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EUROPEAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (ISSN 0392-2936) publishes original peer reviewed works in the fields of female genital cancers and related subjects and also proceedings of gynecologic oncology society meetings all over the world. The Journal is covered by CURRENT CONTENTS, SCIREACH, RESEARCH ALERT, INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica, CURRENT ADVANCES IN CANCER RESEARCH, BIOSIS.
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Robot-assisted laparoscopic surgery in patients with advanced ovarian cancer: Farghaly’s technique

S.A. Farghaly

The Joan and Sanford Weill Medical College of Cornell University, and The New York Presbyterian Hospital
Weill Cornell University Medical Center, New York, NY (USA)

Minimally invasive surgery for gynecological cancers demonstrated its safety and feasibility to treat those disorders [1-3]. Surgeon’s experience, training, and limitations of oncologic laparoscopic surgery that include counter-intuitive emotion, non-wristed instrumentation, and a reliance of skilled surgical assistance contribute to a difficult and long learning curve. The da Vinci surgical system is a robotic surgical platform that was approved by the FDA in April 2005 for gynecologic application. The robot is a telesurgical system that allows the surgeon to operate at a console rather than at the patient’s bedside. The three-dimensional image provided by the camera gives the surgeon a life-like view of the surgical field with magnification. The surgeon manipulates instruments equipped with “endowrist” movements that duplicate the movements of the hand. The small instruments and magnification allow for accuracy. Robot-assisted surgery leverages the advantages of standard laparoscopy while restoring three-dimensional vision, ergonomic and intuitive controls, and wristed instruments that approximate the motion of the human hand. The only absolute contraindications to robotic surgery are: 1) patients who cannot tolerate general anesthesia and 2) patients who cannot tolerate a steep Trendelenberg position.

For many institutions, assisted robotic surgery has become the technique of choice for performing surgery for endometrial and cervical cancer patients. In patients with advanced ovarian cancer, optimal debulking could be achieved, through performing total hysterectomy, bilateral salpingo-oophrectomy, para-aortic lymphadenectomy, bilateral pelvic lymphadenectomy (including obturator, hypogastric, external iliac, and common iliac lymph nodes), and partial omentectomy. It is important to operate in all quadrants of the abdomen. This could be achieved by rotating and redocking the robot at the patient’s head. This position allows para-aortic lymphadenectomy to the level of renal vessels, and performs debulking of cancerous tissue of the upper abdomen, diaphragm, and liver to less than 0.5 cm residual tumor. The advantage of using this method is low blood loss; reasonable operative time with short hospital stay. The preferred surgical technique (Farghaly’s Technique), involves bowel prep beginning one day before surgery with Half Lytely and Bisacodyl Tablet bowel Prep Kit. The empty bowels are less likely to obstruct the surgical field view. The day prior to surgery a pressure-controlled anesthesia is used for ventilating patients in steep Trendelenberg position. After induction of anesthesia, the patient is placed in steep Trendelenberg position with lithotomy position to facilitate exposure. Disposable foam egg crate beneath the torso is used to prevent slippage during surgery. The patient’s arms are tucked to her sides, and shoulder blocks are placed to minimize patient positional shifts and prevent nerve injury. Then a vaginal probe is used to identify the vaginal margin below the cervix. The patient is prepped and draped in a standard fashion. A six-trocar transperitoneal approach is used. A two-mm laparoscopic port is placed in the left upper quadrant two cm below the costal margin in the mid clavicular line. All subsequent ports are placed under direct visualization. The abdomen is then insufflated with CO₂ gas to a maximum pressure of 15 mmHg. The patient is subsequently placed in a steep Trendelenberg position, and the secondary trocars are placed. After that, the two-mm left upper quadrant port is converted to a 10-12 mm assistants’ port. The da Vinci surgical system is then docked between the legs at the foot of the bed. A zero-degree camera is used for the entire procedure. Maryland grasper is used in the left robotic arm; also a bipolar endowrist instrument is placed in the fourth robotic arm and used for retraction. The abdominal cavity is inspected systemically by using atraumatic forceps: the ovaries, fallopian tubes, uterus, pelvic peritoneum, serosa, and mesentery of the large bowel, liver surface, paracolic gutters, and diaphragm are thoroughly visualized. It is important to operate in all four quadrants of the abdomen. The surgical procedure begins with right para-aortic lymphadenectomy, followed by left para-aortic dissection, pelvic lymphadenectomy, and total hysterectomy, bilateral salpingo-oophrectomy, and partial omentectomy. The boundaries of dissection of the pelvic-aortic lymphadenectomy are consistent with the Gynecologic Oncology Group (GOG) surgical procedures manual. For pelvic lymphadenectomy, this includes the middle psoas muscle (laterally), deep circumflex iliac vein (inferiorly), mid-
common iliac vessels (superiorly), and obturator nerve (posteriorly). The aortic lymph node dissection superior boundaries are to the ovarian vessel on the right and to the inferior mesenteric artery on the left. Also, segmental resection and cauterization of the diaphragm, peritoneal ablation, and stripping of pelvic peritoneum are carried out. The cancerous tissues are thoroughly debulked to less than 0.5 mm in diameter residual tumor, by using the electrosurgical loop excision procedure (LEEP) and argon beam coagulator (ABC). A ten-mm loop electrode with several extensions is inserted through a port. The loop electrode extension is attached to a handheld cautery and is used on the cutting mode at 50-W cutting/50-W coagulation setting. Small seedling tumors and bases of tumors are coagulated by using the ABC through the laparoscopic port at a setting of 85. For operating instruments, a monopolar spatula instrument is used in the right hand and a plasma kinetic grasper in the left hand. For large pedicles, a Ligasure tissue Fusion System is used for a combined vessel sealing and cutting through the assistant’s port. A vaginotomy is performed. The specimens are placed in endocatch bags and delivered vaginally. The vaginal cuff is closed with two-0-coated vicryl sutures, 8-18 inches in length on CT-1 36 mm needle, beginning from each corner and meeting in the middle. Pelvic drain is inserted through the ten-mm port and ports are removed under vision. For the trocars site, all layers of the abdomen are closed separately only at level of the umbilical trocar site insertion to avoid trocar metastases, using vycril 1 with J needle for the fascia, monocril 2-0 for the subcutaneous, and nylon 3-0 for the skin with a subcuticular suture. Postoperatively, patient is given a regular diet the night of surgery and oxycodone/acetaminophen for pain relief. The Foley catheter is left in place and discharge from the hospital and a voiding trial is scheduled in clinic within one week. The pelvic drain is kept for 24-48 hours depending on the outflow. Operative time could be maintained at 240 minutes and surgical blood loss of 100 cc. The patient is discharged on postoperative day two but could be discharged one day following surgery. In general, the goal of minimally invasive robot-assisted laparoscopic surgery is to duplicate traditional open procedures via small incisions in the skin with surgical outcomes equivalent or superior to a traditional surgical approach. It has been demonstrated that minimally invasive surgery is associated with less blood loss, shorter hospital stay, less postoperative pain, improved cosmesis, and faster recovery compared to traditional approaches [4-6]. Robotics and laparoscopy appear preferable to laparotomy for the surgical treatment of ovarian cancer patients requiring primary tumor excision alone or with one additional major procedure. Sert and Abeler described their experience with robotic radical hysterectomy with an operative time of 241 minutes and blood loss of 71 cc [7]. Kim et al. reported on ten cases with an operative time of 207 minutes, blood loss of 355 cc, and nodal yield of 27. No conversion to laparotomy was reported [8]. Fanning et al. reported on their experience with robotic radical hysterectomy for cervical cancer. They reported operative time of 390 minutes without conversion to laparotomy. They reported hospital stay of one day and surgical blood loss of 300 cc [9]. Magrini et al. emphasized that optimal debulking is more important than the type of surgical method, as there was no difference in the overall and progression-free survival for robotic and laparotomy patients. However, one of the most important factors to consider is the challenge associated with the need to explore all four quadrants of the abdomen in cases of advanced ovarian cancer with carcinomatosis [10]. They have suggested the rotation of operative table and redocking the robot at the patient’s head. This way, it was easier to excise para-aortic lymph nodes to higher levels and other upper abdominal metastases. Also, the reverse-docking position was helpful when the transverse colon needed mobilization for bowel resection in their study. Farghaly presented a technique of robotic-assisted laparoscopic anterior pelvic exenteration in patients with advanced ovarian cancer, involving the lower urinary tract. He found that it was safe, feasible, and cost-effective with acceptable operative, pathological and short- and long-term clinical outcomes. It retained the advantage of minimally invasive surgery [11]. To conclude, robot-assisted laparoscopic surgery for patients with advanced ovarian cancer is safe and effective alternative to laparoscopic and laparotomy surgery. It has the advantage of three-dimensional vision, ergonomic and intuitive control, and wristed instrument that approximate the motion of the human hand. It can decrease the incidence of intraoperative complications and postoperative wound complications without significantly increasing operative time or blood loss. The procedure is cost-effective with acceptable operative, pathological, and short- and long-term clinical outcomes. It retains the advantage of minimally invasive surgery.

References
Robot-assisted laparoscopic surgery in patients with advanced ovarian cancer: Farghaly’s technique


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18th World Congress on
Controversies in Obstetrics, Gynecology & Infertility
(COGI)
October 24-27, 2013 - Vienna, Austria

www.congressmed.com/cogi
Barrel index of bulky cervical tumours and intrauterine fluid determined by MRI as additional prognostic factors for survival

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¹Department of Gynaecology, ²Department of Radiology, Leiden University Medical Center, Leiden (The Netherlands)

Summary

Objective: to investigate whether morphologic characteristics determined by magnetic resonance imaging (MRI) can discriminate between bulky cervical tumours with a favourable or worse prognosis. Materials and Methods: MRI examinations were performed in 24 patients with cervical cancer Stage ≥ 1B2. The ratio between tumour width and length (barrel index: BI) and the presence of intrauterine fluid retention were related to survival in a multivariate regression analysis. Results: BI and intracavitary fluid were predictors of survival, independent from tumour diameter and other known important factors for survival. A cut-off value of 1.40 for the BI proved to be the best prognostic factor with respect to recurrence and death; the hazard ratios of BI > 1.40 as compared to BI ≤ 1.40 were 18.9 (95% CI 2.8 to 125.6) for recurrent disease and 16.4 (95% CI 2.9 to 93.9) for death by cervical cancer. The hazard ratios of intracavitary fluid retention were 73.6 (95% CI 5.3 to 1,016.4) and 48.1 (95% CI 4.7 to 491.6) for recurrence and death, respectively. Conclusion: The morphologic characteristic BI and the presence or absence of intracavitary fluid as determined by MRI might have predictive value for survival in patients with bulky cervical tumours.

Key words: Uterine cervical neoplasms; MRI; Morphology; Growth pattern; Intrauterine fluid.

Introduction

The staging procedure of cervical cancer is based on the FIGO staging system, which does not routinely include magnetic resonance imaging (MRI), or computer tomography (CT) scan [1]. Accordingly, although used more and more frequently, not all clinics with available MRI or CT use these imaging modalities in the routine work-up of cervical cancer patients. Tumour extension (i.e. tumour diameter and infiltration of surrounding tissue like the parametria, vagina, bladder, and rectum) is the most important factor in the FIGO staging system and is considered to be the deciding factor for the choice of the primary treatment [2].

Due to poor prognostic properties, bulky cervical tumours are assigned to a separate class in the FIGO system (1B2 or above); morphology, however, is not accounted for [3, 4]. A prospective study of 400 surgically-treated bulky (diameter > four cm) cervical cancer patients showed that morphologic characteristics of the tumour are of prognostic significance. Patients with a barrel-shaped tumour had a significantly worse disease-free survival (DFS) and overall survival (OS) after primary surgery compared to patients with the same FIGO Stage but with an exophytic growing tumour. The authors of that study concluded that surgical treatment should be considered for patients with bulky exophytic cervical cancer [5]. There is no general agreement regarding the optimal treatment of bulky cervical tumours. Morphology could play a role in the selection of a subgroup that is suitable for primary surgery.

The purpose of this study was to determine whether MRI could discriminate between patients with morphologically favourable bulky cervical tumours and patients with bulky cervical tumours with a worse prognosis. MRI allows accurate visualization and assessment of extension of the tumour in surrounding tissues, without the need for intravenous contrast [6]. The authors performed a retrospective observational study in patients with surgically-treated bulky cervical cancer of whom MRI of the pelvis was performed prior to surgery. The ratio between tumour width and length and the accumulation of fluid in the uterine cavity were related to DFS and OS of the patients.

Materials and Methods

Patients

All data were obtained in accordance with the medical ethical guidelines of this Hospital. One hundred and eight patients were surgically treated for cervical cancer Stage 1B2 or above in this centre between 1984 and 2000. Twenty-four of these patients had a preoperative MRI scan and were included in the study.

Clinical assessment

The included patients were evaluated preoperatively by the standard staging procedure of this gynaecologic oncology department, which included complete physical and gynaecologic examination under anaesthesia, routine blood and urine analyses, chest radiography, and ultrasound to exclude ureteral dilatation. Additionally, a MRI scan was performed. The indications for the MRI scan were high suspicion of tumour extension into the parametria, bladder, or rectum, and lymph node metastases, based on physical examination under anaesthesia. The MRI scans were performed on a 1.5 T scanner, using a phased
Barrel index of bulky cervical tumours and intra uterine fluid determined by MRI as additional prognostic factors for survival

array torso coil. All patients were scanned in supine position. The imaging protocol consisted of axial T1-weighted fast spin echo images (TR/TE = 575/8 msec, 24 slices, four-mm thickness, field of view 200 mm, matrix 320 x 256), and axial and sagittal T2-weighted fast spin echo images (TR 4800 msec, TE 150 msec, 24 slices, four-mm thickness, field of view 200 mm, 320 x 256 matrix), through the pelvic region. The images were analyzed on a dedicated workstation.

**Treatment**

In this centre, the standard treatment for cervical cancer Stage 1B and 2A is radical abdominal hysterectomy and pelvic lymphadenectomy [7]. For one patient with FIGO Stage 2B, the treatment was individualized to chemotherapy followed by radical hysterectomy. Postoperative pathologic assessment included histological type, infiltration depth, involvement of the parametria, resection margins, tumour diameter, and lymph node metastases. Patients received adjuvant radiotherapy in case of ≥ one tumour positive lymph node, and if parametrial involvement or non-radical surgical resection margins (< five mm free of tumour) were found. An additional criterion for adjuvant radiotherapy from 1997 onwards was the presence of at least two of the following prognostic unfavourably factors: tumour diameter > four cm, invasion depth > 15 mm, and vaso-invasion. In individual cases of severe tumour extension, platinum-based chemoradiation was offered.

**Table 1. — Characteristics of 24 patients with bulky (> 40 mm) cervical tumours.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Min - Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50.8</td>
<td>31 - 75</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>16</td>
<td>67</td>
</tr>
<tr>
<td>Surinam</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>16</td>
<td>67</td>
</tr>
<tr>
<td>2A</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>2B</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Neo-adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Disadvantageous pathological parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive lymph node</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>Resection margins five mm free of tumour</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>Parametria tumour positive</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Invasion depth &gt; 15 mm</td>
<td>19</td>
<td>79</td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td>57.3</td>
<td>45 - 80</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Regional</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Distant</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, by cervical cancer</td>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td>Yes, by other cause</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>DFS (mth)</td>
<td>31.2</td>
<td>0.8 - 110.1</td>
</tr>
<tr>
<td>OS (mth)</td>
<td>44.4</td>
<td>0.8 - 131.6</td>
</tr>
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N = number; DFS = disease-free survival; OS = overall survival.

**Table 2. — Cox regression analysis of the shape of the cervical tumour (BI).**

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>DFS HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.9</td>
<td>0.9 to 1.0</td>
</tr>
<tr>
<td>Positive lymph nodes</td>
<td>0.1</td>
<td>0.01 to 0.5</td>
</tr>
<tr>
<td>Invasion depth &gt; 15 mm</td>
<td>3.7</td>
<td>0.6 to 22.7</td>
</tr>
<tr>
<td>Parametria tumour positive</td>
<td>47.0</td>
<td>3.9 to 562.6</td>
</tr>
<tr>
<td>Resection margins &lt; 5 mm</td>
<td>1.1</td>
<td>0.3 to 4.2</td>
</tr>
<tr>
<td>Barrel Index &gt; 1.40</td>
<td>18.9</td>
<td>2.8 to 125.6</td>
</tr>
</tbody>
</table>

**Table 3. — Inter-observer concordances.**

<table>
<thead>
<tr>
<th>BI &gt; / ≤ 1.40</th>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Observer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa</td>
<td>x</td>
<td>0.74</td>
<td>0.50</td>
</tr>
<tr>
<td>Observer 1</td>
<td>x</td>
<td>0.74</td>
<td>x</td>
</tr>
<tr>
<td>Observer 2</td>
<td>0.50</td>
<td>0.58</td>
<td>x</td>
</tr>
<tr>
<td>Observer 3</td>
<td>0.67</td>
<td>0.75</td>
<td>x</td>
</tr>
</tbody>
</table>

**Table 4. — Cox regression analysis of intracavital uterine fluid retention.**

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>DFS HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.9</td>
<td>0.9 to 1.0</td>
</tr>
<tr>
<td>Positive lymph nodes</td>
<td>1.6</td>
<td>0.3 to 8.4</td>
</tr>
<tr>
<td>Invasion depth &gt; 15 mm</td>
<td>0.2</td>
<td>0.01 to 2.2</td>
</tr>
<tr>
<td>Parametria tumour positive</td>
<td>24.2</td>
<td>1.9 to 304.4</td>
</tr>
<tr>
<td>Resection margins &lt; 5 mm</td>
<td>1.0</td>
<td>0.2 to 5.6</td>
</tr>
<tr>
<td>With intracavital fluid retention</td>
<td>73.6</td>
<td>5.3 to 1016.4</td>
</tr>
</tbody>
</table>

**Measurements**

The maximal cranio-caudal length of the cervical tumour (increased signal on T2-weighted images compared to normal cervical tissue) parallel to the cervical axis and the maximal width perpendicular to the cervical axis were measured (Figure 1). Subsequently the ratio between tumour width and length was calculated and expressed as the ‘barrel index’ (BI = width / length). A barrel-shaped tumour was expected to cause fluid retention in the uterine cavity by obstruction of the endocervical canal. The
authors therefore visually-assessed the presence of fluid in the lumen of the uterus. Because differentiating between fluid and endometrial glands and stroma can be difficult, they defined two categories: ‘no fluid or just a stripe of fluid’, and ‘more than a stripe of fluid’. Presence of intracavital fluid was recognized by its biconcave shape. The two groups are further referred to as ‘without fluid retention’ and ‘with fluid retention’. Figure 2 shows an example of a uterine cavity with fluid retention (contrary to the example in Figure 1). All measurements were independently performed by three different radiologists (AŠ, MW, and IL) who were blinded for the follow-up status of the patient.

Follow-up

Follow-up data and patient characteristics were extracted from the medical records. The follow-up period for this study extended from the individual date of surgery to November 2007.

Statistical analysis

Cox regression was used to analyze the effect of the BI and fluid retention on DFS and OS. First the authors performed univariate analysis for varying cut-off points of the BI to determine the optimal cut-off point for the BI in the subsequent analyses. The multivariate analysis included BI or fluid retention, and the known disadvantageous prognostic factors age, positive lymph nodes, invasion depth > 15 mm, tumour positive parametria, and resection margins < five mm free of tumour. Student’s t-test was used to compare the mean tumour width between the patients with and without intracavital fluid retention. For the statistical analysis with respect to prognosis, the measurements of one investigator (AŠ) were used. Cohen’s kappa coefficient was calculated to evaluate the interobserver concordance of the MRI determinations (BI and presence of intracavital fluid).

Results

General characteristics

General characteristics, pathology results, and results with respect to survival after radical hysterectomy of the 24 patients are summarized in Table 1. The group consisted of 16 (67%) Dutch and eight (33%) Surinamese patients who were referred to the Netherlands for cervical cancer treatment. Two patients received neoadjuvant chemotherapy, which was begun after the MRI scan. The follow-up period ranged from 0.8 to 131.6 months. Mean DFS was 31.2 months, and mean OS 44.4 months. One patient died in the first month after treatment by another cause other than cervical cancer and was excluded from the survival analyses. Three other patients were lost to follow-up after follow-up periods of 4.0, 4.6, and 21.3 months, respectively. Fourteen patients (61%) had a recurrence. All patients with recurrent disease died of cervical cancer.

Barrel index

Univariate Cox regression analysis with varying BIs ranging from 1.10 to 1.90 showed that a cut-off point of 1.40 for the BI was the best prognostic factor with respect to recurrence and death in this sample. Ten of 23 patients (44%) had a BI > 1.40, the rest of the BIs were 1.40 or smaller. The group of patients with a BI > 1.40 consisted of seven patients (70%) with FIGO Stage 1B2, two (20%) with 2A, and one (10%) with 2B. The group with BI ≤ 1.40 consisted of nine patients (64%) with Stage 1B2, and five (36%) with 2A. Eight patients with a BI > 1.40 (80%) and six (46%) with a BI ≤ 1.40 had a recurrence. Table 2 shows the results of the multivariate survival analysis based on this cut-off point. The hazard ratio (HR) of BI > 1.40 as compared to BI ≤ 1.40 was 18.9 (95% CI 2.8 to 125.6) for recurrent disease, and 16.4 (95% CI 2.9 to 93.9) for death by cervical cancer. Exclusion of the two patients that received adjuvant chemoradiation from the analysis increased the HR’s of BI > 1.40 to 32.2 (95% CI 3.3 to 312.9) for DFS and to 20.8 (95% CI 2.9 to 151.7) for OS. The inter-observer concordance of the MRI meas-
urements of BI > / ≤ 1.40 by the three radiologists was moderate to substantial (kappa = 0.50 to 0.74) (Table 3).

**Intracavitual fluid retention**

In 14 of the 24 patients (58%), high intensity fluid was present in the uterine cavity. There was a trend towards lower stages in the fluid retention group (11 patients (79%) with 1B2, and 3 (21%) with 2A) as compared to the group without fluid retention (five patients (50%) with 1B2, four (40%) 2A, and one (10%) 2B). In the 23 patients included for the survival analyses, 11 of 14 patients (79%) with fluid retention, and three of nine patients without fluid retention (33%) had a recurrence. The hazard ratio of fluid retention as compared to a stripe or no fluid was 73.6 for recurrent disease (95% CI 5.3 to 1016.4) and 48.1 for death by cervical cancer (95% CI 4.7 to 491.6) (Table 4). Exclusion of the two patients that received adjuvant chemoradiation from the analysis decreased the HR for DFS of fluid retention to 43.8 (95% CI 3.2 to 602.2) for DFS and increased the HR for OS of fluid retention to 54.8 (95% CI 4.4 to 674.2). Interobserver concordance of the estimation of high intensity retention material in the uterine cavity on MRI was substantial to almost perfect (kappa = 0.67 to 0.92) (Table 3).

**BI and fluid retention with regard to tumour size**

Six of the ten patients (60%) without fluid retention had a BI ≤ 1.40 based on MRI measurements, and six of 14 patients (43%) with fluid retention had a BI > 1.40. The largest tumour width measured on MRI in the group without fluid retention was 59 mm, whereas 57% of patients with fluid retention had a tumour width > 59 mm, with a maximum of 87 mm. The difference between the mean tumour width of the group with fluid retention (63 mm) and without fluid retention (50 mm), was significant (mean difference = 12.5 mm, 95% CI = 2.7 to 22.2).

Inclusion of the maximal tumour width in the multivariate survival analysis for BI > / ≤ 1.40 resulted in a decrease of the HR from 18.9 to 11.3 (95% CI = 1.4 to 92.6) for DFS and from 16.4 to 12.2 (95% CI = 1.8 to 85.2) for OS. In both survival analyses, however, the BI remained an independent prognostic factor. A similar decrease of the HR for fluid retention was observed when the maximal tumour width was included in that multivariate analysis: decrease of the HR from 73.6 to 26.4 (95% CI = 2.2 to 315.5) for DFS and from 48.1 to 24.8 (95% CI = 2.5 to 241.4) for OS. Fluid retention also remained an independent prognostic factor.

**Discussion**

The results of this observational study on growth pattern of cervical tumours in relation to recurrence and survival suggest that the morphologic characteristic BI and presence or absence of intracavitual fluid, as determined by MRI, may have prognostic value.

A division in groups based on the ratio between tumour length and width (BI) was an independent prognostic factor for recurrence and OS in this study. The relation to survival was independent from the known tumour diameter prognostic factor. In previous studies, a barrel-shaped growth pattern and tumour size were also found to be independent disadvantageous prognostic factors [5, 8]. The results of these studies support the present findings. To the best of the authors’ knowledge, this is the first study in which the BI of cervical tumours, determined by MRI, was found to be a prognostic factor for survival.

The results of this study suggest that presence or absence of fluid in the uterine cavity is a strong prognostic factor for recurrence and OS. The HR for recurrence and OS were even higher than for BI. Intrauterine retention material could not conclusively be related to morphology based on MRI assessment, but it had a clear relation with tumour width as measured on MRI. Although intrauterine fluid accumulation is a quite common finding in transvaginal sonography among asymptomatic postmenopausal women, accumulation of fluid in the uterine cavity on MRI and transvaginal sonography imaging has been related to gynaecologic cancer [9-12]. As far as the authors know, this is the first study in which this finding has been correlated to growth pattern and to prognosis. Given the substantial to almost perfect interobserver concordance of this parameter on MRI, and the strong relation the authors found in this study to prognosis, retention material in the uterine cavity is a promising prognostic parameter. Further larger studies are needed to confirm these findings.

In this study, the authors found that tumour diameter is also a prognostic factor for recurrence and OS after surgical treatment of cervical cancer. Previous reports confirm this finding [8]. Multivariate survival analysis including tumour diameter, BI, and fluid retention, however, showed that only BI and fluid retention remained independent risk factors. These findings suggest that tumour diameter, BI, and fluid retention are correlated but that BI and fluid retention are stronger independent prognostic factors.

This study has several limitations. One limitation is that in daily practice in this centre, MRI imaging is not routine in the staging procedure for cervical cancer. In this study group, an MRI scan was performed based on clinical grounds. The studied population might therefore not be a representative sample of the average population of patients with bulky cervical cancer. This probably explains the very high HRs found for BI and fluid retention for recurrence and OS and the unusual finding that lymph nodes appear to be protective in some of the analyses. Furthermore, follow-up was not fully documented in three of the 23 patients (13%) that were included in the survival analyses. When these individuals were completely removed from the analyses, the results did not change substantially (data not shown). The authors therefore do not think that the results of this study are much influenced by the individuals that were lost to follow-up during the study. Another limitation is the small study size. Despite the small study size, these results were highly-significant, suggesting that the BI and presence or absence of intracavitual fluid are strong prognostic factors. Furthermore it...
has already shown that BI is a prognostic factor. The additional value of this study is that these results show that the prognostic factor BI can be determined with MRI prior to therapy. Larger and prospective studies are needed to confirm these results.

In conclusion, the results of this study support the reported finding that morphology of bulky cervical tumours is predictive for prognosis. The morphologic characteristic BI and intracavitary fluid as assessed by MRI might be helpful in identifying a subgroup of individuals with bulky cervical cancer with a better prognosis and who are therefore eligible for primary surgical therapy.

References


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Analysis of failures and clinical outcome of advanced epithelial ovarian cancer in patients with microscopic residual disease at second-look reassessment following primary cytoreductive surgery and first-line platinum-based chemotherapy

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2Division of Gynecology, European Institute of Oncology (EIO), Milan
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Introduction

Epithelial ovarian cancer is the leading cause of gynecologic cancer death in Western countries [1]. Survival is highly-dependent on tumor Stage. As far as patients with advanced disease are concerned, the International Federation of Gynecology and Obstetrics [FIGO] Annual report n. 26 showed that the five-year overall survival ranged from 46.7% for Stage IIIa, to 41.5% for Stage IIIb, 32.5% for Stage IIIc, and 18.6% for Stage IV [2]. Cytoreductive surgery followed by paclitaxel/platinum-based chemotherapy is the standard treatment for advanced disease, which is able to achieve a clinical complete response rate of 50% approximately, a pathological complete response rate of 25%-30%, a median progression-free survival of 15.5 to 22 months, and a median overall survival of 31 to 44 months [3-6]. Almost 75% of the clinically complete responders and 30% to 50% of pathologically complete responders will ultimately relapse after a lead time of 12.5 to 52.5 months [6-12]. Most recurrences develop within the initial two years.

Materials and Methods

Nine-five women were retrospectively analyzed. Residual disease after initial surgery was > one cm in 58 (61.1%) patients, first-line chemotherapy was paclitaxel/platinum-based in 70 (73.7%) patients, second-look findings showed no macroscopic residuum but positive random peritoneal biopsies and/or positive washing (“true” microscopic residual disease) in 79 (83.2%) patients, and a macroscopic residuum which was completely resected (converted complete response) in 16 (16.8%) patients. Results: Eight-one (85.2%) patients developed recurrent disease after a median time of 14 months (range four to 51). The abdomen (29.6%) and the pelvis (28.4%) were the most common sites of failure. Two- and five-year survival after second-look were 78.1% and 31.0%, respectively. The clinical and pathological features with prognostic relevance at presentation (age, histotype, and tumor grade), as well as type of first-line chemotherapy and treatment after second-look were not related to the clinical outcome. There was a trend for a better survival in patients with optimal primary cytoreduction compared with those with suboptimal primary cytoreduction (five-year survival = 42.7% vs 23.4%).

Conclusions: These data confirm the unsatisfactory clinical outcome of patients with microscopic residual disease after first-line chemotherapy and the limited benefit of second-look reassessment.

Key words: Epithelial ovarian cancer; Surgical cytoreduction; Chemotherapy; Second-look surgery; Survival.
completion of chemotherapy; and iii) who had no macroscopic residuum but positive random peritoneal biopsies and/or positive peritoneal washing ("true" microscopic residual disease) at second-look, or who had a macroscopic residuum which was completely resected during the second-look (converted complete response). Patients who underwent neoadjuvant chemotherapy followed by interval debulking surgery were not included in the present analysis.

The hospital records, including surgical notes and pathological reports of the 95 women, were collected using a common form with standardized items and a common database. Some of these patients had been enrolled in phase II multicenter Italian study (After-6 Protocol 2) aimed to assess the efficacy of weekly 60 mg/m² paclitaxel as maintenance treatment in patients who had microscopic residual disease after six cycles of paclitaxel/platinum-based chemotherapy [22].

At presentation, tumor Stage and histological diagnosis were determined according to FIGO criteria and the histological typing system of the World Health Organization (WHO), respectively. Tumors were graded as well (G1), moderately (G2), or poorly (G3) differentiated. The histological material was reviewed by the same pathologists in each center. Additional therapy after second-look was given according to local protocols, and changed at the long-term interval of the study.

The evaluation of the course of disease was based on clinical examination, serum CA 125 assay, chest X-ray, abdominal-pelvic ultrasound, and/or computed tomography (CT) scan. Further investigations were performed where appropriate. An asymptomatic patient with rising CA125 levels and negative clinical and imaging examinations was no longer considered to have recurrent disease and underwent a more stringent follow-up program.

The median follow-up of survivors was 74 months (range 8 to 137).

Statistical methods

The SAS statistical package (release 8.2) was used for computations. The time from second-look surgery to death or last observation was defined as survival after second-look. The analysed prognostic variables included patient age, histological type, tumor grade, residual disease after initial surgery, first-line chemotherapy (paclitaxel/platinum-based chemotherapy vs other), second-look findings ("true" microscopic residual disease vs converted complete response), and treatment after second-look (platinum-based chemotherapy vs weekly paclitaxel vs other). Survival analyses were performed according to the Kaplan-Meier product-limit method. Differences between groups were evaluated by the log-rank test.

Results

Patient characteristics at initial diagnosis are summarized in Table 1. Median age was 53 years, FIGO Stage was IIIC in 82 (86.3%) cases, histological type was serous in 72 (75.7%) cases, tumor grade was G3 in 64 (67.3%) cases, and residual disease was > one cm in 58 (61.1%) cases. First-line chemotherapy consisted of paclitaxel/platinum-based regimens in 70 (73.7%) cases. Second-look reassessment was performed by laparotomy in 42 (44.2%) and by laparoscopy in 53 (55.8%) cases. Second-look findings showed a "true" microscopic residual disease in 79 (83.2%) cases, and a converted complete response in 16 (16.8%) cases. Nine-two (96.8%) patients received additional chemotherapy.

Nine patients did not develop recurrent disease and were still alive after a median time of 37 months (range 9 to 114) from second-look, five patients died due to intercurrent disease with no evidence of recurrent tumor after a median time of 29 months (range two to 84), and 81 (85.2%) patients developed recurrent disease after a median time of 14 months (range four to 51). The abdomen (29.6%) and the pelvis (28.4%) were the most common sites of recurrent disease (Table 2).

Treatment at recurrence consisted of chemotherapy in 62 patients, surgery plus chemotherapy in 16 patients (with additional radiotherapy in one patient), and best supportive care in three patients.

Among the 81 relapsed patients, 69 died after a median death of 53 months (range 9 to 114) after second-look surgery. Median time from second-look to death was 33 months (range 2 to 114) for patients who had microscopic residual disease after six cycles of paclitaxel/platinum-based chemotherapy. Median time from second-look to death or last follow-up was 74 months (range 8 to 137) for the 52 surviving patients.

Table 1. — Patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients: 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>53 years (range 31 to 82)</td>
</tr>
<tr>
<td><strong>FIGO Stage</strong></td>
<td></td>
</tr>
<tr>
<td>IIIA-IIIB</td>
<td>5</td>
</tr>
<tr>
<td>IIC</td>
<td>82</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
</tr>
<tr>
<td><strong>Tumor grade</strong></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>3</td>
</tr>
<tr>
<td>G2</td>
<td>28</td>
</tr>
<tr>
<td>G3</td>
<td>64</td>
</tr>
<tr>
<td><strong>Histological type</strong></td>
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</tr>
<tr>
<td>Serous</td>
<td>72</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>9</td>
</tr>
<tr>
<td>Mucinous</td>
<td>0</td>
</tr>
<tr>
<td>Clear cell</td>
<td>2</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>4</td>
</tr>
<tr>
<td>Mixed</td>
<td>7</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1</td>
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<tr>
<td><strong>Residual disease after first surgery</strong></td>
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</tr>
<tr>
<td>0-1 cm</td>
<td>37</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>58</td>
</tr>
<tr>
<td><strong>First line chemotherapy</strong></td>
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</tr>
<tr>
<td>Platinum-based non taxane-combination</td>
<td>16^</td>
</tr>
<tr>
<td>Single-agent platinum</td>
<td>9</td>
</tr>
<tr>
<td>Paclitaxel + platinum-based CT</td>
<td>70^</td>
</tr>
<tr>
<td><strong>Second-look findings</strong></td>
<td></td>
</tr>
<tr>
<td>&quot;True&quot; microscopic residual disease</td>
<td>79</td>
</tr>
<tr>
<td>Converted complete response</td>
<td>16</td>
</tr>
<tr>
<td><strong>Treatment after second-look</strong></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>92</td>
</tr>
<tr>
<td>Platinum-based non taxane-combination</td>
<td>13*</td>
</tr>
<tr>
<td>Single-agent platinum</td>
<td>7</td>
</tr>
<tr>
<td>Paclitaxel + platinum-based CT</td>
<td>12**</td>
</tr>
<tr>
<td>Weekly paclitaxel (up to 21 cycles)</td>
<td>31</td>
</tr>
<tr>
<td>Other agents</td>
<td>29***</td>
</tr>
<tr>
<td>No treatment</td>
<td>3</td>
</tr>
</tbody>
</table>

^Carboplatin + gemcitabine, 1; platinum + cyclophosphamide ± doxorubicin or epirubicin, 15. **Paclitaxel + carboplatin, 61; paclitaxel + cisplatin, 5; docetaxel + carboplatin, 2; Ifosfamide + paclitaxel + cisplatin, 2. ***Doxil, 4; topotecan + doxil, 1; doxorubicin or epidoxorubicin, 15. *Platinum + topotecan, 4; platinum + doxil, 5; platinum + cyclophospha-mide ± doxorubicin or epidoxorubicin, 4 **. **Paclitaxel + carboplatin, 11; paclitaxel + cisplatin, 1. ***Doxil, 4; topotecan + doxil, 1; doxorubicin or epidurubicin, 7; paclitaxel, 13; unknown, 4. G1: well-differentiated; G2: moderately-differentiated; G3: poorly-differentiated.
Table 2. — Sites of first recurrence after second-look surgery.

<table>
<thead>
<tr>
<th>Sites</th>
<th>Patients (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>24 (29.6%)</td>
</tr>
<tr>
<td>Retroperitoneal nodes</td>
<td>13 (16.0%)</td>
</tr>
<tr>
<td>Distant sites *</td>
<td>10 (12.3%)</td>
</tr>
<tr>
<td>Multiple sites **</td>
<td>11 (13.6%)</td>
</tr>
</tbody>
</table>

* Pleura, 1; auxiliary nodes, 1; liver + spleen, 1; liver; 4 + liver + pleura, 1; lung 1; SNC 1; **abdomen + plevis 3; pleura + abdomen 1; pelvis-retroperitoneal nodes 1; pelvis + retroperitoneal nodes + abdomen 2; pelvis + liver 2; abdomen + retroperitoneal nodes 1; abdomen + sovraclavicular nodes 1.

Discrimination

Carboplatin plus paclitaxel is the standard regimen for advanced epithelial ovarian cancer able to achieve a clinical complete response in approximately 50% of the cases [3-6]. Second-look laparotomy or laparoscopy has long been used for the reassessment of disease status in clinically complete responders. However, this surgical procedure has been less and less employed in the last decade due to its limited clinical benefit. Two randomized trials failed to detect a survival advantage with second-look, although both studies had drawn criticism for their design or for the chemotherapy regimen used [23, 24]. More recently, a non-randomized comparison, using an explanatory analysis of the optimally debulked women enrolled in the Gynecologic Oncology Group (GOG) 152 trial, confirmed that the performance of a second-look laparotomy was not associated with longer survival [25]. At second-look reassessment, only 50% of clinically complete responders are in pathological complete response, whereas 15% have a microscopic residual disease, and 35% have a subclinical macroscopic residuum [26]. Approximately, 30%-50% of pathologically complete responders will ultimately relapse [6-12], and consolidation treatments with intra-peritoneal [27] or systemic [28-31] chemotherapy, immunotherapy [32], whole abdomen irradiation [17], and intraperitoneal phosphorus (P) [33] do not improve the prognosis of these patients. The management and the clinical outcome of patients with microscopic residual disease after second-look represent an even more debated problem, and different therapeutic modalities have been tested with uncertain results [13-22]. Whole abdomen irradiation has been largely used, with five-year overall survival rates ranging from 29% to 66% [15, 17, 19, 21]. Intraperitoneal P or systemic and/or intraperitoneal chemotherapy have obtained conflicting, inconclusive, and generally disappointing results [14, 16, 18, 20]. For instance, Spanos et al. [14], who administered intraperitoneal P to 52 patients with Stage III epithelial ovarian cancer after second-look surgery, reported a five-year survival of 75% for the 23 pathologically-complete responders, 48% for the 15 patients with microscopic residual disease, and 32% for the 14 patients with macroscopic residual disease. McCracken et al. [20] reviewed 262 clinically complete responders who had persistent disease after second-look surgery and who further received systemic and/or intraperitoneal chemotherapy. Median survival ranged from 5.9 years for the patients with optimal primary cytoreduction (macroscopic residual disease ≤ one cm after initial surgery) and microscopic residual disease after second-look, to 3.4 years for those with suboptimal primary cytoreduction and microscopic residual disease after second-look, to 2.1 years for those with suboptimal primary cytoreduction and macroscopic residual disease after second-look (p < 0.001), and no salvage chemotherapy regimen was associated with a survival advantage. A Swedish-Norwegian study reported a five-year survival of 40.5% for the women who had microscopic residual disease after four cycles of first-line epidoxorubicin/plat-
inum-based chemotherapy and who underwent six additional cycles of the same regimen as maintenance treatment [17].

In the present study, 81 (85.2%) of the 95 patients developed recurrent disease after a median time of 14 months from second-look, and the abdomen and the pelvis were the most common sites of failure. Among the 81 relapsed patients, 69 (85.2%) died after a median time of 17 months from recurrence. Two- and five-year survival rates after second-look were 78.1% and 31.0%, respectively. The clinical and pathological features with prognostic relevance at presentation (age, histological type, tumor grade), as well as type of first-line chemotherapy and treatment after second-look, were not related to the clinical outcome. In agreement with the data of McCrea!th et al. [20], there was a trend towards a better survival for the patients with optimal primary cytoreduction when compared with those with suboptimal primary cytoreduction (five-year survival = 42.7% vs 23.4%). These data confirm the unsatisfactory clinical outcome of patients with microscopic residual disease after first-line chemotherapy, and the limited benefit of second-look reassessment. Nonetheless, it is noteworthy that patients with a macroscopic residuum, which was completely resected during second-look, had the same survival of those with no macroscopic residuum but positive random peritoneal biopsies and/or positive peritoneal washing. Similarly, in a GOG study including women with persistent epithelial ovarian cancer at second-look, no difference in survival was detected between the 29 patients who had microscopic disease and the 36 patients who had macroscopic residuum and who were surgically cytoreduced to microscopic disease [34].

Attempts to improve the prognosis of patients with advanced epithelial ovarian cancer should be addressed to the identification of both new first-line regimens able to obtain higher complete response rates and effective treatments to consolidate or maintain the response achieved by first-line chemotherapy [35]. The good results obtained with the addition of bevacizumab during and after carboplatin- and paclitaxel-based chemotherapy appear to offer new interesting perspectives for the treatment of these patients and to further reduce the role of second-look surgery [36, 37].

References


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Bioethical issues on the role of contemporary gynecologists concerning HPV vaccination

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Summary
Debate is heating up whether or not to require girls to be vaccinated against the human papillomavirus (HPV), a leading cause of cervical cancer (CC). Prophylaxis against this plague is mainly focused on early detection with Pap test (screening) and recently with administrating HPV vaccines in youths. Objective: To discuss the increased bioethical role of contemporary gynecologist in the young population, with the aim to contribute to the decrease of this malignancy. Materials and Methods: The authors searched the web (data-warehouse: articles, forums, etc., and data-mining: sequence analysis and classification) for HPV vaccination and related bioethical issues. Results: HPV vaccines have already caused debates on whether they must be mandatory and on whether they cause a pseudo-safeness mental state, making youths “forget” necessary annual Pap tests or even worse, urging them in promiscuity, resulting in an increased occurrence of CC. Conclusions: Greece, in order to appropriately apply the Constitutional Law §5 (All persons have the right to the protection of their health...), needs to train contemporary gynecologists in adequate youth consultation and proper family approaches regarding HPV vaccination issues. Enhancing the gynecologist’s role, vaccination’s effectiveness (sensitivity and specificity) will be increased and on the other hand, a rule of social law will be established in the country.

Key words: HPV vaccination; Cervical cancer; Child’s healthcare; Law frame on HPV vaccination; Bioethics.

Introduction
Bioethics (Greek terminology: bios = life; ethos = behavior), as a study of controversial ethics brought about by advances in biology and medicine [1], should be primarily considered as a vital, as well as an enormous socially important filter involved in the process of achieving and applying several scientific inventions and discoveries within our society. The ethical questions, that arise in the relationships among life sciences, biotechnology, medicine, politics, law, and philosophy [1], have already become a daily issue, which every medical specialist, and mostly gynecologists, must inevitably cope with. The significance of the correlation among medical practice, social and political values, personal beliefs, and several philosophical streams can be noted if we adopt a holistic approach towards the «disease» phenomenon and at the same time, consider «precaution» as humanity’s tension against illness occurrence in the general population. Bioethics is the harmonic joint that connects the above sciences, revealing several different canals of interaction among them in a way that on one hand, practicing medicine can promote personal, social, political, and philosophical consciousness, while on the other hand, applying values of the latter sectors in the medical field, indicators like sensitivity and specificity, may be characteristically improved, and concepts such as «precaution», «therapy», «follow-up», etc. can be securely promoted to high qualitative levels. As medical professionals, we must examine in-depth every accepted achievement in medicine and consequently, apply the several accepted methods for the benefit of our patients using ethos as a key tool in our endeavors.

One of the most frequent malignancies that occur in the female population is cervical cancer (CC), being at the same time the main cause of death by gynecological cancer worldwide (500,000 new cases annually [2]. A complex interplay of factors participates in the formation of this malignancy, as emerging from the various scientific fields: unfavorable psychosocial events, systemic immunity, contraception, nutrition, smoking [3], and the persistence of high-risk human papillomavirus (HPV) infection intervene on CC. Moreover, this complex directly results in the composition of CC etiology and determines the precautionary and therapeutic strategies, follow up, and the prognosis of patients. Bioethics has become essential in understanding and approaching the disease. Furthermore, the analysis of risk factors provides the knowledge that smoking habits, number of sexual partners, parity, positive medical history of sexually-transmitted diseases (STDs), and abnormal cervical cytology (Pap smears (+)) are associated with HPV infection [4]. Likewise, the multiple cytopathologic alterations, CIN (I, II, III), could be confronted, using bioethical methods.

A measure which has recently caused debates, is HPV vaccination and the issue whether it should be mandatory or not [5]. This controversial matter needs to be addressed through its bioethical dimension, while taking into consideration CC and HPV «ethos». The current situation on HPV vaccination’s program in combination with average family’s opinion is presented in this study, emphasizing the role of the current gynecologist towards the desired elimination of CC.

Revised manuscript accepted for publication May 31, 2012
Materials and Methods

The web was searched (using several keywords: HPV vaccination, cervical cancer, etc.), and many articles, forums, and blogs were investigated. All the above data warehouse was very useful in Online Analytical Processing (mandatory or optional. Blogs were investigated. All the above data warehouse was very useful in Online Analytical Processing (mandatory or optional. Data-mining, like association rules [7], sequence analysis [8], classification [9], clustering [10], and forecasting [11]. Statistics and decision-making strategies were major means of applying bioethics, as tools of secure interpretation of the online observations.

Results

The extraction of the conclusions was based on a “population” (web material) which was found interesting and was collected objectively, using criteria as quality and traffic of the website, impact factor of the medical web magazine, voting of the online statement. However, human error [12] can never be excluded from an experiment and the conclusions do remain safe by just accepting the restrictions of the subject’s human nature. Another difficulty was the laborious task in adequately detecting the various of factors mentioned directly or just implied in the collected web texts. The authors evaluated the quality of the written speech, the qualifications and ethos of the writer, and the medical terminology. For example, a forum discussion [13], provided us with the following material: “HPV vaccine for my 17-year-old daughter?? Should I give my daughter this vaccine? Not sexually active yet, but the crowd says give it now. What does the gp/lp community say??”. It is obvious that the quality of writing in combination with the cited aspect reveals a person with a level of low education, with a daughter that has a rather late onset of sexual coitus (> 16 years old), tending mostly to choose an “optional” stance. Her inquiry was made in a forum of dubious quality, showing her prejudiced stance, confusion, low level of information, and increased fear towards the vaccine. In the same website in another page [14], the 11th answer urges women not to be advised by doctors while replying on the question: “Just got a CERTIFIED LETTER stating that I am late for my pap smear”. Studying the above web link, the authors approached a population which has adopted an “optional” stance on both the HPV-vaccination program and the regular Pap-test’s visits.

However, the sensitivity of this type of methodology needs further studies with larger «web populations» in order to be well-established. The authors studied 98 different websites and profiled different tables according to the restrictions of the subject’s human nature. Another difficulty was the laborious task in adequately detecting the various of factors mentioned directly or just implied in the collected web texts. The authors evaluated the quality of the written speech, the qualifications and ethos of the writer, and the medical terminology. For example, a forum discussion [13], provided us with the following material: “HPV vaccine for my 17-year-old daughter?? Should I give my daughter this vaccine? Not sexually active yet, but the crowd says give it now. What does the gp/lp community say??”. It is obvious that the quality of writing in combination with the cited aspect reveals a person with a level of low education, with a daughter that had a rather late onset of sexual coitus (> 16 years old), tending mostly to choose an “optional” stance. Her inquiry was made in a forum of dubious quality, showing her prejudiced stance, confusion, low level of information, and increased fear towards the vaccine. In the same website in another page [14], the 11th answer urges women not to be advised by doctors while replying on the question: “Just got a CERTIFIED LETTER stating that I am late for my pap smear”. Studying the above web link, the authors approached a population which has adopted an “optional” stance on both the HPV-vaccination program and the regular Pap-test’s visits.

However, the sensitivity of this type of methodology needs further studies with larger «web populations» in order to be well-established. The authors studied 98 different websites and profiled different tables according to association rules, sequence analysis, and clustering to be applied. An overall online analytical processing (OLAP) table is shown, in Table 1. An example of association rules is shown in Table 2.

Interestingly, in a «mandatory» group with both high education and parity, but with no Pap tests: “Can HPV-vaccination (for this group) subconsciously become an ‘excuse’ for them to avoid the regular (annual) Pap test and eventually, a cause for a relative increase of CC in these women?”. Sequence analysis revealed several hidden co-relations among the collected contexts that enabled to make proper classifications and clustering. For example, a web-person stated «mandatory» and had had low parity, low education level, and positive for smoking habits, while another stated «optional» and also had had low parity, low education, but without having reported «smoking» as a habit. «Smoking» in this category was an addiction far from «just pleasure», applied to characters full of «health fears» that reflectively support «mandatory» as salvation to smoking addiction. Another reported «optional» had been negative for STDs, with low education, while same choice was selected by an individual who had also been STD-negative, with low education, and had undergone regular Pap tests; something showing the wary eye against new methods in our population, is possibly attributed to a lack of proper information. Classification and clustering revealed that non-regular Pap test groups mainly tended to sexual promiscuous behavior, which resulted in high CC incidence [15]. Apparently, high-educated women had supported «mandatory» in subconscious efforts to psychologically protect themselves from their dangerous sexual attitude, while low-educated women had spontaneously expressed «optional», just honestly reporting their real superficial hazardous lifestyle. Finally, forecasting permitted the authors to make several hypotheses, validating them on the internet.

Discussion

The answer whether HPV vaccination should be mandatory or optional, depends on the culture of the population that this dilemma is addressed to, and is a matter of the quality of established law systems within a democratic society. Some societies will support that it should be mandatory, while others optional. However, bioethics, as a third force that intervenes in the «mandatory vs optional» debate seems to provide a happy medium by just accepting both opinions and applying one according to the underlying educational and cultural matrix. Some societies require mandatory while others require optional HPV vaccination. More precisely, the philosophical, political, sociological, and legal background of the society and the overall population’s stance regarding HPV vaccination issues should be studied, discovering interactions that may possibly exist. In a population where the word «mandatory» means social or ethic suppression, bioethics teaches us that such movements would certainly lead our medical endeavors to inevitable failure, with a possible consequent increase in new CC cases. This has become clear in the previous analysis when the authors concluded that vaccination could be misused by women, playing the role of a reasonable-like «excuse» for not undergoing regular Pap tests, something that is extremely fatal. If youths acquire a pseudo-safeness mental state concerning their sexual health and behavior, just because they tend to think of having become invulnerable after getting the HPV shot, they are going to undoubtly “forget” their future
annually-necessary Pap test or, worse, they will be urged in promiscuity and CC occurrence will eventually increase. On the other hand, in a population where «optional» expresses egotism, bioethics advises us to avoid such a strategy. This was clearly proved above, when the authors concluded that «optional» was an off-the-cuff statement of women having a superficial sexually-hazardous lifestyle, far away from responsible behavior. In both cases, the science of bioethics directly gives the message that we must concentrate on other preceding certain values before we will able to give a straightforward answer regarding the matter in question: mandatory or optional? These values became quite obvious after accessing the data-mining procedures, such as the concern in undergoing regular Pap tests, the emotional stability, and general educational level of the population, and provided information regarding certain topics.

Focus must be particularly dedicated to the role of current gynecologists rather than on the debate that involves the nature of the provided HPV vaccination (mandatory/optional) [16]. As it is widely accepted, the specialist has the obligation to inform the patient with honesty and respect, to the inalienable right to self-determination (informed potential consent or refusal) [17], before taking any indicated medical actions for precautionary, therapeutic, or other medical reasons [18]. In other words, the specialist must cooperate with the patient and provide her with the proper knowledge regarding health matters by using a safe and common terminology, contributing in this way to a deeper understanding of the disease and finally, to reach the best possible behavior, praxis, and ethos; something that is a certain guarantee for the success of a medical method. Having the consent of the patient regarding a following necessary medical praxis (by fulfilling a consent form, as a practical application of the basic principle of freedom and integrity (Greek Constitutional Law, Article 5) [19], the latter becomes an active subject, instead of an irresolute experimental object, that dynamically affects the outcome of any applied medical method [18]. Any possible lack of proper information generates the doctor’s tort liability, because of a direct insult to the patient’s multiple legitimate rights [20]; rights that absolutely have an enormous socio-economic dimension, on the grounds of which the State has to provide civilians with suitable services (the “necessary measure”) aiming in the promotion of the general population’s health [21].

The right to health is an inalienable human right that is found in many law systems, such as: Preamble to the Constitution of the World Health Organization (1948), Article 7 of the Convention C102 concerning Minimum Standards of Social Security (at Geneva by the Governing Body of the International Labour Office) [22-24], the Annex III ((f), (g)) of the Declaration of Philadelphia (International Labour Organization) [25], Article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR-adopted by the United Nations General Assembly in 1966) [26], the Greek Constitutional Law §5 (All persons have the right to the protection of their health...) [19], etc.
Bioethical issues on the role of contemporary gynecologists concerning HPV vaccination

The first necessary measure that should be taken is the empowerment of gynecologist’s role in the direction of the proper practice regarding HPV vaccination, meaning that the specialist has to undertake enhanced responsibilities concerning the health of both the patient and of the general population. Proper patient consulting, as well as children consultation on a regular basis (every 6-12 months) before the latter’s first coitus, would provide quite safe education to the child before, during, and after the administration of this vaccine; something that contrasts ideas as the following one: “most parents do not discuss with their child why he/she needs the MMR or DTaP, when they get regular vaccinations. When children ask their parents why they need to get shots, the normal answer is to keep them healthy. The same can be with the HPV virus…” [27]. Of course, the State must invest to improve the training of the new gynecologists: books, extra training semesters in the specialty, conferences, and programs. When medical doctors comprehend the very nature of the words “mandatory” and “optional”, we will be able to evaluate the educational level, the habits, and the deep feelings of a child, as well as of the surrounding family environment within the current social issue and properly decide on the way to approach and cultivate the sexual consciousness of young individuals. Then, the terms “mandatory” and “optional” will generate a new hybrid, a highly qualitative sexually-responsible attitude in youths, which will eventually become a strong guarantee for the universal establishment of a rule of social law. Moreover, this bioethical solution seems to be the only way to decrease CC incidence and thus, to increase the sensitivity of the CC’s precautionary strategies at large, including that of HPV vaccination. The question that is raised is what measures can the State adopt in the intermediate phase, before reaching the above achievement? The authors believe that the answer depends on the special features that characterize every nation. Some countries present more organized healthcare and at large socio-political systems, inspiring their population with safety and thus, creating strong bonds of reciprocity with the civilians. These nations may accept the mandatory HPV vaccination without any unexpected deviant behaviors, but with an enhanced feeling of altruism. Of course, even in these wise social groups, the State will still have to properly inform and discuss the issue in question, creating a general social feeling of a simple solution-duty that needs to be chosen. On the other hand, in nations in which the aforementioned bond of reciprocity has not yet developed, the “optional” strategy is better with a similar, as previously stated action to be undertaken by the State. In Greece, according to the Constitution, the “optional” method has been applied, but many extra measures must still be taken in order to be able to see optimistic results.

Conclusion

Greece, in order to appropriately apply the Constitutional Law 5§5: All persons have the right to the protection of their health..., needs to train contemporary gynecologists in adequate youth’s consultation and proper family approaches on HPV vaccination issues. Enhancing the gynecologist’s role, vaccination’s effectiveness (sensitivity and specificity) will be increased and on the other hand, a rule of social law will be established in the country.

References


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Clinical picture of infiltrating lobular carcinoma of the breast: an analysis of 96 patients

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Summary

Objective: The aim of this study was to present the clinical picture of infiltrating lobular carcinoma (ILC) of the breast. Materials and Methods: A detailed analysis was performed for the group of 96 ILC patients subject to initial surgical treatment in the Krakow Branch of Centre of Oncology between 1983 and 1996. The investigated group was selected out of 2,347 breast cancer patients treated during that period, based on re-examination of histologic specimens of the initial patient group. Results: The following distinctive demographic and clinical features of ILC were found: average age of patients: 59 years (37 - 83); average duration of pathological symptoms: five months; most frequent site of primary tumor: upper outer quadrant (54.2%); primary tumor Stage: I/II0 (64.6%), III0A (35.4%); tumor size in breast: up to five cm (69.8%), larger than five cm (30.2%); no axillary lymph nodes involvement in 51% of patients; multifocality of lesions in 10% of patients; contralateral disease occurrence in eight percent of patients; atypical pattern of distant metastases, e.g. gastrointestinal system, gynaecologic organs, and cerebral meninges. Conclusions: Based on this analysis as well as on literature reports, it was found that the fundamental differences between ILC and infiltrating ductal carcinoma (IDC) included demographic and clinical features as patient age, primary tumor size at diagnosis, incidence of multifocality and contralateral disease, sites of distant metastases, and histopathological status of axillary lymph nodes.

Key words: ILC; IDC; Tumor; Metastases.

Introduction

Infiltrating lobular carcinoma (ILC) accounts for one to 20% of all mammary malignant neoplasms [1-9]. Such considerable differences in ILC incidence are connected with different demographic characteristics of presented groups of patients, varying diagnostic criteria assumed by different authors, and numerous histopathological carcinom subtype reports in the literature. In 1941, Foot and Stewart presented in detail the morphologic features of ILC and introduced the name “lobular carcinoma” into the literature; the so called “classic” type of ILC, as described by them, accounts for 70% - 85% carcinoma cases. During the following decades, numerous subtypes of ILC have been described. Some of them are widely accepted, e.g. solid variant, alveolar variant, tubulo-lobular variant, pleomorphic variant; others are discussed, and yet another even rejected by the majority of authors, e.g. trabecular variant, signet ring cell variant, histiocytoid variant, apocrine variant, etc. If more than one variant of ILC is found within a neoplastic tumor and none of them constitutes more than 80% - 85% of the histopathological picture, authors recognize it as a mixed subtype [4, 6, 10-13].

Materials and Methods

The detailed analysis was performed in a group of 96 ILC patients subject to initial surgical treatment in Center of Oncology Krakow between 1983 and 1996; the analysis is the basis for the assessment of ILC clinical picture. The investigated group was selected out of 2,347 breast cancer patients treated during that period in Center of Oncology Krakow, based upon re-examination of histologic specimens of the initial patient group. That is, ILC in the presented material accounted for 4.1% of all breast cancer cases. The youngest patient was 37-years-old, the oldest 83 years; average age of patients was 59 years with a median of 57 years. Thirty-one (32.3%) patients were pre-menopausal; 13 (13.5%) were menopausal; and 52 (54.2%) were post-menopausal. Duration of pathological symptoms varied from three to 33 months with an average of five months. Classic ILC was diagnosed in 56 (58,3%) patients; 40 (41.7%) were diagnosed with atypical ILC. The 40 atypical ILC cases included eight (8.3%) cases of solid ILC, four (4.2%) cases of pleomorphic variant, 18 (18.7%) cases of pleomorphic variant of signet ring-like cells, six (6.3%) cases of signet ring cell variant, and four (4.2%) tubulo-lobular variant.

Results

Detailed analysis of demographic and clinical features of the group of 96 ILC patients is shown in Table 1. Forty-eight patients (50%) of the investigated group were between 50 and 70 years old; 22 (22.9%) were older than 70 years, and 26 (27.1%) younger than 50 years. Only five (5.2%) patients in the investigated group were younger than 40 years.

In more than half (54.2%) of the patients, primary tumor was localized in the upper outer quadrant of the breast; in 36 (37.5%) cases, in other quadrants; and only in eight (8.3%) cases, in the central part of the breast. Twelve (12.5%) patients had tumor in Stage T1 (T1b - two patients, T1c - ten patients), 50 (52.1%) in Stage T2, and 34 (35.4%) in Stage T3.
In 30 (31.2%) patients, there was no clinical evidence of axillary lymph node involvement; in 48 (50.0%) patients, metastatic deposits were found in movable ipsilateral axillary lymph nodes; and 18 (18.8%) patients developed metastasis in matted ipsilateral axillary lymph nodes.

Ten (10.4%) patients were in Stage I°, 18 (18.8%) in Stage II°A, 34 (35.4%) in Stage II° B, and 34 (35.4%) in Stage III°A, according to American Joint Committee on Cancer (AJCC) staging system published in 2002 [14].

Examination of resection tissue material showed that breast tumor diameter in 22 (22.9%) patients was less than three cm; in 45 (46.9%), between three and five cm; and in 29 (30.2%), more than five cm.

Histopathological examination revealed metastases in axillary lymph nodes in 47 (49.0%) patients; in 31 (32.3%) cases metastatic deposits were found in one to three lymph nodes, and in 16 (16.7%) cases in four to nine lymph nodes. In seven (7.3%) patients neoplastic infiltration extended outside the lymph node capsule.

Multifocality of neoplastic disease was observed in ten (10.4%) patients of the investigated group. In seven (7.3%) patients, additional tumor foci were found within the same breast quadrant as the primary tumor (multifocal disease); and in three (3.1%) patients, in breast quadrants adjacent to the primarily involved one (multicentric disease).

During the last ten years’ follow-up, eight (8.3%) patients of the investigated group developed contralateral breast cancer; there were two cases of ILC and six cases of infiltrating ductal carcinoma (IDC). Contralateral breast cancer was diagnosed in one patient in the fifth year after treatment, in two patients in the seventh year after treatment, in two patients in the ninth year after treatment, and in three patients in the 11th, 14th, and 15th respective year after treatment.

In all 27 patients of the investigated group who died of ILC, the cause of treatment failure was development of distant metastases. Besides typical breast cancer (IDC) sites of metastases being lungs, liver, brain, and bones (in 14 patients, i.e., 41.8% of cases), atypical sites of metastases were found, such as large intestine (four patients, i.e., 14.8% of cases), cerebral meninges (two patients, i.e., 7.4% of cases), peritoneum (two patients, i.e., 7.4% of cases), ovary (two patients, i.e., 7.4% of cases), rectum (two patients, i.e., 7.4% of cases), and uterine corpus (one patient, i.e., 3.7% of cases).

Discussion

Distinctive demographic and clinical features of ILC found in the investigated group of patients include:

– average age of patients: 59 years (37 - 83),
– average duration of pathological symptoms: five months (3 - 33),
– tumor site most frequently in upper outer quadrant (54.2%),
– Stage III°A according to AJCC 2002 staging system in over one-third of the patients,

Table 1. — Demographic and clinical features in the group of 96 ILC patients.

<table>
<thead>
<tr>
<th>Demographic, clinical, and histopathological characteristics</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:&lt;br&gt; &lt; 50 years</td>
<td>26</td>
<td>27.1</td>
</tr>
<tr>
<td>50-70 years</td>
<td>48</td>
<td>50.0</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>22</td>
<td>22.9</td>
</tr>
<tr>
<td>Tumor site in breast:&lt;br&gt; upper outer quadrant</td>
<td>52</td>
<td>54.2</td>
</tr>
<tr>
<td>remaining parts of breast</td>
<td>44</td>
<td>45.8</td>
</tr>
<tr>
<td>AJCC 2002 Stage of carcinoma [21]:&lt;br&gt; I°</td>
<td>10</td>
<td>10.4</td>
</tr>
<tr>
<td>II°A</td>
<td>18</td>
<td>18.8</td>
</tr>
<tr>
<td>II°B</td>
<td>34</td>
<td>35.4</td>
</tr>
<tr>
<td>III°A</td>
<td>34</td>
<td>35.4</td>
</tr>
<tr>
<td>Primary tumor size in resection tissue material as graded by pathologist (pT):&lt;br&gt; &lt; 3 cm</td>
<td>22</td>
<td>22.9</td>
</tr>
<tr>
<td>3-5 cm</td>
<td>45</td>
<td>46.9</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>29</td>
<td>30.2</td>
</tr>
<tr>
<td>Axillary lymph nodes histopathological status (pN):&lt;br&gt; pN0</td>
<td>49</td>
<td>51.0</td>
</tr>
<tr>
<td>pN1a</td>
<td>31</td>
<td>32.3</td>
</tr>
<tr>
<td>pN1a</td>
<td>16</td>
<td>16.7</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>100.0</td>
</tr>
</tbody>
</table>

– primary tumor size (pT) exceeding five cm in nearly one-third of the patients,
– no axillary lymph node involvement in 51% of patients; metastatic deposits in more than three nodes in only 16.7% of patients,
– multifocality of lesions in breast in over ten percent of patients,
– contralateral disease, most frequently IDC, in over eight percent of patients,
– atypical sites of distant metastases: large intestine, peritoneum, cerebral meninges, ovary, rectum, and uterine corpus.

Demographic and clinical features presented are similar to those widely reported in the literature, though they sometimes differ in terms of intensity and configuration [3-8, 12, 15-20].

Based on the analysis of the investigated group of patients, it was established that fundamental differences between ILC and IDC demographic and clinical features include patient age, primary tumor size, neoplastic growth multifocality incidence, contralateral disease incidence, sites of distant metastases, and axillary lymph nodes histopathological status.
1. Patient age

In the investigated group of 96 ILC patients, the average patient age was 59 years. According to the literature reports, the average age of patients is slightly higher in case of ILC than IDC [4-9, 21, 22, 15-17, 23, 24]. In the study presented by Silverstein et al., the average age of 161 ILC patients was 55.1 years and 52.5 years in case of 1,138 IDC patients [5]; in the report by Sastre-Garau et al., the average age of 726 ILC patients was 57.2 years, and in case of 10,061 patients diagnosed with other histopathological subtypes of breast cancer, 56 years [4]; in the study by Tubiana-Hulin et al., the average age of 118 ILC patients was 52 years (33-72), and of 742 IDC patients, 49 years (25-80). In all the three studies, the observed differences were statistically significant. According to World Health Organization (WHO) data, the average age of ILC patients is one to three years higher than of IDC patients [6]. A part of the authors report little non-statistically significant differences in the average ages of ILC and IDC patients [8, 17, 19].

2. Primary tumor size

In the investigated group of 96 ILC patients, primary tumor exceeded five cm in 30.2% of the cases. Most of the literature data suggest that primary tumor at diagnosis in ILC patients is, on average, in a higher stage than in case of IDC patients [3-8, 15, 17, 21-23].

In the study presented by Yeatman et al., the average size of primary tumor in a group of 74 ILC patients was 3.2 cm, while in the group of 661 IDC patients it was 2.2 cm; in 14.8% of ILC patients and only in 4.5% of IDC patients, primary tumor was graded as Stage T3 [8]. In the study by Sastre-Garau et al., primary tumor larger than five cm at diagnosis was observed in 19% of ILC patients and only in 12% of patients with other histopathological subtypes of breast cancer; the difference was highly significant [4]. Mollanda et al. reported primary tumor staged as T3 in ten percent of ILC patients and only in three percent of IDC patients [17].

In the material presented by Tubiana-Hulin et al., Stage T3 primary tumor was observed in 38.1% of 118 ILC patients and only in 21.4% of 742 IDC patients; the difference was also highly-significant [7]. Mersin et al. in their research did not find any differences in primary tumor size between ILC and IDC patients [16].

3. Multifocality incidence

In the investigated group of 96 ILC patients, multifocality of neoplastic disease was observed in ten (10.4%) patients. In the literature, authors generally agree that ILC is a breast cancer histopathological subtype of particularly frequent multifocality of neoplastic lesions [1, 3, 4, 6, 8, 12, 17]. Estimations of multifocality incidence vary considerably; it is, however, widely-assumed that it is higher for ILC than IDC [4, 25]. In the study by Fisher et al., the incidence was even as high as 54% [26]; usually, the incidence is reported to account for 4.5% to 31% [4, 12, 20, 25].

4. Contralateral disease incidence

In the investigated group of 96 ILC patients during the at least ten-year follow-up, contralateral breast cancer was observed in eight (8.3%) patients (two cases of ILC and six cases of IDC). Incidence rate of contralateral breast cancer in ILC patients, as presented in the literature, varies substantially from one to five percent reported by some authors [3, 4], to 13%-26% [4, 12, 27], 6%-19% [5, 6, 8, 12, 25, 28], and even 6%-47% [1, 9, 21, 29] observed by the others. Based on the literature data (882 ILC patients), Sastre-Garau et al. estimated the incidence rate of contralateral disease as 14%; according to WHO it amounts to 13.3% [4, 6].

Majority of studies show higher risk of contralateral disease development in ILC patients than in IDC patients [1, 3-5, 12, 15, 17, 25, 27, 29]. In the group of 103 ILC patients, Dixon et al. observed contralateral disease in 20% of patients (in case of IDC - in eight percent). Arpino et al. estimated the incidence rate as 20.9% and 11.2% in the group of ILC and IDC patients, respectively [15, 29]. Silverstein et al. found contralateral breast cancer in 14% of 161 ILC patients and only in five percent of 1,138 IDC cases; the difference was statistically significant [5]. Incidence rate of contralateral disease depends, of course, on the span of ILC patients follow-up [3]. McDivitt et al. observed contralateral breast cancer in 10% of patients in follow-up for ten years, and in 15% and 25% of patients in follow-up for 15 and 20 years, respectively [30].

In the reports by Sastre-Garau et al. and Peiro et al., contralateral disease incidence was identical in ILC and IDC patients [4, 31].

5. Sites of distant metastases

In the investigated group of 96 ILC patients, atypical sites of metastases (large intestine, cerebral meninges, peritoneum, ovary, rectum, and uterine corpus) were observed besides typical breast cancer metastases to lungs, liver, brain, and bones. A straight majority of authors emphasize that ILC much more frequently than IDC metastasizes to peritoneum and retroperitoneal region [32-34], gastrointestinal system (stomach, large intestine, rectum, duodenum, and anus) [12, 33-39], gynecologic organs (uterine corpus and ovaries) [12, 40], and cerebral meninges [41].

6. Axillary lymph nodes histopathological status

In the investigated group of 96 ILC patients, microscopic metastatic deposits of neoplastic disease in axillary lymph nodes were observed in 47 (49.0%) patients. Most of the literature data indicate that metastases in axillary lymph nodes are a little less frequent or equally-frequent as in IDC patients [4-7]. This is observed despite the fact that ILC – compared to IDC – is characterized by larger primary tumor at diagnosis, higher incidence of multifocality, and higher incidence of contralateral
Clinical picture of infiltrating lobular carcinoma of the breast: an analysis of 96 patients

et al. was reported by Wasif than IDC patients (51% vs. 36%) [8]; similar observation the authors reported that the metastases in their investigated groups of patients. Therefore, WHO [6], Hussien et al. [3] and Yeatman et al. [8] estimate the incidence as 3% - 10%, 46.5%, and 51%, respectively. The latter of the authors reported that the metastases in their investigated group of patients occurred more frequently in ILC than IDC patients (51% vs. 36%) [8]; similar observation was reported by Wåsif et al. (36.8% vs 34.4%) [42].

Conclusions

Compared with IDC cases, ILC patients are characterized by higher age, higher primary tumor size at diagnosis, higher incidence of multifocality of neoplastic lesions, higher incidence of contralateral disease, lower proportion of patients with metastases in axillary lymph nodes, higher incidence of distant metastases in gastrointestinal system, gynecologic organs, and cerebral meninges.

References


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P16 immunostaining and HPV testing in histological specimens from the uterine cervix

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Summary

Background: The cellular tumor suppressor protein p16INK4a (p16) has been identified as a biomarker for transforming human papilloma virus (HPV) infections. P16 is a cyclin-dependent kinase inhibitor that regulates the cell cycle and cell proliferation by inhibiting cell cycle G1 progression. Purpose of the study: To confirm the role of p16 as biomarker for transforming HPV infections and possible clinical applications in histological samples from the uterine cervix. Materials and Methods: The subject of this study included 56 biopsies of the cervical canal collected from January 2012 to September 2012 in the Institute of Pathology of the University of Sassari. The search for HPV immunohistochemistry was performed with the monoclonal antibody DAKO 1:25, while for the detection of p16 was used CINtecTM p16 (INK4a) histology kit. Results: In 56 biopsies performed in women aged between 23 and 69 years, the authors highlighted, by histological analysis, 24 cases of low-grade squamous intraepithelial lesion (LSIL) - cervical intraepithelial neoplasia (CIN1) and 31 cases of high-grade squamous intraepithelial lesion (HSIL) - cervical intraepithelial neoplasia 2/3 (CIN2/3); 15 CIN2, 14 CIN3, and two cervical squamous cell carcinoma in situ (SCIS). One case was an infiltrating squamous cell carcinoma (ISC). In 24 CIN1, there was a 16.67% positivity for p16 and an equal percentage occurred for HPV. In 15 cases of CIN2 the percentage of positivity for p16 was considerably increased (73.33%), unlike the search for HPV which had a positivity rate of 20%. Finally, in 14 cases of CIN3, and in three carcinomas, the positivity for p16 was equal to 100%, however the search for HPV positivity was between 0% and 7.14%. Conclusions: These results demonstrated that p16 was a highly sensitive marker of cervical dysplasia. The authors have shown that p16 overexpression increased with the severity of cytological abnormalities and that had a greater ability to identify the viral infection compared to the classical immunohistochemical staining for HPV.

Key words: Cervical cancer; Human papilloma virus (HPV); P16INK4a; Immunohistochemistry.

Introduction

P16INK4a (p16), a protein that plays a role in tumor suppression, is a cyclin which has a kinase inhibitory function, whose overexpression has been reported in dysplastic and neoplastic epithelial lesions of the uterine cervix [1]. The overexpression of p16 is indirectly induced by the viral oncoprotein E7 as a consequence of the retinoblastoma protein (pRb) deregulation [2].

Cell replication is, in fact, controlled by means of a complex mechanism involving different regulatory pathways within the cell. One of these is the location of the pRb, which controls cell proliferation. Under normal conditions, Rb binds to the transcription factor E2F, which has the effect of blocking the transcription of genes that promote the proliferation and progression of the cell cycle, but also the p16 gene coding for the inhibitor of cyclin-dependent kinase. Therefore the binding of E2F by pRb is one of the control mechanisms to avoid that the cells continue to replicate and proliferate.

In the course of infection with human papilloma virus (HPV), one of the proteins expressed by the virus inside the cell is the oncogenic protein E7. Its oncogenic activity consists of preventing the function of pRb, which does not bind to transcription factor E2F, and consequently this leads to the transcription of certain genes, in particular the transcription of the p16 gene, which encodes for the protein p16 functional inside the cell. As a result of HPV infection, there will be a final induction of cell proliferation [3].

Usually, p16 is expressed at very low concentrations in healthy cells, whereas it is strongly overexpressed in cervical-cancer cell lines in which pRb has been functionally inactivated by the high-risk HPV E7 oncoprotein [4]. The current literature supports using p16 immunostaining as a surrogate marker for the presence of cervical intraepithelial neoplasia 2/3 (CIN2/3) in cervical biopsy specimens to distinguish CIN2/3 from their mimics, such as immature metaplasia or therapy changes.

The objective of this study was to evaluate the expression of p16 protein in the various types of dysplastic cervical lesions, both low and high grade, with the aim to evaluate the different overexpression of this protein in various types of lesions, in order to permit a judgment of prognosis, especially in low-grade lesions. The aim was to be able to program appropriate protocols for monitoring and personalized follow-ups.

Materials and Methods

Fifty-six biopsies of the cervical canal were collected from January to September 2012 and sent for diagnosis and phenotypic characterization to the Institute of Pathology, University of Sassari, and the Institutional Review Board approved the study.
The samples, which were fixed in 10% formalin and embedded in paraffin sections, underwent microtomic sections of four µ, stained with hematoxylin, and some sections were prepared on slides pretreated with polylysine for performing immunohistochemistry.

The search for HPV immunohistochemistry was performed with the monoclonal antibody DAKO 1:25, while for the detection of p16 was used CINtecTM p16 (INK4a) histology kit.

The slides were rehydrated through descending scale of alcohol (96%, 70%, and 50%) for about two minutes. Subsequently, the slides were completely covered with citrate buffer; brought for five minutes to boiling pressure, and then left to cool in the respective chambers at room temperature; then following a washing in distilled water for one minute and counterstained with hematoxylin, mounted on the slide, and analyzed microscopically.

The immunohistochemical positivity was of nuclear type and the cases were classified positive even in the presence of a single positive nucleus.

The authors assigned a positive evaluation, if the sample showed a continuous staining of cells of the basal and parabasal layers of the squamous cervical epithelium, with or without staining of cells of superficial cell layers.

The authors assigned a negative evaluation, if the sample showed a negative staining reaction in the squamous epithelium or staining of isolated cells or in small groups, however, less than 25% of the cells.

Two pathologists, without knowledge of the tissue biopsy and HPV results, independently reviewed the p16 immunostaining results. In 54/56 (96.43%) of the cases, the pathologists agreed on the p16 immunostaining results; in the remaining cases, consensus was reached after review.

Results

The results obtained from histology and immunohistochemistry are summarized in Table 1.

Immunohistochemical analysis totally (Table 2) showed 32/56 cases positive for p16 (57.14%) and 24/56 (42.86%) negative cases, including eight with focal positivity, while only eight (14.29%) were positive for HPV immunohistochemical staining and 48 (85.71%) were negative.

Analyzing the distribution in the different degrees of lesions (CIN1/CIN2/CIN3). The results were the following (Table 3):

- CIN1: 24 cases examined, four (16.67%) were positive for p16 and 20 (83.33%) were negative, including six with focal positivity, while four (16.67%) were positive for HPV and 20 (83.33%) were negative.

- CIN2: 15 cases examined, 11 (73.33%) were positive for p16 and four (26.67%) negative, two of which had a focal positivity, while three (20%) were positive for HPV, and 12 (80%) negative.

- CIN3: 38 cases examined, 24 (63.15%) were positive for p16, while 24 (63.15%) negative, the former two thirds with a focal positivity, while 14 (36.85%) were positive for HPV, and 24 (63.15%) negative.

Table 1. — Total results.

<table>
<thead>
<tr>
<th>Case</th>
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<th>Diagnosis</th>
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<th>HPV (Immunohistochemistry)</th>
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<tbody>
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<td>1</td>
<td>33</td>
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<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>CIN1</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>CIN1</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>CIN1</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>CIN1</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>CIN1</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>CIN1</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>CIN1</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>CIN1</td>
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<td>Negative</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>CIN1</td>
<td>Focal</td>
<td>Positive</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>CIN1</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>CIN1</td>
<td>Focal</td>
<td>Positive</td>
</tr>
<tr>
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<td>52</td>
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<td>Negative</td>
<td>Negative</td>
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<td>15</td>
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<td>Negative</td>
</tr>
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<td>16</td>
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<td>CIN1</td>
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<td>Positive</td>
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<td>Focal</td>
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</tr>
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<td>30</td>
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<td>Negative</td>
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</tr>
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<td>44</td>
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</tr>
<tr>
<td>21</td>
<td>20</td>
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<td>Focal</td>
<td>Negative</td>
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<tr>
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<td>Negative</td>
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<td>Negative</td>
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<td>25</td>
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<td>CIN2</td>
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<td>Negative</td>
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<td>CIN2</td>
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<td>Focal</td>
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<tr>
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<td>26</td>
<td>CIN2</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>29</td>
<td>47</td>
<td>CIN2</td>
<td>Focal</td>
<td>Negative</td>
</tr>
<tr>
<td>30</td>
<td>35</td>
<td>CIN2</td>
<td>Positive</td>
<td>Negative</td>
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<td>CIN2</td>
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<td>Negative</td>
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</tr>
<tr>
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<td>38</td>
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<td>Negative</td>
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Table 2. — Distribution of positive and negative p16 and HPV (IIC) on total cases.

<table>
<thead>
<tr>
<th></th>
<th>p16 positive</th>
<th>p16 negative</th>
<th>HPV (IIC) positive</th>
<th>HPV (IIC) negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>56</td>
<td>32</td>
<td>24-8</td>
<td>24</td>
</tr>
<tr>
<td>(57.14%)</td>
<td>(42.86%)</td>
<td>(16.67%)</td>
<td>(16.67%)</td>
<td>(83.33%)</td>
</tr>
</tbody>
</table>

Table 3. — Distribution of positive and negative p16 and HPV (IIC) according to CIN.

<table>
<thead>
<tr>
<th>CIN</th>
<th>p16 positive</th>
<th>p16 negative</th>
<th>HPV (IIC) positive</th>
<th>HPV (IIC) negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 CIN1</td>
<td>4</td>
<td>20-6</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>(16.67%)</td>
<td>(83.33%)</td>
<td>(16.67%)</td>
<td>(83.33%)</td>
<td></td>
</tr>
<tr>
<td>15 CIN2</td>
<td>11</td>
<td>4-2</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>(73.33%)</td>
<td>(26.67%)</td>
<td>(20%)</td>
<td>(80%)</td>
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<tr>
<td>14 CIN3</td>
<td>14</td>
<td>0</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>(100%)</td>
<td>(7.14%)</td>
<td>(92.86%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Discussion

P16 is a cyclin-dependent kinase inhibitor, the expression of which is negatively controlled by the RB1 gene product. In differentiated epithelial cells, p16 is expressed in levels typically not evaluated by immunohistochemistry. In the course of infection with HPV, one of the proteins expressed by the virus inside the cell is the oncogenic protein E7. Its oncogenic activity consists of preventing the function of pRb, which does not bind to transcription factor E2F [1].

Some studies [5-7] have investigated the usefulness of the protein p16 as biomarker, especially of high-grade lesions of the uterine cervix HSIL and in situ and ISC and also to assess the ability of progression of low-grade lesions LSIL; CIN1 that, in a certain percentage of cases, may undergo spontaneous regression.

It has been shown, in fact, that there is a significant association between the degree of the cervical lesion and the positivity (also in terms of distribution and intensity) for p16 [8].

There are about 15 types of high-risk HPV, but in any case the effect of the E7 oncoprotein is the same in blocking pRb and lead to overexpression of p16. Since p16 is a cellular protein, it may serve as a biomarker, independent of the type of high-risk HPV, and its overexpression is a direct marker of the oncogenic activity of the virus and the more accurate predictor of cervical cancer.

The use of p16 by immunohistochemistry can be considered a complement of cytology and histology, which allows a better evaluation of women with questionable results and require colposcopy or treatment. The detection of this protein with monoclonal antibodies is a useful parameter both in the interpretation of cytology and because it reduces the variability in the evaluation of suspected cervical biopsies. Regarding the cytological examination, if the outcome is positive for a HSIL there will be a high positive predictive value (PPV), instead for results of lower grade, and therefore for LSIL or atypical squamous cells of undetermined significance (ASC-US), there will be a much lower PPV. For this reason the authors have introduced HPV test in the case of low-grade cytological results. However it has been shown that this test has an important role in identifying the risk lesions and the recurrence of the disease, but HPV test fails in the triage of low-grade lesions. In addition, a single HPV DNA test may confirm if the infection is present in 99% of all cancers of the cervix, but it does not discriminate between chronic and transitory infection. The discrimination between the two types of infection is of fundamental importance, as it is the persistent infection that predisposes to progression of lesions to cervical neoplasia. Consequently, once again the value of p16 was emphasized, especially as a marker of risk of progression of lesions to low-grade dysplasia [9].

Tsoumpou et al. [1], in a systematic review and meta-analysis, have reported the overexpression of the protein p16 in a very high proportion of high-grade lesions close to 82% in cases of CIN3, and a range between 38% and 68% in low-grade lesions.

The authors also wanted to evaluate the overexpression of p16 protein in cervical lesions. Immunohistochemical analysis revealed in total, 32 cases positive for p16 (57.14%) and 24 negative cases, including eight with focal positivity (42.86%), while only eight (14.29%) cases positive for HPV and 48 (85.71%) negative for HPV.
The present data confirm the increased ability of p16 to detect viral infection compared to standard immunohistochemical staining for HPV that can now be considered completely useless.

Observing the distribution of the various degrees of injury, the present results are extremely interesting. In fact, of the 24 cases CIN1, four (16.67%) were positive for p16 and 20 (83.33%) were negative, including six with a focal positivity. In cases CIN2 positivity rose to 73.33% (11/15) and even up to 100% in both cases CIN3 (14) and cervical squamous cell carcinoma (two SCIS and one ISC), with a positivity in the overall total of HSIL of 87.10% (27/31).

According the Bethesda classification and identifying only two groups, LSIL and HSIL had a positivity for p16 by 16.67% (4/24) and 87.10% (27/31).

These results demonstrated that the protein p16 was a highly sensitive marker of HPV cervical dysplasia and in particular was able to discriminate between high-grade and low-grade lesions, especially in terms of follow-up.

In fact the authors believe that the relatively frequent negativity of p16 in LSIL is in relation to infection with a strain of non-oncogenic HPV, whereas cases of LSIL positive for p16 indicate possible infection with oncogenic strain. This is in agreement with what is known about the evolutionary history of LSIL, hence about one-third of these lesions should undergo spontaneous regression and are certainly not due to an infection with oncogenic strain.

Positivity for p16 protein allows then to select, in the context of patients with LSIL, those who need a closer follow-up as it is subject to a possible evolution of the disease.

In conclusion, the authors can state that the overexpression of the protein p16 at immunohistochemistry is certainly useful, not so much in the information it can give us in high-grade lesions, but also for the impact it has in the planning of screening program allowing to identify groups of patients at risk already in the LSIL phase, and rationalizing such program in order to obtain more effective prevention and better cost optimization.

References


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Laparoscopic surgical staging of endometrial cancer: does obesity influence feasibility and perioperative outcome?

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Summary

**Aim:** Laparoscopic treatment of early-stage endometrial cancer is the gold standard to reduce perioperative morbidity. Obesity is a well-known risk factor for endometrial cancer and anesthesiological and surgical complications. The authors’ aim was to examine the effect of body mass index (BMI) on perioperative parameters and complications in laparoscopically-treated patients with endometrial cancer. **Materials and Methods:** A consecutive series of patients affected by endometrial cancer and their demographic and clinicopathological data were collected. Patients were divided in 41 non-obese (BMI ≤ 29.9) and 34 obese (BMI ≥ 30) groups. All patients had been preoperatively evaluated with hysteroscopic procedures and toraco-abdominal computed tomography (CT) and had been submitted to laparoscopic radical hysterectomy according to Querleu-Morrow, pelvic lymphadenectomy, peritoneal washing, and bilateral adnexitomy. **Results:** There was no statistically significant difference in blood loss, number of lymph nodes removed, and hospital stay between the groups, but there was a trend towards a lengthening of surgical time in the obese women. There were no major intraoperative and postoperative complications. **Discussion:** This study demonstrates that laparoscopic approach is feasible and safe in obese women evaluating the anesthesiological risk.

**Key words:** Radical laparoscopic hysterectomy; Endometrial cancer; Obesity.

Introduction

Endometrial cancer is the most common gynecological neoplasia in the developed world and it constitutes six to nine percent of all cancer in women. Seventy-five percent of endometrial cancer are diagnosed at an early stage [1-3].

More than 40% of cases of endometrial cancer can be caused by obesity and more than 50% of women with early-stage endometrial cancer are obese.

Obese patients frequently have metabolic syndrome, diabetes, hypertension, cardiovascular disease, and other comorbidities that increase their anesthesiological risk.

Recommended treatment is abdominal hysterectomy and bilateral adnexitomy, while performing also pelvic lymphadenectomy is still controversial. Some authors demonstrated that lymphadenectomy does not improve overall and disease-free survival [4, 5].

Recently, laparoscopy is becoming the standard care in presumed early-stage endometrial cancer [2, 6, 7] since overall and disease-free survival are comparable to laparotomic surgery, while hospital stay and surgical morbidity are decreased by minimally-invasive surgery [8, 9]. High performance of laparoscopic surgery in the oncological field has also been extended to cases of obese women, but it constitutes a controversy among authors [10, 11]. The randomized trial LAP2 study found that the only difference in the outcome of laparoscopically-treated patients with endometrial cancer related to obesity was the rate of conversion to laparotomy. The conversion rate increased from 17.5% in patients with body mass index (BMI) of 25 to 57.1% in BMI higher than 40 [12]. On the contrary, reduction of postoperative complications, wound infection, thrombosis, ileus, and hospital stay may give even greater advantages in obese than in general population.

The purpose of study is to evaluate the feasibility of total radical laparoscopic hysterectomy (TRLH) and the surgery-related morbidity in obese women with endometrial cancer.

**Materials and Methods**

A consecutive series of 75 patients with early-stage endometrial cancer underwent laparoscopic surgery at the Department of Woman and Child Health-University of Padua, and were operated by the same expert surgeon. BMI was calculated using a standard BMI chart (patients’ height and weight). The authors divided the patients into two groups obese (BMI ≥ 30) and non-obese (BMI ≤ 29.9). The non-obese group consisted of 41 patients and the obese group of 34 patients. The study was restricted to those patients under 75 years of age who had presumed endometrial carcinoma up to Stage 2 (Stage FIGO 2009) and lombo-aortic lymphadenectomy was never performed.

The authors also collected age, parity, menopausal status, BMI, grading, histological type, number, and positivity of pelvic lymph nodes.

The histological diagnosis was obtained by hysteroscopic procedures [13-16], clinical examinations consisted in total body computed tomography (CT) and blood tests. Exclusion criteria included: a documented significant cardiopulmonary disease defined as a history of cardiac failure, myocardial infarction, unstable angina, acute or recent vascular thrombosis, poorly-controlled asthma or pulmonary obstructive disease, or contraindicating prolonged Trendelenburg position; prior pelvic or abdominal radiation therapy; or inadequate bone marrow, clotting factor, renal, and hepatic function.

All women were surgically treated according to the method previously described in other papers by the same authors [9]. All patients underwent laparoscopic surgery under general anesthesia, short-course antibiotic therapy with third-generation cefalosporin and thromboprophylaxis, and with dalteparin sodium 100 UI/kg/die for 30 days.

Revised manuscript accepted for publication November 21, 2012

**Eur. J. Gynaec. Oncol.** - ISSN: 0392-2936

XXXIV, n. 3, 2013
The feasibility of TRLH and pelvic lymphadenectomy was assessed in terms of conversion to laparotomy, surgical time (from the beginning of pneumoperitoneum to suturing of the skin), estimated blood loss (EBL), and length of postoperative hospital stay. Complications during days of admission up to 30 days after discharge were recorded from medical charts.

Statistical analysis was conducted with SPSS 19.0. Continuous variables are expressed as mean value ± standard deviation and were compared using non-parametric Mann-Whitney U test. Categorical variables are expressed as number (percentages).

A p value < 0.05 is considered statistically significant.

Results

Overall, 75 laparoscopic radical hysterectomies, bilateral adnexectomies, peritoneal washing, and pelvic lymphadenectomies were performed for early-stage endometrial cancer. The mean age was 64.1 years (range 36 - 75) and the two groups were homogeneous for age, parity, and menopausal status. There were 34 (45.3%) obese patients (BMI ≥ 30); while 41 (54.7%) were normal or overweight (BMI ≤ 29.9). The average BMI was 29.3 with the heaviest patient having a BMI of 64. Seven patients were morbidly obese with a BMI ≥ 40. Pelvic lymph nodes were positive only in eight patients (10.7%).

Table 1. — Clinical and pathological features of patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>No. patients</th>
<th>BMI ≤ 29</th>
<th>BMI ≥ 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>36 (48%)</td>
<td>13 (31.7%)</td>
<td>23 (67.6%)</td>
</tr>
<tr>
<td>G2</td>
<td>31 (41.3%)</td>
<td>20 (48.8%)</td>
<td>11 (32.4%)</td>
</tr>
<tr>
<td>G3</td>
<td>8 (10.7%)</td>
<td>8 (19.5%)</td>
<td>0</td>
</tr>
<tr>
<td>G4</td>
<td>8 (10.7%)</td>
<td>8 (19.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Blood loss (ml) 44 5-300 15.39 (± 7.63) 17.56 (± 8.83) 0.39
Surgical time (min) 178.89 85-300 15.39 (± 7.63) 17.56 (± 8.83) 0.39
Lymph nodes (number) 15.4 6-40 15.39 (± 7.63) 17.56 (± 8.83) 0.39
Hospital stay (days) 3.27 1-10 3.35 (± 1.742) 3.16 (± 1.214) 0.79

Discussion

Currently, many retrospective studies report that laparoscopic approach includes several advantages for women as minor risk of blood loss, necessity of transfusion, postoperative pain, and length of hospital stay compared to open surgery, in the treatment of early-stage endometrial cancer [17].

In obese women who constitute a high-percentage of women suffering from endometrial cancer, it is controversial if this approach is feasible, cost-effective, and safe. Several issues as higher rate of complications, conversion to laparotomy, reduced feasibility of lymphadenectomy, lengthening of surgical time, as well as hospital stay are often debated [6, 18-26]. Enhancement of already impaired cardiopulmonary dysfunction due to Trendelenburg and high intra-abdominal pressure are challenges for both the anesthesiologist and surgeon. Moreover technical limits due to intra-abdominal fat, can lengthen the surgical time and increase the risk of atelectasis, reduction of functional residual capacity and hypercapnia, and worsen cardiac overload [27]. This data as in other studies show among the evaluated parameters only a lengthening of surgical time in obese women. In these cases, it is necessary to underline that recommending laparoscopic surgery implies a close collaboration between surgeon and anesthesiologist.

A randomized trial has confirmed that in patients with endometrial cancer, quality of life is significantly better during perioperative period after TRLH compared to total abdominal hysterectomy [28]. In a retrospective study comparing laparoscopic and laparotomic procedures in obese women, with or without pelvic lymphadenectomy, laparoscopic approach is safe and feasible with low-risk of serious complications [29]. As in the group of Kohler et al. [21], the authors managed to perform pelvic lymphadenectomy in all patients with complete surgical staging, fulfilling the standard of oncologic surgery, confirming that only in the hands of skilled surgeons laparoscopic approach has allowed to perform a complete surgical staging with a good outcome of the patients. According to some authors, laparoscopic surgery is not cost-effective because of increased laparotomic conversion rate [12, 30]. In a randomized study, Bijen et al. [30] proved that obese women having a BMI of class II (35-39.99), are at high-risk for conversion to laparotomy. In the present consecutive series, even if limited, there was no laparotomic conversion in the obese group. Such a conversion rate can be influenced by the experience of
the surgeon and by not performing para-aortic lymphadenectomy. In the recently published data of Farthing et al., as well as this present study, the feasibility and cost-effectiveness of laparoscopic approach in obese women was confirmed by the low-risk of wound infection, wound dehiscence, post incisional hernia, and intensive care admission [19]. Furthermore, length of hospital stay is not different in obese vs non-obese patients and it has already been demonstrated that quick recovery of laparoscopic treatment decreases the costs of admission compared to laparotomy [20].

Conclusions

Surgical staging is the main prognostic factor in oncological field. Laparoscopic surgery is proved safe and feasible only in case of obese women, but this is attainable only with a close collaboration between surgeon and anesthesiologist.

References

Multidisciplinary approach as the optimum for surgical treatment of retroperitoneal sarcomas in women

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Introduction
Retroperitoneal sarcomas (RPS) represent a heterogeneous group of uncommon malignant tumors and rank among soft tissue sarcomas (STS). STSs represent less than one percent of malignant diseases and 10% - 20% of them occur in the retroperitoneal space [1-6]. The most common histotypes are leiomyosarcomas, malignant histiocytomas, fibrosarcomas, and liposarcomas [2]. So far, more than 50 subtypes are known [7]. Most STS tumors occur within the fifth and the sixth decades of life [8]. The etiology and biologic behavior of these tumors is contingent. The most effective treatment method is complete surgical removal. Although effective, radiotherapy (RT) has restrictions due to the site of a tumor, close to an adjacent organ. Current chemotherapy (CHT) has limited efficacy. The size of RPSs is often very large at the time of diagnosis and their complete surgical removal is not always possible. Local recurrence is the main problem of management of these tumors. Main risk factors of recurrence include the positive surgical margin (PSM) and the histological type of the tumor [5]. Resection of a large RPS in female patients is a demanding and aggressive procedure. In such cases, it is advantageous to combine both oncologic and gynecologic needs of aggressive surgery with the urologist experience in retroperitoneal space surgery. The aim of this study was the evaluation of the results with multidisciplinary collaboration during surgical treatment.

Materials and Methods
A cohort of 17 women who underwent a surgical removal of RPS was subject in this evaluation in the period from 1998-2009. All these patients had abdominal and thoracic computed tomography (CT) before surgery. Magnetic resonance imaging (MRI) or colonoscopy was performed only in exceptional cases of suspected tumor infiltration into adjacent organs, especially into the bowels. Surgery was carried out in general anesthesia with antibiotic prophylaxis. Open surgery was performed in 16 patients while a laparoscopic approach was employed in one patient. Complete resection of the tumor was carried out in all patients. In patients with a tumor close to the ureters with dilatation of the upper urinary tract, a urethral catheter was introduced just before resection.

Complications were assessed as well as surgical results, with a focus on local recurrence, overall survival, and disease-specific survival. The data were statistically analyzed using Kaplan-Meier survival analysis. Sizes of tumors and presence of PSM were statistically analyzed for risk of recurrence or metastases. Wilcoxon rank-sum tests were used and p values less than 0.05 were considered statistically significant.

Results
The median follow-up time was 60 (26 - 128) months. The mean age of patients was 55.4 (35 - 75) years. The mean size of tumor was 14.8 (6 - 45) cm. A complete resection without PSM was performed in 14 (88%) cases. No infiltration into the gastrointestinal tract or main vessels was depicted. Table 1 shows histological types, presence of PSM, and next fate of the patients. Two nephrectomies and one splenectomy were performed during removal of RPS due to proximity of tumors. Bleeding was the most common complication. The median blood loss...
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During surgery amounted to 600 (150 - 2,500) ml. Nine patients received blood transfusion during surgery, and the median volume of transfused packed red cells was 900 ml. The median time of surgery was 196 (68 - 314) minutes. There was no perioperative mortality.

All the patients with PSM underwent CHT and RT after surgery. Disease-free survival was recorded in 13 patients (76%). Local recurrence was recorded in three patients with PSM (18%). Patients without PSM exhibited no local recurrence irrespective of the size of the tumor. There was only one exception in one patient (6%) without PSM who had primary pulmonary and hepatic metastases. The mean time from surgery to local recurrence was 26 (22 - 28) months. The treatment of local recurrence consisted in the surgical resection of a tumor combined with second-line CHT. In two patients, the second recurrence was treated by a third resection of the tumor and complemented by new-line CHT with trabectedin. One patient exhibited remission after the second resection and one patient after the fourth resection. The fourth resection was combined with amputation of the rectum and colostomy for infiltration of the rectal wall. Histologic results with local recurrence confirmed malignant fibrous histiocytomas in two patients and one leiomyosarcoma.

The overall and cancer-specific survival was 87.5%. Two patients died of metastatic disease. One patient died after the fourth resection with RT and CHT after the primary resection and second-line CHT after the second resection. Distant metastases followed at six months after the last resection and the patient died at 38 months after the first surgery. The second patient developed distal metastases without local recurrence at 28 months after the complete resection. Despite the CHT regimen, the patient died at 37 months after primary surgery. The histology of both succumbed patients was leiomyosarcoma as the primary tumors.

The Kaplan-Meyer analysis of the overall survival and the disease-free survival are presented in Figures 1 and 2. The size of the removed RPS exerted no significant influence on the risk of local recurrence. The presence of PSM is the main risk factor for local recurrence.

Discussion

RPS is an uncommon but serious disease. The symptomatology is poor and unspecific and the most common symptoms are pain, weight lost, and a palpable tumor. Some tumors are discovered by chance on ultrasound or CT scans. This minimal symptomatology leads to late diagnosis and hence the RPSs are usually very large. The next reason for an extensive growth of a tumor is the absence of a natural barrier within the retroperitoneal cavity. Lahat et al. considered the size of a tumor was one of important prognostic factors for distant recurrence and disease-specific mortality in high-grade tumors. The higher risk was combined with a tumor size more than 15 cm [8]. The large tumors with their late presentation to surgery often result in an invasion of neighboring retroperitoneal organs, and thus their surgical resection is difficult or even impossible. Lewis et al. presented a cohort of 500 patients who underwent resection of RPS, with their complete resection rate amounting to 83%. The median survival in patients with complete vs incomplete resection was 103 and 18 months, respectively [9]. This short survival is similar to patients without surgical treatment and authors concluded that partial resection would be indicated only for patients with severe symptoms [9]. The most common site of RPS recurrence is localized.
The rate of local recurrence ranges from 40% to 80% despite complete resection [4, 6, 9-12]. Distant metastases are rather rare. The therapy of local recurrence is surgical and often the third or more consequential surgical treatments are necessary. Lewis et al. reported the median survival after local recurrence amounting to 60 months in resected patients vs 20 months in unresected patients. Recurrent tumors were resected in 57% of patients with the first recurrence. This figure declines precipitously with further recurrences, dropping to 20% after the second recurrence, and down to 10% after the third recurrence [9]. The authors' experience was a little bit different: the size of the tumor had no influence on recurrence or survival. The presence of PSM was linked to local recurrence in all cases.

The most effective treatment of RPS consists in its surgical removal, but these tumors are usually very large at the time of diagnosis and complete resection is not possible in some cases. These giant RPSs also invade important organs in the retroperitoneal space and it is necessary to remove these organs, for instance a kidney, a part of the intestine, the uterus or great vessels [13-15]. Stoeckle et al. reported a cohort of 145 patients with RPS without distant metastases but only 94 patients (65%) underwent complete excision. The five-year overall survival rate was 49%. The authors recommended postoperative RT, which significantly increased a local control. On the contrary, grade 3 histology of tumors increased the probability of local recurrence [16]. Lewis et al. reported five-year local control rate in 59% of patients who underwent resection of tumor and five-year cause-specific survival rate was 54%. A significantly worse prognosis was recorded in high-grade tumor and liposarcomas [9]. The authors performed resection of adjacent organ during the removal of RPS in the study patients as well. In three cases, they performed resection of adjacent organ, two times nephrectomy, and one splenectomy. In the course of the removal of the local recurrence, they carried out resection of the rectum in one patient.

Gholami et al. reported about their own experience with regards to the surgical treatment of RPS. The authors emphasized complete resection and they removed the tumor with adjacent organs rather than peeling the tumor off. They reached 93% of complete resection without positive surgical margin. The five-year survival was 46% and local recurrence was the main problem even when complete resection had been achieved. The authors recommend close monitoring aimed at an early detection of the local recurrence. Even a small-sized recurrent tumor resulted in its successful removal. The authors concluded that RT and chemotherapy had no significant impact on the overall or recurrence-free survival [4].

This part of oncologic surgery is an evident example of possible multidisciplinary collaboration between urologists and gynecological oncologists. Historically the biggest experiences with radical surgery in retroperitoneal space belong to urologists. The presence of an oncological gynecologist is profitable, especially for improving aggressive surgical techniques in pelvis and retroperitoneal space.

Local recurrence is the main risk in management of RPSs. In an effort of reduction of local recurrence, RT was recommended. Some studies have demonstrated a certain impact on reduction of local recurrence but no impact on the overall or the tumor-specific survival [17]. Catton et al. reported that adjuvant RT after complete resection only delayed local recurrence [18]. According to other retrospective studies, adjuvant or intraoperative RT had no effect on local control and survival [4, 19, 20]. New techniques of RT such as intensity-modulated radiation therapy (IMRT) offer better results and reduction of adverse effects. The optimal role and timing of RT must be proven through further randomized studies.

CHT exhibits a very limited efficacy in the management of RPS. Older studies described some effects of doxorubicin and ifosfamide treatments [21]. CHT, however, possesses significant side-effects, especially in case of doxorubicin. In an effort to reduce toxicity, pegylated liposomal doxorubicin was administered. It is a modification of doxorubicin with similar antitumor activity and it was tested in the treatment of advanced STS [22, 23]. Trabectedin, originally tested for ovarian cancer, seems to be a promising drug in the treatment of metastatic STS. The given drug was tested in metastatic or non-resectable...
STS with failure of standard doxorubicin and ifosfamide chemotherapy regimens [24, 25].

Some risk factors associated with worse prognosis have been described. The most common risk factor mentioned applies to an incomplete resection of the tumor [18-20, 26-28] and to a high-grade sarcoma [18, 20, 26]. Some authors reported worse survival in case of a large tumor, older patients, and/or male patients [17, 27]. According to the present data, completely removed large tumors had no worse prognosis. The removal of adjacent organs is necessary in individual cases of large tumors.

In conclusion, RPSs represent a rare but serious malignant disease with contingent prognosis. Surgery is the most effective treatment option and radical removal without residual tumor has the most important prognostic significance. Complete resection is the main goal of surgery, because PSM significantly increases the risk of recurrence. Complete resection is the main goal of surgery, because PSM significantly increases the risk of recurrence. The authors prefer multidisciplinary approach in the cases of the retroperitoneal tumors in this oncologic center. They want to emphasize that the presence of an onco-gynecologist and urologist is optimal, because retroperitoneal localization has specific characteristics. These rare surgeries have important educative meaning for both specialists.

References


Nestin expression as an indicator of cervical cancer initiation

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Summary

Nestin is an intermediate filament protein expressed in proliferating cells during embryonic development of the central nervous system (CNS) and considered to be a neuronal stem/progenitor cell marker. This study investigated the difference of nestin expression between pre-cancer (carcinoma in situ - CIS) and cancer of cervix in 129 tissues (49 normal cervix, 41 CIS, and 39 invasive cervical cancer) through the use of a paraffin-embedded tissue array. Immunostaining was evaluated by intensity, proportion of stained cells, and pattern of expression. The expression of nestin was positive in 63.4% (26/41) for CIS and 43.6% (17/39) for invasive cervical cancer, but only 26.5% (13/49) for normal tissues (p = 0.002). Strong positive staining/large proportion staining were 53.7% (22/41) / 36.6% (15/41), 15.4% (6/39) / 61.5% (24/39) in the CIS and invasive cervical cancer tissues, respectively (p = 0.043, p < 0.001). The diffuse stain with basal layer was positive in 90.2% (37/41) for CIS, but only 24.5% (12/49) of the samples were positive in normal tissues (p < 0.001). Based on these results, the authors suggest that nestin expression seems to participate in the step of cancer initiation and could potentially be a useful marker in the early detection of cervical cancer.

Key words: Nestin; CIS; Cervical cancer.

Introduction

Nestin is an intermediate filament protein expressed in proliferating cells during embryonic development of the central nervous system (CNS) and is considered to be a neuronal stem/progenitor cell marker [1]. On differentiation and maturation, nestin becomes down-regulated and replaced by tissue-specific intermediate filament proteins, such as desmin and vimentin [2]. In adult organisms, nestin has been identified in cells which have a reserve function of proliferation, differentiation, and migration and are considered as stem/progenitor cell populations, such as striated muscle precursor cells, hair follicle precursor cells, and islet precursor cells, and can be re-expressed in response to injury of CNS, skeletal muscle, and liver [3-5].

Nestin has been detected in various tumors, such as melanomas, gastrointestinal stromal tumors (GISTs), prostate cancer, pancreatic cancer, and breast cancer, and also correlated with tumor differentiation, invasion, and metastasis [6-8]. Recently, the hypothesis that cancer may arise from somatic stem/progenitor cells has emerged and nestin is also expressed in various immortalized mammalian stem cell lines and is usually used as a marker for detecting cancer stem cells [9].

Cervical cancer is the third-most common cancer worldwide in the female population, with an estimated 529,000 new cases in 2008. It is also well-known that high-risk human papillomavirus (HPV) is the most important factor in the carcinogenesis of cervical cancer [10]. Infection by HPV is thought to occur through micro-wounds of the epithelium that expose cells in the basal layer to viral entry. Then, E6 and E7 viral oncogenic proteins interact with p53 and pRb, and result in cell immor-

talization and the malignant transformation of cells [11]. There are however few studies on cancer stem cell markers which represent the transformation from pre-cancer (carcinoma in situ - CIS) to cancer cells.

In this study, the expression of nestin was compared in normal cervix, CIS, and cervical cancer by the immunohistochemical staining score. In addition, the pattern of expression of nestin in the basal layer, in which stem cells may exist, was investigated to define the possibility of cancer stem cells in carcinogenesis of cervical cancer.

Materials and Methods

Cervical tissues, including 39 cancer tissues and 41 CIS tissues, were collected from patients who were treated in the Department of Obstetrics and Gynecology of Korea University Anam Hospital between 2000 and 2006. All patients received treatment according to the routine protocols in use in this hospital. The Korea University Hospital Institutional Review Board approved the study.

A paraffin-embedded tissue microarray was constructed using cervical tissues, including 39 cancer tissues, 41 CIS tissues, and 49 normal tissue counterparts which were collected from the residual normal cervical region after excision of the pathologic lesions (24 specimens from cancer patients and 25 specimens from CIS patients). All tissues were obtained from the histopathologic archives of the Pathology Department of Korea University Anam Hospital. The construction of the tissue microarray is briefly described as follows.

An experienced pathologist marked the area of normal cervical, CIS, and cancer tissue slides under × 400 microscopic magnification and labelled these areas in the corresponding paraffin-embedded blocks. Then, the paraffin wax blocks were incubated in a 37°C oven for 30 min. The punch needle that was used to punch the paraffin wax block withdrew three-mm in diameter tissue cores that fit exactly. The tissue cylinders were mounted on a tissue microarray (TMA). The TMA slide, which was four-µm thick, was deparaffinized in xylene, and was rehydrated in decreasing concentrations of ethanol to deionized water.
Endogenous peroxidase activity was quenched in methanol containing three percent hydrogen peroxide for five min. The TMA slide was treated twice for three min, each in citrate buffer (pH 6.0) with a pressure cooker heating at 121°C for antigen retrieval. After rinsing in Tris buffer, tissue sections were incubated using an anti-nestin primary antibody (1:500, mouse polyclonal antibody) at 4°C for 40 min. After rinsing with Tris buffer, slides were incubated with a secondary antibody for 30 min followed by a rinse with Tris buffer. Finally, the sections were incubated with diaminobenzidine (DAB; substrate buffer + DAB chromogen × 50) for five min. All slides were lightly counterstained with Harris hematoxylin for one min, washed in running water, dehydrated, and mounted.

The immunohistochemical expression of nestin was evaluated with semi-quantitative scoring system [12]. To determine the extent of positive staining, a proportion score that represents the estimated fraction of positively staining area was utilized: 0 = 0 - 5%; 1 = 5 - 25%; 2 = 25 - 75%; and 3 = 75 - 100%. For staining intensity, the score is represented by the estimated average staining intensity of cells as follows: 0 = none; 1 = weak; 2 = moderate; and 3 = strong. The amount of staining was then expressed as the sum of the proportion and intensity scores (range: 0 - 3 for negative staining and 4 - 6 for positive staining). The immunohistochemical staining patterns were divided into superficial and diffuse staining with the basal layer. All immunohistochemical staining were reviewed twice by one pathologist in a blind test.

The expression of nestin was confirmed by reverse transcription-polymerase chain reaction (RT-PCR). Total RNA was extracted from cervix tissue of cancer patients in TRIzol, followed by chloroform extraction. cDNA was obtained by reverse transcription of one ug of total RNA using a reverse transcription system and oligo dT primer. The cDNA was amplified according to the manufacturer’s instructions. To compute the significance, t-test was performed based on measure of band intensities. The primer sequences were as follows: Nestin forward, 5’-GACCCCCCACAAAAGTGGAT-3’, reverse, 5’-TTCTCTTGTCCCGCAGACT-3’; GAPDH forward, 5’-ACAACCTTGGATCATCGGAA-3’, reverse, 5’-AAATTCGTTGCTATCCAGG-3’.

Statistical analyses were performed using SPSS, version 13.0. The Pearson chi-square test and Fisher’s exact test were used to assess the significance of the associations between categorical data. The level of statistical significance for all analyses was set at 0.05.

**Results**

The level of nestin expression was investigated by the use of immunohistochemical analysis in 129 paraffin-embedded tissue samples presented as tissue microarrays. The immunohistochemical stains of nestin are shown in Figure 1. Nestin positivity as determined by the sum of immunohistochemical staining score was 63.4% (37/41) for CIS, but only 26.5% (13/49) of the samples were positive in normal tissues (p = 0.002; Table 1). There were no significant differences between CIS and invasive cervical cancer tissues (p = 0.116). However, when the intensity of staining and proportion were considered separately, strong positive staining existed in 15.4% (6/39) of the invasive cervical cancer tissues and 53.7% (22/41) of the CIS tissues (p < 0.001). The proportion of specimens with > 75% staining was 61.5% (24/39) in the invasive cervical cancer tissues and 36.6% (15/41) in the CIS tissues (p = 0.043; Table 2).

The diffuse stain with basal layer was positive in 90.2% (37/41) for CIS, but only 24.5% (12/49) of the samples were positive in normal tissues (p < 0.001; Table 3). RT-PCR analysis showed that the relative intensity between normal and cervical cancer tissue are statistically different (p = 0.0049, Figure 2).

**Discussion**

This is the first study to detect a correlation between nestin and cervical neoplasia. Nestin is an intermediate filament protein expressed in proliferating cells during developmental stages and in some adult stem cell populations, such as liver oval cells, vascular endothelial cells, and other pathologic conditions [13, 14]. Nestin correlates with the high proliferative and migration activities of primitive neuroectodermal tumors of the CNS and metastatic melanoma, suggesting that nestin might participate in proliferation and invasion of cancer cells [15]. Brychtova et al. [16] compared nestin expression in melanocytic lesions by immunohistochemical staining and reported that nestin was overexpressed in malignant melanoma compared to dysplastic lesions and common nevi, and as the invasion deepened, the expression of nestin increased, indicating that Nestin was associated with malignant transformation and tumor aggressiveness. Kawamoto et al. [8] also reported that nestin might play an important role in nerve and stromal invasion in pancre-
Figure 1. — Nestin immunohistochemical staining: (a) weak superficial staining in normal cervical tissue; (b) strong diffuse staining in the basal layer of CIS; (c) in invasive cervical cancer, and (d) superficial staining (× 100).
Nestin expression as an indicator of cervical cancer initiation

Figure 2. — Relative intensity of RT PCR of nestin in normal and invasive cervical cancer tissues.

atic cancer. In the present study, nestin was more highly-expressed in CIS and invasive cervical cancer tissues than normal tissues. Especially, nestin was more strongly-stained in CIS than invasive cervical cancer but more widely-stained in invasive cervical cancer than CIS. Based on these findings, the authors suggest that nestin may be associated with the step of cancer initiation leading to invasiveness.

For the confirmation of the correlation between nestin expression and cervical cancer initiation, the authors investigated nestin expression in the basal layer. Because it is believed that reserve cells play a critical role in the pathogenesis of cervical intraepithelial neoplasia (CIN), the authors expected the characteristic expression of nestin in the basal layer.

Chronic infection with high-risk HPV has been established as the main factor in carcinogenesis of cervical cancer. However, not all of the infected cells are transformed to cancer cells, but only some of the cells are transformed. Epithelial stem cells, which are responsible for repair of the epithelium, are located in the basal cell layers of non-infected stratified squamous epithelium, and divide and move vertically through the epithelium without further division. Mii et al. reported that HPV-DNA integrated in the genome of tumor cells and contributed to malignant alteration [17]. Although the precise mechanism remains unclear, the authors presumed that HPV-infection converts the stem cell to cancer stem cell in which nestin expression increases. If so, nestin expression can be a more specific marker of cervical cancer initiation than HPV infection.

Although several studies appeared, the markers of cervical cancer stem cells have not yet been well clarified. A majority of the studies supported the usefulness of nestin as cervical cancer stem cell marker [18-20]. Bortolomai et al. [18] found that the growth of stemness upregulates the expression of nestin, with a less pronounced rise of other marker.

In the present study, nestin, a well-known stem cell marker, was more highly-expressed in the basal layer in CIS, and cervical cancer tissues than normal tissues, which were different from other markers such as p63, Bcl-2 and cytokeratin 17. p63 is localized in the basal and parabasal layers in normal tissues and extends into the upper layer as CIN lesions progress [21]. Bcl-2 is limited in basal layers in normal tissues, but not correlated with CIN and cervical cancer lesions [22]. Cytokeratin 17 is not expressed in normal tissues and cytokeratin 17 is expressed in 40% of CIN 3 lesions and 73.2% of invasive cancer specimens, but the expression of cytokeratin 17 between normal and invasive cancer was significant different, and not between normal tissue and CIN 3 [23]. Another marker which has recently emerged is p16INK4A, which is considered to be a useful marker of high-grade squamous intraepithelial lesions and cancer. Van Niekerk et al. [24] and Zhang et al. [25] reported on the immunohistochemistry of p16INK4A in cervical lesions in which a diffuse strong staining pattern was observed in 81% of the cases of invasive cervical cancer and 59% of the CIN 3 lesions. These findings are similar to this present study, but in this study, nestin was more intensively stained in CIS than invasive cervical cancer lesions.

In this study, one pathologist examined all slides for maintaining the consistency of the results and it was enough to make the conclusions. The authors evaluated only pathologic findings without clinical information. Further study considering the risk factors such as HPV infection, smoking, and parity is desired.

In summary, the authors have demonstrated, for the first time, the characteristic expression of nestin in normal, CIS, and invasive cervical cancer. These results suggest that nestin expression seems to participate in the cervical cancer initiation step arising to invasiveness and could potentially be a useful marker in the early detection of cervical cancer. Further studies to determine the impact of the E6 or E7 oncogene on nestin in cell immortality, and the correlation between nestin and CIN lesion, and various clinical parameters, are warranted.

References


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Morular endometrial metaplasia: review of the literature and proposal of the management

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Summary

Purpose of investigation: Morular endometrial metaplasia is a rare condition that can be often misdiagnosed and overtreated, because it can be mistaken for a malignant disease. The aim of this review was to update the current opinion on the significance of this pathology and its risk for potential malignancies. Materials and Methods: The authors report their experience of two cases of morular metaplasia involving very young women managed conservatively with hysteroscopic resection of the affected areas. Results: Hysteroscopic resection of these lesions can be an adequate and fertility-sparing treatment of morular metaplasia in women of child-bearing age. Conclusions: Morular metaplasia has indeed a mutational origin but it is a benign and hormonally inert condition. The risk to develop cancer is closely associated with premalignant or malignant endometrioid glandular proliferations that are often associated with histological finding of morules rather than with morules themselves. Management of this condition requires trained pathologists and gynecologists and should be adapted to the age of the patient.

Key words: Endometrial metaplasia; Operative hysteroscopy.

Definition

Endometrial metaplasia is a benign adaptive phenomena in which epithelial or mesenchymal endometrial cells are replaced by excessive quantities of homologous elements or partly by heterologous cells [1]. Epithelial metaplasias are the most common and include ciliated and tubal metaplasia, mucinous metaplasia, squamous metaplasia, morules, and reactive changes. Mesenchymal metaplasia uncommonly occurs [1].

The term “morula” was first coined in 1959 by Dutra and refers to the histological similarity of this kind of endometrial metaplasia with a mulberry [2]. Morules have indeed a rounded shape and are composed by oval or spindle-shaped cells aggregated in a regular and well-circumscribed manner. These cells usually show eosinophilic cytoplasm and inactive and uniform nuclei without prominent nucleoli [3, 4]. In the centre of large morulas may exist a comedo-type necrosis, probably due to ischemic phenomena [1]. After their origin from glandular epithelium, morules can extend beyond the glandular lume forming ‘free’ stromal nodules [1]. They may contain optically clear nuclei [3-5, 7] that are biotin-rich inclusions first described in endometrial glands during gestation and puerperium [8].

The main causes of endometrial metaplasia are hormonal or irritative stimuli, as unopposed estrogen exposure [9], progesterone-releasing intrauterine devices [10], use of selective progesterone-receptor modulators [11], chronic inflammation as endometriosis [12], and trauma.

Most kind of metaplasia are benign and hormone-related but morular metaplasia has a mutational origin [1] and seems to be related with glandular complexity and atypia [4, 13, 14].

Since Dutra’s original description [2], morular metaplasia has been separated from squamous differentiation both for the well-differentiated complex glandular architecture and the association between morules and lesions of attenuated malignancy [2, 4]. Although some authors consider morules as a kind of immature or early stage squamous differentiation, their different morphology and immunophenotype warmly support to use the term morular metaplasia instead of squamous morules as used in the past.

Morphologically similar structures have been described in many benign and neoplastic lesions. They can be similar to granulomata and may be present in senile endometrium, chronic endometritis, radiation, submucosal myoma, endometrial hyperplasia, and lesions resulting from the use of an intrauterine contraceptive device [3], but some authors consider this to be incidental rather than with a pathogenetical significance [1].

Morules may be indistinguishable from the spindle cell areas present in some endometrioid carcinomas [1] and have been described in neoplastic lesions in other anatomic sites, such as thyroid adenocarcinoma and cribriform-morular variant of papillary thyroid carcinoma [15, 16], pulmonary blastoma, fetal lung carcinoma [17], gastric mucosa [18], pancreatoblastom [19], and colon carcinoma adenoma [20-22]. Chinen et al. studied HPV infection in morules and found no positive morula to human papillomavirus (HPV) [3].

Although morules can be present in endometrial benign lesions without premalignant potential, they are closely associated with premalignant or malignant endometrioid glandular proliferations in the uterus and ovary [5].

Genetic and immunophenotype features

Morules can be distinguished by normal endometrium and endometrioid neoplasm due to their peculiar immunohistochemical [3, 23] and genetic [14, 23] profiles.
Morules typically exhibit diffuse nuclear CDX2 [5] and b-catenin immunoreactivity [3, 6, 13, 14, 23, 24] and are positive for CD10 [4, 5] and LP34 [5]. On the contrary, well-differentiated glandular epithelium is positive to hormonal receptors and only exhibits membrane bound beta-catenin [4].

Beta catenin is a transcriptional activator of the Wnt signaling pathway whose malfunctioning results in the intranuclear accumulation of beta-catenin and transcriptional activation of specific target genes [3].

As in endometrium, some of the aforementioned neoplastic lesions from other organs exhibit morules with nuclear beta-catenin positivity and/or beta-catenin gene mutation, thus leading to the assumption that the presence of morules in neoplasms is related with beta-catenin gene mutation and nuclear accumulation of b-catenin protein [5].

The process of morular formation seems then to be a characteristic, independent type of neoplastic transformation, involving an aberrant nuclear beta-catenin accumulation probably secondary to beta-catenin mutation [4, 7, 14, 24], as first suggested by Nakatani et al. in 2002 [25] and confirmed afterwards by others [22, 26, 27].

The association between beta catenin gene mutation and morules is well known [17, 22, 25, 28] and is attributed by some authors to a group of endometrioid carcinomas with a good prognosis, most of which originating from previous benign or borderline lesions [28]. Determination of the b-catenin mutation in early-stage ovarian cancer has been suggested as a useful marker for selecting low-risk patients [28].

Many different immunohistochemical markers have been studied to clearly identify morules. It is now established that morules show a diffuse and membranous CDX2 expression and morular formation in endometrial squamous metaplasia [1, 4].

Saegusa et al. in 2007 studied the association between CDX2 expression and morular formation in endometrial carcinomas. They concluded that expression of active form of beta-catenin results in significant CDX2 overexpression in morules and therefore CDX2 and beta-catenin signaling may participate in induction of transdifferentiation of endometrial carcinoma cells from a glandular to a morular phenotype [29].

Houghton et al. suggest that CDX2 is a useful marker of morular identification because of their almost constant positivity for this marker that is only occasionally positive in minor foci of glandular elements, while CD10 may be positive in typical squamous elements, glandular elements, and endometrial stroma [5].

In 2010 Chiarelli et al. proposed CD10 as a more useful marker for morular endometrioid lesions for its strong membranous positivity that helps to differentiate morular components from endometrial glandular epithelium, that appears usually negative. They use the glandular architecture, the nuclear beta-catenine positivity, and the steroid receptor positivity to highlight morules from the surrounding stroma, that is also CD10 positive [4].

From a practical viewpoint, CD10 results as a better marker because it permits identification of morules at low power in various types of surgical specimens and in curettings, particularly in fragmented aspirative biopsies, and its positivity remains even in moderately autolytic endometrial lesions and necrotic debris [4].

It is commonly established that morules in endometrioid proliferations of the uterus and ovary exhibit no alpha-estrogens nor progesterone receptors and are thus hormonally inert [3-6, 30] while associated glands are diffusely estrogen receptor positive. Typical squamous elements are usually estrogen receptor positive but less intense and diffuse [5].

Chiarelli et al. report a clinical follow up in patients with morular endometrial metaplasia and show morular persistence during progesterone treatment and after pregnancy, even in a case of associated atypical hyperplasia. The only different finding after progesterone treatment was an intramorular keratinization in two cases [4].

**Risk of malignancy**

The association between endometrial metaplasia and cancer, although clearly described [31-34], differs between each kind of metaplasia, being rare for squamous metaplasia, frequent for tubal and mucinous metaplasia, and almost constant for morular metaplasia [1]. Although morules can be present in benign lesions without premalignant potential, they are closely associated with premalignant or malignant endometrioid glandular proliferations in the uterus and ovary [5]. Nevertheless, the morule being a benign [1, 3] and hormonally inert [3-6, 30] lesion that can often be marker of complex endometrioid glandular architecture [1], does not represent, in the authors’ opinion, a preneoplastic lesion itself.

Indeed, morules show a very low proliferative index [1], mitotic figures are not usually seen, and they result negative to overexpression of p53 and proliferative cell antigens PCNA and Ki-67, nor do they express blood group antigens as morular thyroid carcinoma [3]. Consequently they are not supposed to actively work in the neoplastic transformation compared with their estrogen-sensitive glandular counterpart [1].

As a matter of fact, only the glandular elements keep their responsiveness to the cancer-promoting effects of estrogens, or involutive effects of progestins, and thus premalignant glandular lesions associated with morules will eventually result in glandular, rather than squamous, carcinomas [30].

Furthermore, morules are observed, since their first description by Dutra in 1959, to be associated to well-differentiated lesions with attenuated malignancy [1, 2, 4, 6, 14, 22, 27, 35] that are usually diagnosed at an early stage [4, 14, 23], with long survival rate [24], and low propensity to recur or metastasize [4]. This finding is also supported by the observation by Chiarelli et al. in 2006 that morules are usually absent in high-grade glandular malignant lesions [4].
So which is the predicting factor of a lesion showing morular element to progress into adenocarcinoma? According to Lin et al., the progression strictly depends on the architectural and cytological atypia of the glandular component still responding to estrogens. Thus is the coexistence of atypical hyperplasia or endometrial intraepithelial neoplasia (EIN) among the glandular components, and not morules themselves, responsible for the developing of cancer? [30].

Management

The clinical management of patients showing a morular metaplasia in an endometrial sampling is neither clear nor sufficiently investigated in the current literature. Based on the assumption that lesions associated with complex glandular proliferation, with or without atypia, can develop in adenocarcinomas, Lin et al. suggest to re-evaluate patients with morular lesions without EIN and report a 6.5% of samples revealing an undetected carcinoma [30]. However, he did not specify which was the follow-up technique.

Nicolae et al. suggest that patients with finding of morules in apparently normal glands or in aspiration biopsies should be addressed to a curettage in order to exclude a coexisting under-sampled or occult glandular lesion [1, 30].

In the authors’ opinion, curettage is not the correct technique to approach this kind of follow up, while hysteroscopy being a more accurate and precise exam that allows the surgeon to identify and define the lesion [36, 37], perform a targeted biopsy, and obtain a material that is most suitable to histology.

Relying on these observations, the authors propose a long-term hysteroscopic follow up of morular metaplasia in order to both exclude unsampled complex glandular components and allow a conservative approach to a benign lesion that can occur at a young age, thus preserving fertility of the patients.

Although the present experience is still limited by the rarity of this kind of metaplasia, the authors can report two cases of successful conservative treatment for morular lesions in very young patients. The first patients, aged 24, come to the authors’ observation in February 2012 for menorrhagia and underwent a diagnostic hysteroscopy with biopsy that revealed hyperplasia of endometrial glands with architectural complexity and a large quantity of confluent morules, some with central necrosis. The immunophenotype was congruent with morular hyperplasia with CD10 positivity and negativity for estrogen and progesterone receptors. The authors performed a partial endometrial resection with histological finding of glandular endometrial hyperplasia and morules but without significative atypia. Subsequently the patient was subjected to other two endometrial resections of hyperplastic areas on the posterior uterine wall, the first with the same histological findings of the first biopsy, the second revealing only focal morules and she is still being followed up.

The second patient had a first diagnosis of atypical endometrial hyperplasia after polypectomy performed in another hospital in April 2007. The authors performed another office hysteroscopy with evidence of polyp residue and achieved a wide focal resection of the affected area that revealed histological finding of endometrial glands with architectural complexity and a large quantity of confluent morules, some with central necrosis. She was followed up with transvaginal ultrasound every six months and office hysteroscopy if necessary. Histological examination of biopsies was negative until May 2008 when a focal resection with 21-French hysteroscope was performed on a suspect area in the uterine isthmus which microscopic examination again revealed the presence of morules.

After two negative controls at six and 12 months, a hyper-vascularized area of about one cm was found that revealed again the presence of morules and rare atypia. The subsequent follow up was negative until January 2012 when the biopsy performed during office hysteroscopy revealed a glandular hyperplasia without atypia nor morules. The patient became pregnant only one month later. After a physiological pregnancy, an elective cesarean section was carried on in November 2012 because of the four previous endometrial wide resections at isthmus level and the risk of scar dehiscence in labour. The authors planned to perform a diagnostic hysteroscopy six months after delivery.

In both cases the treatment of morular findings in biopsies was restricted to the complete resection of macroscopic lesions, eventually evidenced during diagnostic hysteroscopy, and no hysterectomy nor progesterone therapy were suggested. No progression of the glandular hyperplasia associated with morules was found during this follow up. The authors propose that in very young patients, a conservative approach is safe and effective and allows for a normal reproductive outcome [36, 38].

Conclusions

Morular metaplasia is a rare, benign [3, 4], and a hormonally inert [3, 6, 30] condition closely associated with premalignant or malignant endometrioid glandular proliferations [5] that can result in glandular carcinomas [29] with attenuated malignancy [1, 2, 4, 6, 14, 22, 25, 27, 35]. Patients with histological finding of morules should be strictly followed up [1, 4, 30].

The authors’ proposal of treatment in fertile women is to perform a hysteroscopic full resection of the affected areas [37, 39] instead of a blind revision of the uterine cavity. For the first year follow up they suggest to perform a transvaginal ultrasound every four months and address patients with suspect hyperencogenic areas to a diagnostic hysteroscopy, each time performing a biopsy of any suspicious areas. If the first year follow up is negative, they suggest a transvaginal ultrasound endometrial evaluation every six months searching for any focal hyperencogenicity that would require once again a diagnostic hysteroscopy. If the two-year follow up remains
negative, the patient can perform an annual transvaginal ultrasound. If the diagnosis of morular metaplasia occurs in menopause or at the end of the personal reproductive plan, a demolition approach should be preferred. Given the rarity of this condition, patients should be carefully followed up by expert gynecologists and a collaboration with trained pathologists is important for management and counselling to avoid unnecessary hysterectomy in fertile women.

References


Morular endometrial metaplasia: review of the literature and proposal of the management


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The effects of simple and radical hysterectomy and radiotherapy on lower urinary tract symptoms and urodynamics

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Summary

Purpose: To evaluate effects of simple/radical hysterectomy, radiotherapy, and their combination on lower urinary tract symptoms (LUTS) and urodynamics. Materials and Methods: Four groups were formed as simple hysterectomy; Group 1 (n = 20), Type-II hysterectomy; Group 2 (n = 11), Type-II hysterectomy + radiotherapy; Group 3 (n = 16), radiotherapy; Group 4 (n = 20). LUTS, bladder diary, pad test, Q-tip test, stress-test, urodynamics, bladder-wall-thickness measurement, King’s Health Questionnaire (KHQ) performed prior and at six and 18 months after treatment. Results: Pre-treatment prevalence of LUTS was higher in Group 1 and decreased at six and 18 months. LUTS increased in Groups 2, 3, and 4 at six months; some of the symptoms decreased to pre-treatment levels at 18 months. Quality of life improved in Group 1 and worsened in the others. Maximum bladder capacity increased in Group 1 and decreased in Groups 2 and 3. Bladder-wall-thickness, maximum detrusor pressures increased, urine sensation decreased in Groups 2 and 4. Maximum vesical pressure increased and compliance decreased in Groups 2 and 3. Conclusion: LUTS may decrease after simple hysterectomy. Radical hysterectomy and radiotherapy result in voiding dysfunction; however some of the symptoms may decrease to pre-treatment levels during follow-up.

Key words: Cervical cancer; Endometrium cancer; Hysterectomy; Lower urinary tract dysfunction; Radiotherapy; Urinary incontinence.

Introduction

Urinary incontinence (UI) is defined as the involuntary loss of urine that is a social or a hygienic problem [1]. The prevalence of UI is affected by age, parity, obesity, smoking, menopausal state, and previous gynecologic or surgical operations. In addition, gynecologic neoplasms and their surgical and non-surgical treatments are associated with UI. There are three possible mechanisms in this association; the direct invasion of the neoplasm, the mass effect of the neoplasm leading to urinary tract compression, and short and long-term effects of treatment modalities leading to temporary or permanent urinary tract symptoms [2].

Simple hysterectomy and radical hysterectomy have been evaluated for their effects on lower urinary tract functions [2, 3]. A decrease in bladder sensations and flow rate, incomplete emptying, and stress urinary incontinence or urge urinary incontinence may develop after surgery [4]. Radiotherapy (RT) also has an important role in the treatment of gynecologic neoplasms and may lead to acute and chronic lower urinary tract problems such as irritative symptoms and nocturia, pollakiuria, dysuria, and diminished bladder capacity [5, 6].

In recent years, survival rate after gynecologic malignancies has increased. In addition to increase in survival rate and life expectancy, it has become quite important for these patients to maintain their quality of life. It is well-known that lower urinary tract symptoms including UI lead to a decrease in quality of life in patients. In this study, the authors aimed at evaluating the effects of simple hysterectomy, radical hysterectomy, RT, and combined treatment modalities on lower urinary tract symptoms and urodynamics.

Materials and Methods

Sixty-seven patients applying to the Istanbul University, Istanbul Medical Faculty Department of Obstetrics and Gynecology and Department of Radiation Oncology were included in this prospective study. Informed consent was obtained from all patients. Ethics approval was obtained from the Istanbul University Ethics Committee on July 6, 2005. Patients were divided into four groups according to the procedure performed. Group 1 (n = 20) and Group 2 (n = 11) underwent simple hysterectomy for benign gynecologic conditions and type II hysterectomy for either endometrial or cervical carcinoma, respectively. All the procedures were performed by laparotomy. Group 3 (n = 16) underwent simple/radical hysterectomy, pelvic ± para-aortic lymphadenectomy and omentectomy for either endometrial or cervical carcinoma and received adjuvant RT. Group 4 (n = 20) received primary RT for Stages IB2, II, and III cervical carcinoma. The former FIGO staging was used while the new staging system was not available during this study. The Foley catheter was removed one day after simple hysterectomy and ten days after type II hysterectomy. All the complications that developed during or after the surgeries were noted.
For RT, total mean 4,500-5,000 cGy dosage with daily 180-200 cGy doses was given. Dosages of 8,500-9,000 cGy was given on the vaginal stump for brachytherapy and 5,000-6,000 cGy was given for the parametrium and pelvic side walls. All the complications that developed during or after RT were noted.

Pelvic organ prolapse evaluation with Baden-Walker-Halfway-System, bladder diary, stress-test, Q-tip-test, one-hour pad test, pelvic floor muscle strength measurement, cystometry, uroflowmetry, and bladder-wall-thickness measured with Doppler ultrasonography was performed in each group pre-treatment and at six and 18 months after treatment. Urodynamics was performed using MMS UD 2000 urodynamics system.

Bladder wall thickness was measured with transvaginal ultrasonography (TVUS) using a 5-9 MHz transvaginal probe. Bladder wall thickness was measured in the lithotomy position after the patients emptied their bladder. All measurements were done at maximum magnification. The bladder wall thickness was measured perpendicular to the bladder lining at the thickest parts of the trigone, dome, and anterior wall of the bladder [7].

The King’s Health Questionnaire (KHQ) has been developed to assess quality of life and includes 21 questions organized in nine domains including general health, incontinence impact, role limitations, personal limitations, social limitations, personal relationship, emotions, sleep and energy, severity of measures, and global score. Each domain has a separate score that specially investigates UI symptoms [8]. KHQ validated in ranges from 0 to 100. The KHQ has a specific domain, which investigates UI symptoms [8]. KHQ validated in Turkish was used to assess the impact on the quality of life [9].

Statistical analysis

Statistical analysis was performed with the computer program Statistical Package for the Social Sciences (SPSS) 15.0 for Windows by a professional statistician. Data were expressed as mean ± standard deviation. One-Way Analysis Test (ANOVA), Kruskal Wallis, Paired t-test, Fisher’s exact test, Wilcoxon rank, and Chi-squared test were used for statistical analysis. A p value less than 0.05 was considered statistically significant.

Results

Sixty-seven patients were included in the study. Fifty Group 1 (n = 16), Group 2 (n = 11), Group 3 (n = 12), Group 4 (n = 11), and 55 patients Group 1 (n = 19), Group 2 (n = 10), Group 3 (n = 15), Group 4 (n = 11) participated in the urogynecologic examination at six and 18 months after treatment, respectively.

The demographic variables of the groups are summarized in Table 1. The mean age of the patients was similar. Ten patients (50%) in Group 1, three patients (27.3%) in Group 2, six patients (37.5%) in Group 3, and three patients (15%) in Group 4 had second-degree prolapse. Mean body mass index (BMI) of Group 3 was significantly higher than the other groups at pre-treatment evaluation and at six months. However, at 18 months, mean BMI of Group 1 was significantly higher than the pre-treatment level and other groups. Q-tip test was positive in all of the patients before treatment. Stress-test was positive in two patients in Group 1, one patient in Group 2, and three patients in Group 3. None of the patients had undergone anti-incontinence or surgery for pelvic organ prolapse.

The indications for hysterectomy in Group 1 were leiomyomas (n = 7, 35%), ovarian cysts (n = 3, 15%), atypical endometrial hyperplasia (n = 2, 10%), dysfunctional uterine bleeding (n = 2, 10%), and Stage IA endometrial cancer (n = 6, 30%). The distribution of patients in Group 2 according to Stage and grade of tumors was as follows; two patients (18.1%) Stage IA2 grade 1, four patients (36.3%) Stage IB1 grade 1, four patients (36.3%), Stage IB1 grade 2, and one patient (9%) Stage IB2 grade 2 squamous cell cervical carcinoma. The surgical treatment and the results of the postoperative histopathologic evaluation of Group 3 who underwent hysterectomy + RT are summarized in Table 2. Nine patients (56.3%) received brachytherapy, five patients (31.2%) received RT + brachytherapy, and two patients (12.5%) received chemotherapy in addition to brachytherapy + RT. Group 4 received only RT + chemotherapy for advanced stage cervical carcinoma. Nine patients (45%) had Stage IB1 and IB2, eight patients (40%) had Stage II, and three patients had Stage III cervical cancer. Mean combined dosage was 4,320 cGy in Group 3 whereas it was 8,859 cGy in Group 4.

Lower urinary tract symptoms of the patients are sum-

Table 1. — Demographic variables of the four groups.

<table>
<thead>
<tr>
<th>Stage - Grade - Histology</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB grade 2 endometrioid type endometrial adenocarcinoma*</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC grade 1 endometrioid type endometrial adenocarcinoma*</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC grade 2 endometrioid type endometrial adenocarcinoma*</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa grade 1 endometrioid type endometrium adenocarcinoma +</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IC grade 2 endometrioid type endometrium adenocarcinoma +</td>
<td>1</td>
<td></td>
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<tr>
<td>IC grade 3 endometrioid type endometrium adenocarcinoma +</td>
<td>1</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>In situ grade 2 squamous cell cervical carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB grade 2 squamous cell cervical carcinoma LVI (+), surgical border &lt; 1 cm*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Total abdominal hysterectomy, pelvic lymphadenectomy, and total omentectomy
* Total abdominal hysterectomy
* Type II hysterectomy
LVI: lymph vascular space invasion.
Table 3. — Results of the King’s Health Questionnaire total score pre-treatment at six and 18 months after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 11)</th>
<th>Group 3 (n = 16)</th>
<th>Group 4 (n = 11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>22.5 ± 17.5</td>
<td>9.1 ± 13.2</td>
<td>19.9 ± 23.2</td>
<td>7.4 ± 7.9</td>
<td>0.022*</td>
</tr>
<tr>
<td>6 months</td>
<td>14.2 ± 12.8</td>
<td>26.9 ± 16.7</td>
<td>20.2 ± 14.6</td>
<td>8.4 ± 7.3</td>
<td>0.019*</td>
</tr>
<tr>
<td>18 months</td>
<td>17.3 ± 18.5</td>
<td>23.1 ± 21.1</td>
<td>22.2 ± 28.3</td>
<td>12.0 ± 11.9</td>
<td>0.730</td>
</tr>
</tbody>
</table>

Table 4. — One-hour pad test results before treatment and at six and 18 months after treatment. Results are expressed in grams.

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>6 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>9.5 ± 21.9</td>
<td>5.2 ± 12.9</td>
<td>0.3 ± 0.8</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.4 ± 1.2</td>
<td>11.5 ± 16.4</td>
<td>10.1 ± 19.2</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.9 ± 6.9</td>
<td>6.0 ± 14.2</td>
<td>14.3 ± 28.4</td>
</tr>
<tr>
<td>Group 4</td>
<td>2.6 ± 7.3</td>
<td>4.3 ± 7.1</td>
<td>0.2 ± 0.6</td>
</tr>
<tr>
<td>p</td>
<td>0.083</td>
<td>0.657</td>
<td>1.176</td>
</tr>
</tbody>
</table>

Table 5. — Pre-treatment cystometry results of the four groups.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 11)</th>
<th>Group 3 (n = 16)</th>
<th>Group 4 (n = 11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>First sensation of urine (ml)</td>
<td>148.1 ± 183.5</td>
<td>209.3 ± 195.1</td>
<td>52.07 ± 55.77</td>
<td>44.2 ± 47.9</td>
<td>0.079</td>
</tr>
<tr>
<td>Strong sensation of urine (ml)</td>
<td>441.25 ± 431.73</td>
<td>389.64 ± 417.33</td>
<td>69.98 ± 52.38</td>
<td>67.49 ± 65.23</td>
<td>0.031</td>
</tr>
<tr>
<td>Max bladder capacity (ml)</td>
<td>85.76 ± 75.81</td>
<td>72.26 ± 65.47</td>
<td>59.69 ± 52.77</td>
<td>72.26 ± 65.47</td>
<td>0.062</td>
</tr>
<tr>
<td>Max detrusor pressure (cm H2O)</td>
<td>30.35 ± 24.20</td>
<td>24.69 ± 23.39</td>
<td>17.00 ± 15.49</td>
<td>24.69 ± 23.39</td>
<td>0.352</td>
</tr>
<tr>
<td>Max detrusor (ml/cm H2O)</td>
<td>41.83 ± 32.77</td>
<td>28.58 ± 23.39</td>
<td>41.83 ± 32.77</td>
<td>28.58 ± 23.39</td>
<td>0.134</td>
</tr>
<tr>
<td>Compliance</td>
<td>75.76 ± 59.69</td>
<td>36.37 ± 28.81</td>
<td>36.37 ± 28.81</td>
<td>36.37 ± 28.81</td>
<td>0.176</td>
</tr>
</tbody>
</table>

Table 6. — Cystometry results of the four groups at six months.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 11)</th>
<th>Group 3 (n = 16)</th>
<th>Group 4 (n = 11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>First sensation of urine (ml)</td>
<td>142.57 ± 131.91</td>
<td>202.00 ± 145.64</td>
<td>26.97 ± 27.77</td>
<td>107.59 ± 85.47</td>
<td>0.123</td>
</tr>
<tr>
<td>Strong sensation of urine (ml)</td>
<td>404.57 ± 373.40</td>
<td>399.04 ± 368.55</td>
<td>72.57 ± 91.18</td>
<td>101.49 ± 72.06</td>
<td>0.412</td>
</tr>
<tr>
<td>Max bladder capacity (ml)</td>
<td>512.79 ± 440.45</td>
<td>472.83 ± 436.64</td>
<td>75.81 ± 87.53</td>
<td>63.77 ± 118.51</td>
<td>0.041*</td>
</tr>
<tr>
<td>Max vesical pressure (cm H2O)</td>
<td>132.14 ± 135.67</td>
<td>127.55 ± 20.69</td>
<td>43.12 ± 31.11</td>
<td>20.69 ± 40.33</td>
<td>0.199</td>
</tr>
<tr>
<td>Compliance</td>
<td>44.79 ± 31.11</td>
<td>43.83 ± 31.11</td>
<td>43.83 ± 31.11</td>
<td>43.83 ± 31.11</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The pre-treatment stress and urge UI, urgency, frequency, pad usage, and coital leakage were higher in Group 1. UI, urgency, nocturia, dysuria, pad usage increased in Group 2 at six months. There was an increase in obstructive symptoms such as 63.6% of the patients had hesitancy, 72.7% of the patients had voiding dysfunction and intermittent stream. These symptoms except for nocturia and slow stream decreased to pre-treatment levels at 18 months. The urinary frequency, pad usage, nocturia increased in Group 3 at six months; some of the symptoms decreased to pre-treatment levels at 18 months. Urgency, frequency, urge UI, nocturia, dysuria, recurrent urinary tract infections, straining for voiding, slow urinary stream increased in Group 4 at six months and some of the symptoms regressed at 18 months. Three patients in Group 4 had hematuria and two patients developed mild hemorhagic cystitis that responded to medical treatment. Also, one patient in Group 2 and two patients in Group 4 suffered from fecal incontinence at 18 months.

The pre-treatment total score of KHQ was significantly higher in Groups 1 and 3 (Table 3). At six months, the total score of Groups 2 and 3 was significantly higher. At 18 months, the total score of KHQ was higher than the baseline in Groups 2, 3, and 4, but had decreased from the levels at six months in Groups 2 and 4.

No significant difference was observed in the pre-treatment urodynamic stress urinary incontinence (SUI) analysis except for the first sensation of urine which was significantly lower in Group 1 (Table 5). At the first urodynamic evaluation, one patient (5%) from Group 1 had urodynamic stress urinary incontinence (SUI). One patient (5%) from Group 1, two patients (18.2%) from Group 2, three patients (18.75%) from Group 3, and one patient (5%) from Group 4 had detrusor overactivity.

At six months after treatment, the maximum bladder capacity of Group 1 increased (Table 6). Group 2 showed a decrease in the maximum bladder capacity.
ance and an increase in the maximum vesical pressure and residual urine volume. Maximum detrusor pressures of Groups 2 and 4 were significantly higher than the other groups. Nineteen of the patients had UI during cystometry. One patient had mixed UI whereas the rest of the patients had detrusor overactivity.

The cystometry results at 18 months after treatment showed a significant difference in maximum bladder capacity in Group 1 (Table 7). In Group 2, obstructive voiding pattern, decrease in urinary flow rate, and high residual urine volume disappeared, but decrease in maximum bladder capacity and compliance and abnormalities in sensation of urine persisted. Almost half of the patients developed urgency and urge urinary incontinence.

De novo SUI developed in two patients in both Groups 3 and 4 at 18 months after treatment. Two patients had type III SUI and two patients had type I SUI. At 18 months, the incidence of UI in Group 1 was 21%, in Group 2 was 50%, in Group 3 was 50.3%, and in Group 4 was 63.6%. There was no SUI in Group 2.

The patients suffering from UI as a late complication were offered treatment. Five patients received anticholinergic treatment and bladder training. One of the patients suffering from SUI underwent transobturator tape operation in Group 3 and received anticholinergic treatment after surgery.

Intraoperative bladder injury occurred in only one patient in Group 1 and was repaired during the operation. No postoperative complications developed. One patient in Group 2 had a lymphocele at the left iliac region leading to grade 2 hydrenephrosis and a unilateral double-J catheter was introduced. One patient in Group 3 receiving brachytherapy and estrogen replacement therapy (ERT) developed radiation cystitis. Two patients in Group 4 with advanced cervical cancer died during the study due to bilateral grade 3 hydrenephrosis and acute renal failure. Ureterovaginal fistula and unilateral grade 3 hydrenephrosis developed in one patient in Group 4, six months after RT. Bilateral double-J catheter was introduced.

**Discussion**

UI may accompany gynecologic tumors and has an adverse effect on the quality of life and psychologic, social, and general well-being. Anatomical closeness makes lower urinary tract symptoms quite common in advanced stage gynecologic neoplasms [10]. In addition, surgery, RT, and chemotherapy lead to temporary or permanent lower urinary tract symptoms [2].

The authors could not find any detrimental effect of simple hysterectomy on lower urinary tract symptoms and urodynamics. On the contrary the prevalence of pretreatment symptoms was highest in Group 1, but these symptoms decreased at six and 18 months after the operation. The increase in BMI was linked to postmenopausal changes in the basal metabolic rate seen after bilateral salpingo-oophorectomy [11].

There are studies with contradictory results regarding the effects of simple hysterectomy on the lower urinary tract. It was suggested that simple hysterectomy led to
lower urinary tract dysfunction [12]. However prospective studies have not supported this idea [13-17]. In the only prospective study suggesting an association between UI and simple hysterectomy, the incidence of urinary symptoms increased from 58% to 75% [18]. In a recent meta-analysis, no association between hysterectomy and UI was found in women younger than 60 years of age [19].

There was a significant increase in the maximum bladder capacity after simple hysterectomy. The patients that developed detrusor overactivity at six and 18 months already had low compliance during the pre-treatment evaluation. The only patient that developed SUI had chronic pulmonary disease and an increase in BMI after surgery. According to these results, the authors can say that simple hysterectomy does not have an adverse effect on lower urinary tract function. El-Toukhy et al suggested that lower urinary tract symptoms occurred less frequently and urodynamic studies remained unchanged after hysterectomy [20].

The discrepancy between clinical findings may be seen because of a couple of factors such as hysterectomies performed in the old age group in whom lower urinary tract symptoms are nonetheless commonly encountered, the reduction of pelvic organ prolapse after hysterectomy, and the misinterpretation of short-term effects [21]. Another factor is that most of the patients relate their lower urinary tract symptoms to their hysterectomy date. In addition, if the indication for hysterectomy leads to more severe symptoms, the patient may put off mild UI.

The radical hysterectomy group (Group 2) showed a decrease in the maximum bladder capacity, mean flow rate, compliance, and an increase in the maximum vesical pressure, residual urine volume, urgency, urinary incontinence, and obstructive symptoms. At the 18 month evaluation, obstructive voiding pattern, decrease in urinary flow rate, and high residual urine volume disappeared, but a decrease in maximum bladder capacity and compliance and abnormalities in sensation of urine persisted.

Radical hysterectomy may lead to lower urinary tract symptoms as high as 80% in some series [2]. The most significant morbidity in the postoperative period has been bladder dysfunction including loss of bladder sensations, hypertonic bladder, hypo/acontractile bladder, urgency, and SUI [22]. However; approximately 80% of women do not report their symptoms as bothersome [2]. Changes in the intrinsic sphincter functions are thought to be responsible for the development of UI after radical hysterectomy [23]. Decrease in maximal urethral closure pressure, flow rates, compliance, and a significant increase in maximum intravesical filling pressure and residual urine volume have been observed [24]. However, these changes may normalize during follow-up. In one study, UI following radical hysterectomy showed a significant spontaneous improvement rate within the first 12 months following surgery. Urodynamics should be a mandatory investigation in patients who complain of persisting problems thereafter [25].

Nerve-sparing radical hysterectomy techniques may eliminate these lower urinary tract symptoms seen after radical hysterectomy [26, 27]. The aim of contemporary oncologic surgery should be to minimize the morbidity and adverse effects on quality of life while performing optimal surgery.

RT has early and late effects on bladder and urethral functions. In Group 3, there was a significant decrease in bladder capacity and an increase in intravesical pressure and resting detrusor pressures at six months. The results showed that at six months radical hysterectomy alone led to more severe symptoms, but the results of Groups 2 and 3 were similar at 18 months. In a study on the short-term effects of RT on urinary symptoms and urodynamic assessment, voiding dysfunction was more common after radical hysterectomy and radical hysterectomy + RT group as compared to RT group [28]. Bladder compliance was significantly reduced in those patients receiving more than 3,000 rads to the entire bladder from RT.

Group 4 had a significant increase in bladder wall thickness, resting detrusor pressures, UI episodes, and a decrease in flow rate and compliance. At 18 months, there was a further decrease in the first sensation of urine, strong sensation of urine, maximum bladder capacity, and compliance, but there was no significant difference between Groups 2 and Group 4 regarding the reduced bladder capacity and obstructive symptoms.

The maximum bladder capacity and compliance was significantly lower and maximum detrusor pressure was higher in Group 4 when compared with Group 3 at 18 months. This might be due to the difference in dosage and the chosen route of treatment in primary and adjuvant RT. In a study evaluating the effect of RT on bladder functions with urodynamics, UI developed in all of the patients at two years after RT [29]. Radiation fibrosis of the bladder and reduction in bladder capacity was thought to be responsible and symptoms could be at least partially reversible in some patients. No change was observed in urethral closure pressures and the SUI cases were attributed to pre-treatment SUI.

The authors could not show a relation between simple and radical hysterectomy and SUI. In contrast; in the two groups receiving RT, SUI was observed after treatment. SUI after RT might be related to bladder neck fibrosis, damage to urethral mucosa, and decrease in compliance [30].

Fecal incontinence was observed in two patients in Group 4 and in one patient in Group 2. Damage to pelvic autonomic nervous system by RT or radical hysterectomy may lead to fecal incontinence and colorectal dysfunction [26].

The quality of life was worsened at six and 18 months except for the patients in Group 1. KHQ has a special domain that evaluates the effect of urinary symptoms on the quality of life. Therefore the detrimental effect on the quality of life might be attributed to an increase in lower urinary tract symptoms in these patients.

The number of patients in this study was quite restricted. Studies with more patients and longer follow-up are needed for more accurate results. While treating malig-
nant disease, the aim should include increasing survival without affecting the quality of life. The understanding of the exact mechanism of urinary dysfunction may result in decreasing or preventing dysfunction. Lower urinary tract symptoms developing after treatment may be severe and require treatment.

Conclusion

Simple hysterectomy does not lead to lower urinary tract symptoms, instead lower urinary tract symptoms present before treatment may decrease after simple hysterectomy without affecting the urodynamic parameters. Radical hysterectomy and RT alone or in combination result in UI, urgency, frequency, and obstructive symptoms with decrease in bladder capacity and compliance; however some of the obstructive symptoms may regress during follow-up.

Acknowledgements

This work was supported by Scientific Research Projects Coordination Unit of Istanbul University [Project number: T725-13092005]. The authors would like to thank for their support. In addition, they would like to thank Habibe Ayilidiz Erkan and Nurcihan Alper for performing the urodynamics of all the patients and Ahmet Cem Iyibozkurt, MD for the performance of oncologic operations.

References


Immunohistochemical evaluation of epithelial antigen Ber-Ep4 and CD10: new markers for endometriosis?

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¹Gynaecologic and Obstetric Clinic, Department of Surgical, Microsurgical and Medical Sciences, University of Sassari, Sassari (Italy)
²Gynecologic and Obstetric Clinic, University of Geneva (Switzerland)
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Summary

Background: Early and certain diagnoses of endometriosis are mandatory to begin the correct treatment and to exclude the risk of endometriosis-associated ovarian carcinoma (EOC) and endometrial stromal sarcoma (ESS). Purpose of the study: To assess the immunohistochemical expression of Ber-Ep4, an epithelial antigen, and CD10 in endometriosis. Materials and Methods: Forty-eight women underwent laparoscopic surgery for endometriosis and endometriotic samples were recovered for histology. In all surgical specimens Ber-Ep4 and CD10 were searched by an immunohistochemical method. The authors evaluated the correlations among the immunohistochemical positivity and the location of endometriosis. Results: Most cases (40/48 83.34%) were represented by ovarian endometriosis. Among the eight remaining cases, three (3/48, 6.25%) were pelvic endometriotic lesions, two (2/48, 4.17%) peritoneum of vesico-uterine pouch, one vaginal lesion (2.08%), one salpinx lesion (2.08%), and one inguinal lesion (2.08%). Ber-Ep4 and CD10 were expressed in 90% and 100% of the ovarian lesions, respectively. In pelvic lesions Ber-Ep4 and CD10 showed both 66.67% of positivity and had the same pattern in peritoneal, salpinx, vaginal, and inguinal lesions (50%, 100%, 100%, 100%, respectively). Ber-Ep4 was negative in 6/48 (12.5%) cases whereas CD10 was negative in 2/48 (4.17%) cases of endometriosis. The sensitivity of Ber-Ep4 and CD10 for endometriosis diagnosis were 87.50% and 95.83%, respectively. Immunohistochemistry for Ber-Ep4 showed positivity in all cases of endometriosis with typical cubic epithelium, whereas CD10 was positive in 1/2 (50%) atypical case. Conclusion: Immunohistochemical expression of Ber-Ep4 and CD10 was positive in most cases of endometriosis and was useful in differential diagnosis with mesothelial cysts. Ber-Ep4 was negative in cases of hyperplastic epithelium or cytological atypia; these cases are not well-differentiated and could be optimally treated by surgery and not by hormonal therapy because of the risk of cancer degeneration.

Introduction

Endometriosis is a common gynecologic pathology affecting about 10%-22% of all women in their reproductive age [1]. Endometriosis is characterized by the presence of endometrial tissue outside the uterine cavity. Endometriotic lesions are usually found in the pelvis, e.g. on the ovaries, peritoneum, pouch of Douglas, and recto-vaginal septum [2]. Endometriosis, although benign, because of its destructive, invasive, and metastatic nature, mimics presentation of malignant tumors and could progress to biological malignant tumors such as endometriosis-associated ovarian carcinoma (EOC) and endometrial stromal sarcoma (ESS) [3, 4].

Several immunohistochemical markers for endometriosis have been introduced in clinical research. Nakayama et al. [5] demonstrated that normal peritoneal mesothelium showed negative staining for Ber-Ep4, ER, and PR whereas the mesothelium of the peritoneum adjacent to the endometriotic lesions showed focal positivity for Ber-Ep4, ER, and PR. Guedj et al. [6] studied through an immunohistochemical approach eight cases of thoracic endometriosis with Ber-Ep4 and CD10. Ber-Ep4 is a marker for cells with epithelial origin [7].

CD10 (CALLA) is expressed by haematopoietic neo-plasms (acute lymphoblastic leukemia and follicular lymphomas) [8]. Sumathi and McCluggage showed CD10 expression in a limited number of non-haematopoietic tissues, including normal endometrial stromal cells and endometrial stromal sarcoma [8].

To the authors knowledge, there are few data on Ber-Ep4 antigen and CD10 in endometriosis reported in the literature.

The aim of this study was to evaluate immunohistochemical positivity of Ber-Ep4 and CD10 in women undergoing surgery for endometriosis.

Materials and Methods

The authors studied 48 cases of endometriosis and searched the presence of Ber-Ep4 and simultaneously of CD10 antigens by immunohistochemistry. All the women underwent laparoscopic surgery for endometriosis at Gynecologic Clinic of the University of Sassari in the period 2011-2012. The study was approved by the local ethical Committee. The immunohistochemical study was performed at the Institute of Pathology of the University of Sassari.

Histology of surgical specimens confirmed the laparoscopic diagnosis of endometriosis according the histologic diagnostic criteria as the presence of endometrial tissue outside the endometrium and myometrium. Usually, both epithelium and stroma are seen, but occasionally the histologic diagnosis of endometriosis can be made when only one component is
Immunohistochemical evaluation of epithelial antigen Ber-Ep4 and CD10: new markers for endometriosis?

The mean age of the women was 33.50 years (range 20-50). Table 1 shows the distribution of cases according to age classes and corresponding positivity for Ber-Ep4 and CD10. The authors divided the cases in three age classes and corresponding positivity for Ber-Ep4 and CD10.

Results

The mean age of the women was 33.50 years (range 20-50). Table 1 shows the distribution of cases according to age classes and corresponding positivity for Ber-Ep4 and CD10. The authors divided the cases in three age classes and corresponding positivity for Ber-Ep4 and CD10.

<table>
<thead>
<tr>
<th>Age classes</th>
<th>N° cases</th>
<th>Ber-Ep4+</th>
<th>CD10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 30 years</td>
<td>14 (29.17%)</td>
<td>12/14 (85.71%)</td>
<td>13/14 (92.86%)</td>
</tr>
<tr>
<td>31 - 40 years</td>
<td>27 (56.25%)</td>
<td>25/27 (92.59%)</td>
<td>26/27 (96.30%)</td>
</tr>
<tr>
<td>41 - 50 years</td>
<td>7 (14.58%)</td>
<td>5/7 (71.43%)</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (100)</td>
<td>42/48 (87.5%)</td>
<td>46/48 (95.83%)</td>
</tr>
</tbody>
</table>

Discussion

The authors have already studied Ber-Ep4 as a marker in gynecologic oncology [10, 11].

In a study [10] on endometrial carcinoma, Ber-Ep4 did not show any correlation with grading, histotype, and Stage of disease or receptorial status of the endometrial carcinoma.

On the other hand, Ber-Ep4 was positive in 72.58% of primary epithelial ovarian cancers studied, with a prevalent membranous staining but with no characteristic topographic distribution. The presence of the antigen seemed related to the histotype and grading but not to clinical Stage [11].

The aim of the present study was to evaluate immunohistochemical positivity of Ber-Ep4 and CD10 in women undergoing surgery for endometriosis in order to achieve information on prognosis of disease.

Ber-Ep4 was not positive in cases of hyperplastic epithelium or cytological atypia; these cases are not well-differentiated and could be optimally treated by surgery.

Table 1. — Distribution of cases according to age classes and corresponding positivity for Ber-Ep4 and CD10.

<table>
<thead>
<tr>
<th>Location</th>
<th>N° cases</th>
<th>Ber-Ep4+</th>
<th>CD10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>40 (83.34%)</td>
<td>36/40 (90%)</td>
<td>40/40 (100%)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>3 (6.25%)</td>
<td>2/3 (66.67%)</td>
<td>2/3 (66.67%)</td>
</tr>
<tr>
<td>Peritoneum (vesico-uterine plaque)</td>
<td>2 (4.17%)</td>
<td>1/2 (50%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Salpinx</td>
<td>1 (2.08%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Vagina</td>
<td>1 (2.08%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Inguinal</td>
<td>1 (2.08%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (100)</td>
<td>42/48 (87.5%)</td>
<td>46/48 (95.83%)</td>
</tr>
</tbody>
</table>

Table 2. — The location and positivity for the two tested antigens.

<table>
<thead>
<tr>
<th>Epithelium</th>
<th>N° cases</th>
<th>Ber-Ep4+</th>
<th>CD10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubic</td>
<td>42</td>
<td>42 (100%)</td>
<td>42/42 (100%)</td>
</tr>
<tr>
<td>Not represented</td>
<td>3</td>
<td>0</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atypical</td>
<td>2</td>
<td>0</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>42/48 (87.5%)</td>
<td>46/48 (95.83%)</td>
</tr>
</tbody>
</table>

Table 3. — Distribution of cases according to type of epithelium and corresponding positivity for Ber-Ep4 and CD10.
and not by hormonal therapy because of the risk of cancer degeneration.

Ber-Ep4 was negative in 6/48 (12.5%) cases whereas CD10 was negative in 2/48 (4.17%) cases of endometriosis. Two out of six ovarian cases negative for Ber-Ep4 staining were associated with mesothelial cysts. Ber-Ep4 and CD10 were expressed in 90% and in 100% of the ovarian lesions, respectively. In pelvic lesions Ber-Ep4 and CD10 showed both 66.67% of positivity and had the same pattern in peritoneal, salpinx, vaginal, and inguinal lesions (50%, 100%, 100%, 100%, respectively).

Conclusion

Immunohistochemical expression of Ber-Ep4 and CD10 was positive in most cases of endometriosis and was useful in differential diagnosis with mesothelial cysts. The sensitivity of Ber-Ep4 and CD10 for endometriosis diagnosis were 87.50% and 95.83%, respectively.

Further studies on larger series are necessary in order to formulate definitive conclusions on the expression of these antigens in endometriotic lesions and their value as a marker of endometriosis.

References


Prevalence and distribution of high-risk human papillomavirus genotypes in cervical carcinoma, low-grade, and high-grade squamous intraepithelial lesions in Jordanian women

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Summary

Purpose: To assess high-risk human papillomavirus (HR-HPV) prevalence, and genotype distribution in invasive cervical cancer (CC) and its precursors in Jordanian patients. Materials and Methods: A total of 124 different specimens of formalin-fixed, paraffin embedded samples, including 18 low-grade squamous intraepithelial lesions (LSILs), 28 high grade squamous intraepithelial lesions (HSILs), and 78 CCs were included in this study. HPV detection and typing was done using HPV High Risk Typing Real-TM Kit that enables the concomitant detection of the 12 most common HR-HPVs. Results: Overall, HR-HPV prevalence was 87.2%, 78.6%, and 72.2% in CC, HSIL, and LSIL respectively. Genotype 16 was the most predominant in all cervical lesions, detected in 53.8%, 46.4%, and 38.9% of CC, HSIL, and LSIL respectively. Among all HPV genotypes, HPV-16 and HPV-18 were found separately or together in 50% of LSILs, 60.7% of HSILs, and 76.9% of CC specimens. HPV-31 was the second most common type detected in LSILs (22.2%) and HSILs (21.4%). HPV-45 was the third most common type detected in CC (11.5%). Conclusion: The prevalence and genotypes distribution patterns of HR-HPV types among patients with CC and its precursors in Jordan are similar to known international patterns. The results of this study provide baseline information on the HPV type distribution, which may guide the development of CC prevention and control programs in Jordan.

Key words: HPV; Cervical cancer; Jordan; Genotypes; Prevalence.
newly-diagnosed cancer cases. However, most cases are diagnosed at advanced stage due to the lack of national screening program.

Despite the knowledge of HPV prevalence and its etiologic association with CC development, there is no information about HPV genotype distribution in Jordanian women. The objective of this study was to gain an understanding of circulating HR-HPV genotypes in this geographically distinct region and to compare HPV prevalence patterns with data from international studies. This will help us to estimate the benefits of administering HPV vaccines.

Materials and Methods

Sample collection

A total of 124 formalin-fixed, paraffin-embedded samples with histologically-proven diagnosis of CC or preinvasive cervical disease were obtained from the archives of the Pathology Departments at three hospitals in Jordan during the period from 2003 to 2010. Of these, 18 cases were LSIL, 28 cases were HSIL, and 78 cases were CC. All samples were reviewed, and the diagnosis was confirmed by two pathologists.

The study was performed on archival materials and the samples were coded and processed anonymously with no patients’ identifiable scripts. The study was approved by the institutional review board at Jordan University of Science and Technology.

DNA extraction

Genomic DNA from cervical biopsies was extracted using commercially available kit for purification of total DNA from formalin-fixed, paraffin-embedded tissues according to the manufacturer’s instructions. Genomic DNA was amplified using HPV High Risk Typing Real-TM Kit to detect DNA of HPV of high carcinogenic risk in the urogenital swabs and biopsies. Real time amplification test was used for qualitative detection and genotyping of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) by multiplex Real Time amplification of four tubes for each sample according to the manufacturer’s instructions using Rotor Gene-Q. Each tube contained primers directed against regions of three HPV types and β-globin gene by polymerase chain reaction (PCR), indicating adequate DNA extraction and PCR conditions. Overall, HR-HPV DNA was detected in 103 cases (83.1%).

The prevalence of HR-HPV in LSIL was 72.2% (13/18). HPV-16 was the most common type and detected in 38.9% (7/18) of the samples. HPV-31 was the second most common type and detected in 22.2% (4/18) of the samples. There were three samples with double infections (16/18, 16/31, 16/35). Results of HPV distribution in LSIL are summarized in Table 1.

The prevalence of HR-HPV in HSIL was 78.6% (22/28). HPV-16 was the most common type, detected in 46.4% (13/28) of the samples. HPV-31 was the second most common type (21.4%), followed by HPV-18 (14.3%), as shown in Table 2. There were five double infections, with genotypes 16/31 being the most common combination (3/5).

In the 78 CC specimens, a total of nine different HR-HPV genotypes were detected. Overall, 91 infections were identified. The prevalence of HR-HPV in CC was 87.2% (68/78). HPV-16 was the most common type, detected in 53.8% (42/78) of the samples, either separately or in combination with other types. HPV-18 was the second most common type, detected in 23.1% (18/78) of samples, followed by HPV-45 (11.5%). Other HPV genotypes which were relatively less common are described in Table 3. Together, HPV-16 and HPV-18 were found in 60/78 specimens (76.9%) either singly or in combination. There were 48 single infections (70.6%), 17 double infections (25%), and three triple infections (4.4%). In multiple infections, HPV-16 was the most common occurring genotype associated with other HPV types (18 of 20 combinations [90%]). HPV types 16 and 18 were associated together in 45% of multiple infections.

Discussion

To the authors’ knowledge, this is the first formal study on the prevalence of HPV in Jordanian women with cervical diseases. It is also the first study to describe the distribution of HR-HPV genotypes in histologically confirmed CC specimens in Jordan. The only published data regarding the distribution of HPV in CC in Jordan is a small series involving 41 cases of CC which showed that HPV types 16 and/or 18 were found in 75.6% of the cases [11].

Overall, HR-HPV genotypes have been identified in 87.2% of these CC specimens. The yield from paraffin-embedded tissue is similar to that reported in other studies [12, 13]. As observed in this study, HPV-16 and HPV-18 were identified as the most common HPV types prevalent among Jordanian women and the overall prevalence of these two HPV types was 76.9%. This is comparable to the prevalence observed in other countries, in Jordan [14-16], and worldwide [8, 12]. HPV-45 was the third most common type detected in this series of CC specimens (11.5%). This is in agreement with the literature [3, 4, 9]; however, the present results showed that the prevalence of HPV-45 in CC in this area was higher than described in other studies. According to a meta-analysis
Prevalence and distribution of high-risk human papillomavirus genotypes in cervical carcinoma, low-grade, and high-grade etc.

Table 1. — HPV genotypes in low-grade lesions (n = 18 cases).

<table>
<thead>
<tr>
<th>HPV genotype</th>
<th>Number of samples detected in either single or multiple infections</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>7</td>
<td>38.9</td>
</tr>
<tr>
<td>HPV-18</td>
<td>2</td>
<td>11.1</td>
</tr>
<tr>
<td>HPV-31</td>
<td>4</td>
<td>22.2</td>
</tr>
<tr>
<td>HPV-35</td>
<td>2</td>
<td>11.1</td>
</tr>
<tr>
<td>HPV-56</td>
<td>1</td>
<td>5.6</td>
</tr>
</tbody>
</table>

HR-HPV genotypes not detected in five cases (5/18) = (27.8%).

Combined infection in three cases (3/18) = (16.7%)
(HPV 16/18, HPV 16/31, HPV 16/35).

Table 2. — HPV genotypes in high-grade lesions (n = 28 cases).

<table>
<thead>
<tr>
<th>HPV genotype</th>
<th>Number of samples detected in either single or multiple infections</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>13</td>
<td>46.4</td>
</tr>
<tr>
<td>HPV-18</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>HPV-31</td>
<td>6</td>
<td>21.4</td>
</tr>
<tr>
<td>HPV-35</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>HPV-56</td>
<td>2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

HR-HPV genotypes not detected in six cases (6/28) = (21.4%).

Combined infection in five cases (5/28) = (17.9%)
(HPV 18/31, HPV 16/31 x 3, HPV 16/35).

Table 3. — HPV genotypes in cervical cancer cases (n = 78 cases).

<table>
<thead>
<tr>
<th>HPV genotype</th>
<th>Number of samples detected in either single or multiple infections</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>42</td>
<td>53.8</td>
</tr>
<tr>
<td>HPV-18</td>
<td>42</td>
<td>53.8</td>
</tr>
<tr>
<td>HPV-31</td>
<td>6</td>
<td>7.7</td>
</tr>
<tr>
<td>HPV-35</td>
<td>6</td>
<td>7.7</td>
</tr>
<tr>
<td>HPV-39</td>
<td>4</td>
<td>5.1</td>
</tr>
<tr>
<td>HPV-45</td>
<td>9</td>
<td>11.5</td>
</tr>
<tr>
<td>HPV-51</td>
<td>4</td>
<td>5.1</td>
</tr>
<tr>
<td>HPV-56</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>HPV-58</td>
<td>1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

HR-HPV types not detected in ten cases (10/78) = 12.8.

Combined infection in 20 cases (20/78) = 25.6%

Three triple infections and 17 double infections:
– HPV-16 detected in 18 cases of combined infections
– HPV-18 detected in 10 cases of combined infections

of Smith et al. [9], the worldwide prevalence of HPV-45 was 4.6% in CC and 2.3% in HSIL. According to a meta-analysis of Bao et al., in Asia, the prevalence of HPV-45 was 2.8% in CC and 1.7% in HSIL [17]. However, HPV-45 was found to be the second most predominant HPV type in CC (16.9%) and HSIL (11.1%) in some areas of China [18]. Other HR-HPV genotypes detected in the present study included 31, 35, 39, 51, and 58, which is comparable to the universal distribution of these genotypes.

In this study, the prevalence of HR-HPV DNA in LSIL was 72.2%. This is comparable with the reported prevalence worldwide. A meta-analysis by Clifford et al. [19] showed that overall, 71.1% of LSILs tested positive for HPV DNA. They found that geographic variation in overall HPV prevalence did exist, with the prevalence highest in North America (80.2%) and lowest in Africa (59.1%). With respect to the type-specific HPV prevalence, similar to the other regions of the world, HPV-16 was the most predominant HPV type followed by HPV-31. However, their prevalence in this present study was higher than the reported worldwide prevalence (38.9% and 22.2% vs 26.3% and 11.5%, respectively) [19]. However, if combined infections were excluded, there would be comparable results. HPV-18 was the third most common type in this series with comparable prevalence to other regions in the world.

In HSILs, the reported worldwide HPV prevalence was 84.2% [20], which is slightly higher than in this study (78.6%). The genotype distribution in this study is similar to the worldwide distribution, with HPV-16 being the most common type followed by HPV-31 and then HPV-18. However, their prevalence is higher than their overall worldwide prevalence [20]. Again this may be explained by the inclusion of combined infections in this analysis.

The findings in this study suggest that among all HPV genotypes, HPV-16 and HPV-18 are found separately or in combination in 50% of LSILs, 60.7% of HSILs, and 76.9% of CC specimens. This is in agreement with the literature [8]. Published literature reports HPV-45 to be an important oncogenic type, which is usually indicated in invasive CC cases and is responsible for the progression from infection to malignancy [9, 21]. Data from this study also provides evidence of the association between HPV-45 and CC (11.5%).

Several reports have shown that multiple HPV infections are less common among CC biopsies than among cervical intraepithelial neoplasia biopsies; given that precursor lesions of CC develop to cancer after several years, and most HPV infections are cleared with only a small proportion of HPV persisting, it was assumed that the proportion of multiple infections would be higher in patients with cervical intraepithelial neoplasia than in patients with CC [22-24]. Opposite results have been demonstrated in this present study, with multiple HPV infections found in 16.7 of LSIL, 17.9% of HSIL, and 25.6% of CC. A possible explanation for this disagreement is that the distribution of only HR-HPV types have been studied in this report; which are more frequent in CC specimens. Moreover, the frequency of multiple infections in the present CC specimens is similar to the frequency reported in other studies [18, 25].

Primary prevention of CC can be achieved by introduction of efficacious HPV vaccines. Vaccines were developed against HPV infection to prevent CC and other HPV-related diseases [26]. Two types, a bivalent (Cervarix) vaccine that protects against HPV-16 and HPV-18 and a quadrivalent (Gardasil) that is effective against HPV types 6, 11, 16, and 18, are being widely introduced in Western countries [26, 27], and promising new broad-spectrum HPV vaccines are in development [28]. The present results showed that 87.2% of cervical tumors are infected with HR-HPV, of which 76.9% are HPV-16 and HPV-18 genotypes are covered by both available vaccines. Therefore, vaccination is expected to protect against more than two-thirds of CCs in Jordan as it has been estimated worldwide [27], although undoubtedly a
larger study is needed to confirm these findings. In addition, both the bivalent and quadrivalent vaccine formulations may offer a degree of cross-protection against phylogenetically related HPV types [29, 30].

In conclusion, the prevalence and type distribution of HR-HPV types in patients with CC and its precursors were investigated in the present study. The genotype distribution is similar to other comparable geographical regions. The current study provides some valuable information showing that CC in Jordan has a high correlation with HPV. This is an indication that the epidemiology of this disease is similar to the known international consensus. This will also help the healthcare authorities to plan for possible initiation of an HPV national vaccination program.

Acknowledgment

The study was funded by the Deanship Research at Jordan University of Science and Technology.

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Left fallopian tube primitive serous adenocarcinoma presenting as a cardiac tamponade - a case report and review of literature

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Summary
A 61-year-old woman presented to the emergency room complaining of anterior left thoracic pain and shortness of breath even after minor efforts. Her previous medical history was unremarkable. Pulmonary angiographic tomography showed a considerable pericardial effusion that had collapsed inferior lung lobes, a large pericardial effusion, and several enlarged lymph nodes in the anterior mediastinum. Echocardiogram (ECG) showed a considerable pericardial effusion with some degree of heart function impairment. Pericardiocentesis and thoracocentesis revealed neoplastic cells in both pericardial and pleural fluids. Abdominal and pelvic ultrasound showed a complex cystic mass with a 13-cm diameter located at left adnexal region and another complex cystic tumor with five-cm diameter at right adnexal region, with small amount of peritoneal effusion. Surgical staging was performed. Pathologic diagnosis was primitive left fallopian tube serous adenocarcinoma with peritubal involvement and multiple peritoneal and lymphatic metastases (FIGO Stage IV; TNM pT3c M1). Chemotherapy was initiated. Death occurred 25 months after diagnosis, with secondary dissemination (breast and lung). No recurrence of pericardial effusion was registered after chemotherapy, suggesting a high susceptibility of pericardial metastasis.

Key words: Fallopian tube adenocarcinoma; Cardiac tamponade; Gynecological cancer.

Introduction
Although pericardial metastasis is frequently found in autopsies of patients whose cause of death was cancer, they are usually not symptomatic [1]. Sometimes enough quantity of pericardial fluid accumulates leading to cardiac tamponade which may be fatal if left untreated. Urgent pericardial drainage might be life-saving, but a work-up to find primary tumor’s localization is necessary for proper management of the patient.

In women, those that most frequently complicate with cardiac metastasis are lung, lymphoma, breast, and pancreatic cancers [1]. Very few cases of cardiac tamponade originating from ovarian cancer have been reported [2-7]. No clinical cases of cardiac tamponade as the presenting manifestation of primary carcinoma of the fallopian tube have been previously reported, probably because it is one of the rarest malignancies of female reproductive tract [8]. Its estimated incidence ranges from 0.15%-0.30% to 1.1%-1.8% of all gynecological cancers [8-11].

Case Report
A 61-year-old woman presented to the emergency room complaining of anterior left thoracic pain and shortness of breath even after minor efforts. These symptoms had commenced a few days prior and came to the hospital when dyspnea of growing intensity began. She denied any recent fever, nausea or vomiting. Her previous medical history was unremarkable, except for asthma, but had been asymptomatic for the previous 15 years, and a depressive syndrome for which she was medicated with alprazolam and escitalopram for three years.

Blood samples were collected for analysis. Hemogram and ionogram showed no abnormalities; D-dimmers were 2,908 ug/l. Initial proposed diagnosis was pulmonary embolism, based on acute onset of the symptoms. Pulmonary angiographic tomography showed a moderate bilateral pleural effusion that collapsed inferior lung lobes, a large pericardial effusion, and several enlarged lymph nodes in anterior mediastinum.

The patient was admitted to the Intensive Care Unit (ICU) for further evaluation and therapy. Echocardiogram (ECG) showed a considerable pericardial effusion with some degree of heart function impairment. Pericardiocentesis and a thoracocentesis were then performed. Neoplastic cells were present in cytopathological analysis of both pericardial and pleural fluids. An abdominal and pelvic ultrasound showed a complex cystic mass with a 13-cm diameter located at left adnexal region and another complex cystic tumor with a five-cm diameter at right adnexal region, with small amount of peritoneal effusion. Enlarged lymph nodes in the right iliac chain – 2.5 cm was the largest diameter – were imaged with abdominal and pelvic tomography.

Twenty days after admission, complete surgical staging was performed. Pathologic diagnosis was primitive left fallopian tube serous adenocarcinoma with peritubal involvement and multiple peritoneal and lymphatic metastases (FIGO Stage IV; TNM pT3c M1).

The patient was scheduled for chemotherapy with paclitaxel 175 mg/m² and carboplatin every three weeks, commencing at 41 days after admission. No grade III toxicity was reported. After six courses of chemotherapy, a partial response was
obtained with no recurrence of pericardial effusion. She was asymptomatic and chemotherapy was stopped. A second-line chemotherapeutic treatment was begun 12 months after initial admission due to abdominal disease progression with doxorubicin 50 mg/m² every two weeks. No response was documented after the third cycle of chemotherapy. A third-line chemotherapeutic treatment was attempted with carboplatin 300 mg/m² and cyclophosphamide 600 mg/m² every four weeks. Grade III toxicity with severe anemia and neuropathy developed and chemotherapy was stopped by the second course. At 25 months after initial diagnosis, a left breast metastasis with cutaneous infiltration was diagnosed and confirmed by trucut biopsy. At that time, a pulmonary carcinomatosis was also diagnosed. She was no longer considered suitable for further chemotherapy and palliative care was proposed. The patient died 25 months after initial diagnosis as a consequence to cardio-pulmonary insufficiency with no signs of cardiac tamponade recurrence. No autopsy evaluation was done.

Discussion

As it was previously emphasized, primary malignancies of the fallopian tube are very rare diseases [8-12]. Most likely, this is the reason why the described case is, according to the authors’ knowledge, the first clinical case reporting a cardiac tamponade as first manifestation of primary fallopian tube carcinoma.

In the present case, cancer cells in pericardial effusion were detected before any gynecological symptoms. The work-up of the patient showed a complex bilateral adnexal tumor. Staging laparotomy allowed the diagnosis of fallopian tube primitive serous adenocarcinoma.

The diagnosis of primitive fallopian tube cancer is very rare before surgery. Usually it is made during laparotomy for staging a suspicious adnexal tumor and is almost always considered an ovarian cancer. In the described case, the adnexal tumors were a delayed diagnosis, after cardiac tamponade, and they were assumed as ovarian cancer.

Most cases of primary fallopian tube adenocarcinomas are serous and diagnosed at FIGO Stage I [9, 13, 14]. FIGO staging for ovarian cancer has been adopted for primary fallopian tube cancer staging. Prognosis is strongly dependent on FIGO Stage [12]; Stage IV patients have a median survival time that can be as low as 20 months [11]. As in this presented case, diagnosis is usually made in menopausal patients, in their fifth to sixth decades of life [9, 11, 13, 14]. However, fallopian tube carcinoma has been described in patients ranging from 14 to 85 years of age [8].

Initial treatment for primary fallopian tube adenocarcinoma is surgical [8, 11]. Hysterecetomy with bilateral salpingo-oophorectomy is considered the standard therapy [12]. Less radical surgery has been attempted in some Stage I fallopian tube carcinomas, but this is a controversial approach [8, 15]. Adjuvant chemotherapy seems to increase survival and is advisable for patients with proper medical conditions [11]. Platinum-based chemotherapy should be the first-line treatment [8, 11]; other recommended agents are doxorubicin and cyclophosphamide [8]. Radiotherapy is a controversial treatment for primary fallopian tube cancer.

Individualized treatment for metastatic primary fallopian tube carcinoma should be offered to those patients and chemotherapy is usually the initial treatment. In the present case, after an initial partial response to chemotherapy, a progression of the disease was documented resulting in the patient’s death 25 months after diagnosis. However, it is interesting to note that no recurrence of pericardial effusion was registered, suggesting a high susceptibility of pericardial metastasis to chemotherapy. This finding may be taken in account for other patients diagnosed with cardiac metastasis from primary fallopian tube carcinoma.

References


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Hemoperitoneum and acute abdomen caused by the rupture of ovarian granulosa cell tumor: a case report

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Department of Obstetrics and Gynecology, Istanbul University School of Medicine, Istanbul (Turkey)

Introduction

Granulosa cell tumors (GCT) constitute 70% of all ovarian sex-cord stromal tumors, which account for less than five percent of all ovarian carcinomas [1, 2]. Microscopically GCTs are composed of granulosa cells and fibroblasts or theca cells [3]. GCTs may secrete estrogen, inhibin, and Müllerian-inhibiting substance (MIS) [4]. The hormonal activity of these tumors is the cause of clinical manifestations of the disease. Most patients present non-specific symptoms such as abdominal pain, distension, and bloating due to the tumor [4]. Isosexual precocious pseudopuberty may be seen in prepubertal girls. Patients in the reproductive age may complain of abnormal uterine bleeding, including menorrhagia and intermenstrual bleeding. In postmenopausal women, the only symptom of this tumor may be vaginal bleeding [4]. Acute abdomen and hemoperitoneum are usually the initial presentations of GCTs, while bleeding is rare [1, 2]. The authors herein report a rare case of a ruptured GCT of the ovary in a 43-year-old female who was admitted to the emergency department with signs of acute abdomen.

Case Report

A 43-year-old woman was admitted to the emergency department of Istanbul University School of Medicine with complaints of abdominal pain, fatigue, and dizziness. Her medical history revealed the diagnosis of an ovarian cyst. Her family history was normal and reported no previous surgery. General examination revealed hemodynamic instability, her pulse was 133 bpm, and her blood pressure was 100/60 mm Hg. A beta-human chorionic gonadotropin (β-hCG) biochemical pregnancy test was negative. Her gynecologic examination was within normal limits. Her abdominal examination showed generalized abdominal tenderness with rebounding pain and muscle guarding. Transabdominal and transvaginal ultrasounds revealed presence of hemoperitoneum and fluid in the abdominal cavity. A laparotomy was indicated.

The abdomen was opened under general endotracheal anesthesia, revealing 3,000-4,000 ml of hemoperitoneum, a ruptured left ovarian tumor, and bleeding from the infundibulopelvic ligament on the patient’s left side. Based on the intraoperative findings, a left-sided oophorectomy was performed. The frozen section confirmed a GCT. The surgical procedure consisted of a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentum biopsy.

The patient received five units of red blood cells and three units of plasma preoperatively and two units of red blood cells postoperatively. Her postoperative course was then uneventful.

Discussion

GCTs are very rare, accounting for only five percent of all ovarian malignancies [4]. Known initial presentations of this tumor are hemoperitoneum and acute abdomen. In fact, there are many case reports, which have described acute abdominal pain secondary to rupture of GCT. To the authors’ limited knowledge, this is one of the few cases of ruptured GCT of the ovary that presented with an acute abdomen in the literature. Habek et al. reported a case of GCT with signs of acute abdomen [2]. As the pain of their patient was predominantly in the iliocecal region, the clinician’s initial diagnosis was acute appendicitis. When the abdomen was opened, the surgeons saw hemoperitoneum and the rupture of a right-sided ovarian mass. They performed a right unilateral salpingo-oophorectomy and appendectomy. The pathological diagnosis was GCT. One month postoperatively, re-laparotomy was required, when unilateral salpingo-oophorectomy, hysterectomy, and omentectomy were performed. Poma reported a postmenopausal woman who presented with acute abdomen [5]. The medical history of this obese patient, whose body mass index (BMI) was 41, revealed gallstones and complained of right upper quadrant pain. The authors started IV fluid infusion with the diagnosis of cholelithiasis. At follow up, when the urine output became minimal and the hemoglobin decreased to 8.3 g/dl from 10.2 g/dl, the sur-
geons performed a laparotomy and saw a ruptured left ovary. The pathological diagnosis of GCT was made after surgery which consisted of left oophorectomy. Her post-operative care was uneventful. Lee et al. reported a case of a 44-year-old patient of known GCT who was admitted with acute abdomen ten years after her first operation [1]. The medical story revealed a laparotomy at the age of 34 with the diagnosis of Stage 1A GCT. In order to preserve her fertility, the surgeons performed unilateral salpingo-oophorectomy and complete staging. She delivered a normal baby at the age of 37. Ten years after the initial treatment, she was admitted with acute abdomen and she was hemodynamically unstable. Laparotomy showed hemoperitoneum and rupture of the other ovary. The frozen section reported GCT and abdominal hysterectomy; lymph node sampling and omentectomy were performed. The Stage was I C and she received six courses of adjuvant chemotherapy (cisplatin, adriamycin, and cyclophosphamide).

In conclusion, GCT is an unusual ovarian malignancy that may present with signs and symptoms including vaginal bleeding. Tumor rupture causing acute abdomen and hemoperitoneum is a less common but dramatic presentation that may be confused with a ruptured ectopic pregnancy or appendicitis. Surgery is the initial choice of management and is necessary for diagnosis, staging, and removal of the tumor. Therefore, especially when faced with an intense presentation such as acute abdomen, clinicians should keep in mind that the cause may be the rupture of an ovarian GCT, especially if the patient has a previous history of an ovarian cyst or GCT.

References

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Late recurrence of malignant melanoma mimicking primary peritoneal cancer

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Summary

Background: Malignant melanoma is an extremely malignant tumor with an unpredictable metastatic profile with variable periods of remission. Case: A 41-year-old woman presented with recurrent malignant melanoma which had clinical features of an acute state mimicking primary peritoneal cancer. The case was an unusual recurrence of malignant melanoma occurring seven years after diagnosis and treatment of malignant melanoma in the patient’s arm. The diagnosis was established postoperatively by immunohistochemistry. Conclusion: A variety of imaging methods and pathological methods, including an exploratory laparotomy, may be necessary in cases of patients suspecting primary peritoneal cancer with a previous history of melanoma with possible metastatic dissemination. Urgent diagnosis and treatment of these patients seems to be critical.

Key words: Malignant melanoma; Late recurrence; Primary peritoneal cancer.

Introduction

Malignant melanoma is a malignant tumor of melanocytes, which are the cells that produce the pigment melanin and are derived from the neural crest. Although most malignant melanomas originate in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate [1].

Malignant melanoma is an extremely malignant tumor with an unpredictable metastatic profile with variable periods of remission. Late recurrence of malignant melanoma after diagnosis and treatment is also rare [2]. When late recurrence of malignant melanoma occurs, the most common sites of metastasis are the skin, subcutaneous tissue, and lymph nodes. However, late recurrent cases of malignant melanoma to other organs such as lung, liver, brain, bone, heart, ovary, and adrenal gland have been reported [2-4]. The late recurrence of malignant melanoma to the peritoneum is very rare. To the authors’ knowledge, there is only one report of late recurrence of malignant melanoma presenting with diffuse peritoneal carcinomatosis [5].

The authors present a rare case of a late recurrence of malignant melanoma exhibiting clinical features of an acute state mimicking primary peritoneal cancer.

Case Report

A 41-year-old woman was initially diagnosed in January 2005 with malignant melanoma on the skin of her right forearm. The tumor was excised with a five-mm margin, and the diagnosis of the excisional biopsy was malignant melanoma. At the time of excision of the primary tumor, no evidence of regional lymph node or distant metastasis was observed. She was diagnosed with malignant melanoma Stage IIB (pT3bN0M0). Postoperatively, the patient received three courses of DA-V-feron chemotherapy using dacarbazine, nimustine, vincristine, and interferon-beta. In the following seven years, the patient underwent regular physical examinations with no evidence of recurrence or metastasis.

Seven years after excision of the primary tumor, in October 2011, the patient noticed diffuse abdominal distention. The patient underwent computed tomography (CT) examination of the abdomen and chest, which demonstrated extensive nodularity of the peritoneal surfaces, soft tissue thickening of the omentum, and large amount of ascites (Figure 1). The patient also underwent magnetic resonance imaging (MRI) examination of the pelvis, which demonstrated extensive nodularity and thickening of the peritoneum (Figure 1). The colon fiberoscopy and photogastroscopy examination was negative. Laboratory investigations showed a normal lactate dehydrogenase (LDH) level at 128 IU/l. Tumor markers showed an elevated CA125 at 884 U/ml and a slightly elevated but almost normal 5-S-CD (5-S-cysteyldopa) at 8.4 nmol/l. Other tumor markers were within the normal ranges (CEA: 0.7 ng/ml; CA19-9: 19 U/ml). The cytological examination of the ascites showed a few atypical cells. The cytological examination of cervix and endometrium examinations with no evidence of recurrence or metastasis.

Seven years after excision of the primary tumor, the patient underwent an exploratory laparotomy. Macroscopically, there was a large amount of yellowish serous ascites in the peritoneal cavity. A number of white-yellow rubbery nodules of tumor were present diffusely in the ovaries and omentum and on the uterine serosal surface. The ovaries and uterus were unremarkable (Figure 2). The frozen pathological examination of the resected specimen showed poorly-differentiated adenocarcinoma of peritoneum, including a dense proliferation of cellular oval cells with vesicular nuclei. The cytological examination of the ascites showed poorly-differentiated adenocarcinoma. At this time, the authors diagnosed the patient as primary peritoneal cancer and performed hys-

Revised manuscript accepted for publication October 18, 2012
terectomy, bilateral salpingo-oophorectomy, partial omentectomy, and debulking of the peritoneal tumor.

Finally, the pathological examination showed poorly-differentiated adenocarcinoma of peritoneum, including a dense proliferation of cellular oval cells with vesicular nuclei. The tumor cells showed strong positivity by immunohistochemistry for S-100, melan A, and vimentin, although HMB-45 was negative (Figure 3). The authors confirmed the diagnosis of metastatic malignant melanoma.

The patient received a course of chemotherapy consisting of dacarbazine and tamoxifen. To date, seven months after detection of recurrent malignant melanoma, the patient is alive with disease.

Discussion

Malignant melanoma is a malignant tumor of melanocytes, which are the cells that produce the pigment melanin and are derived from the neural crest. Although most malignant melanomas originate in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate [1]. The incidence of malignant melanoma has been increasing over the last several decades. Malignant melanoma is the sixth most common malignancy in the United States; there were an estimated 68,120 new cases of invasive melanoma in 2010 with 8,700 deaths due to the disease [6].

Malignant melanoma is an extremely malignant tumor with an unpredictable profile of spread and variable periods of remission. Late recurrence of malignant melanoma after diagnosis and treatment is also rare [2]. Several reports have proposed possible factors that might predispose a patient to late recurrence of malignant melanoma.

Koh et al. suggested that changes in the immune system of the host might be a possible reason for the occurrence of late metastasis and emphasized the importance of host defense mechanisms [7]. Some reports suggested the importance of female gonadal hormones, which may have an inhibitory effect on malignant melanoma, contributing to a more favorable prognosis in women than in men [8, 9]. However, Filizel et al. disagreed about the importance of the influence of female gonadal hormones based on their studies indicating no advantage for premenopausal women in avoiding the late recurrence of malignant melanoma [3].

When late recurrence of malignant melanoma occurs, the most common sites of metastasis are the skin, subcutaneous tissue, and lymph nodes. However, late recurrent cases of malignant melanoma to other organs such as lung, liver, brain, bone, heart, ovary, and adrenal gland have been reported [2-4]. The late recurrence of malignant melanoma to the peritoneum is very rare. To the authors’ knowledge, there is only one report of late recurrence of malignant melanoma presenting with diffuse peritoneal carcinomatosis [5].

The authors present a rare case of a late recurrence of malignant melanoma exhibiting clinical features of an acute state mimicking primary peritoneal cancer. It was very difficult to diagnose the present case, which was established postoperatively by immunohistochemistry. As conventional imaging test for preoperative screening, the patient underwent CT examination of the abdomen and chest, which demonstrated extensive nodularity of the peritoneal surfaces, soft tissue thickening of the omentum, and large amount of ascites. The patient also under-
Late recurrence of malignant melanoma mimicking primary peritoneal cancer

The patient went MRI examination of the pelvis, which demonstrated extensive nodularity and thickening of the peritoneum. The ovaries and uterus were unremarkable on CT and MRI examinations. Therefore, primary peritoneal cancer was initially considered the most likely diagnosis. Several reports showed that positron emission tomography (PET) was a useful imaging test for evaluating recurrence of malignant melanoma [10]. The patient did not undergo PET in this case, but it did not seem to be diagnosed as recurrence of malignant melanoma.

Laboratory investigations showed that a normal LDH level at 128 IU/l. LDH seems to be a predictor of survival in patients with metastatic malignant melanoma [11]. In the present case, LDH was not a predictor of recurrence of malignant melanoma. Tumor markers showed an elevated CA125 at 884 U/ml and a slightly elevated but almost normal 5-S-CD (5-S-cysteinyldopa) at 8.4 nmol/l. Other tumor markers were within the normal ranges (CEA: 0.7 ng/ml; CA19-9: 19 U/ml). The elevated 5-S-CD was reported as a useful tumor marker in some recurrent cases of malignant melanoma [12]. In the present case, 5-S-CD was not a predictor of recurrence of malig-

Figure 2. — The macroscopic image of resected specimen. A diffuse numerous number of white-yellow rubbery nodules of tumor are present in the ovaries and omentum and on the uterine serosal surface.

Figure 3. — A) Microscopic image of tumor cells (Hematoxylin & Eosin, x2). B) Microscopic image of tumor cells (Hematoxylin & Eosin, x20). C) Image of S-100-positive tumor cells. D) Image of melan A-positive tumor cells.
nant melanoma and elevated CA125 was concordant with considering it as a primary peritoneal cancer. The cytological examination of the ascites preoperatively showed a few atypical cells. The frozen pathological examination of the resected specimen showed poorly-differentiated adenocarcinoma of peritoneum, including a dense proliferation of cellular oval cells with vesicular nuclei. The cytological examination of the ascites showed poorly-differentiated adenocarcinoma. At this time, the authors diagnosed the patient as primary peritoneal cancer. Finally, the pathological examination showed poorly-differentiated adenocarcinoma of peritoneum, including a dense proliferation of cellular oval cells with vesicular nuclei. The tumor cells showed strong positivity by immunohistochemistry for S-100, melan A, and vimentin, although HMB-45 was negative. The authors confirmed the diagnosis of metastatic malignant melanoma. The diagnosis was established postoperatively by immunohistochemistry.

The incidence of malignant melanoma has been increasing over the last several decades [6]. Late recurrence of malignant melanoma may frequently be seen in the future. A variety of imaging methods and pathological methods including an exploratory laparotomy may be necessary in cases of patients suspecting peritoneal cancer with a previous history of melanoma with possible metastatic dissemination. Urgent diagnosis and treatment of these patients seems to be critical.

References


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Amelanotic malignant melanoma of the perineum: a case report

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Summary

The case of a patient diagnosed and surgically treated for amelanotic malignant melanoma of the perineum, accompanied by several local relapses, metastases to iliac-femoral lymph nodes, and distant metastases to both lungs is presented. Survival, up to date, equals 12 years. Amelanotic malignant melanomas are very rare tumors. Perineal and perianal localization of these tumors is especially rare. References cite about 500 cases with survival limited to between six months and one year after diagnosis.

Key words: Amelanotic malignant melanoma; Survival; Perineum.

Introduction

Malignant melanoma is one of the most malignant human tumors. It is characterized by extremely fast growth and fast formation of hematogeneous and lymphogeneous generalized metastases. While 80% of all primary malignant melanomas are located in the skin and 19% in the eye, the remaining one percent comprise malignant melanomas localized in mucous membranes of the oral cavity, esophagus, bowels, rectum, nose, urethra, and vagina. They are seldomly found in the vulva, perineum, palms or soles, i.e., in places not exposed to ultraviolet solar radiation. Amelanotic melanomas comprise only two percent of all melanomas [1] and are most commonly subungual [2]. Urogenital and perianal localization of such tumors is extremely rare.

Amelanotic malignant melanomas are the most aggressive of all histological types of malignant melanomas. Tumor cells in these histological types of tumors are undifferentiated to such a degree that they are not able to create melanin. This renders them highly malignant. Amelanotic melanoma diagnostics is a special problem because macroscopic forms of these tumors can be very diverse; due to the lack of pigment, melanoma is often excluded from consideration in the process of early diagnostics [3]. On the other hand, deep tumor invasion into dermis and hypodermis, or even deeper, is present in a significant percentage of cases. Data cited in references show a positive correlation between depth of invasion and final outcome of the disease.

Case Report

The case is presented of a patient whose survival after diagnosis and surgical treatment of amelanotic malignant melanoma primarily localized in the perineum, followed by several relapses and distant metastases equals 12 years. Discomfort which caused the 60-year-old patient to report for a medical exam were tingling sensation in the perineal area, occasional contact bleeding, and occasional bleeding during defecation. These discomforts appeared several months before the first visit to the physician during which a small, protuberant tumor lesion was visualized, around ten mm in size, macroscopically polypoid in appearance, localized on the skin of the perineum some two cm above the anus. Macroscopic appearance of the lesion did not contain any elements which would lead to suspect that the malignant tumor, especially not malignant melanoma, was present. The lesion was surgically removed. Amelanotic malignant melanoma was verified by histopathological examination; it was characterized by dominantly trabecular, partly solid organization with strong invasion into dermis and hypodermis, Breslow III, Clark level V.

Considering this unexpected histopathological finding, computed tomography (CT) exam of the abdomen and pelvis was performed postoperatively. Lymphadenopathy was found in the right inguinal, while one month after the control check-up following the surgical removal of the tumor, a local relapse was detected. A dissection of the right inguinal was performed accompanied by lymphadenectomy and excision of the local relapse. Metastases were verified in lymph nodes. Histopathological examination of the local relapse also confirmed the existence of amelanotic malignant melanoma, infiltrating only hypodermis, without any deeper invasion. The patient underwent regular quarterly check-ups over the next two years. A metastatic lesion in the upper lobe of the left lung was diagnosed by radiographic exam during the third year; it was subsequently surgically removed. Metastasis of amelanotic malignant melanoma was confirmed. The tumor did not affect the visceral pleura and edges of the resection did not contain malignant cells. A month later a local relapse appeared in the perineum and was surgically removed. Over the following three years, the patient remained symptom-free. However, a solid metastasis was subsequently discovered in the right lung as well. Resection was performed again, this time of the right lung and metastasis of the amelanotic malignant melanoma was histopathologically verified; edge of the resection did not contain malignant cells. One year later, another local relapse in the perineum appeared and was surgically removed. Histopathological examination showed that the depth of invasion of this relapse was even smaller than that of previous local melanoma relapse in the perineum. One possible explanation for the smaller depth of invasion of the relapse is the existence of scar tissue in deeper...
layers formed as a result of surgical removal of primary tumor and several local relapses. Since then the patient has been subjected to regular check-ups. There are no symptoms and the malignant disease has been in remission phase for the last five years. Survival period since the moment of primary diagnostics of this tumor until the present day is 12 years.

**Discussion**

Perineal amelanotic malignant melanoma is a very rare tumor. References up to date cite only about 500 cases [4, 5]. Recent epidemiological analyses indicate, however, that the incidence of malignant melanoma in the world is increasing. Supported by references, a clear adult female predominance with involvement of the lower genito-urinary tract was identified [6]. Literature reviews describe three cases of amelanotic malignant melanoma of the vagina, two cases each originating from the cervix, ovary, and urethra; such cases were also identified in cerebral cortex (frontal and fronto-parietal area), rectum, nasal cavity, tongue, breast, and tonsillar sinuses [7-9].

Early detection, accurate staging system that rates the level of invasion according to Clark and Breslow, surgical therapy, regular check-ups, and prompt treatment of relapses are all important for survival [10-14].

**Prognosis** is dependent on the Breslow’s level at time of diagnosis. In amelanotic melanoma, the cues leading to diagnosis are often absent, leading to reports of missed diagnoses and poor prognoses.

According to data presented by American Joint Committee on Cancer, the five-year survival of patients suffering from malignant melanoma is under ten percent [15]. References cite cases of patients with rare malignant melanoma localizations whose survival ranged from six months to one year after being diagnosed. Cases of survival around five years are extremely rare, while ten or more years survival are only sporadic.

It is a fact that malignant melanomas can arise in unconventional areas. Gross tumor appearance and the unavailability of an immunohistochemical panel may result in their misdiagnosis.

Considering the fact that malignant melanomas are predominantly tumors of the skin, an organ easily accessible for regular self-examination, education of the entire population with emphasis on self-examination of skin, and all new lesions appearing on it is very important. The relationship between sun ultraviolet (UV) radiation and appearance of “de novo” tumors on completely healthy skin is well-known. However, it is very important to perform exams on those skin regions not exposed to UV radiation, yet posing as possible predilection sites for development of various macroscopic forms of amelanotic melanoma, the most aggressive malignant tumors characterized by very poor prognosis and short survival rate. Early diagnostics and early surgical treatment can prolong remission and survival periods even with these most aggressive human malignant tumors.

**References**


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Acute hemorrhage related to spontaneous rupture of an uterine fibroid: a rare case report

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Summary

The authors present smooth muscle tumors of uncertain malignant potential (STUMP) diagnosis and surgical management of a spontaneously-raptured degenerated uterine fibroid. A 48-year-old nulliparous presented with a two-day history of abdominal pain, bloating, constipation, and menorrhagia. Within eight hours, her distress level increased. Computed tomography (CT) scanning of the abdomen showed a large, 31 × 25 cm solid-cystic lesion. An emergency laparotomy was indicated. Surgery revealed approximately 2,000 cc of blood and a 30 cm degenerated uterine fibroid with a fundal rupture, cystic, and solid components extending to the lower pole of the liver. Pathology results noted mild nuclear atypia, six mitoses per ten high-power fields (hpf) and necrosis spread that was not coagulative with a STUMP diagnosis. STUMP presents a problematic group of uterine smooth muscle tumors for any clinician. In addition, STUMP can rarely cause acute complications like a rupture. Therefore, prompt diagnosis and effective management are important.

Key words: Leiomyoma; Leiomyosarcoma; Smooth muscle tumors; STUMP; Uterine fibroid.

Introduction

Uterine smooth muscle tumors arise from the uterine myometrium and include leiomyomas (or uterine fibroids) and uterine leiomyosarcoma (LMS). In addition, Kempson and Hendrickson acknowledge that a small group of uterine smooth muscle tumors exists for which we have insufficient understanding to predict the clinical outcome [1]. The authors apply the term smooth muscle tumors of uncertain malignant potential (STUMP) to these neoplasms [2]. One way to define STUMP is by exclusion, namely if the tumors do not fit the definition for any of the other uterine smooth muscle tumors, then they are classified as STUMP. Bell et al. have established the most extensively used classification system of uterine smooth muscle tumors [3]. In this system, LMS is defined as tumors with at least two of the following three features: (1) diffuse cytologic atypia, (2) moderate to severe tumor cell necrosis, and (3) ≥ ten mitoses per ten high-power fields (hpf). In contrast, leiomyomas are defined as tumors with a flat appearance, no tumor cell necrosis, and ≤ four mitoses per ten hpf. Tumors that do not meet these definitions are classified as STUMP.

LMS is a rare malignant tumor, while leiomyomas are the most common benign uterine masses occurring in women over 35 years. On the other hand, spontaneous rupture of a degenerated fibroid is an uncommon manifestation that can cause acute complications such as intra-abdominal hemorrhage and result in mortality. The authors herein present STUMP diagnosis and surgical management of a spontaneously ruptured degenerated uterine fibroid.

Case Report

A 48-year-old nulliparous woman was admitted to the emergency department of Istanbul University School of Medicine presenting with a two-day history of abdominal pain, bloating, constipation, and menorrhagia. On examination, the patient’s blood pressure was normal (110/70 mm Hg) and her pulse was 98 beats per minute. Pelvic examination revealed mild vaginal bleeding and a mass that extended the umbilicus. There was also abdominal distention. Abdominal rebound tenderness or defense was not noted. Complete blood count revealed anemia (Hct 29.6%, Hb 9.62 g/dl), an elevated white blood cell (WBC) count of 13.5 × 10^3/µl, and hs-CRP of 21.62 mg/l. Her past medical history revealed hypothyroidism. An ultrasound examination showed a large 20 × 10 cm mass in the pelvic region but no free fluid was detected. The patient was admitted to the clinic for further observation.

Within eight hours, the patient’s distress level increased. Abdominal rebound tenderness and defense began abruptly. Emergency computed tomography (CT) scanning was performed. The CT scan of the abdomen and pelvis showed a large, 31 × 25 cm solid-cystic lesion extending toward the liver’s periphery. A fluid collection was noted on the right side of the lesion. Free fluid was detected in Douglas’ pouch and the right and left paracolic gutters. Other intra- and retroperitoneal organs were normal. Patient’s level of distress increased as her blood pressure decreased along with rapidly-dropping hemoglobin and hematocrit counts that are associated with acute blood loss. An emergency laparotomy was indicated. Blood pressure and complete blood count prior to surgery were 100/60 mm Hg, Hct 24.6%, Hb 7.91 g/dl, WBC 9.4 × 10^3/µl, and hs-CRP 8.7 mg/l, respectively. Antibiotic treatment was also administered before surgery to prevent infection.

The abdomen was opened in general endotracheal anesthesia, revealing approximately 2,000 cc of blood and a large 30-cm degenerated fibroid with a fundal rupture, cystic, and solid components on the right side of the uterus extending to the lower pole of the liver (Figure 1). The rupture caused a separation of approximately ten cm of the fibroid, which extended loosely to the abdomen. The surgical procedure consisted of a total...
abdominal hysterectomy and bilateral salpingo-oophorectomy. The patient received two units of erythrocyte suspension during surgery and two more units postoperatively. Her postoperative course was uneventful and she had a normal recovery. The patient was discharged from the hospital six days after surgery.

Pathology results revealed mild nuclear atypia, six mitoses per ten hpf, and necrosis spread that was not coagulative. The case was diagnosed as STUMP.

Discussion

Uterine smooth muscle tumors range from leiomyomata to LMS. A relatively rare subgroup is called STUMP and presents a dilemma for clinicians due to an uncertain clinical behavior [4]. The present case falls into the category of STUMP since it had a mitotic index of six MFs/ten hpf, a mild nuclear atypia rather than moderate to severe, and necrosis spread that was not coagulative.

Leiomyomas typically undergo degeneration, which produces no characteristic symptoms. Some degree of degeneration is present in nearly all tumors. The cystic degeneration represents at late stage. Necrosis can occur in a large tumor as a result of poor circulation. Interestingly, in the present case, the fibroid features were also compatible with degeneration similar to a leiomyoma and possibly ischemic necrosis because of its large size. The authors speculate that extensive degeneration with areas of necrosis in the large fibroid may have led to thinning of the wall of the necrotic cavity, causing a spontaneous rupture of the fibroid in the patient. There are fewer than a hundred case reports of massive bleeding from uterine fibroids in the literature, indicating that it is a rare complication.

In conclusion, STUMP presents a problematic group of uterine smooth muscle tumors for any clinician. The malignancy potential poses a significant risk. Therefore, patients with STUMP should be counseled on the potential of recurrence and disease progression to LMS. In addition, STUMP can rarely cause acute complications like a rupture. The complications are uncommon, but can result in serious and catastrophic mortality. Therefore, prompt diagnosis and effective management are important. The treatment consists of immediate laparotomy. While there are no established guidelines for follow-up care after treatment, it may be advisable that patients with STUMP who have had surgery should be seen by their gynecologic oncologist three months postoperatively for a physical examination, blood tests, and a CT scanning. After that, follow-up may include a physical examination and blood tests about every six to 12 months, with additional imaging tests on an as-needed basis.

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Multiorgan thrombotic disorder in a young patient with primary antiphospholipid syndrome (APS) and ovarian tumor

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Summary
Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening condition with high mortality rate besides aggressive multimodal treatment. Underlying triggers of “thrombotic and cytokine storm” include pregnancy, inflammation, trauma, surgery, and infection. The authors present a case of a young female patient with primary antiphospholipid syndrome (APS) who was admitted to the hospital due to abdominal pain caused by ovarian tumor with elevated tumor markers. After the prophylactic anticoagulants and antibiotic treatment, surgery was performed. Suddenly after treatment, her clinical status deteriorated and she died regardless of intensive immunosuppressive and anticoagulant therapy attempts. This condition requires all clinical awareness, timely diagnosis, and therapeutical approach, including a better understanding of the pathophysiology that leads to CAPS.

Key words: Catastrophic antiphospholipid syndrome; Multiorgan thrombotic disorder; Systematic inflammatory response syndrome.

Introduction
An acute multiorgan thrombotic dysfunction known as catastrophic antiphospholipid syndrome (CAPS) is triggered with one of the events as infection, minor surgical trauma, malignant disease, or even pregnancy. These events activate thrombotic and cytokine storm that results in small vessel occlusion and systematic inflammatory response. With the current therapeutical approach, the mortality rate is still near 50% [1]. According to new investigations, potential genetic risk factors may predispose APS-positive patients to CAPS. Current knowledge is mostly based on international web CAPS registry.

Case Report
The authors present a case of a young nulliparous 22-year-old female patient with primary antiphospholipid syndrome (APS) who was admitted to the hospital with acute abdominal pain caused by adnexal tumor followed by high level of CA-125 markers (1,034 U/ml). Pulmonary embolism and thrombosis of the inferior vena cava and iliac-femoralis in both lower limbs were her previous APS manifestation at the age of 16. After discovering primary APS and surviving from her first attack, she was treated with oral anticoagulant therapy.

Laboratory tests, pelvic, and abdominal ultrasound examination were performed upon admission to hospital. Ultrasound examination revealed a right adnexal bilocular hypoechogenic tumor size 7 × 6 cm. Hematological, pulmonal, and vascular examinations were also performed as a preoperative diagnostic procedure. A vascular surgeon performed a color venous duplex scan of the lower limbs and confirmed no thrombotic masses in their vessels.

Upon admission to the Clinic, laboratory test were normal but her clotting test showed prolonged activated partial thromboplastin time (aPTT) 51.2 (normal range 22 - 31.5), prothrombin time was 57.7% (normal range 70% - 130%) with also strong lupus anticoagulant (LA) activity with LA1 - 118.6 (< 45 sec.) and kaolin clotting time (KCT) > 200 sec (range 70 - 90).

Her immunological test revealed high alkaline phosphatase (APL) activity with value of anticytadioplin (aCL) IgG > 100 (< 11 GPL) and aCL immunoglobulin M (IgM) 20.4 LU/ml (< 10 MPLU / ml). Hematologist had ordered anticoagulant therapy with low-molecular weight heparin twice daily.

Besides lower abdominal pain, the patient developed gastrointestinal disorder with upper abdominal pain in right hypochondrium followed with nausea, vomiting, and increased bilirubin levels. Abdominal and gastroenterologist examination diagnosed calculosis cholecystitis confirmed by abdominal ultrasound and laboratory tests. The patient was treated with wide-spectrum antibiotics, which were given for ten days.

After using antibiotics and prophylactic anticoagulants therapy, surgery was performed with an intraoperative findings: enlarged right Fallopian tube, multiple right ovarian cysts and liquid in Douglas pouch, with multiple adhesions. Also, enlarged gallbladder and liver were detected. Surgery consisted of tumorectomy of the right ovary, right salpingectomy, and cytology of the peritoneal liquid. Patient’s general status deteriorated rapidly immediately after surgery, manifested as cardiopulmonary insufficiency and the patient was administered intermittent positive pressure ventilation (IPPV) with 100% O₂, but saturation was only 50% - 60%. Cardiologist and vascular consultation had been made due to cardiac ultrasound which showed decreased ejection fraction (EF) of 30%, asymmetrically enlarged right ventricle with decreased contractility, and paradoxal moving of interventricular septum. Laboratory tests showed high level of creatine-kinase 90 (normal < 24) and S-troponin 25, 144 (normal < 0.1) and high value of lactate-dehydrogenase 1,611 (normal l,220 - 460). She was administrated anticoagulant therapy with parenteral unfractionated heparin 5,000 twice in bolus, and also corticosteroids. Furthermore, antithrombin III and fibrinolytics were administrated, as the other supportive therapy (bronchodilators, diuretics, cardiotonics) and at least inotropic drugs (dopamine, atropine, and adrenaline) followed by external heart massage.

Revised manuscript accepted for publication August 18, 2012
Despite continuous intensive therapy, permanent asystolia was recorded. The patient died due to cardiopulmonary insufficiency, and the final diagnosis was CAPS affecting lungs, heart, and kidneys.

Autopsy revealed multiorgan thrombotic involvement, cardiac (multiple myocardial infarction with thrombotic masses in the vessels), pulmonary respiratory distress syndrome with capillary hyaline thrombosis and bilateral hydrothorax, and renal involvement in a lesser extent (glomerular thrombosis). The other findings of the autopsy included pancreas autolysis, hepatomegaly, and middle cholecystitis calculosa.

Pathohistology of the operation revealed: chronic purulent salpingitis and ovarian follicular and cystic simplex.

Discussion
CAPS is a severe devastating disease with wide-spectrum of clinical appearances.

Owing to an international web-based registry called CAPS registry, analyses of the characteristics of almost 300 patients with diagnosed of CAPS is available. Among the patients in the registry, most of them (84.5%) had APL syndrome (primary or secondary), and in 82% were positive for IgG aCL antibodies [1, 2].

Although pathogenesis of CAPS is not clear at all, microthrombosis and consequent extensive tissue damage are supposed to be the cause. Autopsy revealed thrombotic microangiopathy (TMA), as well as occlusion of the larger vessels in a lesser extent [1, 2].

Systemic inflammatory response syndrome (SIRS) secondary to cytokine activation is another pathogenic mechanism in CAPS, besides thrombosis. The cytokines that are released during tissue damage initiate and amplify an inflammatory reaction in CAPS. SIRS can be the cause of pulmonary injury that leads to acute respiratory distress syndrome (ARDS), which is a main pulmonary manifestation of the disease [3, 4].

Even minor surgical intervention or infection are precipitating factors than can initiate rapid and progressive multiorgan thrombotic failure. The most common event is infection, which besides surgical trauma, was a trigger in the case presented [3].

The mechanism is still unclear, but it is hypothesized that surgical trauma by affecting endothelial cells, could activate procoagulant moleculars, complements, and cytokine production leading to thrombosis and tissue necrosis [3].

The most frequent CAPS involve organs such as kidneys, lungs, and brain with a variety of clinical manifestations. Pulmonary manifestations are both thrombotic and non-thrombotic. It includes ARDS but also pulmonary hemorrhage and embolism. Intra-abdominal thrombotic complications may involve the pancreas, adrenal glands, and intestinal and splenic vasculatures. Skin complication and bone marrow infarction can also occur in some cases [5, 6].

Based on the CAPS patient registry, almost half of patients did not survive, and the cerebral involvement was the major cause of death. Causes of death usually include cerebral stroke and cardiac involvement as in the present case [6, 7].

According to algorithm of treatment guidelines for catastrophic APS, prophylactic therapy recommends using wide-spectrum antibiotics for treating any infection and parenteral anticoagulants, before and during the surgical procedure [8].

First-line therapy consisted of anticoagulants plus corticosteroids which had been given in the case of patients. If plasmapheresis or/and intravenous immunoglobulins are added, clinical improvement is increased. Other therapeutic choices include cyclophosphamide, fibrinolytics, and supportive treatment (mechanical ventilation, blood, fresh frozen plasma (FFP) transfusion, and oxygen) [8].

CAPS is life-threatening condition with potentially lethal outcome besides aggressive multimodal treatment, which needs better understanding pathophysiology that leads to CAPS.

Although there are still no randomized clinical trials, information from CAPS registry can help in analyzing clinical form of the disease, management, and outcome. This condition needs all clinical awareness, timely diagnosis, and also a therapeutical approach.

Acknowledgements
This work was supported by research grant number 41021 for 2011-2015, issued by Ministry of Science of the Republic of Serbia.

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Uterine tumor resembling ovarian sex cord tumor.

Case report and review of literature

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Introduction

Uterine tumors resembling ovarian sex cord tumors (UTROSCT) belong to miscellaneous category of uterine tumors that consist of different amounts of sex cord-elements. Clement and Scully divided the ovarian sex cord tumors of the uterus into two groups: Group I of tumors are endometrial stromal tumors with sex cord like elements (ESTSCLE) whereas sex cord elements are minor components (40%) of tumors, characterized by increased risk of recurrence and metastasis. Group II tumors are UTROSCT consisting of more than half of sex cord tissue and characterized by low recurrence rate and metastasis [1, 2].

According to some authors, distinction of UTROSCT from endometrial stromal tumors can be subjective, but UTROSCT is reserved for tumors with predominant or exclusive sex cord differentiation. Classification of tumors of the female genital tract by World Health Organization (WHO) make a distinction between UTROSCT from endometrial stromal neoplasms, but there is still debate of its histogenesis [1, 2].

Uterine tumor resembling ovarian sex cord tumor shows a poly phenotypic immunophenotype with coexpression of markers of epithelial, myoid, and sex cord markers, as well as hormone receptors [1].

Case Report

A 59-year-old multiparous woman was admitted to the Institute of Gynecology and Obstetrics Clinical Centre of Serbia in January 2010 due to prolonged vaginal bleeding and abdominal discomfort. Her last period was 15 years ago and two explorative curettages were performed because of abnormal vaginal bleeding during the last five months. Pathological findings of the procedure included phlogistic fibroglandular polyp in both samples. Patient was biochemically and clinical assessed and ultrasound-examined. The vaginal ultrasound showed an enlarged uterus sized 100 x 74 x 81 mm, with extended cavity filled with unhomogenic content and myomas sized 54 x 69 mm located in fundus with secondary changes. She underwent abdominal hysterectomy with adnexectomy.

Microscopic examination revealed submucosal uterine tumor with variable histological organization that had anastomotic trabeculae with solid cellular grupations. Rare mitotic figures (2/10 HPF) were found. Additional immunohistochemistry showed immunophenotype: the sex cord areas were positive for vimentin(++) , aSMA(++) , AE1/AE3(+), PR(+), and ER(+). The poly phenotypic immunophenotype can be useful in differential diagnosis from other neoplasms but also suggests an origin of UTROSCT from uncommitted stem cell enabling for multidirectional differentiation.

Discussion

UTROSCT distinguish from ESTSCLE in clinicopathological features, although they seem at first sight very similar. Only 48 cases of UTROSCT have been reported in earlier international literature and usually the...
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Diagnosis was made after hysterectomy or polypectomy [1, 2]. This rare tumor is mostly revealed incidentally, as it was in a new reported case of UTROSCT in patient with neoplasm which seemed to be the consequence of tamoxifen treatment for breast carcinoma. In latest citations, few new cases of these rare tumors have been published, but mortality from the UTROSCT has not yet been described [2, 3]. Recently the role of conservative therapeutic approach has become more acceptable in young patients, besides the standard procedure that considers hysterectomy.

UTROSCT are myometrial tumors that consist of predominantly ovarian sex cord tissue that resembles granulosa cell or Sertoli cell neoplasms. They are usually located in the uterine fundus, but have also been seen in endometrial cavity and in the cervix as in the present case. Macroscopic appearance of these tumors often reveal lobulated and yellow structures. The microscopic image shows that the tumor is composed of anastomotic trabeculae, corded, nested, and glandular arrangements of tumor cells. Infiltrating borders of tumor can be seen but with rare lymphovascular invasion. Although 36% of UTROSCT have infiltrative margins, almost all of them behave as benign tumors. Nuclear atypia is mild to moderate and mitotic index is low in UTROSCT group [4, 5].

Diagnosis of UTROSCT is usually based on histologic pattern and immunohistochemical phenotype. These neoplasms have a variable immunophenotype sometimes with coexpression of epithelial (AE1/3, epithelial membrane antigen), myoid (desmin, smooth muscle antigen), sex cord (inhibin, CD99, melan A, calretinin), neuroendocrine (chromogranin, CD56) markers, as well as hormone receptors, vimentin, and CD10 [6, 7].

Immunohistochemistry shows that the majority of UTROSCT express α inhibin, CD99, and vimentin. Some tumors are positive for smooth muscle antigen and myoglobin, and up to one-third are positive for desmine. Cytokeratin was expressed in 50% of cases and 10% patients with UTROSCT express epithelial membrane antigen [6, 7].

The poly phenotypic immunophenotype can be useful in differential diagnosis from other neoplasms, such as
endometrial stromal sarcoma or a low-grade mixed Müllerian tumor. The diverse immunohistochemical profile also suggests an origin of UROSCT from uncommitted stem cell, enabling multidirectional differentiation. Other studies suggest that UROSCT are variants of endometrial stromal neoplasms [6, 7].

These rare uterine tumors occurred in women both in reproductive and postmenopausal ages and usually presented with abnormal vaginal bleeding. Preoperative assessment includes curettage that sometimes reveals endometrial hyperplasia that can be caused by hormonal production of this rare neoplasm. Sonographically, intramyometrial sex cord tumor is similar to leiomyoma and its intracavitary form is difficult to distinguish from endometrial polyp or submucosal myoma. A pelvic magnetic resonance image (MRI) can demonstrate if the endomyometrial junctional area is disrupted and if there is a possible invasion of the uterine wall. Final diagnosis of UROSCT is based on histologic pattern and immunohistochemical phenotype [8].

Although UROSCT behave in benign manner, some of them might undergo malignant transformation and have a metastatic potency. First described metastasis was in a 86-year-old patient, detected on omentum during a hysterectomy with bilateral salpingoophorectomy, with no relapse at five-years follow-up. In one of the latest publications, a case of metastatic disease was discovered four years after hysterectomy. Patient developed obstructive ileus due to a large infiltrating tumor within the small bowel presenting same morphology and expression pattern as the previously diagnosed UROSCT. Two benign gastrointestinal stromal tumors were also detected in the same patient [2, 9].

Recurrence of the disease was also published. Recent case of recurrence in literature was described in young patient with galactorrhea three-years after hysterectomy because of UROSCT. The extensive debulking surgery was performed because of relapses and it included partial bladder and colon resection, followed by chemotherapy. Galactorrhea and elevated prolactin level increased with tumor relapse, suggesting a hormonal imbalance due to the UROSCT endocrine function [9].

Because of the occasional recurrence of these rare tumor, they should almost be considered as low-grade malignant potential. It has been suggested that the malignant potential of UROSCT can be assessed by criteria for endometrial stromal sarcomas-like mitotic count, vascular invasion, infiltrative borders, and even serosal infiltration. However some authors suggest that the current histological features are still not sufficient for prediction of the behaviour of this tumor [3, 9].

On the basis of the uncertain malignant potential and low recurrence rate, these tumors are treated with hysterectomy. Conservative treatment has been proposed as an alternative to hysterectomy, in patients who want to preserve fertility [10, 11]. One of the first conservative treatments of UROSCT was reported seven years ago, with local excision of the tumor performed in young nuliparous patient [12].

Recently, sparing procedures consist of tumor resection usually using resectoscopic surgery. There have been described four cases of UROSCT that were managed by minimally-invasive hysteroscopic surgery [10, 11]. Up until now, three spontaneous pregnancies after conservative treatment of UROSCT have been described. One pregnancy after hysteroscopic resection of tumor resulted in uneventful delivery [11, 13].

As the quality of life becomes even more important in medicine, fertility-sparing procedure should be reasonably considered in therapeutic approaches, without compromising patient survival. However, careful short- and long-term follow-ups are necessary in patients with UROSCT.

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A rare case of lymphangiomyomatosis treated with leuprolide acetate: five-years follow-up

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Summary

Lymphangiomyomatosis (LAM) is a rare and systemic disease that is characterized by the abnormal proliferation of smooth muscle-like cells in the lungs and along the axial lymphatic system. The authors herein present a rare case of LAM that was treated with long-term use of leuprolide acetate, a gonadotropin-releasing hormone analogue (GnRHa).

Key words: Lymphangiomyomatosis; Gonadotropin releasing hormone; Leuprolide acetate.

Introduction

Lymphangiomyomatosis (LAM) is a rare and systemic disease that is characterized by the abnormal proliferation of smooth muscle-like cells in the lungs and along the axial lymphatic system [1]. The main symptoms include progressive dyspnea, cough, recurrent pneumothorax, chylothorax, and hemoptysis [2]. Diagnosis is made via pulmonary high-resolution computed tomography (HRCT), which shows the presence of thin-walled cysts and pathological confirmation. Since LAM is a rare disease, there is inadequate number of randomized controlled trials (RCTs) on its management. However, treatment options include anti-estrogen hormonal treatment, letrozole, sirolimus (rapamycin), doxycycline, and lung transplantation.

LAM mainly affects women in their reproductive age. The clinical manifestations of the disease worsen during pregnancy [2] and with the administration of estrogens [3]. The cells specific to LAM have progesterone and estrogen receptors [3, 4]. Treatment has long been based on the use of hormonal therapy like progesterone, tamoxifen, gonadotropin-releasing hormone analogue (GnRHa), and oopherectomy. Nowadays, researchers are studying administration of letrozole, which is an aromatase inhibitor, as a potential treatment option. All these factors indicate that LAM is an important disease not only for pulmonologists but also for gynecologists.

The authors herein present a rare case of LAM that was treated with the long-term use of leuprolide acetate, which is a GnRHa.

Case Report

In 2006, a 32-year-old Caucasian woman was admitted to the Gynecology Clinic of Istanbul University School of Medicine with a previous diagnosis of LAM. Her medical history revealed that in 1997, she was first admitted to a pulmonary hospital. In 1997, her computed tomography (CT) scans revealed diffuse thin-walled cysts in both lungs and pointed LAM. A tumor in left surrenal gland was also detected. A biopsy obtained from the lung revealed smooth muscle-like cells and cystic destruction of the lungs. During 1997, she underwent five consecutive surgeries: (1) closed-tube drainage of the left lung due to spontaneous pneumothorax, (2) left surrenalectomy, (3) right thoracotomy, partial parietal pleurectomy, and bullae resection due to pneumothorax in the right lung, (4) closed-tube drainage of the left lung due to spontaneous pneumothorax, and (5) left thoracotomy, partial parietal pleurectomy, and bullae resection. Between 1997 and 2006, she received numerous drug therapies as well. The clinicians of this pulmonary hospital decided to begin an anti-estrogen treatment and referred the patient to Istanbul University in 2007. After discussing the case in the medical committee of this university, the authors decided to treat the patient with leuprolide acetate 11.25 mg, once every three months. She was invited for follow-up every six months. Her condition began to improve after treatment. She was examined by a pulmonologist every year. Her general physical examination, radiologic workup, and spirometry did not show any worsening. In 2011, regression of disease was detected. Annual ultrasound imaging of the urinary system did not reveal any masses consistent with angiomyolipomas.

In 2007, the authors also began an add-back treatment but the patient did not regularly use the hormone-replacement therapy (HRT). Subsequently, annual bone mineral densitometry revealed a decreased bone mineral density. The authors collaborated with the osteoporosis clinic of this university and began the patient on daily oral calcium and vitamin D supplementations and weekly oral alendronic acid tablets.

Discussion

The treatment of LAM is controversial. The European Respiratory Society (ERS) Task Force proposed a guideline, which recommends maintaining normal weight, smoking cessation, vaccination, and pulmonary rehabilitation [5]. Since estrogen plays a role in the development of LAM, pregnancy and exogenous estrogen replacement must be avoided. Doxycycline is a member of the tetracycline antibiotics group and widely-used in the treatment of LAM, but the clinical data is limited. Sirolimus, which is an immunosuppressant drug, stabilizes lung function in patients with LAM but does not prevent the...
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evolution of the disease, as lung function declines once again when treatment is suspended [5]. Recently, letrozole is an aromatase inhibitor and has been studied as a potential treatment option of LAM [6]. Lung transplantation is the therapeutic measure of last resort.

HRT is another option in the treatment of LAM. It includes bilateral oophorectomy, tamoxifen, GnRHα, and progesterone [2-4]. Progesterone does not seem to slow the progression of the disease but decreases the rate of decline in lung function [7]. As far as GnRH analogues are concerned, Rossi et al. reported a LAM case that responded to the treatment with an analog of luteinizing-hormone-releasing hormone, namely goserelin [8]. Desurmont et al. treated one patient for three months with tamoxifen and 20 months with triptiline (3.75 mg/month) and another patient for 40 months with triptiline (3.75 mg/month) [9]. These authors concluded that GnRH analogues seem to provide an attractive alternative in the treatment of LAM [9]. Conversely, Radermecker et al. reported two cases in which 13 and five months of buserelin therapy failed to control LAM [10]. Drug therapy might have failed due to two reasons: the advanced stage of the disease when the therapy initiated and the ineffective agent that was chosen for drug treatment. Furthermore, Baldi et al. argued that the response to the treatment with GnRH analogues is dependent on the specific agent used and on whether the agent is administered at an earlier or at a more advanced stage of the disease [11]. In the present case, the patient benefited from leuprolide acetate treatment.

Conclusion

There is a significant lack of controlled trials and, in particular, comparisons of drugs generally used in the treatment of LAM. Despite the fact that further research is required to achieve a definitive assessment, current data obtained from a limited number of studies along with this reported success with leuprolide acetate indicate that GnRHα may present a useful alternative in the treatment of LAM.
Endometrial stromal sarcoma with intracaval extension at initial presentation

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Summary
Endometrial stromal sarcoma (ESS) is a rare uterine neoplasm. Tumor involvement of the large vessels is extremely rare. This is a case report of ESS with tumor invasion of the inferior vena cava at initial presentation.

Key words: Endometrial stromal sarcoma; Tumor thrombus; Vena cava inferior.

Introduction
Endometrial stromal sarcoma (ESS) is a rare uterine neoplasm; it comprises 0.2% of all uterine malignancies and 7%-15% of all uterine sarcomas [1]. The diagnosis is often only made postoperatively after examination of the surgical specimen [1, 2]. Despite its well-recognized propensity to spread throughout the lymph nodes and vessels, involvement of the large vessels is extremely rare [1-3].

Case Report
A 46-year-old woman presented to this Clinic, complaining of abdominal discomfort and enlargement over the past two months, and acute swelling of the right leg. Her previous history was significant for transurethral bladder resection on two different occasions, six and four months prior to admission. Histopathological examination of the first specimen reported transitional cell carcinoma of the bladder; however, the repeated transurethral resection yielded a diagnosis of chronic cystitis, with no signs of malignancy.

On admission, a bimanual gynecological examination revealed a large, non-mobile, non-tender mass filling the pelvic cavity, approximately ten cm in diameter. The right leg was pale and swollen, with pedal pulses palpable. Laboratory analysis including tumor markers and chest radiograph were within normal limits.

Magnetic resonance imaging (MRI) of the pelvis and abdomen detected organized tumor thrombus in the right common iliac vein and the inferior vena cava. The bladder wall appeared thickened, with suspect tumor infiltration on the right side. The imaging of the uterus was significant for the presence of tumor mass in the posterior wall, 80 x 50 mm in diameter. No rectal infiltration was seen.

The patient was administered low-molecular-weight heparin. Repeated cystoscopy reported no evidence of tumor infiltration. Fractional curettage followed, with the histology examination reporting a fibroglandular endometrial polyp.

With no conclusive diagnosis of the tumor histological origin one month after the initial examination, the patient underwent explorative laparotomy. The uterus was enlarged and firm, approximately 11 cm in diameter with no pathologic findings on the serosal surface. Ovaries and tubes exhibited normal macroscopic features. There were no signs of pelvic lymphadenopathy. Total hysterectomy and bilateral salpingo-oophorectomy were performed, without further surgery on the major vessels.

Histologic examination and immunohistochemistry revealed the diagnosis of ESS. There was extensive lymphatic and vascular invasion; mitotic count was 1/10 high power field.

Postoperative course was uneventful. The patient was discharged from the Clinic ten days after the surgery.

During the first visit six weeks after surgery, the patient reported to be in a good condition. Since the MRI showed organized tumor thrombus, and the satisfactory patency of the ilio caval axis was confirmed on pulsed Doppler examination, it was decided, in consultation with the vascular surgeon, not to proceed with second-stage surgery to remove tumor thrombus from the inferior vena cava. The patient was administered isophosphamide and cisplatin chemotherapy and scheduled for regular two-month follow-up visits.

Discussion
To the best of the authors’ knowledge, the present is the 20th reported case of ESS with extension to the inferior vena cava [1-3]. Caval involvement is usually seen with the recurrent tumor, and the presented case is only the sixth to describe the invasion of the vena cava on initial presentation [1, 2]. An advanced stage of the disease at presentation may be contributable to the delay in the diagnosis, which is not uncommon [4]. In this case, however, it is debatable whether the stage at presentation could be explained by the delay of approximately three months, including the period during which reported symptoms did occur, but the patient did not seek medical support.

Preoperative confirmation of ESS is based on histological examination of the endometrial sample, obtained either by endometrial biopsy or by dilation and curettage [5]. However, as was the case with the present patient, in a considerable proportion of patients the diagnosis is only established after hysterectomy [1, 2].

The optimal therapy for ESS is surgical resection. Hor-
monal, chemotherapy, and radiotherapy have been reported either as an adjuvant treatment or primary treatment for the recurrent disease [1, 2, 6, 7]. In this case, adjuvant chemotherapy was initiated, consisting of ifosfamide and cisplatin, and the patient is to be monitored at two-month follow-up controls.

References


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