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Intraperitoneal recurrence of low-grade endometrial stromal sarcoma in the shape of huge polycystic tumors – 10 years after primary treatment

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There is no standard therapy for cases of recurrence low-grade endometrial stromal sarcoma (LESS). Nowadays, chemotherapy is commonly used. We describe a case of a 55-year-old woman with the third, consecutive, abdominal, intraperitoneal recurrence of LESS in the shape of two huge (16 kg in weight) polycystic tumors – 10 years after primary treatment.

Key words: low-grade endometrial stromal sarcoma, recurrence, surgery treatment

Introduction

Initial therapy for patients with low-grade endometrial satromal sarcoma (LESS) is surgery. Approximately 50% of them develop recurrent disease, mainly in the pelvis or the lung [1]. There is no standard therapy for cases of recurrence, although chemotherapy is commonly used, but unfortunately well-defined protocols are inexistent. We describe the case of the third, consecutive, abdominal recurrence of disease in the shape of huge polycystic tumors, 10 years after primary treatment.

Case

A 55-year-old woman with recurrence of LESS in the shape of huge abdominal tumors was admitted to the Gynecological Oncology Department of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in September 2004. In July 1994, after the appearance of irregular bleeding, D&C was performed and endometrial stromal sarcoma (LESS) was recognized. She was operated and total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. The histopathological findings confirmed LESS. In August 1994 she underwent radiotherapy. External irradiation was delivered to the pelvis with 18 MeV photons with total dose 46 Gy.

After 53 months of disease free survival, in February 1999, three cystic tumors: 50, 100, 110 mm in diameter, in pelvis were found. She was operated again and the tumors and infiltrated omentum were totally removed. Pathological exam recognized metastatic LESS. After that, there was no adjuvant therapy. Between March and July 2000, due to pulmonary metastases, recognized by a chest CT scan, she was given six cycles of chemotherapy CAP (cisplatin, doxorubicine, cyclophosphamide) with complete radiological remission .

In July 2001 consecutive recurrence was recognized (by CT scan) in the shape of two, pelvic and abdominal tumors 80 and 60 mm in diameter. She started second-line chemotherapy (cisplatin, doxorubicine). After three cycles, due to progression, chemotherapy was terminated. Palliative care with Tamoxifen 20 mg and Megestrol 160 mg a day was introduced. Thereafter, increasing ascites was periodically observed. Several times we performed abdominal paracentesis, evacuating from 3000 to 6000 ml of ascites. In time, despite repeated paracenteses, abdominal circumference remained increased. When the symptoms of ileus and respiratory disturbances with dyspnea occurred, we decided to operate her.

In September 2004, after 4 days of parenteral nutrition and a transfucion of 600 ml of packed red cells, explorative laparotomy was performed. We found two cystic, multilocular tumors: the first one was 20 cm in diameter and weighed 4 kg; it was situated under the greater curvature of the stomach and transverse colon, over the pancreas. The second one was located in the middle part of the abdominal cavity and pelvis. It was 35 cm in diameter and weighed 12 kg. (Figure 1) The polycystic tumor was accreted with the abdominal wall, the small bowel, the colon and the mesosigmoid. We found a lot of link vessels between tumor and abdominal wall. Injury of these vessels caused massive bleeding. Hemostasis was secured with hot gauze packs compression or local coagulation. She underwent recto-sigmoid resection en block with the tumor, and stapled side-to-side anastomosis. The smaller tumor was sepa-

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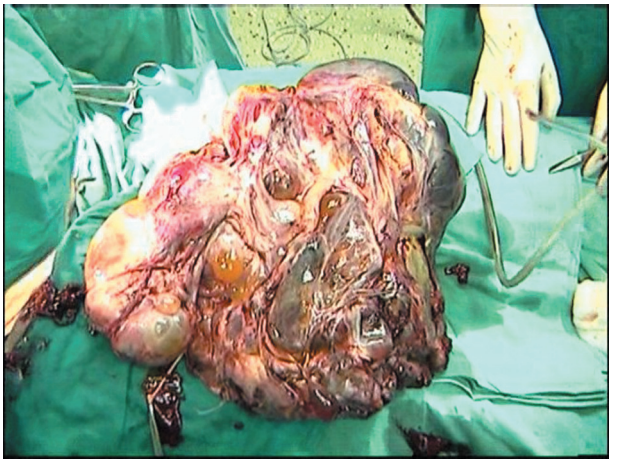

Figure 1. The larger tumor (12 kg) after resection

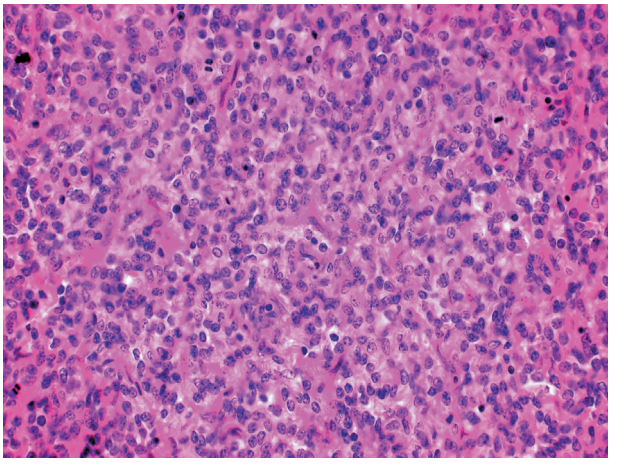

Figure 2. LESS hematoxiline-eosine staining

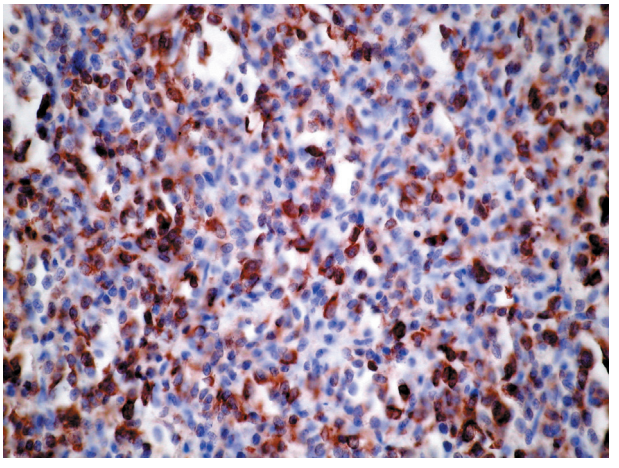

Figure 3. Positive CAM5.2 immunohistochemical staining

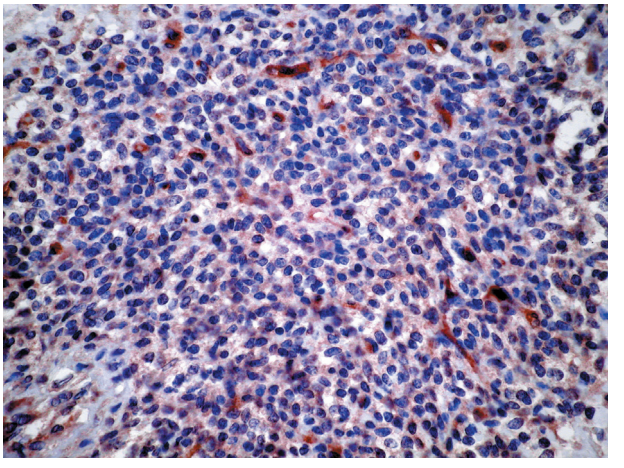

Figure 4. 30% positive CD117 (c-kit) immunohistochemical staining

rated from the stomach and the transverse colon and removed as a whole. After that, there was no macroscopic pathological mass in abdominal cavity. The overall blood loss was 1200 ml and she required transfusion of 2 units packed red cells and 600 ml of fresh-frozen plasma. There were no complications during the postoperative period and parenteral nutrition was continued for 5 days. Final postoperative histopathology report confirmed LESS with one mitosis per 20 high-power fields and moderate nuclear pleomorphism (Figure 2). Immunohistochemical study analyzed the following antigens: estrogen receptor (ER), progesterone receptor (PR), smooth muscle antigen (SMA), low molecular weight cytokeratin (CMA5.2), MIB1, CD117 (c-kit) and CD34.

ER was noted in 30% of cells. PR was absent. We noted strong positive reaction with CAM5.2 and SMA. In 30% of the cells, the CD117 (c-kit) was expressed. There was no expression of MIB1 and CD34 in all the cells (Figures 3 and 4).

Now, eleven months after debulking, she is in complete clinical and radiological (abdominal and pelvic CT scan) remission. Her quality of life is good and all respiratory disturbances have disappeared.

Discussion

Uterine sarcomas are aggressive gynecological malignancies even at an early stage of disease. The most common histological types are represented by leiomyosarcoma, endometrial stromal sarcoma (ESS), and mixed mullerian tumors. Estimated 5-year overall survival rate for all types of tumors is 62%. ESS is characterized by proliferations composed of cells with endometrial stromal cell differentiation. A breakpoint of 10 mitoses per 10 high-power fields is used to distinguish between low-grade and high-grade endometrial stromal sarcoma and to evaluate the prognostic value of mitotic count in patients with ESS [2]. All authors agree, that LESS has the best prognosis of these tumors. In the Royal Marsden Hospital study Livi et al. estimated that 3-years survival rate was 63% in patients with LESS. It was significantly related to stage, grade and histological type [3].

Immunohistochemical analysis can provide some prognostic information regarding LESS in early stages. Geller et al., have described the outcomes and patterns of failure in 28 patients with ESS (19 LESS and 9 HESS) diagnosed over 31 years and the relationship to proto-oncogene c-kit expression (CD 117). Positive tumors had more than 10% of cells comprising the neoplasm display

immunoreactivity. The median survival of patients with c-kit-positive versus c-kit-negative tumors was 12 and 47 months, respectively [4]. Our patient was c-kit-positive in 30% of the cells.

Bhargava et al. studied soft-tissue neoplasm including 17 ESS. Immunohistochemically, detecting the following antigens: CD10, ER, PR, bcl-2, CD34, SMA, epithelial membrane antigen and cytokeratin (AE1/AE3). Most ESS stained positively for CD10 (16/17), ER (17/17), PR (15/17), and bcl-2 (17/17). Staining with SMA was seen in 11 of 17 cases of ESS, with more intense staining seen in areas showing smooth muscle differentiation. Staining with AE1/3 was seen in four of 17 ESS, with two of the positive cases containing epithelioid cells. None of the ESS expressed epithelial membrane antigen or CD34. Differences between ESS and other soft-tissue tumors were detected for all of the immunohistochemical markers ($P<0.05$), except anti-bcl-2 and AE1/3 [5]. In our case of LEES we fined ER in 30% of the cells and no PR expression. None of the cells expressed CD34. In addition we noted strong positive reaction with SMA and CAM5.2. Humble et al. described CAM5.2 positive reaction in all examined epithelioid sarcomas in different localization [6].

Optimal primary treatment of early stages of disease is total hysterectomy with bilateral salpingo-oophorectomy. Unfortunately, it is not clear whether adjuvant therapy improves prognosis. In the Royal Marsden Hospital group, adjuvant radiotherapy with doses higher than 50 Gy, decreased the local recurrence rate, but did not have a significant impact on survival[3]. Our patient, after postoperative radiotherapy with a dose 46 Gy, had disease-free period of 53 months. Adjuvant chemotherapy may form an approach, since distant recurrences are more frequent than local failures. Unfortunately, there are no standard programs for the treatment of recurrent disease. The regimen of adjuvant chemotherapy currently used in the treatment of uterine sarcomas is based on ifosfamid and doxorubicin. There are some papers about CYVADIC as adjuvant treatment in stage I uterine sarcomas. Odunsi et al. have examined the efficacy and results of long-term follow-up of 24 valuable patients with completely staged uterine sarcomas. They received adjuvant multiagent chemotherapy with vincristine, doxorubicin, cyclophosphamide and dacarbazine for a total of nine monthly cycles or until recurrence of disease was documented. Overall, the patients received 206 of the planned 216 cycles of chemotherapy. The median follow-up of the patient population was 93 months (range 11-213 months). Eight patients (33%) developed recurrent disease. The median time to recurrence was 19 months (range 7-184 months) [7]. Wall and Starkhammar have described the effect of palliative chemotherapy on soft tissue sarcomas given outside controlled trials. Thirty-six patients were treated with first-line chemotherapy CYVADIC, with a response rate of 28% (median response duration 5.5 months). Etoposide and ifosfamide (includes granulocyte colony-stimulating factor (G-CSF)) were used in the treatment of 18 patients. The response rate was 22% (median response duration 4.5 months); Nineteen patients were treated with doxorubicin+ifosfamide and one patient responded. Four patients received other first-line treatments. Thirty-eight patients were given second-line chemotherapy and 4 (10%) patients responded. Thirteen patients were given third-line treatment and 5 patients received fourth-line treatment, but without any response. Disease progression was the dominant reason for discontinuation of therapy. The authors have concluded that the treatment with CYVADIC yields at least as high a response rate as the more recently described doxorubicin + ifosfamide combination, but third- and fourth-line therapy is not beneficial [8].

After second recurrence with pulmonary metastases our patient underwent six cycles of chemotherapy consisted of cisplatin 100 mg, doxorubicin 100 mg, cyclophosphamide 1000 mg with complete radiological remission.

Both lung and pelvis metastases are the main points of LESS relapse, approximately in 50% of patients after first line of therapy. However, there are rare cases, like those described by Matsuura et al., of multiple bone and lung recurrence in a patient with LESS. Metastases in thoracic spine, ribs, iliac bone and sacrum area were treated with external beam irradiation. It was effective as a form of pain relief, although the size of the recurrent tumor remained unchanged [1].

LESS, especially in its early stage, has the best prognosis of all uterine sarcomas. Even in cases of recurrent disease, overall survival may be long. Second line therapy and further therapy are reasonable, although the choice of the treatment method is difficult. Sometimes, during a consecutive relapse, surgery is only way of therapy to save the patient's life. We suggest that it should be performed safety, but radically, whenever possible.

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