Introduction

Brenner tumor of the ovary is a relatively uncommon neoplasm. It constitutes about 1.5% of all ovarian tumors with a peak of incidence in the fifth decade. The vast majority of Brenner tumors is benign, while only 1% is malignant and associated with a poor prognosis. Diagnosis could be made only with histological examination, and surgery is the mainstay of treatment.

Materials and methods

Here we present the case of a patient affected by a malignant Brenner tumor of the ovary, with metastases to brain, lung and liver and by a concomitant low grade endometroid adenocarcinoma of the uterus. A postoperative platinum based chemotherapy (CHT) was planned. The adjuvant treatment was discontinued for hematologic and liver toxicity and the patient died one month later due to a cardiorespiratory arrest.

Results and discussion

For what concerns adjuvant therapy, it is supposed that chemotherapy is profitable in the survival of these patients, but what agents would really provide an objective response in the presence of metastatic disease is not standardized.

Conclusion

Because of the rarity and the limited good quality research reports, multicentric prospective trials are needed to improve preoperative diagnosis of MBTs and investigate the best treatment.

KEY WORDS: Ovarian neoplasms - Brenner tumor - Ovarian cancer - Metastases.
V. Di Donato et al.

severe abdominal pain refractory to medical care. She reported a history of abdominal pain and abdominal swelling, persistent indigestion and nausea, changes in bowel habits, such as constipation and changes in bladder habits, including urinary urgency.

Abdominal and transvaginal ultrasound showed a pelvic right mass of 90 x 80 mm with mixed echogenicity, without evidence of vascularization and an endometrium thickness of 10 mm with poor vascularization, without signs of myometrial invasion. The liver and kidneys were unremarkable. Routine biologic tests results were all within normal ranges and CA-125 was 77.8 U/ml (normal 0-35 U/ml). A preoperative CT scan confirmed the presence of a right mass, excluding signs of extra-pelvic disease.

A diagnostic open laparoscopy plus hysteroscopy was planned, however the patient signed an informed consent also for laparotomic ovarian debulking in case of malignancy. Indeed diagnostic open laparoscopy was immediately converted to longitudinal laparotomy for the presence of macroscopic characteristics suspicious of malignancy. After en-block removal of the mass, intraoperative histological examination made diagnosis of malignant undifferentiated ovarian tumor. Complete ovarian debulking as staging procedure was performed. Final pathological examination reported diagnosis of right ovarian Brenner malignancy and concomitant low grade endometroid adenocarcinoma of the uterus. In particular the pathological examination of the right mass showed areas of benign Brenner tumor and areas with frankly malignant histological features, made of neoplastic epithelial elements infiltrating the stroma and calcifications. Immunohistochemical examination of the mass showed positive cytokeratin 7 and negative cytokeratin 20, CDX2, ER, vimentin and CA125. Outbreaks of metastases were also present in the left parametrium, pararectal periitoneal surface, anterior rectal seromuscular tunic and appendix. The cytology of ascites was positive for Brenner tumor.

A postoperative platinum based chemotherapy (CHT) with carboplatin and paclitaxel was planned. The adjuvant treatment was discontinued for hematologic and liver toxicity (G3 neutropenia, increased liver enzymes and bile salts, jaundice, itchiness). After three cycles of CHT, a total body CT scan showed new multiple secondary lesions in the lung and liver (Figure 1) and furthermore a diffuse peritoneal carcinomatosis. There were no significant pathological changes in load of spleen, pancreas, kidneys and adrenal glands, nervous system and skeleton.

In the meanwhile a gynaecological visit revealed the
presence of two little epithelialized vaginal areas of about 30 and 15 mm, which were removed. The final diagnosis put down for metastatic repetition of malignant Brenner tumor in the vagina. Due to this reason she continued palliative chemotherapy until she complained for weakness at the right arm.

A neurological visit revealed slight fall of the upper right limb and right pronation. A cerebral MRI showed abnormal signal intensity in multiple cortical areas and in the cerebellar vermis, as for brain metastases of malignant Brenner tumor (Figure 2).

The patient died one month later due to a cardiorespiratory arrest.

Results and discussion

Malignant Brenner Tumor (MBT) represents a very rare tumor of the ovary. Since the signs and symptoms are nonspecific it is difficult to make a diagnosis based on clinical suspicion. Moreover, little information exists in literature about Brenner tumors instrumental evaluation: no ultrasound criteria are reliable for clear identification of malignant Brenner tumors (10, 11) and no specific tumor markers exist.

The largest retrospective study from databases of the International Ovarian Tumor Analysis (IOTA), conducted on 29 patients who had undergone an ultrasound scan before surgery for adnexal mass that proved to be a Brenner tumor, failed to demonstrate ultrasound features specific for Brenner tumors (12).

Calcifications may occur in Brenner tumors and have also been reported in most Brenner tumors (13), but this feature can be found in several more frequent benign gynecological conditions like dermoid cysts. So calcifications cannot be accepted as a diagnostic criterion (12). However some sonographic features like higher color scores or irregular internal cyst walls - as in all malignant masses - are reported more in MBT than in benign ones (12).

Histological examination after surgery is the only way to make diagnosis of MBT; moreover, diagnosis is not always easy. Different Authors (14, 15) have tried to formulate the histological diagnostic criteria of MBTs.

The presence of frankly malignant histological features intimately associated with a benign Brenner tumor is mandatory for diagnosis of MBT (14, 16). In these histological types the epithelial nests are more angulated and have a disorderly infiltrating growth pattern; mild or moderate atypia may be present; mitotic activity may be prominent; mucinous cystadenomas should preferably be absent or must be well separated from both the benign and the malignant Brenner tumor; finally, stromal invasion by epithelial elements of the malignant Brenner tumor must be demonstrated.

In our case, the histopathologic diagnosis was performed according to these mentioned criteria. Since diagnosis of MBT is difficult, specialized pathologists should assess these cases for a better diagnostic accuracy and, if possible, a second opinion should be sought.

Nevertheless, because of the rarity and variable histological criteria, there are no established tumor markers for malignant Brenner tumors. Furthermore these rare tumors of the ovary usually have no hormonal activities, although there are reports of steroid hormone-producing Brenner tumors. Several studies indicate that MBT may have a functional effect, usually that of hyperestrinism (17-22), but pathogenesis is still unclear.

Fox et al. (23) showed cases of MBT presenting abnormal vaginal bleeding and mild degrees of endometrial hyperplasia, explained by estrogenic activity. Moreover, histologically confirmed endometrial hyperplasia has been reported in 4-14% of women affected by Brenner tumors (24) and in postmenopausal women this incidence ranged from 7 to 25% (25).

Isolated reports of endometrial adenocarcinoma associated with Brenner tumors can also be found (26-30). A final pathological report demonstrated, in our
patient, a concomitant low-grade endometroid adenocarcinoma of the uterus. Some Authors suggested a multifocal primitive independent origin of concomitant MBT and endometrioid tumor, originating from the primary and secondary Mullerian epithelium (28).

Otherwise, in patients affected by MBT and hyperestrogenism (high pre-operative serum and urinary estrogen concentrations, low serum LH and FSH levels, and histologically confirmed atypical endometrial hyperplasia) some Authors have described a reduction in serum and urinary estrogen level and an increase in serum LH and FSH concentrations after tumor removal, assuming that the tumor was synthesizing estrogen. Furthermore, Seldenrijk et al. (24) supposed that high estrogen may induce a negative feedback on the hypothalamic-pituitary axis, resulting in the reduction of serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) below the normal postmenopausal values, as they observed in their patient.

As generally occurs in cases of unbalanced hyperestrogenism, synchronous tumors tend to be low grade and early stage (28).

For what concerns adjuvant therapy, it is supposed that chemotherapy is profitable in the survival of these patients, but what agents would really provide an objective response in the presence of metastatic disease is not standardized. In the study conducted by Gezginc et al. (2), 9 out of 10 patients (90%) who underwent postoperative chemotherapy achieved complete response. The most common adjuvant chemotherapy regimen is platinum-based, with paclitaxel 175 mg/m², and carboplatin, at dosage ranging between 4 to 6 area under the curve (AUC) or cisplatin 75 mg/m² (2, 29, 31, 32).

An experience with short-term combination of cyclophosphamide, 5-fluoruracil and vincristine in a patient with an unresectable malignant Brenner tumor without any objective response is reported (33). Literature also describes the case of a patient treated with radiotherapy and subsequent chemotherapy with alkalin (1 mg/kg over a 5-day period every 4 weeks), who remained disease-free 15 months following discontinuation of her chemotherapy (34).

Although data from this study have to be interpreted with caution due to the small analyzed populations, some interesting observations can be made. The association between carboplatin and paclitaxel represents a drug combination which several gynecologic oncologists would consider as a standard in patients affected by MBT.

Since MBTs are rare, there are few reported cases of metastatic disease. Searching in literature, we found four cases of liver and lung metastases (2) treated with standard chemotherapy for ovarian mali-

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>Sites of metastases</th>
<th>Management</th>
<th>Follow-up (status)</th>
<th>Follow-up duration (months)</th>
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<td>DOD</td>
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<td>Lung</td>
<td>CT</td>
<td>NED</td>
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<td></td>
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CT: chemotherapy; NA: not available; NED: no evidence of disease; DOD: died of disease.
Brain metastases from malignant Brenner tumor of the ovary: a case report and a literature review

Gestations. In another case the patient presented with a 6-month history of intracranial hypertension as a result of dural metastases (6), and unfortunately died after a dural hemorrhage. Subcutaneous (7) and cutaneous (8) metastases are reported too, and in these cases malignant Brenner tumor presented a more aggressive clinical course, as the patients expired within few months of diagnosis of disease. In the report by Friedman et al. (35), they presented a patient with FIGO Ia malignant Brenner tumor in whom metastatic disease was found in retroperitoneal lymph nodes, stressing the importance of selective biopsies of retroperitoneal lymph nodes in the staging laparotomy for ovarian carcinoma. Skeletal metastases are described (33) too, in a patient whose tumor was apparently confined within the ovaries at initial laparotomy. Then multiple skeletal metastases developed 4 months later and the patient died of the disease 6 months after diagnosis. Peritoneal metastases can also occur, as in the case report of a 67-year-old woman by Hayashi et al (37). In the end, as affirmed by Han et al. (32) in their retrospective analysis on 10 patients with ovarian MBT, the role of adjuvant chemotherapy in MBT remains unclear because of its rarity. However their results showed that systemic chemotherapy is beneficial in patients with recurrence of a primary MBT of the ovary especially in the locoregional recurrence. In their series disease recurrence occurred in 4 of the 6 patients initially subjected to postoperative chemotherapy, and the median time to recurrence was 11 months (9-18 months). Two patients with locoregional recurrence showed favorable results after chemotherapy, regardless of the initial stage of the tumor: the woman with the stage IIIC tumor was alive at 13 months after recurrence on current chemotherapy and the other with the stage IV tumor showed no evidence of the disease > 12 years after the last chemotherapy. Nevertheless the two patients with distant recurrence died after showing a long-term survival of 49 months and 88 months, respectively, after recurrence and intensive chemotherapy.

Basically, surgery remains a cornerstone of treatment for women with MBT. However extensive procedures should be performed only after a careful systemic evaluation, in order to avoid wide surgery and related risk of complications in those patients in which absent residual tumor could not be reached (38-40).

Conclusions

To our knowledge, this case is the first reported instance of a Brenner tumor with cerebral metastases. Because of the rarity of such neoplasms and the limited good quality research reports, a more comprehensive study including interventional trial is needed in the future to better understand this cancer.

References