CASE REPORTS

Malignant mixed müllerian tumor of the ovary and false negative punctures

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Summary

Malignant mixed müllerian tumour (MMMT) of the ovary is a rare and aggressive tumour with a poor prognosis. We present a case of a 57-year-old woman with a large pelvic mass, omental cake, ascites and pleural effusions, clinically highly suspect of an ovarian neoplasm. Paracentesis and ultrasound-guided biopsy of the ovary were negative for malignant disease. Therefore a CT-guided true cut biopsy was performed. The latter gave a histopathologic diagnosis of an endometrioid adenocarcinoma of the ovary. However after cytoreductive surgery anatomopathologic examination revealed a malignant mixed müllerian tumour of the ovary with heterologous differentiation. Apparently only one of the two components was found in the puncture. Adjuvant chemotherapy, active against the sarcomatous and the carcinomatous component, was given. At present the patient is well and disease free 35 months after the initial diagnosis. Cytological examination of ascites may be negative in the presence of malignant disease. If a tumour consists of two components, puncture can miss one, which may lead to undertreatment. Punctures should be discouraged as a diagnostic tool in patients in whom an ovarian malignancy is suspected.

Key words: Ovarian neoplasm; Biopsy; Malignant mixed müllerian tumour; Puncture.

Introduction

Malignant mixed müllerian tumour (MMMT) of the ovary is an infrequently occurring neoplasm that represents 1-2% of all malignant ovarian tumours. Less than 500 cases have been reported in the literature [1].

Like epithelial ovarian tumours, MMMT of the ovary affects mainly postmenopausal women and consists of proliferating sarcomatous and carcinomatous elements. Two different types are seen: the homologous type and the heterologous type. The homologous type (carcinosarcomas) contains sarcomatous elements originating from tissue normally present in the ovary. The heterologous type contains elements such as bone, cartilage, fat or striated muscle [1].

The management of ovarian MMMTs presents a difficult problem for two reasons: they are highly aggressive neoplasms and their rarity has made it impossible to determine the optimal treatment for this neoplasm. The preferable approach, like in epithelial tumours, consists of optimal cytoreductive surgery followed by adjuvant platinum containing polychemotherapy. In general the diagnosis of MMMT carries a survival of less then two years. The histopathologic recognition is of the utmost importance for the type of chemotherapy. A therapy which combines two drugs, one active against the sarcomatous component, the other specifically active against the carcinomatous component, would still prove superior in advanced disease [7].

The symptoms are comparable with epithelial ovarian tumours and include abdominal swelling, vague abdominal discomfort, dyspepsia, constipation, and urinary frequency and weight change. On the basis of physical examination, symptoms and level of CA 125, ovarian cancer can be suspected. The diagnosis needs to be confirmed by histology. The treatment, in general, consists of a laparotomy in order to confirm the diagnosis and at the same time optimal surgical cytoreduction with appropriate intraoperative staging. An alternative approach to conventional surgery is neoadjuvant chemotherapy as the initial management of bulky ovarian cancer [2, 3]. A prospective randomised study of neoadjuvant chemotherapy and primary cytoreductive surgery is ongoing. A correct histopathologic diagnosis is important to determine the type of chemotherapy. In MMMT, therapy which combines two drugs, one active against the sarcomatous component and the other specifically active against the carcinomatous component, should be given. We present a case where several punctures failed to make the correct diagnosis.

Case report

In November 1999, a 57-year-old woman, G4P4, was admitted because of a large pelvic mass and ascites. Her complaints were anorexia, weight loss and epigastric pain of three months duration. The past medical history showed a cholecystectomy, appendectomy and sterilisation. She had been menopausal since 1994 and did not use any hormonal substitution therapy. Clinical examination showed a large pelvic mass, omental cake, ascites and pleural effusions, clinically highly suspect for an ovarian malignancy. Ultrasound examination revealed a pelvic polycystic structure (76 x 131 mm), accompanied by a large amount of ascites. Computerised tomography confirmed a large pelvic mass as well as ascites and the presence of pleura fluid. Different omental deposits were found and spleen metastases were presumed.

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Puncture of the ascites (twice) showed acute inflammatory cytology; no abnormal cells were found. Pleura puncture did not reveal any malignancy non did ultrasound-guided puncture of the ovarian cyst. A true-cut biopsy was performed which revealed the presence of an endometrioid adenocarcinoma. Laboratory work-up showed ferriprive anaemia and a high value of CA 125 (1580 U/ml, normal value < 35 U/ml). The patient was included in EORTC trial 55971 with randomisation between neo-adjuvant chemotherapy and up-front debulking; our patient was randomised for upfront debulking. Cytoreductive surgery was performed in December 1999. Besides the pelvic mass, there was tumoral involvement of the bladder, sigmoid, colon ascendens, liver, diaphragm and uterus. Together with the cytoreduction a total abdominal hysterectomy and bilateral salpingo-oophorectomy, infracolic omentectomy, and pelvic lymphadenectomy were performed. At the end of the procedure a tumour mass was left up to 4 cm in the upper part of the abdomen and less than 1 cm in the Douglas pouch. Anatomopathologic examination showed a MMMT with heterologous differentiation of the ovary (Stage IIIc).

From December 1999 until March 2000, the patient was treated by a combination of chemotherapeutic agents (epirubicine, paclitaxel and carboplatin: TEC) for three cycles (EORTC trial 55981). At the third cycle a dose reduction (75%) was given because of pancytopenia. Clinical, biochemical and radiological examination showed good partial remission.

In March 2000 our patient underwent interval debulking; supra-colic omentectomy, splenectomy and para-aortal lymphadenectomy (a difficult procedure because of retroperitoneal fibrosis) were performed. After surgery there was no macroscopic tumour left in the abdominal cavity. Anatomopathologic examination showed the presence of some MMMT (heterologous type) deposits in the fat tissue in front of the rectum and in the left fossa paracolica, as well as in the proximal mesenterium and in one para-aortal lymph node. The spleen was free of malignancy.

From March 2000 until May 2000 the patient received adjuvant chemotherapy: ifosfamide, adriamycin and cisplatin (PIA) for three cycles. For the second cycle doses reduction of ifosfamide was given due to hematotoxity. For the last cycle (May 2000) monotherapy of cisplatin was given because of the severe hematotoxity. The patient recovered well. At present, 35 months after her initial diagnosis, the patient is alive and disease free.

Discussion

MMMTs are highly malignant but rare tumours of the ovary with a poor prognosis. Several studies have reported a mean survival time between 12-25 months [1]. The most important predictors for survival seem to be stage (Stage I-II versus III-IV), optimal cytoreductive surgery and type of chemotherapy. Unfortunately, there are only small studies published on patients in several stages. Morrow *et al.* showed in a study involving 30 patients that the most important factors for survival were stage and the amount of residual tumour following initial surgery [5]. There is controversy regarding the prognostic importance of the pathologic subtype. Most of the studies demonstrate significantly better survival for the homologous MMMT compared to the heterologous type [1]. Other studies by Prendiville *et al.* [4], Morrow *et al.* [5] and Bicher *et al.* [6] dispute this and argue that stage was a confounding variable not taken into account by the authors who found a more favourable outcome for homologous tumours. In the most recent study by Hellström *et al.* a better prognosis for homologous tumours was seen when Stages I-II were compared to Stages III-IV [1]. The therapy of patients with MMMT preferably consists of optimal debulking surgery [7], followed by chemotherapy. Irradiation may have some place in cases localised to the pelvis [1]. Adjuvant radiotherapy for patients with more extensive disease did not improve their outcome, probably because these tumours tend to metastasize outside the abdominal cavity [7]. Numerous chemotherapeutic regimes have been tried in MMMT. Basically, these regimes fall into two groups: regimes effective in soft tissue sarcomas and regimes effective in epithelial ovarian cancer. The platinum-containing combinations seem to give a better response and longer survival than other regimes [1, 6-8]. The sensitivity of MMMT to cisplatin supports the view that MMMT of the ovary is possibly a high grade carcinoma with metaplastic sarcomatous elements [7].

Nevertheless, therapy which combines two drugs, one active against the sarcomatous component and the other active against the carcinomatous component, would still prove superior in advanced disease [7]. This makes histopathologic recognition of MMMT of the ovary important, in order to avoid undertreatment.

However in the current case of a clinically obvious tumour, it was necessary to have a preoperative histological diagnosis in order to decide whether or not the patient could participate in a randomised study between neo-adjuvant chemotherapy and up-front debulking. For this reason punctures were performed. First, cytological examination of the ascites (twice), pleura fluid and the ovarian cyst was performed which showed no tumour cells. Second, a true cut biopsy was performed which showed only one of the two components of the tumour, which could lead to undertreatment if neoadjuvant chemotherapy is considered.

Conclusion

Although the prognosis in cases of MMMT of the ovary is poor, aggressive cytoreductive surgery followed by combination chemotherapy active against both components of the tumour seem to improve the progression-free intervals for women with advanced ovarian MMMT. The current report shows that if you have a tumour consisting of two components, it is possible that only one of the two is diagnosed. In our patient the true-cut biopsy was not representative of the two components of the tumour. This manuscript stresses further the importance of a correct histological diagnosis in order to give optimal medical treatment.

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