Malignant Peritoneal Mesothelioma in Women

a report by
Professor Bilal M Sert

Council Member, European Society of Gynecology (ESG)

Professor Bilal M Sert is a Council Member of the European Society of Gynecology (ESG). He is also a Senior Consultant in the Division of Gynecologic Oncology at the Norwegian Radium Hospital.

Introduction

Primary peritoneal mesothelioma is a rare disease with an annual incidence of only one case per million in the US,[1] with pleural malignant mesotheliomas by far more common than the peritoneal variants (2.2 cases per one million in the US).[2] It was first described, in 1908, as *"a malignant tumor arising from the endothelium of the peritoneum and producing mucoid ascitic fluid."*[3] In 1909 the term mesothelioma was first used *"to refer to a highly malignant tumor of the serosal membranes involving mostly the pleura and the peritoneum, and less often the pericardium and tunica vaginalis testis."*[4] The first documented case of mesothelioma, according to current diagnostic criteria, was published in 1947.[5] Primary peritoneal mesothelioma represents 20% to 37% of all mesotheliomas.[6–8]

In 1960, the clear relationship between occupational and environmental crocidolide exposure and diffuse pleural mesothelioma was demonstrated.[9] A recent study from Norway has also shown a high incidence of mesothelioma and a high ratio of mesothelioma to lung cancer among asbestos and cement workers. No peritoneal mesothelioma was found.[10] The ratio of mesothelioma to lung cancer cases was 1: 2 for the total cohort. Rare cases of mesothelioma have been associated with radiation exposure,[11] with studies in rats supporting the notion that radiation exposure can cause mesothelioma.[12] It seems safe to state that intensive radiation exposure can cause mesothelioma; however, the overall number of mesotheliomas caused by radiation is probably small. There is some evidence that Simian Virus (SV 40) and asbestos might be carcinogens in human mesothelial cells in tissue culture.[13–14] Genetic and erionite may co-operate in causing mesothelioma in the Cappadocian region of Turkey.[15] Mesothelioma may be a cancer in which genetics, radiation, viruses and erionite interact to cause malignancy.

Diagnosis of Primary Peritoneal Mesothelioma

The common presenting symptoms of primary peritoneal mesothelioma are non-specific abdominal pain, abdominal distention and weight loss. Examination reveals ascitis in 90% and an abdominal mass in 16% of patients. Approximately one-third present with abdominal distention, one-third present with abdominal pain and one-third present with combined symptoms of pain, abdominal distention and other findings. Among women, 24% presented as a perforated appendix and incarcerated umbilical hernia.[15]

Computed tomography (CT) examination aids in the diagnosis of peritoneal mesothelioma. The two clinical types of peritoneal mesothelioma – wet or dry – have profoundly different appearances under CT examination. The dry type of peritoneal mesothelioma may disclose several mass lesions and the tumour mass commonly associated with the greater omentum. The symptomatic mass lesion seen on the CT is thought to be a large primary carcinoma (ovarian, gastrointestinal, borderline) or other benign lesions such as abscesses and benign cysts. Only laparotomy has the definitive diagnosis evident in these patients presenting with solid tumour without ascites. In the wet type, there is little or no evidence of solid tumour. Occasionally, small nodules lining the parietal peritoneal surface are evident, especially beneath the right hemidiaphram.[16]

Cytology of fluid removed by paracentesis, combined with the sophisticated use of an extensive panel of immunohistochemical (IHC) markers, can also be used to confirm the diagnosis of peritoneal mesothelioma. Diagnostic laparoscopy with biopsy can be used for definitive diagnosis when it is indicated. Calretinin and Ber-EP4 are very useful markers especially in distinguishing peritoneal mesothelioma from serous papillary ovarian and peritoneal carcinoma.[17] Ber-EP4 to be a discriminant marker between epithelium and mesothelium.[18] Calretinin is a most useful marker for positive identification of malignant mesotheliomas.[19]

Leu-M1 is also very useful since practically no cases of malignant mesothelioma express this antigen, which is present in the majority of adenocarcinomas.[20,21]

Analysis of DNA content by flow cytometry may provide further help in the distinction between

malignant mesothelioma and benign mesothelial proliferation, but distinguishing mesotheliomas from adenocarcinomas by ploidy analysis appears to be controversial at present.[21] It is important to make the definitive histologic diagnosis because the well-differentiated papillary mesothelioma of the peritoneum is a special variant characterised by an indolent clinical course and prolonged survival.[22,23] Furthermore, deciduoid peritoneal mesothelioma is another uncommon variant that affects young women.[24,25] Differential diagnosis of the simultaneous occurrence of colon carcinoma and peritoneal mesothelioma was only possible as a result of IHC studies.[25]

Treatment

Cytoreductive surgery is essential. The size of residual tumour nodules after cytoreduction has been documented to influence strongly the efficiency of post-operative therapy. The correlation between the completeness of cytoreductive surgery and survival rate for peritoneal carcinomatosis from colonic and appendiceal cancer.[27,28] A laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy and tumour debulking is recommended. Right and left subphrenic peritonectomy and complete pelvic peritonectomy has been described.[29]

Antman, et al. reported significantly better survival in a small group of patients (six women) treated after aggressive surgical debulking with a combination of intraperitoneal cisplatin and doxorubicin (Adriamycin®) and whole abdominal radiotherapy when compared with surgically inoperable cases treated with chemotherapy.[30] Although there was no statistical indication that intraperitoneal chemotherapy resulted in survival benefit, palliation of ascitis may be an important outcome with intraperitoneal chemotherapy. Sebbag, et al. reported that patients were treated by cytoreductive surgery with peritonectomy and perioperative intraperitoneal chemotherapy (cisplatin, doxorubicin) has 33% morbidity and the perioperative mortality rate was 3%.[31]

There are several reports regarding long-term survival in patients with malignant peritoneal mesothelioma treated with irradiation and combined modality treatment. An extended Phase II trial of ifosfamide plus mesna in malignant mesothelioma showed no objective response but significant side effects.[34] Continuous hyperthermic peritoneal perfusion has shown promising results in 18 patients with primary peritoneal mesothelioma, five of which were women and no operative or treatment-related mortality was reported and morbidity was minimal.[35] Prospective trials for the treatment of primary peritoneal mesothelioma with cytoreductive surgery combined with intraperitoneal hyperthermic chemotherapy perfusion are encouraging.[36]

Figure 1: Scattered small nodules involving both visceral and parietal peritoneal surfaces

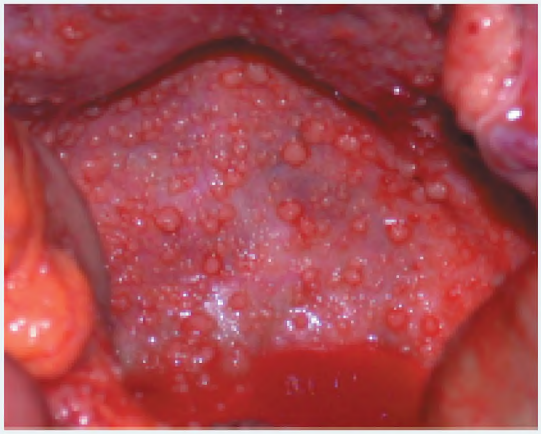


Figure 2: These small nodules also covered all pelvic peritoneum inclusive uterine serosa and both adnex

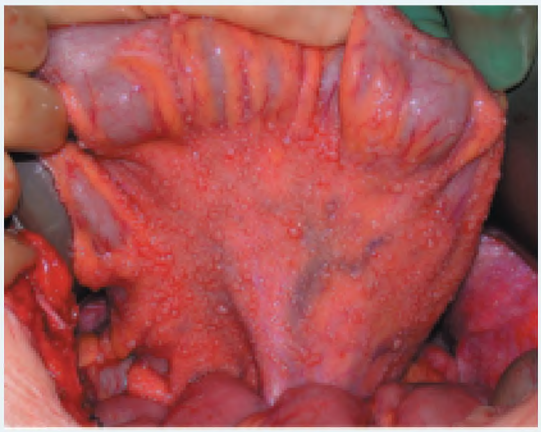
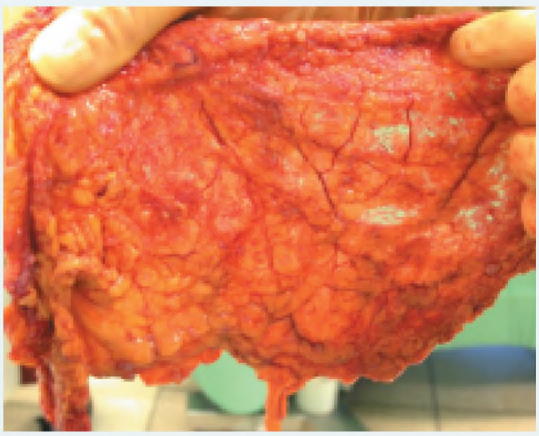


Figure 3: There are many small nodular metastases to omentum



Although malignant mesothelioma is not a classically immunologic cancer, there is clear evidence for immune recognition. A Phase I study of intraperitoneal recombinant human interleukin-12 use in peritoneal mesothelioma was reported.[37] To date, there is no standardised therapy for patients with peritoneal mesothelioma. The evaluation of gene therapy, vaccination, immunotherapy and novel cytostatic agent is still in infancy.

Box 1: Case Report of a 60-year-old Woman

Normal obstetric and gynaecologic history, with no cancer history in family anamnese. Menopause at 55 years of age and no hormonal replacement therapy. The patient was examined in 1998 by her own specialist as a routine when fluid in the *fossa douglasi* was found. Aspiration cytology showed benign mesothelial cells but no atypia and fractional curettage was also normal. Ca 125 = 4. The patient had normal Rontgen examinations both thorax and abdominal CT at that time, followed up yearly with gynaecologic examination, tumour marker and vaginal ultrasound. Ascitis fluid in the *fossa douglasi* had increased from 4cm in 1998 to 5.5cm in September 2002. Ca 125 = 7. The patient was referred to a local hospital where ascitis fine-needle aspiration (FNA) cytology revealed papillary malignant cells. Rontgen thorax and mammography was normal. CT scan showed ascitis otherwise normal organ status. Patient referred to our institutions in December 2002 for further evaluation, examination and treatment.

On physical examination, the patient is found to have ascitis but no definitive intra-abdominal masses. Pelvic examination under anaesthesia fails to reveal any specific abnormal findings. Transvaginal ultrasound-guided FNA cytology revealed malign mesothelioma after immunohistochemical staining.

Through-cut biopsy from omentum also showed the same diagnosis. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and total omentectomy has been performed and post-operative course was uncomplicated and the patient discharged from hospital post-operatively on the fifth day. Final histopathology confirmed the preoperative diagnosis well-differentiated papillary malign peritoneal mesothelioma, involving superficially uterus serosa, both ovaries and meso-ovarium and omentum but no evidence of invasive pattern. Patient has been discussed in the tumour board and no additional therapy recommended.

Controls of ascitis alone is worthy of therapeutic goal and surgical technical improvements and could enhance the degree of cytoreduction and might improve clinical results.

Although prospective randomised trials of combined treatment with cytoreductive surgery and chemotherapy are theoretically attractive, the rarity of peritoneal mesothelioma makes accrual to appropriately powered trials highly unlikely.

It is important to distinguish this disorder from the malignant variants. In view of the indolent course of this subtype of mesothelioma, avoidance of treatment is justified unless there is evidence of progressive disease. Of course, patients should be fully informed about additional therapy alternatives such as systemic or local chemotherapy. ■

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