Diffuse malignant epithelial peritoneal mesothelioma in pregnancy. A case report and literature review

T. Pekin[1], *Assoc. Prof.*; **E. Coşar**[1], *Resident*; **N. Dedeoğlu**[1], *Resident*; **F. Çakalağaoğlu**[2], *Assoc. Prof.*; **H. Gökaslan**[1], *Assist. Prof.*; **Z. Kavak**[1], *Prof.*

[1]*Department of Obstetrics and Gynecology,* [2]*Pathology, Marmara University Hospital of Medical School, Istanbul (Turkey)*

Summary

A 33-year-old pregnant woman of 38 weeks' gestation with massive peritoneal ascites presented. A cesarean section was performed and a viable 3,100 g male infant was delivered. Biopsy of the nodular enlargements from the omentum revealed a malignant epithelial peritoneal mesothelioma. Malignant mesothelioma is a rare malignancy which has not been described in term pregnancy and appears to be unaffected by the pregnant state.

Key words: Diffuse malignant epithelial peritoneal mesothelioma; Pregnancy; Histochemistry; Immunohistochemistry.

Introduction

Malignant peritoneal mesothelioma is a rare peritoneal malignancy, representing approximately one-third of all mesotheliomas in females, and the majority of lesions are epithelial forms [1-3]. It is increasing in frequency, and the increase is anticipated to continue, especially in industrialized nations [3, 4]. The number of large series of malignant mesothelioma is still few. A review of the literature revealed no cases of malignant epithelial peritoneal mesothelioma complicating term pregnancy. Mesothelioma may involve the pleura, less frequently the peritoneum and rarely, the pericardium. Peritoneal mesothelioma is usually a rapidly fatal peritoneal surface malignancy with a median survival of less than one year [1]. Asbestos is the leading etiologic factor for malignant mesothelioma [1, 3]. Limited data are available regarding this malignancy in pregnancy.

We present a case of malignant epithelial peritoneal mesothelioma complicating pregnancy and provide a review of the literature.

Case Report

The following clinical information was retrieved from the patient's medical records at another institution: A 33-year-old female, gravida 1, para 1 presented with the complaint of secondary infertility in November 2001. Clinical examination revealed abdominal discomfort and mild abdominal swelling, temperature 37°C, blood pressure 110/75 mmHg, pulse 90 beat/min, mild shortness of breath, weight loss and weakness. Complete blood count revealed Hgb 10.5 g/dl, Hct 32.3%, platelets 339000/mm^3, WBC 13200/mm^3. Abdominal ultrasonography showed ascites in the abdomen and computerized tomography revealed widespread small nodular findings over the parietal and visceral peritoneum. Evaluation of the aspirated yellow-gray fluid by abdominal puncture was consistent with "chronic nonspecific infectious reaction". A tuberculin skin test and HIV serology were negative.The referring physician probably misdiagnosed the neoplasm or was uncertain of its nature. The patient underwent antituberculous therapy with a "poor" response.

In April 2002 the patient was referred to the Department of Ob/Gyn of Marmara University Hospital with the complaint of abdominal swelling and delayed menstruation. Ultrasonographic examination of the patient revealed a 9-weeks' gestation and ascites in the abdomen. Laparoscopy was performed and multiple small nodular tumors over the parietal and visceral peritoneum were found. Cytologic examination of the aspirated fluid and histology of the biopsy specimens revealed the diagnosis of atypical mesothelial cells and malignant epithelial mesothelioma, respectively. The patient denied any chemotherapy or surgery for subsequent treatment.

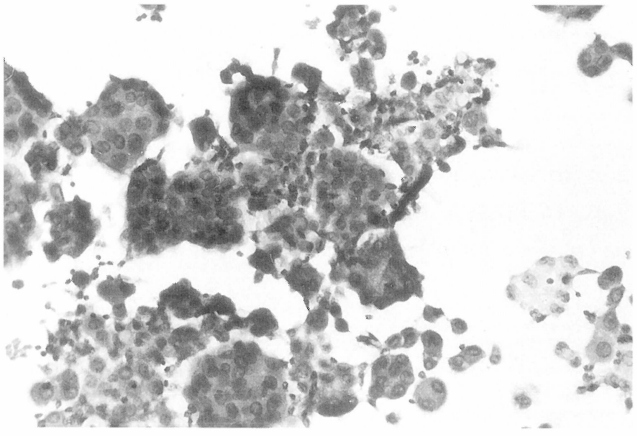
On November 11, 2002 the patient presented again to the Perinatal Department of Marmara University Hospital with the complaint of labor pains and abdominal distention with her term pregnancy (38 weeks, 6 days). A cesarean section was performed and a healthy 3,100 g male infant was delivered. At the same time two liters of yellowish-gray fluid from the abdominal cavity was removed. Evaluation of the abdomen revealed widespread tumoral nodules, typically solid, and the parietal and visceral peritoneum were diffusely thickened and partly studded with minute foci of tumor resembling grains of sand which were partly necrotic and fragile, less than 2 cm (0.5-2 cm) in diameter. The surface of the liver, spleen, and omentum were also involved with tumoral nodules. Both ovaries were normal in size, but there was scanty involvement of their surfaces with tumoral nodules less than 5 mm in diameter. Partial omentectomy and adequate biopsies from different sites of the abdominal cavity were taken. The omentum material, biopsied tumors, 50 cc of fluid, and placenta were submitted to the Department of Pathology, Marmara University Hospital for histologic evaluation.

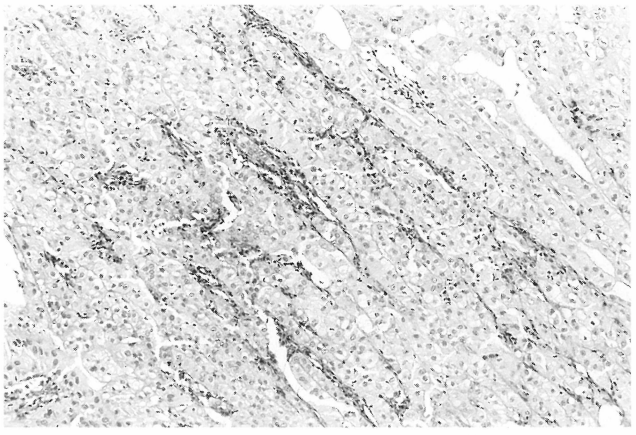
Histopathology

In this case, the diagnosis of mesothelioma was made using currently accepted histologic and cytologic criteria, combined with histochemical and clinical features.

Revised manuscript accepted for publication June 18, 2003

Fig. 1





Fig

Figure 1. — Atypical mesothelial cells in ascitic fluid (Pap x 200).
Figure 2. — Atypical mesothelial cell islands of cords and glandular structures in omentectomy specimen (H&E x 100).

Macroscopic findings

Sampled biopsies were described as white-gray nodules, varying in size from 0.5 to 1.5 cm. The omentum was 4.5 x 3 x 2 cm in size, involved with multiple tumors less than 2 cm in diameter. The mature placenta revealed no evidence of metastasis and 50 cc of yellowish-brown fluid was aspirated.

Microscopic findings

The tumor was diagnosed histopathologically as malignant mesothelioma using hematoxylin-eosin stained sections and specialized immunohistochemical tests for differentiation from other peritoneal surface malignancies [5-7]. The histologic features were an exclusively sheet-like pattern composed of polygonal cells with abundant eosinophilic cytoplasm. They contained a prominent inflammatory infiltrate which included a dense lymphocytic infiltrate with granulomas. The stroma within the epithelial patterns varied from scanty to abundant. It was typically hyalinized and confluent papillae with hyalinized cores were a striking finding (Figure 1). The nuclear grade of the cells was 3.

Cytology of ascitic fluid revealed atypical mesothelial cells of epithelial type (Figure 2).

Special stains and immunohistochemistry

Immunohistochemical studies were performed using the avidin-biotin-peroxidase complex method of Hsu *et al.* [8]. Sections were cut 3-4 mm thick, deparaffinized in xylene, and rehydrated in descending grades (100-70%) of ethanol. Endogenous peroxidase activity was blocked by a 10-minute treatment with 3% hydrogen peroxide in absolute methanol.

Results

The histochemical and immunohistochemical findings for the mesothelioma are as follows:

PAS. With PAS/D and without diastase staining revealed focal granular intracytoplasmic positivity in the neoplastic cells.

Vimentin. Mesothelioma expressed vimentin. The staining was focal at the cells

Cytokeratin 5/6. Mesothelioma reacted with the 5/6 antikeratin antibody. Staining was strong and was evenly distributed throughout the cytoplasm. Cytokeratin 5/6 could be a useful marker for mesothelioma [9, 10].

EMA. Mesothelioma reacted for epithelial membrane antigen. The staining was cytoplasmic with accumulation of the reaction along the cell membranes.

Calretinin. Mesothelioma exhibited calretinin reactivity. The staining was strong and occurred in both the cytoplasm and in the nucleus of the cells.

p53. Staining was strong and diffusely distributed throughout the cytoplasm.

CEA. Mesothelioma did not react for carcinoembryonic antigen.

Discussion

This is the first study of diffuse peritoneal epithelial mesothelioma complicating term pregnancy in women to date. The link between mesothelioma and exposure to asbestos is widely accepted; its incidence is increasing in industrialized nations [11, 12]. The incidence in asbestos-exposed patients is 3%, a 300-fold increase over the general population. Latency from asbestos exposure to onset of disease may be 20-40 years [1]. Asbestos-exposure history can be identified in 60-70% of affected patients, with direct occupational exposure noted in nearly 30% [13]. Peritoneal mesothelioma represents 20-37% of all mesotheliomas [1, 2]. Because of its rarity and the small size of published series, an estimation can only be made of 200-400 new cases annually in the USA [14]. No clear history of asbestos exposure was noted with our patient.

The most common initial complaints for peritoneal mesothelioma of the patient were gradually increasing abdominal distention, abdominal pain, and weight loss. Ascites were present at the time of diagnosis. Our case indicates that a substantial proportion of diffuse peritoneal epithelial mesothelioma behaved indolently. The mean interval from onset of symptoms to diagnosis was approximately five months. Diagnosis of peritoneal

mesothelioma was made by paracentesis and cytology, and by laparoscopic biopsy.

A difficult distinction for most pathologists, however, is between peritoneal mesothelioma and serous epithelial tumors of either ovarian or peritoneal origin. Distinguishing mesotheliomas from far more common serous epithelial tumors is important because of their differences in epidemiology, clinical behavior, and treatment [15, 16]. Surface serous carcinomas and ovarian serous carcinomas with peritoneal metastases typically present as widespread "carcinomatosis" and usually are accompanied with ascites. Their intraoperative appearance may be suggestive of a malignant mesothelioma. Serous carcinomas however, are composed of epithelial cells which have more overtly malignant histologic features with a greater degree of cellular and nuclear pleomorphism, mitotic activity, and infiltration of underlying tissues and organs than are generally seen in mesotheliomas. While peritoneal malignant mesotheliomas in women have grade 3 nuclei, they are typically well differentiated tumors composed of relatively uniform cells with a low level of mitotic activity [17]. A recent paper by the United States-Canadian Mesothelioma Reference Panel reviewed in detail the histologic features that are useful in distinguishing benign mesothelial reactions from malignant mesothelial neoplasms [18]. Histologic features that favor the diagnosis of mesothelioma over serous carcinoma include a prominent tubulopapillary pattern, polygonal cells with eosinophilic cytoplasm, the absence of marked nuclear pleomorphism, the absence of high mitotic rate, and the presence of intracellular acid (PAS negative) mucin rather than neutral (PAS positive) mucin [19]. Several studies have reviewed the use of immunohistochemical markers in distinguishing mesotheliomas from serous carcinomas [20, 21]. In our patient the special staining, such as PAS and PAS/D and immunohistochemistry markers such as vimentin, cytokeratin 5/6, EMA, calretinin, p53 and CEA investigations were in favor of the diagnosis of malignant epithelial mesothelioma. We also are confident that the tumor was malignant epithelial mesothelioma and not serous carcinoma based on the histologic appearance, lack of PAS staining and the available immunohistochemistry.

Malignant mesothelioma carries a poor prognosis irrespective of treatment modality. In a review of the literature no dominant therapeutic guideline for peritoneal mesothelioma was found. A few articles were clinicopathological retrospective reviews and most were case reports compiling disparate and deceptive therapeutic experiences, including use of systemic chemotherapy, whole abdomen irradiation, and intraperitoneal treatments with compounds such as colloidal radioactive ^{32}P and ^{198}Au, thiotepa and bleomycin [2, 22, 23]. Combination chemotherapy has demonstrated a response rate of 30-40% [3]. Responses, however, are typically limited to palliation of symptoms and prolonged survival.

More recent reports show a more systematic approach to peritoneal mesothelioma, with debulking surgery and systemic chemotherapy with paclitaxel, cisplatin alone or doxorubicin [24, 25]. A phase I trial with 18 patients reported a similar approach to the present one, with promising preliminary results [26]. The prognosis is grim after diagnosis of peritoneal mesothelioma. Median survival is 8-14 months from onset of initial symptoms or 4-12 months after diagnosis [1-3, 22, 27].

Malignant peritoneal mesothelioma has not been described in term pregnancy. It is not known whether pregnancy affects progression of malignant mesothelioma. The clinical course of our patient did not appear to be influenced by the gravid state. Careful examination of the placenta and infant revealed no metastases although this is more commonly associated with melanoma and hematopoietic malignancies [28].

At the time of last follow-up, the patient was alive and clinically well with the disease five months after delivery.

In conclusion, peritoneal mesotheliomas occasionally occur in women. This tumor, which diffusely involved the peritoneum, had an infiltrative growth pattern and had grade 3 nuclei usually acting in a clinically aggressive manner, often causing death of the patient within a few years. Distraction of peritoneal mesotheliomas in women from serous adenocarcinomas can usually be accomplished with careful light microscopy but may require histochemical stains and immunohistochemistry studies.

With the current state of knowledge, there is no standardized therapy for patients with mesothelioma, although limited evidence suggests that tumor-reduction surgery and chemotherapy may improve survival [24].

References

[1] Sridhar K. S., Doria R., Raub W. A. Jr., Thurer R. J., Saldana M.: "New strategies are needed in diffuse malignant mesothelioma". *Cancer,* 1992, *70,* 2969.

[2] Asensio J. A., Goldblatt P., Thomford N. R.: "Primary malignant peritoneal mesothelioma. A report of seven cases and a review of the literature". *Arch. Surg.,* 1990, *125,* 477.

[3] Antman K. H.: "Malignant mesothelioma". *N. Engl. J. Med.,* 1980, *303,* 200.

[4] Walker Am., Loughlin J. E., Freidlander E. R.: "Projections of asbestos-related disease, 1980-2009". *J. Occup. Med.,* 1983, *25,* 409.

[5] Hammar S. P., Bolen J. L.: "Pleural neoplasms". In: Dail H. D., Hammar S. P. (eds.): "Pulmonary Pathology" 1st ed., New York, Springer-Verlag, 1988, 973.

[6] Johnsen B. L., Lee I., Gould V.: "Epidemiology, pathogenesis, and pathology". In: "Mesothelioma Diagnosis and Management". Kittle F. C. (ed.), Chicago, Year Book Medical, 1987, 1.

[7] Donna A., Betta P. G., Bellingeri D., Marchesini A.: "New marker for mesothelioma: an immunoperoxidase study". *J. Clin. Pathol.,* 1986, *39,* 961.

[8] Hsu S-M., Raine L., Fauger H.: "Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures". *J. Histochem. Cytochem.,* 1981, *29,* 577.

[9] Clover J., Oates J., Edwards C.: "Anti-cytokeratin 5/6: A positive marker for epithelioid mesothelioma". *Histopathology,* 1997, *31,* 140.

[10] Ordonez N. E.: "Value of cytokeratin 5/6 immunostaining in distinguishing epithelial mesothelioma of the pleura from lung adenocarcinoma". *Am. J. Surg. Pathol.,* 1998, *22,* 1215.

[11] Yates D. H., Corrin B., Stidoph P. N., Brownek.: "Malignant mesothelioma in southeast England: Clinicopathological experience of 272 cases". *Thorax,* 1997, *52,* 507.

[12] Price B.: "Analysis of current trends in United States mesothelioma incidence". *Am. J. Epidemiol.,* 1997, *145,* 211.
[13] Ramsey P. S., Danilenko-Dixon D. R., Ramin K. D., Ogburn P. L. Jr.: "Malignant pleural mesothelioma in pregnancy". *J. Materno-Fetal. Med.,* 2000, *9,* 373.
[14] Sebbag G., Yan H., Shmookler B. M., Chang D., Sugarbaker P. H.: "Results of treatment of 33 patients with peritoneal mesothelioma". *Br. J. Surg.,* 2000, *87,* 1587.
[15] Kannerstaein M., Churg J.: "Peritoneal mesothelioma". *Hum. Pathol.,* 1977, *8,* 83.
[16] McCaughey W. T. E.: "Papillary peritoneal neoplasms in females". In: "Pathology Annuals, Part 2". Sommers S. C., Rosen P. P., Fechner R. E., (eds.), New York, Appleton-Century-Crofts, 1985, 387.
[17] Goldblum J., Hart W. R.: "Localized and diffuse mesotheliomas of the genital tract and peritoneum in women". *Am. J. Surg. Pathol.,* 1995, *19* (10), 1124.
[18] Churg A., colby T. V., Cagle P., Corson J., Gibbs A. R., Gilks B., *et al.*: "The separation of benign and malignant mesothelial proliferations". *Am. J. Pathol.,* 2000, *24,* 1183.
[19] Clement P. B., Young R. H.: "Atlas of Gynecologic Surgical Pathology". Philadelphia, W. B. Saunders, 2000, 456.
[20] Ordonez N. E.: "Role of immunohistochemistry in distinguishing epithelial peritoneal mesotheliomas from peritoneal and ovarian serous carcinomas". *Am. J. Surg. Pathol.,* 1998, *22,* 1203.
[21] Bollinger D. J., Wick M. R., Dehner L. P., Mills S. E., Swanson P. E., Clarke R. E.: "Perithoneal malignant mesothelioma versus serous papillary adenocarcinoma: A histochemical and immunohistochemical comparison". *Am. J. Surg. Pathol.,*1989, *13,* 659.
[22] Rogof E. E., Hilaris B. S., Huvos A. G.: "Long-term survival in patients with malignant peritoneal mesothelioma treated with irradiation". *Cancer,* 1973, *32,* 656.
[23] Rose R. G., Palmer J. D., Lougheed M. N.: "Treatment of peritoneal mesothelioma with radioactive colloidal gold. Report of a case". *Cancer,* 1955, *8,* 478.
[24] Eltabbakh G. H., Piver M. S., Hempling R. E., Recio F. O., Intengen M. E.: "Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma". *J. Surg. Oncol.,* 1999, *70,* 6.
[25] Markman M., Kelsen D.: "Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma". *J. Cancer Res. Clin. Oncol.,* 1992, *118,* 547.
[26] Park B. J., Alexander H. R., Libutti S. K., Wu P., Royalty D., Kranda K. C. *et al.*: "Treatment of primary peritoneal peritoneal mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP)". *Am. Surg. Oncol.,* 1999, *6,* 582.
[27] Tsavaris N., Primikiros N., Mylonakis N., Varouchakis G., Dosios T., Pavlidis N. *et al.*: "Combination chemotherapy with cisplatin and/or doxorubicin in malignant mesothelioma. A retrospective study". *Anticancer Res.*, 1997, *17,* 3799.
[28] Read E. J., Platzer P. B.: "Placental metastasis from maternal carcinoma of the lung". *Obstet. Gynecol.,* 1981, *38*, 387.

Address reprint requests to:
T. PEKIN, M.D.
Cemil Topuzlu cd. 103/15
81060 Caddebostan
Istanbul (Turkey)