Cystic mesothelioma of the peritoneum

Report of a case with multiple recurrences and review of the literature[1]

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A case of cystic peritoneal mesothelioma with repeated local recurrences is presented. Ultrastructural and immunohistochemical studies confirmed the mesothelial character of the lesion. The literature was reviewed and 20 previously reported cases tabulated. Cystic mesothelioma is a relatively "benign" tumor characterized by frequent intra-abdominal recurrences without distant metastases. Morbidity associated with the lesion is due to local tumor recurrence. Patients are usually women of reproductive age with complaints of abdominal pain. Some tumors are discovered initially as incidental findings. No specific factors are helpful in predicting which tumors are most likely to recur. Recurrences are independent of lesion size at initial or recurrent presentation, adequacy of tumor resection, or the use of adjunctive therapy. No consistent etiologic factor has yet been identified in the pathogenesis of this rare neoplasm.

Index terms: Mesothelioma · Pathology features · Peritoneal neoplasms

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Cystic, or multicystic, mesothelioma is a rare "benign" tumor of the peritoneum characterized by multiple free and attached cysts of the abdominal or pelvic cavity. The cysts are lined by cytologically bland mesothelial cells, which are indistinguishable from those of normal or reactive peritoneal surfaces. The tumor was probably originally described by Plaut in 1928 as loose cysts of the pelvis incidentally discovered during surgery for uterine leiomyomas.[1] Since then, case reports and small series have appeared in the literature.[2–11] While the tumor appears to be nonmalignant, local recurrences have been described.[2–7] The clinical behavior of the tumor, however, has not yet been well defined. We report a case of cystic mesothelioma with repeated local recurrences evaluated ultrastructurally and immunohistochemically. The literature is reviewed and all reported cases evaluated for useful clinical and pathologic features.

Case report

A 32-year-old, gravida 1, para 1, white woman first complained of acute lower abdominal pain in June 1975. With a presumed diagnosis of acute appendicitis, an exploratory laparotomy was performed at an outside hospital and a ruptured left ovarian cyst was found. A cystectomy, with preservation of the left ovary, and appendectomy were done. No other cystic lesions were identified and the postoperative course was uncomplicated.

In November 1977, she again presented with acute abdominal pain in association with an intrauterine device. Exploratory laparotomy revealed a large pelvic abscess involving the right tube and ovary. Numerous cystic struc-

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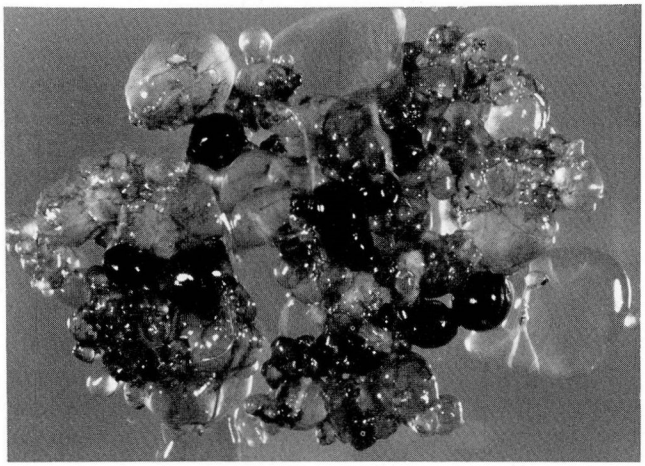

Fig. 1. Gross photograph of recurrent cystic mesothelioma, showing numerous cysts ranging in size from 0.5 to 0.6 cm. Cysts are both solitary and in clusters.

tures, many in grape-like clusters and containing clear fluid, were seen involving the uterus, both tubes and ovaries, peritoneum, small bowel, and omentum. Because of the clinical impression of ovarian carcinoma with peritoneal and mesenteric seeding, a bilateral salpingo-oophorectomy and omentectomy were performed. The uterus was not removed because of "technical inaccessibility" due to the right tubo-ovarian abscess.

The patient did well postoperatively and was asymptomatic until December 1980 when she complained of abdominal pain and an enlarging abdomen. Diagnostic laparoscopy showed the presence of ascites and multiple fluid-filled cysts studding the entire peritoneum, large and small bowel, and liver.

In April 1981, she underwent laparotomy at the Cleveland Clinic for removal of the lesions. At operation, multiple loculated cystic structures containing serous fluid were identified throughout the pelvis and serosal surfaces of the gastrointestinal tract, extending from the stomach to the sigmoid colon. A total of 2,950 g of cysts were excised, although a complete excision was not possible and multiple small cysts remained after operation. Seven months postoperatively, the patient complained of abdominal discomfort, dyspareunia, and increasing abdominal girth. Ultrasound demonstrated a large cystic and solid mass posterior to the bladder.

She continued to be followed until May 1982 when a fourth laparotomy was done for symptomatic relief. Intraoperative findings included cystic lesions similar to those previously described involving the entire pelvic peritoneum. A subtotal excision was done. The uterus was not removed because of concern that the cysts might recur in the vaginal vault. Postoperatively, the patient was begun on a course of medroxyprogesterone acetate in an empiric attempt to prevent further recurrence.

In August 1983, she again complained of abdominal discomfort, increasing abdominal girth, and irregular bleeding. The medroxyprogesterone was discontinued, and she was followed until August 1984 when significant abdominal pain and dyspareunia prompted another laparotomy. Multiple cystic structures of variable size and containing clear, watery fluid were present. A subtotal excision and lysis of adhesions were done, with an aggregate of cysts (18.0 x 14.0 x 1.8 cm) excised. The postoperative course was uncomplicated, and the patient continues to survive with the disease.

She was last seen in May 1985—10 years after her initial complaints of abdominal pain and eight years after the cystic lesions were discovered at operation.

Results

Gross pathologic features

All biopsy and resection specimens from operations performed at the Cleveland Clinic were similar in gross appearance, varying only in the amount of the cystic masses removed. The lesions consisted of multiple cysts from 0.5 to 6.0 cm in diameter (*Fig. 1*). Many cysts were present in grape-like clusters; solitary cysts were also identified. All the lesions appeared to be uniloculated with smooth, pliable walls. The cysts contained watery fluid, which varied in color from clear to amber to purplish-red. No excrescences or solid areas were identified.

Light microscopic features

Routinely processed paraffin sections stained with hematoxylin and eosin showed numerous cysts of variable size lined by uniform low cuboidal or flattened cells, which had cytologic features of benign mesothelial cells (*Figs. 2* and *3*). No mitotic figures were seen. The stroma separating the cysts consisted of loose connective tissue containing capillaries. Several clusters of mature lymphocytes were present, often in a perivascular arrangement.

Immunohistochemical stains with monoclonal antibodies to cytokeratins AE1-3 were strongly positive in the cytoplasm of the cells lining the cysts (*Fig. 4*). Immunohistochemical stains for factor VIII-related antigen were negative in the lining cells and positive in endothelial cell cytoplasm of stromal capillaries. Neither the lining cells nor the endothelial cells were positive with immunohistochemical stains for carcinoembryonic antigen. These immunohistologic features confirm the mesothelial characteristics of the cysts.

The outside hospital pathology report from the initial ovarian cystectomy and appendectomy from 1975 indicated a ruptured endometriotic ovarian cyst and a normal appendix. The report from the bilateral salpingo-oophorectomy and omentectomy in 1977 described bilateral acute

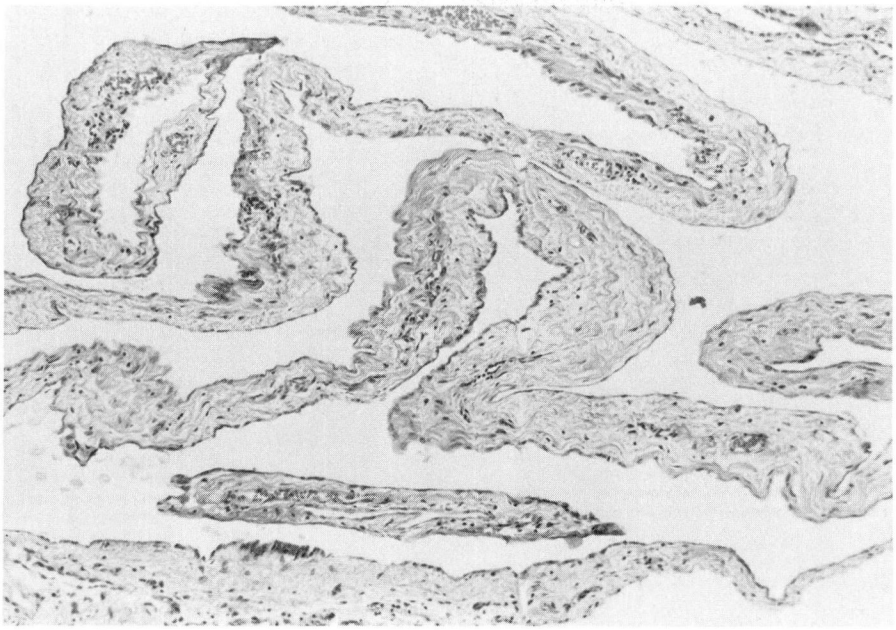

Fig. 2. Cystic mesothelioma. Cysts have smooth walls and are separated by thin septa composed of connective tissue (× 100).

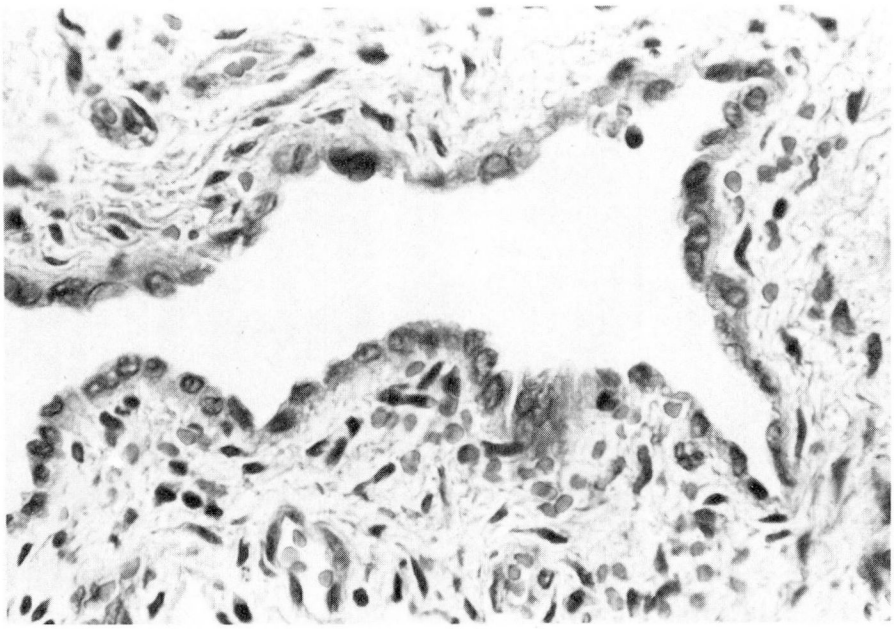

Fig. 3. Cyst wall. The flat to low cuboidal lining cells resemble mesothelial cells. The connective tissue stroma contains collagen, fibroblasts, and small capillaries (× 340).

and chronic salpingo-oophoritis, severe acute serositis, and multiple cysts lined by benign flattened and cuboidal cells consistent with mesothelial cysts.

Electron microscopic findings

Ultrastructural studies were performed on formalin-fixed tissue embedded in plastic and rou-

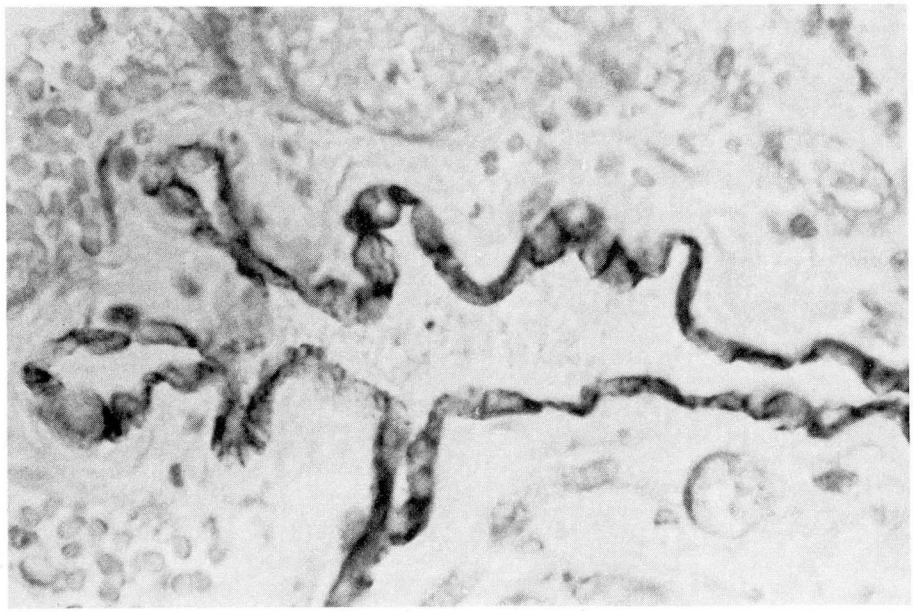

Fig. 4. The mesothelial lining cells exhibit strongly positive (dark black) immunohistochemical staining with monoclonal antibodies to cytokeratins AE1-3. The adjacent endothelial cells and fibroblasts are negative (× 550).

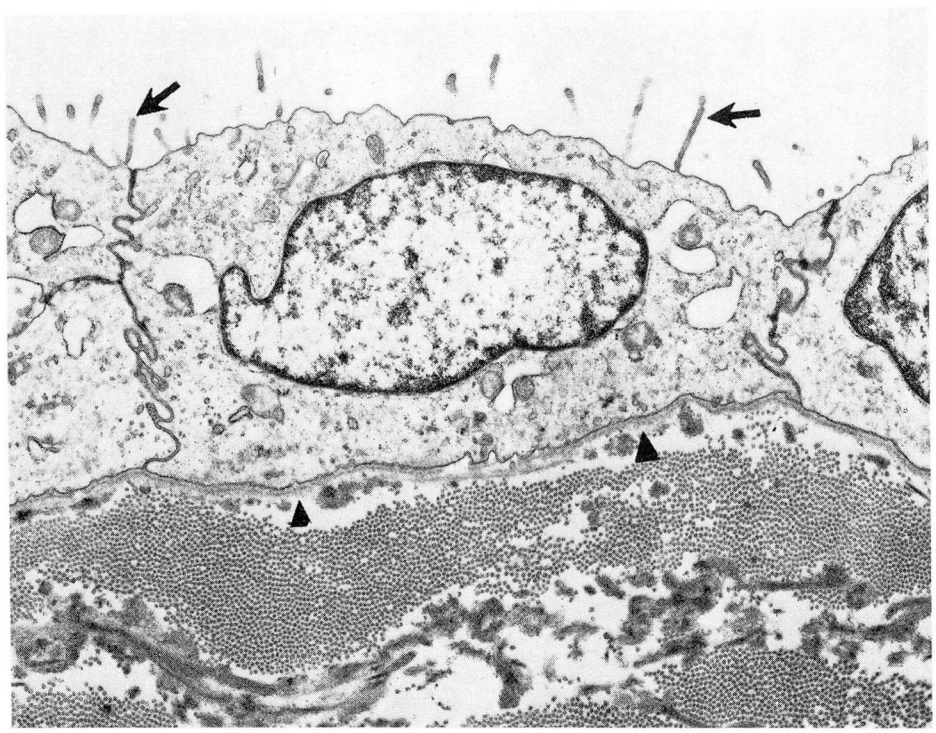

Fig. 5. Electron micrograph of cyst wall. Mesothelial lining cells have numerous microvilli projecting from their luminal surfaces (arrows). The lining cells have intercellular junctions and rest on a well-developed basal lamina (arrowheads) (× 4,500).

tinely processed for transmission electron microscopy. Cystic spaces were lined by both cuboidal and flattened cells having numerous microvilli along their luminal surface (*Fig. 5*). Cells were supported on a continuous basal lamina and joined by well-formed desmosomal junctions. The cytoplasm contained numerous polyribosomes and short, dilated segments of endoplasmic reticulum. Mitochondria were small, oval, and few in number. Numerous cytoplasmic microfilaments converged at the intercellular junctions. Weibel-Pallade bodies were absent in the cells lining the cysts. Nuclei were flattened to oval with a dispersed chromatin pattern and contained prominent nucleoli. These electron-optic features also supported the interpretation of the mesothelial nature of the cysts. Bundles of mature collagen with interposed endothelial-lined vascular spaces surrounded the cysts in the interstitium.

Discussion

Our case brings the total number of well-documented cases of benign cystic, or multicystic, mesothelioma reported in the English literature to 21. This rare tumor occurs most commonly in women of reproductive age. Of the 21 patients, 19 were women. Median age was 36 years (range, 23 to 67 years). No clinical history of asbestos exposure was obtained in any of the cases, in contrast with the known association of asbestos exposure and the development of malignant mesothelioma. Parity and previous peritoneal trauma did not appear to be closely related to tumor development. Eleven of the women were parous, 3 were nulliparous, and the parity was not known in five cases. Only 5 (24%) patients had a documented history of previous abdominal surgery.[3,7,10] The most common presenting complaint was abdominal pain, occurring in 9 patients. In 7 patients, the tumor was an incidental finding.[2,8–10] Three of the patients presented with a pelvic or abdominal mass, and the chief complaint was not stated in two cases.[7]

Follow-up information was available in 19 of the 21 patients. Nine (47.3%) experienced a total of 16 recurrences.[2–11] The average time to first recurrence was 32.2 months (range, four months to seven years). The recurrences were most commonly associated with abdominal pain or an abdominal mass. In 2 patients, a recurrent tumor was unexpectedly found in a hernia sac.[2,6] All of the other recurrent lesions involved the visceral and parietal peritoneal surfaces. Distant metastasis did not develop in any of these patients. All patients were alive at last known follow-up, which ranged from four months to 22 years after the initial diagnosis was made.

No factors were helpful in predicting which tumors were more likely to recur. Size of the tumor at initial presentation did not differ significantly in the group of patients with recurrence. Tumor bulk ranged from 4 to 20 cm in the tumors that subsequently recurred, and from 4 to 17 cm in those that did not recur. No significant difference was found in tumor size in patients who experienced more than one recurrence. Tumor bulk also had no apparent effect on the time to first or repeated recurrence.

Adequacy of initial tumor resection was not helpful in predicting tumor recurrence and had no apparent effect on outcome. Two patients had incomplete initial resections and both experienced recurrences 2½ years and 11 months postoperatively, respectively.[2,3] The latter patient is alive without evidence of disease 29 months after initial therapy. The status of the other patient is unknown. The remaining 7 patients who had recurrent tumor had resections that initially had been thought to be complete.

Adjunctive therapy was given in only two cases: intraoperative cyclophosphamide in 1 patient[2] and progesterone therapy for recurrent tumor in the patient described here. In both patients, recurrence of tumor was documented after adjunctive therapy was given.

While the differential diagnosis of cystic mesothelioma may include several diverse lesions, the histologic recognition that the cysts are lined by benign mesothelial cells excludes such tumors as malignant mesothelioma, metastatic carcinoma, lymphangioma, hemangioma, and pancreatic microcystic adenoma. Microscopic examination of a single small cyst without knowledge of the size, number, and location of the lesions could cause difficulty in distinguishing cystic mesothelioma from a solitary mesothelial inclusion cyst or a cystic variant of an adenomatoid tumor[12] since they are also composed of benign mesothelial cells. The multiplicity and large sizes of the mesothelial cysts and their extensive involvement of peritoneal and serosal surfaces, however, are characteristic operative and gross pathologic features that identify cystic mesothelioma as a dis-

tinctive clinicopathologic entity when coupled with accurate histologic identification of the benign mesothelial lining of the cysts.

Summary

Cystic mesothelioma appears to be a relatively "benign" tumor with no documented potential for distant metastases. Morbidity associated with the lesion is due to local tumor recurrence. Patients usually are women of reproductive age with complaints of abdominal pain. Some tumors are discovered as incidental findings. No specific factors are helpful in predicting which tumors are most likely to recur. Recurrences are independent of tumor size at initial or recurrent presentation, adequacy of tumor resection, or use of adjunctive chemotherapy. No consistent etiologic factor has yet been identified in the pathogenesis of this rare tumor.

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