Malignant Peritoneal Mesothelioma in Women

A Study of 75 Cases With Emphasis on Their Morphologic Spectrum and Differential Diagnosis

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Abstract

Seventy-five malignant mesotheliomas of the peritoneum in women were reviewed to highlight their morphologic spectrum. The patients ranged from 17 to 92 (mean, 47.4) years of age. The clinical presentation was usually abdominal or pelvic pain, abdominal swelling (sometimes due to ascites), or a pelvic mass. On microscopic examination, the majority of the tumors had only an epithelial morphology, but 4 were biphasic and 1 was sarcomatoid. The most common epithelial patterns were tubular and papillary (which often coexisted), but 5 tumors were purely diffuse; 2 had cells with abundant glassy eosinophilic cytoplasm (so-called deciduoid mesothelioma). The cells in the tubular and papillary patterns were generally cuboidal with scant to moderate amounts of eosinophilic cytoplasm. Nuclear atypia was usually only mild, although a minority of cases had moderate or even, occasionally, severe atypia. Many tumors had foci that, viewed in isolation, resembled so-called well-differentiated papillary mesothelioma, and accordingly that diagnosis should be made cautiously. Unusual features were lymphoid follicles (13 cases), striking myxoid stroma (5 cases), prominent foamy histiocytes (5 cases), and a striking vascular proliferation (1 case). The varied morphology of peritoneal malignant mesotheliomas may raise a broad differential diagnosis, but in most cases the resemblance to other tumors is limited. Histochemistry, immunohistochemistry, and electron microscopy may provide important aid, particularly when tissue is limited, but should be needed only occasionally.

The histologic diagnosis of mesothelioma often is considered problematic when based only on routine light microscopic findings, and much has been written on the undoubted value in some cases of immunohistochemical analysis in the differentiation of mesothelioma from other tumors, especially extraovarian serous carcinomas in females.[1-6] In our experience, however, features seen on H&E-stained sections usually allow differentiation of mesotheliomas from serous and other tumors. To highlight the morphologic features of peritoneal mesothelioma in females and emphasize the features that should enable it to be recognized and distinguished from other tumors, we reviewed the histologic features of 75 cases. The immunohistochemical features of the tumors were not analyzed because these features specifically were not the focus of this study and have been well described in the literature. Patient outcome also was not the focus of this study, because that topic was addressed in a recent study that included 15 of the cases in this report,[7] and many of the cases in this series are recent with limited follow-up intervals.

Materials and Methods

Of the cases, 60 were from the consultation files of two of us (P.B.C. and R.H.Y.) and 10 were from the files of Robert E. Scully, MD. The remaining cases were from the surgical pathology files of the Massachusetts General Hospital, Boston (2 cases); University of British Columbia, Vancouver (1 case); and the United States–Canadian Mesothelioma Panel (2 cases). Fifteen cases were published in a study of diffuse malignant epithelial mesotheliomas of the peritoneum in women,[7] and 1 case was reported in a study of deciduoid

mesotheliomas.[8] Cases from a previous study of 9 cases of malignant mesothelioma with prominent ovarian involvement were not included because the histopathologic features of these tumors were described in detail in that report.[9] Tumors fulfilling our strict criteria for the diagnosis of well-differentiated papillary mesothelioma (see the "Discussion" section) were excluded. The number of H&E-stained sections available for review ranged from 1 to 31 (mean, 14). Mitotic counts were performed on 5 sets of 10 high-power fields (HPF), and the mitotic count in the highest set of 10 fields was recorded.

Results

Clinical and Operative Findings

The patients were 17 to 92 years old (mean, 47.4 years). The clinical manifestations were known in 65 cases. Of these patients, 49 had abdominal or pelvic pain, abdominal swelling that in some cases was due to ascites, a pelvic mass, or combinations thereof. In 3 of these cases, a diagnosis of florid reactive or atypical mesothelial hyperplasia was made at initial operation, but laparotomy 2 months later (1 case), 3 years later (1 case), and at an unspecified interval for persistent symptoms (1 case) revealed malignant mesothelioma. In a fourth patient who initially had an acute bowel obstruction thought to be due to adhesions and was treated with a colostomy, a diagnosis of malignant mesothelioma was made on biopsy specimens obtained at the time of colostomy closure. In an additional case, a diagnosis of well-differentiated papillary mesothelioma was made on a tumor that at a subsequent operation 9 months later was shown to be malignant based on its infiltrative features.

The tumor was an incidental intraoperative finding in 13 patients who underwent an operation for other reasons. One patient with a history of ovarian endometrioid carcinoma treated by surgery and chemotherapy had mesothelioma diagnosed at the time of "second-look surgery," and in 1 patient initially given a diagnosis of stage III ovarian carcinoma that was treated with chemotherapy, subsequent reexploration and pathology review led to a change in diagnosis to malignant mesothelioma. In 1 case, the tumor was an autopsy finding. A history of asbestos exposure was given in 1 case, and 2 patients had received radiotherapy.

At the time of laparotomy, widespread disease was identified in 59 cases. In many of these cases, the peritoneal surfaces were described as studded with tumor. In other cases, their appearance was less striking and characterized by terms such as granules, papillae, adhesions, or combinations thereof. The remaining cases lacked the diffuse distribution of disease seen in the cases just noted. In 3 of these cases, disease was limited to a segment of bowel: one of them was described as diffusely fibrotic with no evidence of a dominant mass, another as being fibrotic with numerous adhesions on the serosal surface and within the mesentery and adjacent omentum, and another as "bowel-to-bowel" adhesions forming a tumor-like mass. Disease limited to the omentum was found in 2 cases, and in an additional 2 cases, disease involving both ovaries and portions of the omentum was found. In another case, there was a 10-cm mass adjacent to the left ovary with focal disease involving 2 additional sites. In 3 cases, a single lesion was identified at the time of operation: a soft, red-tan, 4.0-cm right paratubal mass (1 case); a soft, tan-gray, 0.9-cm broad ligament mass (1 case); and a solid, tan, 2.2-cm nodule in the pelvic side wall (1 case). In the case found at autopsy, the abdominal and pelvic cavities were obliterated by tumor that encased the viscera. In 4 cases, the extent of the disease was unknown.

Thirty-six patients were treated with a total abdominal hysterectomy and bilateral salpingo-oophorectomy, often with omentectomy and peritoneal biopsies that were accompanied by appendectomy (13 cases), bowel resection (3 cases), pelvic or para-aortic lymph node dissection (9 cases), liver biopsy (2 cases), or splenectomy (1 case). Three patients had a simple hysterectomy with peritoneal biopsies performed in 2 of them, and 1 patient had a total abdominal hysterectomy and unilateral salpingo-oophorectomy with biopsies. In 7 patients, bilateral salpingo-oophorectomy and multiple peritoneal biopsies were accompanied by an appendectomy (1 case) and a resection of bowel (1 case). In 1 case, a single mass was excised; in 1, a single nodule was biopsied; and in 1, only a segment of bowel was removed. In 15 cases, only peritoneal biopsies were performed. In 8 cases, the extent of the surgery was unknown, and in 1 case, as noted, the examination was postmortem.

Pathologic Findings

Gross Findings

Gross examination revealed that the tumor usually took the form of nodules or, less commonly, plaques, or papillary excrescences or, rarely, polyps that in 1 case were described as cauliflower-like. The neoplastic tissue usually was solid or occasionally solid and cystic and variously described as soft, friable, firm, or rubbery and white, red, yellow-tan, pink, or gray. In 1 unusual case, the tumor nodules were described as cartilaginous. In some cases, removed organs (including bowel and ovaries) were encased by tumor, and in 1 case, tumor invaded and compressed the bowel wall, constricting the bowel lumen. In the patient in whom the diagnosis was made at autopsy, the entire abdominal cavity was grossly obliterated by tumor and the viscera had to be removed en bloc. In 5 cases in which tumor microscopically involved the omentum, it was described grossly as having no distinct

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masses. In 1 case in which a large mass involved the colonic mesentery, lymph nodes were involved grossly by tumor.

Microscopic Findings

Seventy tumors had purely or predominantly epithelial morphologic features **Image 1**, **Image 2**, **Image 3**, **Image 4**, **Image 5**, **Image 6**, **Image 7**, **Image 8**, **Image 9**, **Image 10**, and **Image 11**, 4 tumors were biphasic (epithelial and sarcomatoid) **Image 12**, and 1 tumor was purely sarcomatoid **Image 13**. In 5 cases in the epithelial group, there was a transition from obvious epithelial patterns, which predominated, to areas with spindled morphologic features. When this transition was abrupt, it resulted in a striking picture because of the marked change in morphologic features, a low-grade

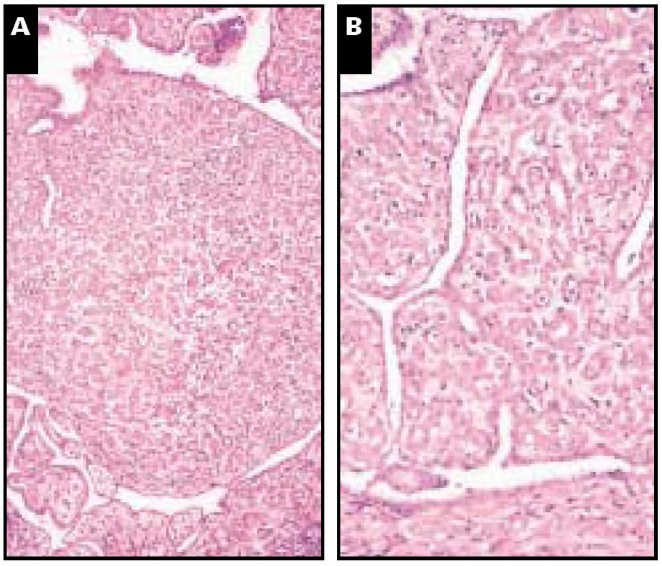

Image 1 Tubulopapillary pattern. **A**, A polypoid nodule composed of small tubules occupies most of the image, but a few papillae also are present (H&E). **B**, Typical small tubular pattern (H&E).

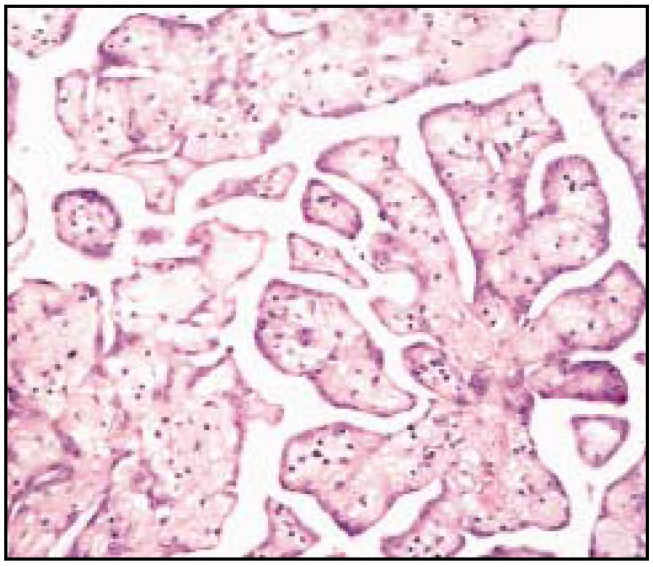

Image 2 Papillary pattern. The papillae are lined by a single layer of bland cuboidal to flattened cells with scant cytoplasm. Viewed in isolation, the picture is consistent with so-called well-differentiated papillary mesothelioma (H&E). See text for discussion.

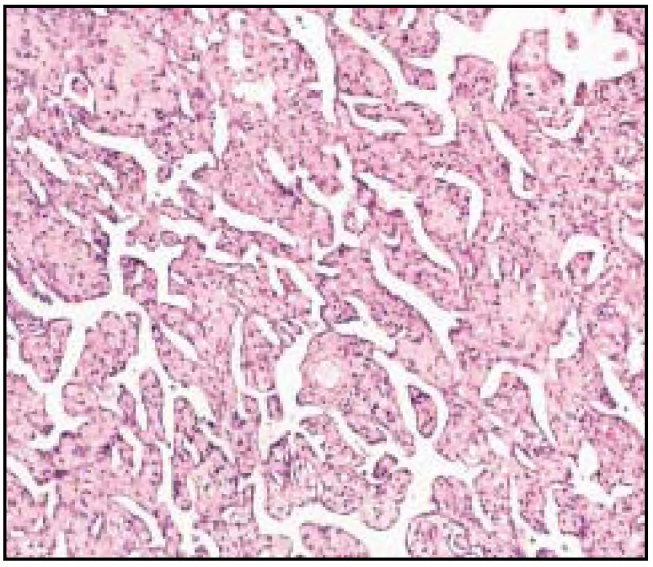

Image 3 Branching slit-like tubules. The pattern might suggest a serous neoplasm, but note the lack of the cellular intraluminal papillae that are frequent in such neoplasms. The cytologic features also were blander than those of most serous carcinomas (H&E).

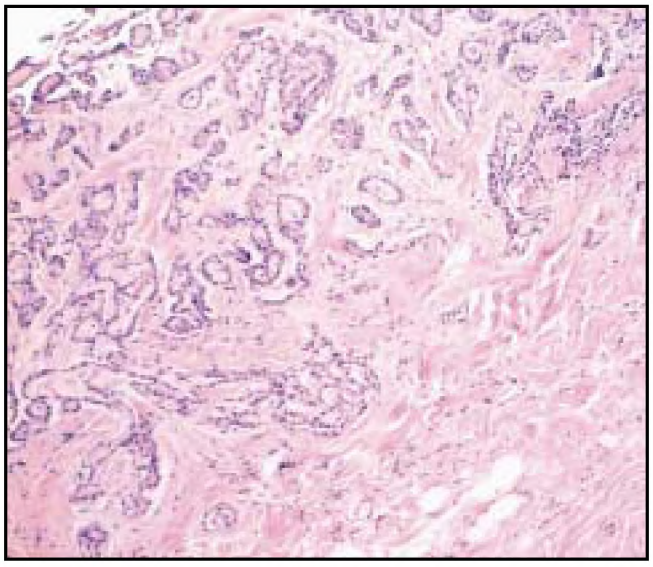

Image 4 Small clusters with focal tubular differentiation infiltrating in a fibrous stroma (H&E).

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papillary pattern merging with a sarcomatoid pattern **Image 14**. The architectural and cytologic spectra varied from case to case and within individual cases, but the greatest variation was seen in tumors that were purely epithelial.

Three major epithelial patterns were identified: tubular, papillary, and solid. The most common was tubular, which was present at least focally in 56 cases, most often in combination with papillary architecture (Image 1), and was the predominant pattern in 24 cases (Image 4). The tubules generally were small and uniform and relatively evenly spaced (Image 4) but sometimes were dilated and in 5 cases were compressed and irregular in size and shape (Images 3 and 6). In occasional cases, slit-like spaces were striking and, to an extent, focally simulated the slit-like spaces of serous carcinomas. In 3 cases, closely packed tubules, sometimes with a cribriform pattern, formed well-circumscribed rounded

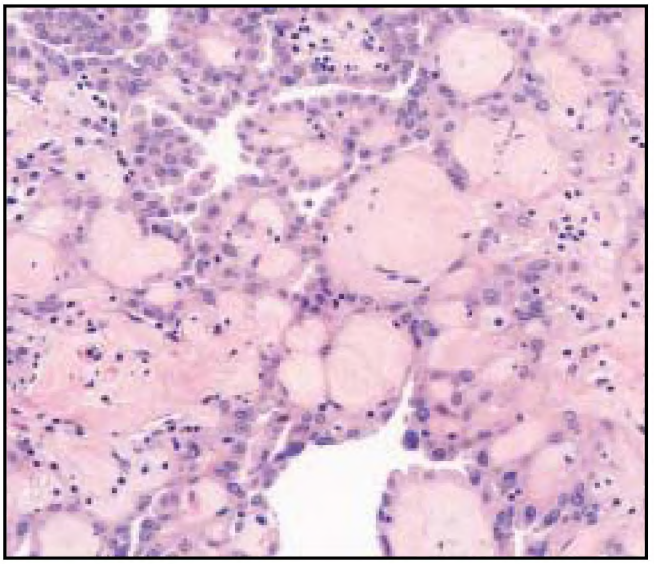

Image 5 Papillae with hyalinized cores. Most of the papillae have become fused together (H&E).

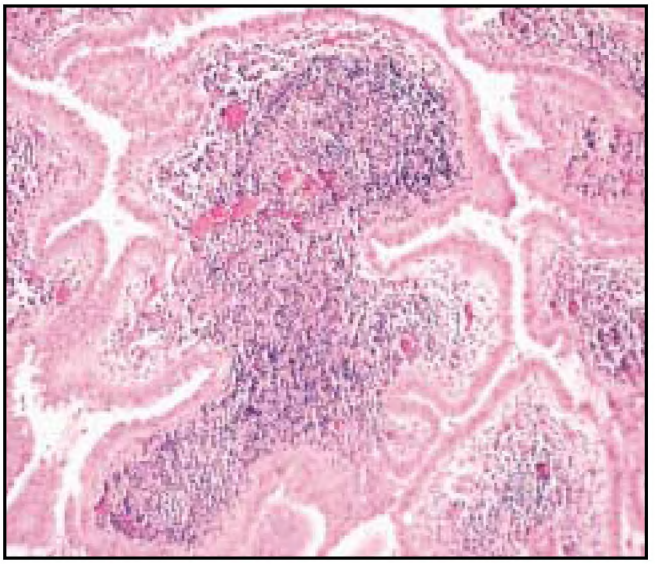

Image 6 Anastomosing tubules lined by cells that had eosinophilic cytoplasm and associated prominent lymphocytic infiltrate imparting a low-power appearance reminiscent of that seen in Warthin tumor (H&E).

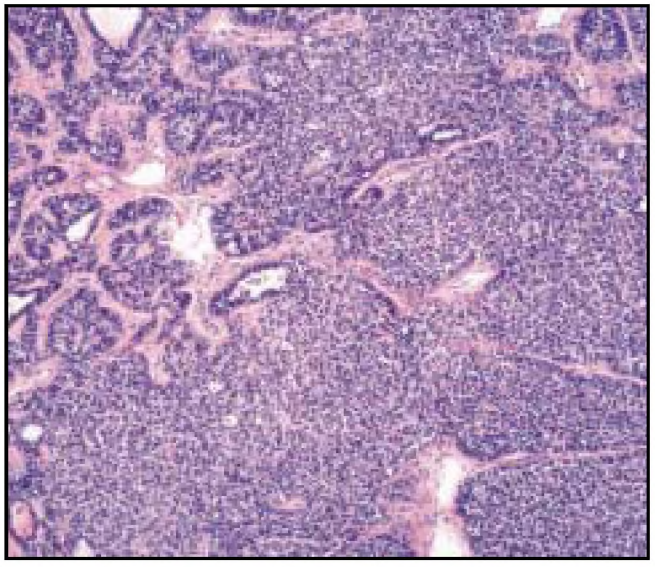

Image 7 Insular and tubular patterns resembling those of ovarian sex cord tumors (H&E).

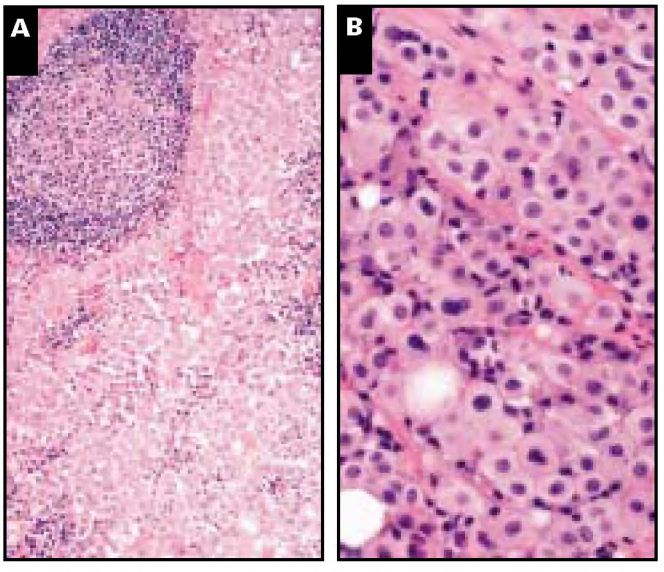

Image 8 **A**, Diffuse growth of mesothelioma cells with obliteration of most of the underlying omental adipose tissue. Lymphocytic aggregates also are present (H&E). **B**, High-power appearance of diffuse growth showing typical eosinophilic cytoplasm and relatively uniform nuclei (H&E).

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aggregates or filled broad polypoid structures (Image 1). In 2 other cases, the tubules were focally cystically dilated, creating a microcystic appearance. The tubules had lumens that were empty or contained pale eosinophilic to slightly basophilic material. Occasional other epithelial patterns were small nests, irregular clusters, or thin cords **Image 15B**.

A papillary pattern (Images 2, 5, and 11) was present in 45 cases and was the predominant pattern in 23 cases. The papillae generally were broad, often with a fibrous core, and lacked hierarchical branching. Budding of cells from the surfaces of the papillae generally was absent or inconspicuous but was conspicuous in 3 tumors.

A solid pattern (Images 8 and 9) was identified in 45 cases; sometimes it was only focal, but in 23 cases, it formed a conspicuous component of the tumor, most commonly associated with a tubular pattern. In 2 tumors, solid sheets of cells were interrupted by irregular follicle-like cystic spaces that contained lightly eosinophilic to basophilic extracellular material and exfoliated tumor cells. In 1 case, solid nests, trabeculae, cords, and sertoliform tubules bore a striking resemblance

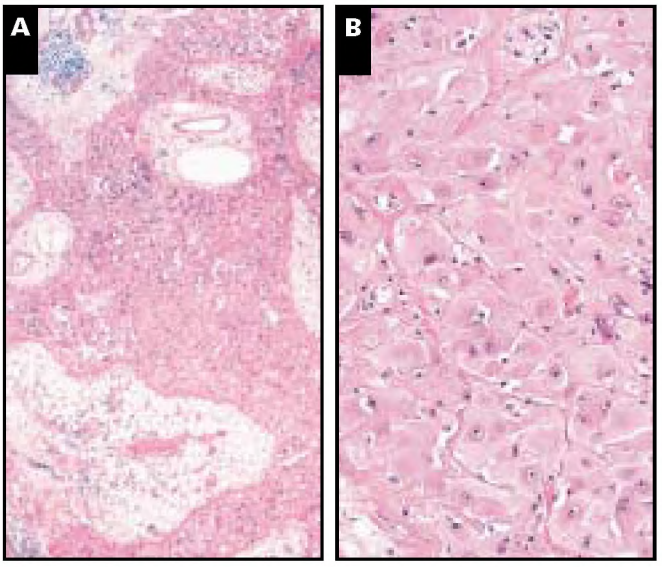

Image 9 Deciduoid variant. **A**, One tumor had a prominent trabecular pattern (H&E). **B**, The tumor cells have abundant glassy cytoplasm that was eosinophilic (H&E).

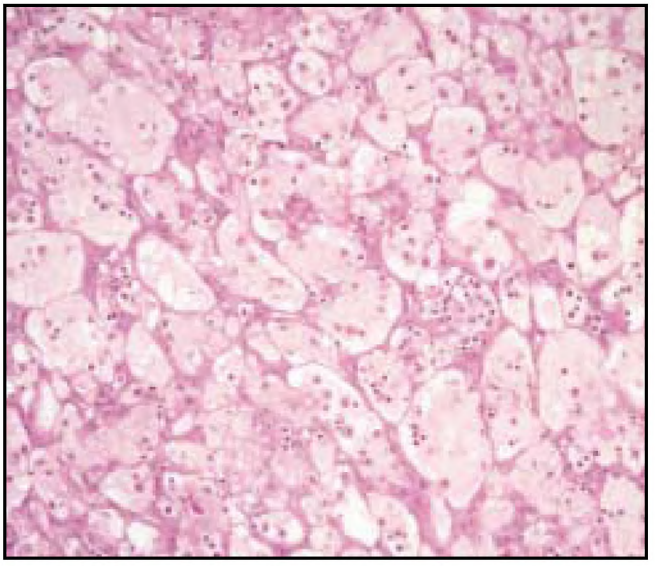

Image 10 Tumor cells with conspicuous foamy cytoplasm (H&E).

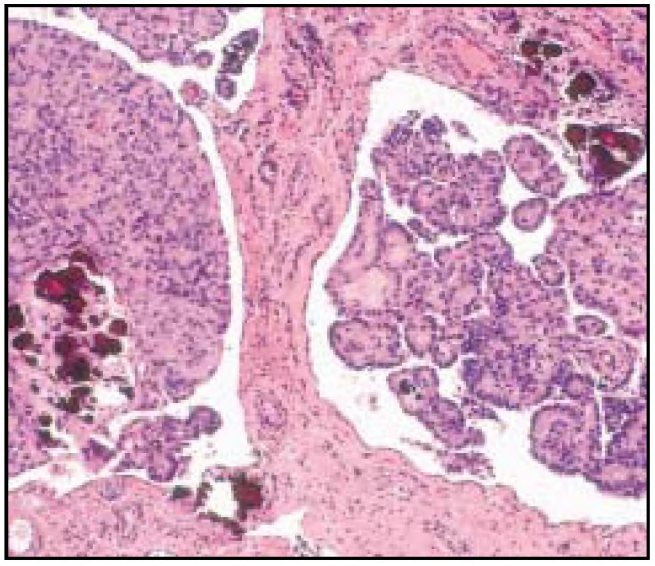

Image 11 Psammoma bodies in neoplasm with a papillary pattern (H&E).

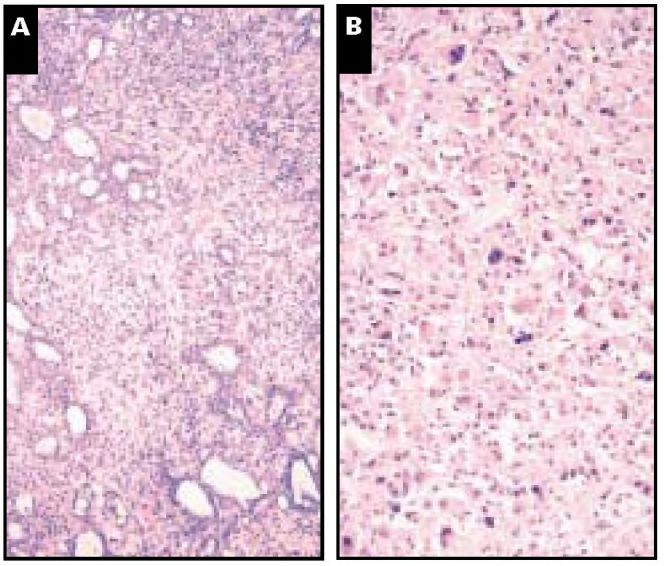

Image 12 Biphasic pattern. **A**, Tubules lined by relatively bland cuboidal cells on a background of spindle-shaped cells (H&E). **B**, Anaplastic morphologic features in tumor that in other areas had a biphasic pattern (H&E).

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to patterns encountered in ovarian granulosa and Sertoli cell tumors (Image 7). In 5 tumors, only a solid growth pattern was identified. In 1 case with so-called deciduoid morphologic features (see next paragraph) the cells focally were arranged in broad intersecting bands (Image 9A).

The neoplastic cells in the epithelial patterns generally were polygonal, cuboidal, or low columnar, with pale to eosinophilic cytoplasm that ranged from scant to moderate, to infrequently abundant, sometimes being glassy or squamoid. The polygonal cells often had sharp "squared-off" cytoplasmic borders that imparted a cobblestone appearance (Image 8B). Cells lining cysts usually were flattened and those covering papillae, low cuboidal (Image 2). In 3 cases, striking hobnailed cells were seen, and in 2 cases, they covered large areas of the omental surface. Cells with clear cytoplasm were present focally in many cases, usually in small numbers, although in 1 tumor, they were conspicuous. In 1 case, the mesothelial cells had striking abundant foamy cytoplasm (Image 10), and in 1 case in which the cells had abundant eosinophilic cytoplasm, "apical snouts" were seen. The cells in the 2 deciduoid tumors were very large, round, oval, or polygonal with abundant eosinophilic, glassy cytoplasm (Image 9B), with occasional multinucleated cells in 1 case and, in the other case, pleomorphic, often multinucleated cells that vaguely resembled intermediate trophoblasts. Variably sized cytoplasmic vacuoles were found in scattered tumor cells in many tumors, and in 3, they were prominent enough to result in a pattern resembling that of an adenomatoid tumor. In 5 cases, signet-ring–like cells were focally conspicuous, and in 2 cases, some cells had a rhabdoid appearance with eccentric nuclei and prominent, dense, eosinophilic cytoplasm.

The degree of nuclear atypia varied greatly among the epithelial-dominant tumors from mild (31 cases) (Image 8B), to mild to moderate (29 cases), and moderate to severe (10 cases). Nucleoli varied from tumor to tumor and within tumors from inconspicuous to prominent and eosinophilic but generally were more conspicuous in tumors with greater degrees of atypia. Nuclear grooves were striking in 1 tumor, which, combined with its growth patterns, resulted in a close resemblance to an ovarian sex cord tumor. Nuclear pseudoinclusions were seen in several tumors. Mitotic figures were rare to absent in 37 tumors (<1 mitotic figure per 10 HPF) and ranged from 1 to 5 mitotic figures per 10 HPF in 24 tumors

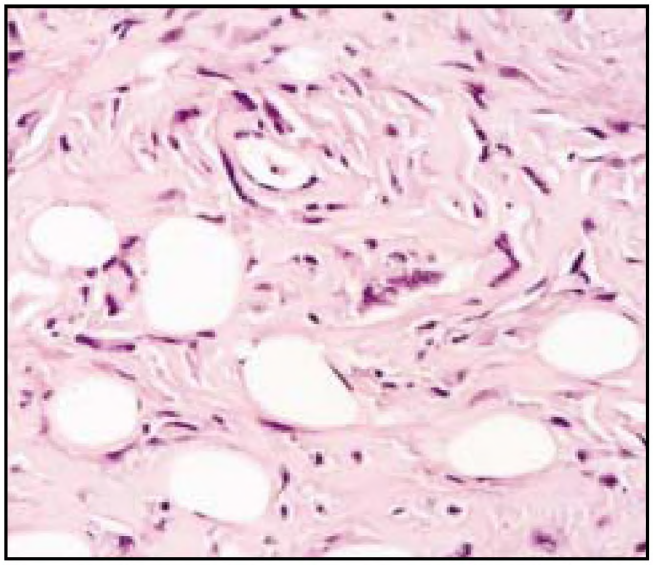

Image 13 Desmoplastic malignant mesothelioma infiltrating omentum (H&E).

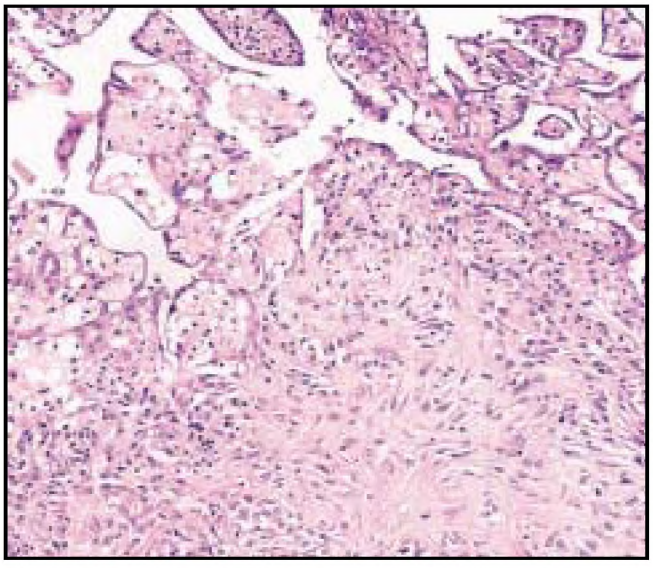

Image 14 Papillary pattern (top) with underlying sarcomatoid pattern (H&E).

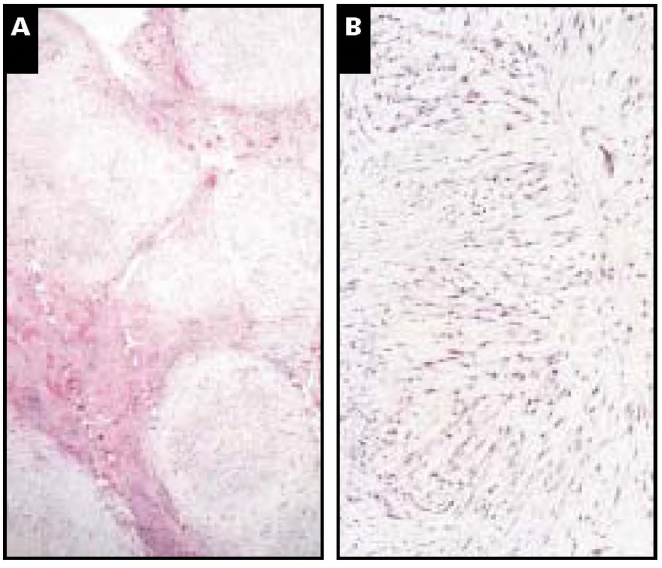

Image 15 **A**, Nodular growth in case with prominent myxoid stroma (H&E). **B**, Scattered mesothelial cells growing mostly in a myxoid background (H&E).

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and from 6 to 15 mitotic figures per 10 HPF in 6 tumors. In 3 cases, mitotic counts were difficult to assess accurately owing to paucicellularity, including one case with abundant myxoid stroma and another with numerous apoptotic bodies.

The stroma within the epithelial patterns varied from edematous to fibrous and, in some of the latter, was sclerotic or hyalinized. The stroma also was focally myxoid in 19 tumors and was conspicuously so in 5 of them, sometimes forming rounded nodules **Image 15A** (left). In one such case, the stroma of the entire tumor was composed of large pools of paucicellular, lightly basophilic, myxoid material.

The cores of the papillae often were hyalinized, and in 5 cases, this was striking (Image 5). In 2 cases, hyalinized fibrous tissue formed spherical structures surrounded by epithelium, resulting in a vague resemblance to an adenoid cystic carcinoma. A mixed inflammatory infiltrate consisting predominantly of lymphocytes and plasma cells, but also neutrophils and occasional eosinophils, was present in almost all tumors. The inflammatory infiltrate generally was present in the stroma but occasionally was admixed with the tumor cells. Small collections of neutrophils formed microabscesses in several of the tumors, and in 5 cases, a striking predominance of neutrophils was seen, usually in association with areas of acellular necrotic debris. In 13 cases, a heavy infiltrate of lymphocytes and plasma cells, including lymphoid aggregates (Image 6 and Image 8A) and follicles, was present, typically within the omental fat or omental fibrous tissue surrounding areas of invading tumor. Foamy histiocytes, rarely containing hemosiderin pigment (2 cases), were present in 14 cases and were prominent in 5 of them. The foam cells most often were found in the cores of the papillae, sometimes expanding them, but also occasionally were found as single cells, small clusters, or solid sheets in nonpapillary areas (Image 10). Necrosis was present at least focally (sometimes as single cell necrosis) in 27 tumors and was prominent in 8 of them.

Psammoma bodies were present in 16 cases and were prominent in 6 of them (Image 11). They typically were seen in the papillary areas, but in 2 cases occurred in the solid areas. In one unusual tumor, a peculiar and very prominent reactive vascular proliferation was present diffusely throughout the tumor. In 3 cases, striking perivascular fibrosis was seen.

An infiltrative pattern of invasion was seen in 45 cases, usually involving omentum, ovaries, bowel wall, or uterine serosa (in order of decreasing frequency). In the autopsy case, tumor destructively infiltrated the spleen and liver. In the omentum, the tumors typically dissected through the omental fat. On the ovarian surface, the invasion was often at the base of a papillary lesion as haphazardly arranged groups of tubules. In 1 case with striking myxoid stroma (Image 15A), rounded nodules involved the ovary and, viewed in isolation, could have been misconstrued as an unusual ovarian sex cord–stromal tumor. In 10 cases, the invasion had a pushing front involving the ovary (3 cases) or omentum (7 cases). In 1 case in which there was no obvious invasion in the slides available for review, lymph node metastases were present. Destructive invasion was not identified in 7 cases in which the tumor grew over the involved tissues in a plaque-like manner, including 1 case with a single focus of tumor confined to a structure resembling a mesothelial cyst. Invasion could not be assessed in 7 cases.

Lymph node metastases were present in 6 cases; the intranodal tumor had a predominantly solid pattern, but focal tubulopapillary areas were seen in 1 case, and in 1 case, psammoma bodies were identified. Lymphovascular space invasion, however, was not identified in any of the tumors.

The 4 biphasic tumors (Image 12) contained an epithelial component that varied from less than 10% (2 cases) to 30% (1 case) to 50% (1 case). In the regions in which both epithelial and sarcomatoid components were present, they were associated intimately with each other. In 3 of the tumors, the epithelial component was purely tubular, and in the fourth, it was solid and papillary. The degree of cytologic atypia in the epithelial component varied greatly among the 4 cases; in 1 case in which the epithelial component was minor, the epithelial cells were very monotonous with minimal atypia and no mitotic activity. In the other 3 cases, the epithelial component showed moderate to severe cytologic atypia, including bizarre mononucleated and multinucleated tumor giant cells that in 1 case simulated anaplastic carcinoma. A brisk mitotic rate was seen in the epithelial component of 1 tumor, and in 3 cases, the mitotic activity was difficult to assess owing to the limited amount of epithelium.

The cells in the sarcomatoid component of the biphasic tumors often were arranged in sheets, but fascicular and storiform patterns also were focally prominent, and 1 was prominently myxoid. The cellularity in these areas varied from highly cellular to paucicellular. The cells were moderately to severely atypical and epithelioid to spindled with multinucleated tumor giant cells, large vesicular multilobated nuclei, occasional nuclear pseudoinclusions, and nucleoli that varied from inconspicuous to prominent. In 3 cases, the spindle cells focally merged with the epithelial component, and in 1 case, the epithelial and sarcomatous components were distinct, with a tendency of the spindle cells to focally condense around the epithelial component. The mitotic rate in the spindle cells usually was brisk. Extensive tumor necrosis was seen in the sarcomatoid component of all tumors. All 4 biphasic tumors were highly infiltrative, with involvement of omental fat (3 cases), ovaries (2 cases), and the spleen and liver (1 case).

The single sarcomatoid mesothelioma had diffuse storiform and fascicular patterns and extensively infiltrated omental fat (Image 13). Abundant collagen focally invested individual tumor cells, resulting in a desmoplastic appearance (Image 13). Necrosis, severe cytologic atypia, and brisk mitotic activity were found.

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Discussion

Peritoneal mesotheliomas are much less common than their pleural counterparts, and the literature on them predominantly concerns a consideration of tumors occurring in males, who often have a history of asbestos exposure.[10] The largest series of 82 cases, reported by Kannerstein and Churg[10] in 1977, included only 6 females. Two series, however, focused on these tumors in women,[7,11] both of which found no definite link with asbestos exposure. In addition, one of the studies[7] found that a substantial number (40%) of peritoneal malignant mesotheliomas in women had an indolent behavior compared with their usually aggressive behavior in males.[10] A few additional female cases are present in some other studies, such as one emphasizing presentation as lymph node metastasis[12] and one emphasizing presentation as an ovarian mass.[9] The present study is the largest series describing the histopathologic features of peritoneal malignant mesotheliomas in females.

The male/female ratio in patients with peritoneal malignant mesotheliomas is 2:1, but because of the rarity of pleural mesotheliomas in women,[13] the ratio of peritoneal to pleural mesotheliomas is higher in women (1:2) than in men (1:5).[14-22] As previously described in the literature[23-25] and as exemplified by 2 of our cases, there is an occasional association with previous radiation therapy. The rarity of peritoneal mesotheliomas in women contributes to the confusion with other tumors, such as serous tumors, which are much more common. In our experience, this situation frequently leads the pathologist to not consider the diagnosis of mesothelioma and, when it is considered, a lack of experience with its histopathologic features can result in misdiagnosis. In our series, only a minority of the cases were submitted with a diagnosis of mesothelioma made or strongly favored; most were submitted with no diagnosis or considered to be neoplasms of other types. The distinction of malignant mesothelioma from various nonmesothelial tumors, which can be done by evaluating routinely stained slides in almost all cases, is the focus of this discussion.

Although other neoplasms can involve the peritoneum in a manner that is grossly indistinguishable from that of malignant mesothelioma, the typical gross presentation of mesothelioma, as represented by most of the cases in this series, merits emphasis. Characteristically, there is limited invasion of the intra-abdominal organs, although occasionally the latter can be replaced by tumor. Indeed, in rare cases, striking ovarian involvement can result in the clinical or intraoperative appearance of a primary ovarian cancer with intraperitoneal spread.[9] In a minority of cases, mesothelioma has a much less impressive clinical, intraoperative, or gross appearance. Indeed, in some cases, the mesothelioma might be an unexpected microscopic finding in a patient undergoing an operation with a clinical impression of another type of abdominal disorder. For example, in a recent study, the intraoperative appearance of the tumor mimicked appendicitis, acute cholecystitis, or an incarcerated umbilical hernia.[26] In these cases, the typical multifocal involvement of the peritoneum was not evident at the initial surgical exploration and the diagnosis subsequently was made on microscopic examination of the resected specimen. Similarly, we have seen a recent case (not included in the present study) in which a patient underwent laparotomy for voluminous ascites. No obvious tumor masses were encountered, but microscopic examination of an omentectomy specimen and peritoneal biopsy specimen revealed malignant mesothelioma.

The results of the present study indicate that a tubular pattern, frequently accompanied by a papillary or solid pattern (or all 3 in combination), and lesional cells that resemble normal or hyperplastic mesothelial cells represent the most frequent morphologic features of peritoneal mesothelioma. In the majority of cases, these features impart a characteristic appearance that makes the diagnosis straightforward. The tubules typically are small and usually uniformly arranged and are lined by cuboidal cells that in most cases have scant cytoplasm but occasionally have more abundant eosinophilic cytoplasm. The cells covering the papillae are similar to those lining tubules and usually show less stratification and fewer cellular buds than those encountered in serous carcinomas, as discussed later.

Much less common than tumors that are tubular or tubulopapillary, with or without minor solid foci, are neoplasms with a uniform or almost uniform solid growth of cells that have more abundant eosinophilic cytoplasm than is usually seen in tumors with other patterns. In some of these cases, the appearance of the tumor can resemble ectopic decidua, leading to this pattern being descriptively referred to as "deciduoid mesothelioma."[8,27-30] We had 2 tumors of this type in our series; 1 was included in a previous study of this subtype.[8] Two of the well-known patterns of mesothelioma of the pleura are biphasic and sarcomatoid, but they are much less common in peritoneal mesothelioma[31,32]; only 4 of the former and 1 of the latter were present in our study. Occasional tumors with tubular or papillary patterns exhibit an abrupt transition to a sarcomatoid pattern, a finding that we distinguish from biphasic growth. In the latter, there is an intimate admixture of the epithelial and sarcomatoid patterns, whereas in the former, individual regions exhibit one or the other of the 2 patterns.

The stroma in mesotheliomas with a solid pattern usually is inconspicuous, whereas tumors with a tubular or papillary pattern tend to have a more appreciable fibrous to hyalinized stroma, although even in these tumors, rarely is it striking. In particular, the papillae of mesotheliomas are more likely to have hyalinized cores than the papillae of serous tumors. Noteworthy are the occasional cases in which the stroma is conspicuous and strikingly myxoid,[33] a finding that can result

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in peculiar arrangements of tumor cells (clusters and cords) within the myxoid matrix that might suggest esoteric diagnoses such as yolk sac tumor or, should the cells appear spindled, a mesenchymal neoplasm. Evidence of merging with more typical foci of mesothelioma, such as characteristic papillae, usually will resolve the problem.

The differential diagnosis of malignant mesothelioma of the peritoneum is broad[34-36] and obviously includes other peritoneal mesothelial lesions. A diagnosis of well-differentiated papillary mesothelioma was considered by the referring pathologist in 8 of our cases. These indolent tumors[37,38] are small (most <2 cm) and generally solitary and show no invasion of the underlying tissues. Microscopic examination reveals that they are characterized, according to our criteria, by a well-developed, orderly, papillary architecture in which the papillae are covered by a single layer of benign, mitotically inactive, mesothelial cells. In 5 cases in which this diagnosis was considered, multiple nodules or multiple sites of involvement were identified intraoperatively, a finding that should have suggested the possibility of a malignant process.[11] In 1 of the 3 cases with a solitary lesion, the surgeon noted numerous "adhesions" that were not biopsied but later raised concern about the potential malignant nature of the process. As Goldblum and Hart[11] correctly emphasized, it is crucial to be aware that individual foci within neoplasms that, based on their overall evaluation represent peritoneal malignant mesothelioma, might be indistinguishable from well-differentiated papillary mesothelioma (Image 2). Thus, it is imperative in this situation that most or all the lesions be removed or biopsied for microscopic examination. Evaluation of the morphologic features in the context of the overall gross and other histopathologic findings should, in practice, make the differential diagnosis of well-differentiated papillary mesothelioma and diffuse malignant mesothelioma an infrequent problem. We should point out that our criteria for well-differentiated papillary mesothelioma are more restrictive than those of Daya and McCaughey.[38] Indeed, the complexity of the morphologic features of some of their cases and the presence of multiple foci of disease would have led us to place them in the category of malignant mesothelioma, not otherwise specified. The latter neoplasm might be indolent in a substantial minority of cases.[7] Notably, Daya and McCaughey[38] did not categorize their cases as benign, an important feature of their study that occasionally is overlooked.

The rarity of malignant mesothelioma of the peritoneum has precluded the clear establishment of morphologic categories with differing outcomes. However, by using a common sense approach when signing out individual cases, one should comment not only on the amount of disease based on the tissue available but also on its histologic features. It is logical to conclude that at least some well-differentiated malignant tumors will have more indolent behavior than tumors with more ominous morphologic features, as suggested by Kerrigan et al,[7] although their findings did not reach statistical significance. On the other hand, as we hope our comments have already indicated, the use of "well-differentiated" terminology may be overly reassuring if applied to tumors with multifocal, particularly bulky, disease.

The most common mesothelial neoplasm in females is the adenomatoid tumor, but its distinction from malignant mesothelioma is rarely a problem because it typically is a grossly well-circumscribed, small tumor occurring in the myometrium, the fallopian tube, or, rarely, the ovary. Despite this, a malignant mesothelioma showing prominent vacuolization of the cells raised the possibility of an adenomatoid tumor to the referring pathologist in 2 of our cases. In these cases, however, the intraoperative, gross, and other histologic findings, including cytologic atypia, mitotic activity, and overt invasion, were all incompatible with a diagnosis of adenomatoid tumor. It should be noted, however, that although adenomatoid tumors are grossly well circumscribed, they might infiltrate adjacent tissues microscopically, a finding that should not lead to a misdiagnosis of malignant mesothelioma in the presence of the otherwise typical gross and microscopic findings of adenomatoid tumor, including their typical locations. Rarely, a bona fide peritoneal adenomatoid tumor seems to arise out of a papillary mesothelioma as in 1 case recently shared with us **Image 16**. We are aware of another such case (R.E. Scully, MD, oral communication, September 2003) in which the material is no longer available for review.

A rare subset of adenomatoid tumors, those with striking cystic change, conceivably could be a consideration in the differential diagnosis of a cystic malignant mesothelioma. However,

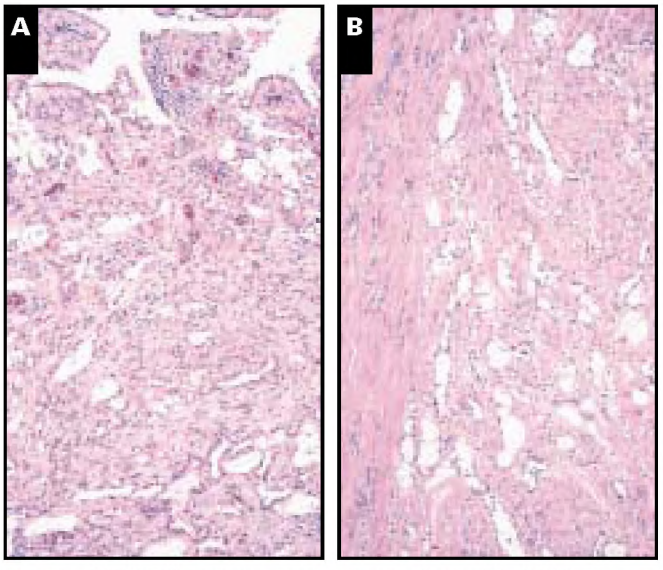

Image 16 Papillary pattern of mesothelioma (**A**, H&E) merging with adenomatoid tumor (**B**). **B**, Typical morphologic features of the adenomatoid tumor (H&E).

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gross cysts are rare in malignant mesotheliomas, and there were no cases in our series that could be considered "cystic" malignant mesotheliomas. In our experience, the most realistic differential diagnosis of the rare cystic adenomatoid tumors is with peritoneal inclusion cysts,[39] a lesion that, although classified by others as "cystic mesothelioma" or in similar terms,[40-42] is, in our opinion, a nonneoplastic lesion with an inflammatory or reactive basis that we categorize separately for reasons given in detail elsewhere.[43]

Distinguishing a florid reactive mesothelial proliferation from a malignant proliferation can be challenging, particularly if the amount of tissue present for examination is limited.[34,36,43] Indeed, in 4 of our cases, the submitting pathologist strongly favored a reactive process. Rare cases of reactive peritoneal disease have manifested with ascites and at laparotomy have shown marked thickening of peritoneal surfaces,[44,45] raising the consideration of malignant mesothelioma and enhancing the potential for pathologic misdiagnosis. Hyperplastic mesothelial cells, however, rarely form grossly visible nodules. Normal mesothelial cells show well-defined cytoplasmic borders, small centrally located nuclei with an even chromatin pattern, and inconspicuous nucleoli. Mesothelial cells showing mild reactive changes have nuclei that are slightly larger and have a slightly more vesicular chromatin pattern and still inconspicuous nucleoli. As the reactive features increase, the cells show a higher nuclear/cytoplasmic ratio, chromatin irregularity, prominent nucleoli, mitotic figures, and multinucleated cells. Although reactive mesothelial cells are more likely to be positive for desmin and less likely to be positive for epithelial membrane antigen and p53 than the cells of malignant mesothelioma,[1] exceptions to these observations occur,[46] limiting the value of immunohistochemical studies in this differential diagnosis.

Unequivocal destructive invasion is diagnostic of malignancy, but it must be evaluated cautiously. In the peritoneal cavity, invasion of omental fat or invasion of an organ must be distinguished from entrapment of mesothelial cells in reactive connective tissue or fibrin on their surfaces or between omental fat lobules. Atypical reactive mesothelial cells might grow in linear parallel arrays (which can be a helpful clue), small clusters, or form tubules.[39] Necrosis, although suggestive of malignancy, is not diagnostic because it can be seen in benign mesothelial proliferations. The presence or absence of cytologic atypia or mitotic activity also is not reliable because malignant mesothelial proliferations can be very monotonous, whereas exuberant reactive mesothelial proliferations, as noted, can show cytologic atypia and mitotic activity, although not abnormal mitoses. Marked nuclear atypia obviously favors malignant mesothelioma although, as noted, this feature is uncommon in these tumors. Similarly, desmoplasia in an organized pattern (such as storiform) strongly favors a diagnosis of malignant mesothelioma over that of a reactive fibrosis associated with mesothelial hyperplasia, but again, the rarity of this finding limits its usefulness.

The most frequently proffered diagnosis in the cases submitted to us was papillary serous carcinomas of ovarian or peritoneal origin. Confusion is enhanced by the overlap in the clinical manifestations of müllerian epithelial tumors and peritoneal mesothelioma that often include elevation of the CA-125 level.[47] Two thirds of the patients in our study had abdominal or pelvic pain, ascites, or a pelvic mass, alone or in combination. The last finding, particularly in a postmenopausal woman, might bias the clinician or pathologist toward a primary ovarian neoplasm, a much more common tumor.

The distinction of papillary serous carcinoma of ovarian origin from malignant mesothelioma, including those with striking ovarian involvement and rare primary ovarian mesotheliomas,[9,11] usually can be done on the basis of histologic features alone **Table 1**. Although both tumors show a papillary architecture and might have slit-like spaces and psammoma bodies, both of the latter features are uncommon in mesothelioma. In addition, the papillae in serous carcinomas generally show more hierarchical branching, cellular stratification, and detached cell clusters, whereas the papillae in typical mesotheliomas are broader, lack budding, and have hyalinized cores more often than do serous carcinomas. Papillary serous tumors in general show a much greater degree of nuclear atypia, often with areas of anaplastic or bizarre nuclei, much higher mitotic rates, and a higher frequency of abnormal mitotic figures. If one were to grade peritoneal malignant mesotheliomas based on their cytologic features, most of them would be grade 1 or grade 2 with only a minority being grade 3.[7] This is the converse of the spectrum of grades of peritoneal serous carcinoma. The differential diagnosis with serous carcinoma is more difficult, not surprisingly, in the occasional case of high-grade malignant

Table 1
Mesothelioma and Serous Carcinoma

	Mesothelioma	Serous Carcinoma
Cellular papillae	Rare to occasional	Typical
Papillae with prominent, often hyalinized stromal cores	Frequent	Rare
Slit-like spaces	Rare to occasional	Typical
Psammoma bodies	Rare to occasional	Typical
Conspicuous eosinophilic cytoplasm	Typical	Rare
Nuclear atypia	Usually mild to moderate	Usually severe
Mitoses	Occasional	Frequent
Cytokeratins 5 and 6, calretinin, thrombomodulin*	Positive	Negative
Ber-EP4, B72.3, Leu-M1 (CD15)*	Negative	Positive

* A panel of antibodies is recommended, including the 6 listed. A diagnosis based on the staining result of a single antibody is not reliable.

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mesothelioma, but even in these cases, typical foci of better differentiation often are present and helpful. Although rarely indicated, the potential role of immunohistochemical analysis and electron microscopy in this differential diagnosis is summarized in the subsequent text.

Another ovarian tumor that rarely might enter the differential diagnosis with malignant mesothelioma is clear cell carcinoma, which rarely is of peritoneal origin.[48] Clear cell carcinoma, like malignant mesothelioma, frequently has tubular and papillary patterns (including papillae with hyalinized cores), and, as exemplified by a few of our cases, malignant mesotheliomas can rarely contain clear cells or hobnail cells, two characteristic cell types of clear cell carcinoma. The cells of clear cell carcinoma typically contain intracytoplasmic glycogen, often contain intracytoplasmic or intraluminal mucin, and generally show much greater cytologic atypia and mitotic activity than seen in malignant mesotheliomas. The latter may contain glycogen, but intracytoplasmic neutral mucin is almost always absent. Immunohistochemical staining and electron microscopy might be helpful in the rare case in which routine morphologic features and histochemical stains are inconclusive.

In one of our cases, a diagnosis of an ovarian sex cord tumor initially was made owing to striking architectural similarities with an adult granulosa cell tumor, including solid, microfollicular, and trabecular patterns. Many of the cells in this case also showed prominent longitudinal nuclear grooves, enhancing the diagnostic confusion. Other areas, however, were typical of mesothelioma, and no ovarian neoplasm was identified, facilitating the diagnosis.

Malignant mixed mesodermal tumors (MMMTs) of the peritoneum are rare.[49] Some of these tumors have arisen from foci of endometriosis, whereas others lacking this association might have arisen directly from the peritoneum. An MMMT might enter the differential diagnosis of biphasic mesothelioma as it did in one of our cases. MMMTs usually show much greater nuclear atypia and mitotic activity of the epithelial component than is present in the epithelial component of a biphasic mesothelioma, which usually resembles the epithelial component of a pure epithelial mesothelioma. Also, the epithelial components of an MMMT usually show typical müllerian features, most commonly endometrioid or serous. Heterologous elements might be present in MMMTs, a finding that is extremely uncommon in malignant mesotheliomas.[50] Rarely, the distinction of malignant mesothelioma from müllerian adenosarcoma might arise, although it was not a realistic issue in any of our cases. Should it be, adenosarcoma usually shows prominent intraglandular stromal papillae of the sarcomatous component, which characteristically forms periglandular cuffs, features not seen to an appreciable extent in mesothelioma.

Two of our tumors had the features of a so-called deciduoid mesothelioma (Image 9), and a few other tumors had a less striking resemblance to decidual cells. Ectopic decidua rarely might form grossly visible nodules on the peritoneal surfaces or in the omentum[51]; patients with such findings are almost always pregnant. Microscopic evaluation reveals that the cells of ectopic decidua, in contrast with those of malignant mesothelioma, have bland nuclear features and usually no mitotic activity.

When the epithelial component of a biphasic mesothelioma is minor or not represented in the biopsy specimen and the sarcomatous component is hyalinized extensively or shows a prominent storiform pattern with relatively bland cytologic features, as in one of our cases, a solitary fibrous tumor of the peritoneum might be considered.[52-54] In contrast with the generally bland cytologic features of a solitary fibrous tumor, the sarcomatoid component of a biphasic mesothelioma shows focal moderate to marked cytologic atypia; mitotic activity, including abnormal forms; stromal invasion; and sometimes necrosis. Sampling obviously is crucial in this situation, and the diagnosis of a benign fibromatous tumor of the peritoneum of any type should be made cautiously and considered in the context of the gross features. In other words, a biopsy showing only bland morphologic features in a patient with peritoneal disease that has not been well sampled does not lend itself to a confident interpretation.

Of the 3 "classic" forms of mesothelioma, epithelial, biphasic, and sarcomatoid, the last is the rarest in the peritoneum and was represented by only 1 case in the present series. The gross distribution of disease is likely to be a helpful clue to the diagnosis of sarcomatoid mesothelioma rather than sarcoma, but it is in rare cases like this that the supportive findings of immunohistochemical analysis are particularly indicated, as they were in our case (Image 13). The tumor, also diagnosed as mesothelioma by Andrew Churg, MD, was positive for keratin and negative for carcinoembryonic antigen, Leu-M1 (CD15), Ber-EP4, and B72.3. Because of its rarity, sarcomatoid malignant mesothelioma should be diagnosed with great caution. For example, we have seen 1 sarcomatoid carcinoma that involved the peritoneum extensively and, after light microscopic examination, sarcomatoid mesothelioma was a realistic differential diagnosis. In that case, positivity for neutral mucin and the immunologic profile strongly favored carcinoma, indicating the usefulness of those techniques in problematic cases. However, even in that case, routine light microscopy was not to be discounted because careful scrutiny showed rare glands more consistent with the glands of adenocarcinoma than the tubules of mesothelioma.

Several rare morphologic variants of mesothelioma, largely restricted to case reports, have been described but were not represented in pure form in our case material.[55-58] One such previously reported peritoneal malignant mesothelioma had a massive infiltrate of foamy histiocytes that with Sudan III stains was shown to be lipid.[59] In 5 of our tumors,

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foamy cells were conspicuous, but appropriate stains to document intracellular lipid were not performed; based on the appearance of the cytoplasm with routine stains, we consider the presence of intracytoplasmic lipid within histiocytes to be the likely explanation for most of our cases. Neoplastic mesothelial cells themselves can be foamy (Image 10) owing to lipid accumulation, as has been described in a pulmonary mesothelioma.[60]

Numerous studies have indicated the value of histochemical and immunohistochemical analyses in distinguishing malignant mesothelioma from adenocarcinoma. Adenocarcinomas typically contain neutral mucins that stain with the periodic acid–Schiff stain after diastase pretreatment (PASD). Mesotheliomas, on the other hand, secrete acid mucins (predominantly hyaluronic acid) that stain with alcian blue but not with PASD. Rare mesotheliomas, however, have been reported to stain with PASD.[61,62]

For reasons stated earlier, immunohistochemical analysis was not performed in most of the cases reported in this study. Many previous studies, however, have stressed the value of this technique, especially when an antibody panel is used in the diagnosis of malignant mesothelioma and in its differential diagnosis with adenocarcinoma. Mesotheliomas usually are negative for "epithelial" antigens. Of these, Ber-EP4, B72.3, Leu-M1 (CD15), MOC-31, and CA19-9 are the most useful in the differential diagnosis with primary peritoneal serous carcinoma.[4]

However, exceptions to these observations occur, as exemplified by one of the cases in the present study in which the submitting pathologist was uneasy about making the diagnosis of malignant mesothelioma in a tumor that was immunoreactive for B72.3, and yet one study found that 3.5% of mesotheliomas were positive for B72.3.[5] Similarly, another study found that 11% of mesotheliomas were positive for Ber-EP4.[4] The most useful markers that usually are present in epithelial malignant mesotheliomas are cytokeratins 5 and 6, calretinin, and thrombomodulin, although experience is largely with pleural tumors.[63] Ordoñez[4] found that 100% of peritoneal malignant mesotheliomas were immunoreactive for cytokeratins 5 and 6 (vs 24% of extraovarian serous carcinomas), 100% were positive for calretinin (vs 9% of serous carcinomas), and 74% were positive for thrombomodulin (vs 2% of serous carcinomas). Thus, no single marker is diagnostic in the separation of malignant mesothelioma from adenocarcinoma, and the results of a panel of antibodies should be interpreted in conjunction with the H&E and mucin stains.

The value of electron microscopic examination of mesotheliomas also has been noted in the literature because these tumors characteristically have long, slender, nonbranching, bushy microvilli,[64] but these features are not pathognomonic of mesothelioma, particularly when the mesothelioma is atypical.[18] Moreover, some ovarian papillary serous carcinomas can show electron microscopic findings similar to the features of malignant mesothelioma.

Malignant peritoneal mesothelioma in females has frequently encountered typical patterns, which, in combination with the cell type and gross characteristics, should enable the diagnosis to be made on H&E-stained slides in most cases. As with most categories of neoplasia, aberrant morphologic features occasionally are seen, and, in such cases, histochemical, immunohistochemical, and electron microscopic studies might be important aids in diagnosis and certainly are recommended in problematic cases. The frequency of their use will, to a significant degree, be related to the confidence of individual pathologists with the morphologic features of mesothelioma. Even in these cases, however, a time-honored principle of surgical pathology—extensive sampling—might have as great or greater importance by disclosing minor foci of typical mesothelioma. The clinical findings and gross characteristics of disease also should be given appropriate consideration.

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