Well-Differentiated Papillary Mesothelioma of the Peritoneum

A Clinicopathologic Study of 22 Cases

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Twenty-two cases of well-differentiated papillary mesothelioma of the peritoneum (WDPMP) are described. Eighteen of the 22 patients were women. The peritoneal tumor was usually multifocal. Many of the tumors appear to be indolent or inactive and for practical purposes are benign. However, a few patients receiving adjuvant therapy have died under circumstances that make it difficult to determine whether the tumor was responsible for the death. It is suggested that adjuvant therapy be withheld from patients with WDPMP, unless there is clear evidence of progression. The cause of these rare tumors is not apparent, although three patients had had possible exposure to asbestos and two were sisters.

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ALTHOUGH DIFFUSE MALIGNANT MESOTHELIOMA is a highly malignant cancer, there are other forms of mesothelial neoplasm that are much less aggressive or are benign. These include multicystic mesothelioma,[1] adenomatoid tumor, and the histogenetically contentious localized fibrous mesothelioma. Not as well known is the well-differentiated papillary mesothelioma of the peritoneum (WDPMP). From the small number of examples described, it would appear that WDPMP is usually an indolent tumor that occurs mostly in women.[2–7]

In this report, we describe our experience with 22 WDPMP tumors.

Patients and Methods

The 22 cases were obtained from the Canadian Reference Centre for Cancer Pathology, Ottawa, Ontario, Canada, and from the consultation files of one of us (W.T.E.M.). Between two and 17 hematoxylin and eosin (H & E)-stained slides were available in each case. Stains for mucin (mucicarmine or periodic acid–Schiff [PAS]) had been performed in eight cases. Four cases that had been reviewed by the US–Canadian Mesothelioma Panel had had immunostaining for keratin, carcinoembryonic antigen (CEA), Leu M1, and HMFG-2. Follow-up information was obtained for 18 cases. Six cases have been reported previously.[2]

Results

Table 1 summarizes the salient clinical and pathologic findings of the cases.

Clinical Features

The ages of the 22 patients ranged from 25 to 69 years (average age, 41 years; median age, 40 years). Eighteen patients (82%) were women (Patients 1 through 18) and four patients (18%) were men (Patients 19 through 22). The lesions were usually discovered incidentally during surgery for conditions such as gallstones, hernia, or aortic aneurysm, but some patients had abdominal pain, weight loss, or evidence of "chronic pelvic inflammatory disease." Occasionally, ascites was present. Two patients were sisters (Patients 6 and 9).

Gross Pathologic Findings

In most patients, there were multiple omental and pelvic tumor nodules. From the limited information available, the size of these nodules was obviously variable. Most of them appeared to have been in the 0.5-cm to 2.0-cm range, but in many the largest nodules were at least several centimeters in diameter. Sometimes the tumor nodules were described as "papillary." In two patients, the serosal nodules were solitary. Four of the 18 female patients had small tumor foci on the ovarian surfaces, in addition to

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TABLE 1. Clinical, Pathologic, and Follow-Up Data on 22 Cases of WDPMP

Patient no.	Age (yr)	Sex	Clinical manifestations	Gross findings	Treatment	Follow-up
1	60	F	Incidental finding at cholecystectomy	Calcified nodule, omentum (4 × 3.2 × 2.5 cm) + several small nodules in pelvis Normal ovaries	Nil	14 yr, alive and well
2	41	F	Chronic pelvic inflammatory disease	Nodules in omentum and pelvis	Nil	Died, 29 yr later, of carcinoma of the pancreas Multiple nodules of WDPMP on peritoneum at autopsy
3	28	F	Chronic pelvic inflammatory disease	Nodules (1.5 × 2.1 cm) omentum Pelvic adhesions Normal ovaries	Nil	1 yr, alive and well
4	29	F	Right lower quadrant pain	Tumor nodules 2.5 cm maximum diameter	Nil	7 yr, alive and well
5	57	F	Ascites	Diffuse tumor, peritoneum (2 cm nodules) Cystic ovaries, not removed	Nil	Continued to have ascites. Died 7 yr later of aplastic anemia (?)
6	39	F	Incidental finding at cholecystectomy	Omental nodules Normal ovaries	Nil	5 yr, alive and well
7	41	F	Intestinal adhesions	Papillary lesions mesentery Normal ovaries and uterus	Nil	Recent case
8	35	F	Ectopic pregnancy	Nodule on right fallopian tube	Left oophorectomy	Recent case
9	35	F	Abdominal pain Menorrhagia	Tumor nodules cul-de-sac, pelvis, serosa, uterus, and ovaries	TAH + BSO Omentectomy	2 yr, alive and well Persistence of disease with probable increased bulk
10	37	F	Intermittent abdominal pain	Nodules in pelvis and mesentery	TAH + BSO	8 yr, alive and well
11	43	F	Menorrhagia and left adnexal mass	Papillary excrescences (both ovaries) Pelvic nodules	TAH + BSO	N/A
12	45	F	Menorrhagia	Tumor nodules 0.5–1.0 cm	TAH + BSO for adenomyosis	N/A
13	39	F	Incidental finding of tumor nodules at hysterectomy for menorrhagia	Numerous papillary growths in omentum. Normal ovaries	Radiotherapy (abdomen and pelvis)	6 yr, alive and well
14	48	F	Ascites	Disseminated tumor pelvis, serosal surface of uterus, and ovaries.	Radiotherapy and intraperitoneal chemotherapy (thiotepa)	4 yr, alive and well Persistence of tumor nodules (found during surgery for ventral hernia)
15	69	F	Left ovarian mass	Pelvic nodules	TAH + BSO Chemotherapy for associated endometrioid ovarian cancer	2 yr, alive and well
16	29	F	Left pelvic mass	Papillary tumor nodules, pelvis, and ovarian serosa	Radiotherapy (cobalt)	Died 6 weeks after surgery
17	25	F	Ascites and suspicious left pelvic mass	Studding of serosal surface of peritoneum with plaques	TAH + BSO omentectomy, radiotherapy, chemotherapy	Died 7 yr later, after episodes of intestinal obstruction No autopsy
18	31	F	Dyspareunia, spotting, ovarian cyst	Left ovarian mass (benign cystic teratoma) numerous nodules 0.7–1.5 cm omentum	Radiotherapy and chemotherapy Left oophorectomy	Died 2 yr later Developed radiation enteritis
19	48	M	Incidental finding during hernia operation	Papillary nodule 0.5 cm	Nil	1 yr, alive and well
20	54	M	Incidental finding during abdominal aortic aneurysm resection	Papillary nodules on serosa of large bowel and numerous mesenteric implants	Nil	1 yr, alive and well
21	34	M	Ascites and weight loss	Nodules omentum	Nil	8 yr, alive and well.
22	75	M	Incidental finding during surgery for aortic aneurysm	Patchy nodules	Nil omentum	1 yr, alive and well Persistence of disease

WDPMP: well-differentiated papillary mesothelioma of the peritoneum.

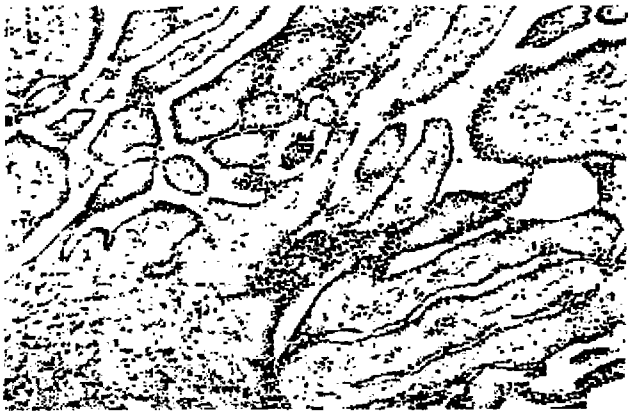

FIG. 1. WDPMP showing coarse papillae covered by cuboidal cells.

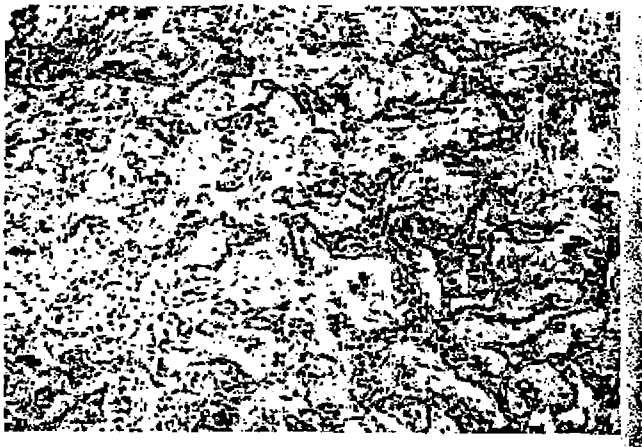

FIG. 3. WDPMP in which the tumor cells form branching cords.

tumor nodules elsewhere in the abdomen. In other instances, the ovaries were said to be normal grossly (five cases) or cystic (one case), or their status was not mentioned (six cases). The remaining two female patients had masses in the ovarian region. In one of these patients, the mass was an ovarian endometrioid carcinoma; in the other patient, it was a benign cystic teratoma (Patients 15 and 18).

Microscopic Findings

There was some variation in the histologic appearances. All had a well-developed papillary architecture in at least some areas, and sometimes the papillae were coarse (Fig. 1). A tubulopapillary pattern also was prominent in some tumors. The papillae and tubules in these areas were often lined by a single layer of relatively uniform cuboidal or flattened epithelium (Fig. 2). Also, branching cords of tumor cells were sometimes seen (Fig. 3). Several tumors showed extensive fibrosis and this was associated with irregularity of the glandular elements in places (Fig. 4). More solid areas of tumor cells were seen in several tumors (Fig. 5). In two cases, scattered multinucleated giant cells were noticed in the stroma. Psammoma bodies were present in five cases (Fig. 6). Mitoses were noticed in only one case and occurred in a cellular component of the tumor. In two instances, isolated tumor nodules showed great congestion. Tiny "seedling" foci of tumor were occasionally observed beside larger masses (Fig. 7).

In three of the four male patients, the tumor had a coarse papillary structure. The fourth case had a more solid growth pattern.

PAS or mucicarmine stains were negative in the eight cases examined. In the four cases in which immunostaining was done, the reaction for cytokeratin was positive and the reactions for CEA, HMGF-2, and Leu M-1 were negative.

Treatment and Follow-Up

Follow-up information for 1 year or more was available for most patients (Table 1). Of the 12 patients (Patients

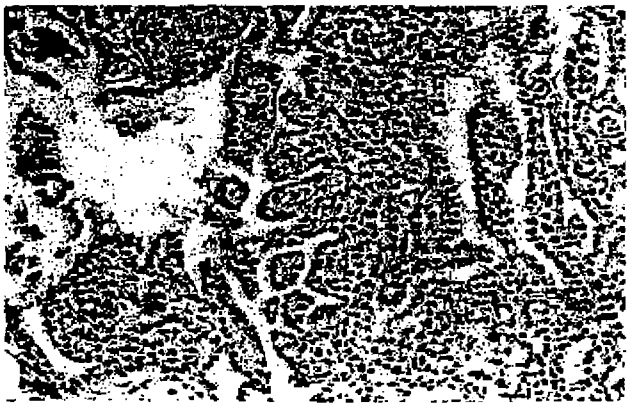

FIG. 2. WDPMP showing a tubulopapillary pattern. The tumor cells are cuboidal and regular.

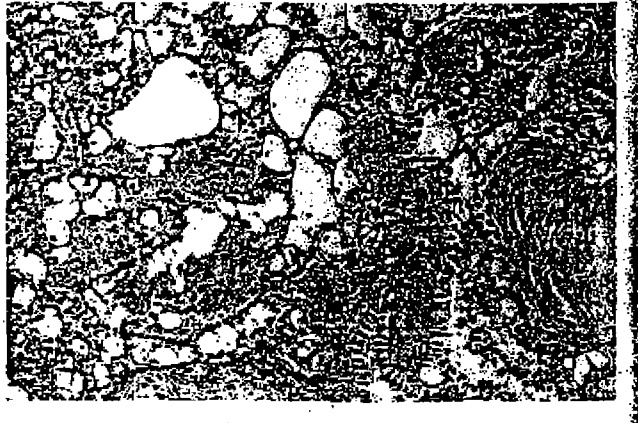

FIG. 4. WDPMP showing extensive fibrosis associated with some irregularity of the tubuloglandular elements.

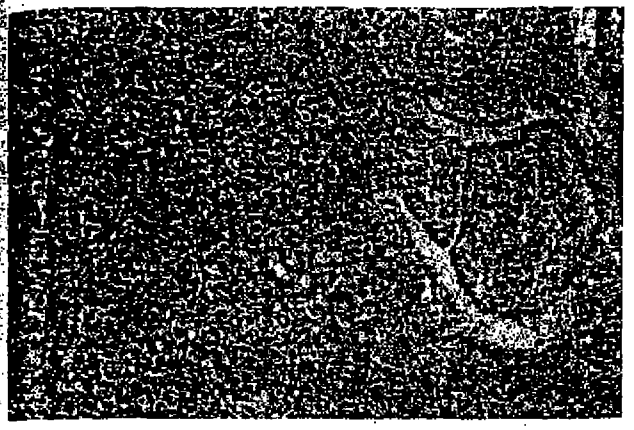

FIG. 5. WDPMP showing a solid area of tumor.

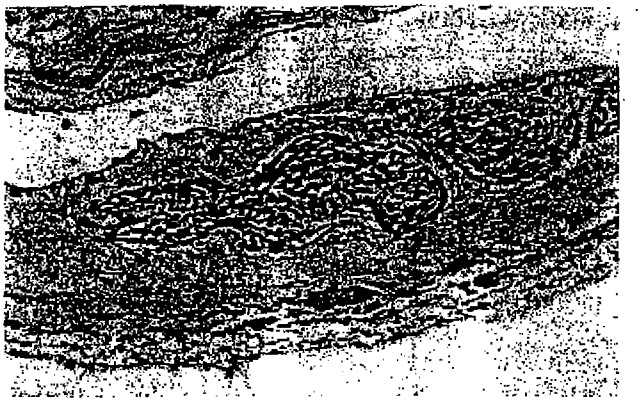

FIG. 7. Seedling foci of tumor that lay close to a large mass.

1 through 12) who did not receive any postoperative adjuvant treatment, two had died. In the first patient (Patient 2), who has been reported previously,[2] death occurred from carcinoma of the pancreas 29 years after the mesothelial tumor was first recognized. At autopsy, nodules of peritoneal tumor, similar in microscopic appearance to those seen in the biopsy specimen 29 years earlier, were observed. The second patient (Patient 5) continued to have ascites and died 7 years after diagnosis, apparently of aplastic anemia. Six of the ten remaining patients in this group have been observed for 1 to 14 years after surgery (mean length of follow-up, 6.2 years). All six patients are alive and well. Follow-up information was not available for two patients and two others were of recent origin.

Of the six female patients who received postoperative adjuvant therapy (Patients 13 through 18), three have died. One of these patients (Patient 16) died 6 weeks after diagnosis. Another patient (Patient 18) died 2 years after diagnosis and was thought to have radiation enteritis. The third patient (Patient 17) died 7 years after diagnosis. She had been treated intensively with radiation and chemotherapy; intestinal obstruction developed in the later stages of her illness. Autopsies were not performed in any of these cases and the contribution of tumor to death is uncertain from the available information. Of the three treated patients who are alive, one is free of clinical disease 6 years after surgery (Patient 13). The second patient (Patient 14) is alive and well 4 years after diagnosis, although residual tumor has been found in tissue removed from a ventral hernia. The third patient (Patient 15) is well 2 years after diagnosis. At the time of the diagnosis of mesothelial tumor this patient also was found to have an endometrioid ovarian cancer and subsequently received chemotherapy for this cancer.

None of the four male patients has received adjuvant therapy. All are alive and well from 1 to 18 years after surgery (Patients 19 through 22).

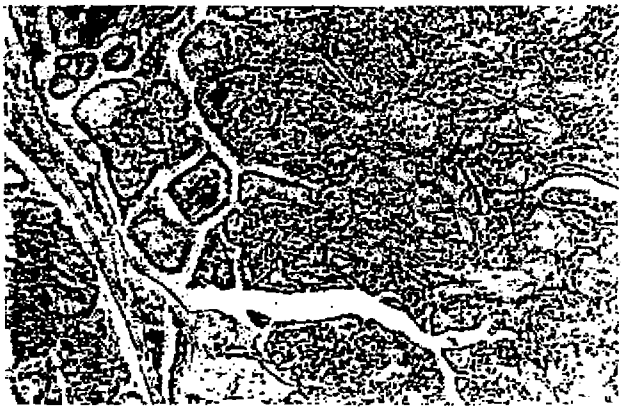

FIG. 6. WDPMP showing two psammoma bodies.

Discussion

Although mesotheliomas are often thought of as highly aggressive neoplasms, it is important to remember that one common form, the adenomatoid tumor, is benign. Two other forms, WDPMP and multicystic mesothelioma,[1] are either benign or of no more than low-grade malignant potential. The localized fibrous mesothelioma also is benign in most cases.[5]

From the gross standpoint, the common presenting sign of multiple peritoneal nodules in WDPMP may lead to confusion with peritoneal carcinomatosis. Pathologically, however, the uniformity of the tumor cells in WDPMP, together with the absence of the nuclear features of malignancy and the absence of multilayering of the epithelium in papillary areas, should usually distinguish it from primary or secondary papillary carcinoma. Confusion with carcinoma is more likely in those uncommon cases of WDPMP in which there is some irregularity of the tubulopapillary elements associated with fibrosis. In such situations, an examination of the nonfibrotic areas of the

tumor should indicate the correct diagnosis. Another major source of diagnostic confusion is the occasional example of diffuse peritoneal malignant mesothelioma where well-differentiated papillary elements are prominent. In cases of the latter type that we have seen, the tumor masses were bulkier than in WDPMP and adequate histologic sampling showed obvious cancerous areas. When the lesions of WDPMP are small, the possibility that they represent hyperplasia rather than neoplasia may come under consideration. However, the papillary nature of the lesion, the absence of any reactive changes in adjacent serosal surfaces, and the absence of antecedent disease or surgery make this improbable. Papillary changes may occur in reactive mesothelial hyperplasia[2,11-12] but are rarely conspicuous.

The occurrence of WDPMP in men is rare. Only three cases appear to have been described in the English literature; one was located in the tunica vaginalis,[15] one in the epicardium,[16] and one in the pleura.[17] In three of our four male patients, the peritoneal tumor was an incidental finding during abdominal surgery for other purposes. The fourth patient (Patient 21) had ascites and weight loss. At laparotomy, nodules were noticed in the omentum. Three of the men were alive and well 1 year after surgery; the fourth was well after 8 years.

The picture that emerges from the current study of WDPMP is that of a predominantly benign tumor. In occasional cases, however, it is possible that the tumor may behave like a low-grade cancer. Two patients in our series (Patients 17 and 18) died 2 and 7 years after diagnosis under circumstances (radiation enteritis in one case and intestinal obstruction in the other) that made it difficult for us to distinguish between the effects of adjuvant therapy and the effects of the tumor. One patient (Patient 5) had continuing ascites and died with query aplastic anemia after 7 years. In another patient (Patient 9) there was evidence that the disease had increased in bulk 1 year after initial surgery. Unfortunately, the quality of follow-up information in referred cases, which constituted our material, varies greatly. The need for long-term follow-up studies is obvious. In the meantime, we believe that the available evidence justifies withholding adjuvant therapy from patients with WDPMP unless there is a clear indication that the tumor is progressing.

Until further information emerges concerning the long-term behavior of WDPMP, the designation of well-differentiated seems more appropriate than that of benign.

Currently, there is no indication of the cause of WDPMP. In three of our patients, there was a history of possible exposure to asbestos; however, as two of these patients were sisters, a familial influence also may have been involved. Evidence of familial clustering has been occasionally reported in cases of malignant mesothelioma.[13,14] The female predominance for WDPMP, its frequent occurrence in younger women, its peritoneal localization, and its indolent nature are all features that it shares with multicystic mesothelioma. There is no evidence that multicystic mesothelioma is related to asbestos.[1]

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