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Well-Differentiated Papillary Mesothelioma

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Well-differentiated papillary mesothelioma is an unusual variant of epithelial mesothelioma considered to be of low malignant potential. The majority of previously reported cases developed in the peritoneum of young women without a history of asbestos exposure. The authors report 14 cases of well-differentiated papillary mesothelioma, seven of which originated in the pleura, six in the peritoneum, and one in the tunica vaginalis. Eleven of the patients were male and three were female, with an average age at presentation of 58 years (range 32–82 years). Six of the patients had a quantifiable history of asbestos exposure. Of the nine cases with complete follow-up, six had clinically indolent disease, one showed resolution after adjuvant chemotherapy, one pursued an aggressive course, and one died of other causes. These findings indicate that well-differentiated papillary mesothelioma is a rare variant of mesothelioma with a variable clinical prognosis that is etiologically related to asbestos exposure in some cases.

Key Words: Papillary mesothelioma—Mesothelioma—Well-differentiated papillary mesothelioma—Immunohistochemistry—Peritoneum—Pleura.

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Well-differentiated papillary mesothelioma (WDPM) is an uncommon tumor arising principally in the peritoneum of women in the third and fourth decades.[6] WDPM occurs rarely at other sites, including the pericardium,[25] tunica vaginalis,[2,4,17,28] and pleura.[29] Unlike the conclusive link between asbestos exposure and diffuse malignant mesothelioma (DMM),[26,27] an association between asbestos and WDPM has not been definitely established.[6,9]

The majority of tumors with histologic features of WDPM have behaved in a benign or indolent fashion.[1–4,6–9,12,13,15,16,18,20,22,24,25,28] However, several WDPMs have pursued a more aggressive course, resulting in death after the development of DMM.[7,8,14]

This report details our experience with 14 WDPMs and expands the clinical and pathologic spectrum for this unusual variant of malignant mesothelioma.

MATERIALS AND METHODS

Fourteen cases of WDPM were identified from the consultation files of two of the authors (S.P.H. and V.L.R.). Demographic and clinical information, including age, gender, occupation, and tumor location, were obtained in all cases by reviewing the medical records. Detailed follow-up data were available from the medical records in nine cases.

Two to thirty-three hematoxylin and eosin-stained slides were available for review in each case. Histochemical studies (periodic acid–Schiff [PAS] with and without diastase pretreatment) had been performed in one case. Immunohistochemical staining on formalin-fixed, paraffin-embedded tissues had been performed in nine cases using an avidin-biotin-peroxidase complex method. Sections from the paraffin block were cut at 4–5 μm, placed on positively charged slides, deparaffinized in organic solvents, treated with methanolic H_2O_2 to quench endogenous peroxidase activity, and rehydrated. Cytokeratin (AE1/AE3, Cam 5.2) (murine IgG monoclonal, Zymed Laboratories, South San Francisco, CA, USA, 1:50; murine IgG monoclonal, Becton Dickinson, San Jose, CA, USA, 1:50) and Leu-M1 (CD15) (murine IgM monoclonal, Becton Dickinson, 1:15) antibodies required proteolytic enzyme digestion of sections, which were pretreated with pepsin (0.25%, pH 2.0, for 12 minutes), followed by nonimmune serum (normal goat serum, 1:20, for 15 minutes). Carcinoembryonic antigen (CEA) (rabbit IgG polyclonal, Dako, 1:4000), epithelial membrane antigen (EMA) (murine monoclonal, Dako, Carpinteria, CA, USA, 1:100), and HBME-1 (murine IgG monoclonal, Dako, 1:1500) antibodies did not re-

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quire proteolytic enzyme digestion of sections. Immunostaining for calretinin (murine IgG monoclonal, Zymed, 1:100) and TAG-72 (B72.3) (murine IgG monoclonal, Signet Laboratories, Dedham, MA, USA, 1:100) was performed after antigen retrieval by heating the unstained sections at 95°C in 10 mM citrate buffer, pH 6.0. Pre-immune rabbit immunoglobulins (Dako) were used as a negative control, and appropriate positive tissue controls were also tested. The unlabeled bound primary antibody was linked with biotinylated goat anti-rabbit IgG (Vector Laboratories, Burlingame, CA, USA, 1:300) and was detected with horseradish peroxidase-labeled streptavidin (Jackson Immuno Research Inc., West Grove, PA, USA, 1:800). Immunoreactivity was visualized using diaminobenzidine as the chromagen, with Harris' modified hematoxylin as the counterstain.

Transmission electron microscopy had been performed in two cases, from which electron photomicrographs were available for review. In another case asbestos body content was determined by light microscopy using a sodium hypochlorite digestion procedure as previously described.[23]

RESULTS

Clinical Features

Salient clinical features of the cases are summarized in Table 1. The age of the patients ranged from 32 to 82 years (mean 58 years). Eleven of the patients were men (case nos. 1–8, 10, 12, 14), five of whom had tumor arising from the pleura, five with peritoneal tumor, and one with WDPM of the tunica vaginalis. The other three patients were female, two of whom had WDPM of the pleura and one with WPDM of the peritoneum. In cases of peritoneal WDPM the lesions were associated with ascites, abdominal pain, cramping, and/or constipation. Patients with tumors arising in the pleura most commonly presented with dyspnea of gradual onset and/or recurrent pleural effusions. The case of WDPM of the tunica vaginalis manifested as a hydrocele.

Detailed history with regard to asbestos exposure was available in 12 cases. Nine patients (case nos. 1–7, 10, and 14) worked in occupations with a high likelihood of asbestos exposure. Contact with a household member occupationally exposed to asbestos was the only known exposure in three cases (case nos. 8, 9, and 11). The duration of exposure was known in four occupational cases (case nos. 1, 3, 4, and 6) and two household contacts (case nos. 9 and 11), which ranged from 2.5 to 35 years (mean 21 years). Pleural plaques were detected radiographically and confirmed histologically in three cases, including one of the household contacts (case nos. 1, 11, and 14). Elevated lung parenchymal asbestos fiber content was found in one occupational case (case no. 10) (see below). Limited medical records precluded determination of asbestos exposure in two cases (case nos. 12 and 13).

Radiologic Findings

Radiographic data were available in seven WDPMs (three pleural, three peritoneal, one tunica vaginalis). Unilateral free-flowing pleural effusions were observed on chest roentgenograms and computed tomography of the thorax in two pleural WDPMs (case nos. 2 and 9). The effusion was accompanied by nodular pleural thickening in one case (case no. 9), whereas pleural nodularity

TABLE 1. *Clinical features in well-differentiated papillary mesothelioma*

Case no.	Age (yrs)	Sex	Site	Presentation	Occupation	Asbestos exposure (yrs)	Treatment	Follow-up	Pleural plaque
1	58	M	Pleura	Dyspnea	Insulator	35	INA	Recent case	Yes
2	56	M	Pleura	Dyspnea, effusion	Power plant	ND	Nil	1 yr, AWD	No
3	46	M	Peritoneum	Constipation	Machinist/HHC	17/12	Chemo	3 yrs, NED	No
4	64	M	Pleura	INA	Rigger	30	INA	INA	No
5	38	M	Peritoneum	Abdominal pain	Furnace worker	ND	Chemo	3 yrs, DOD	No
6	43	M	Peritoneum	Abdominal cramping	Merchant Marine	2.5	Nil	5 yrs, AWD	No
7	64	M	Pleura	INA	Railroad machinist	ND	INA	INA	No
8	32	M	Tunica vaginalis	Hydrocele	HHC	ND	Nil	2 yrs, AWD	No
9	51	F	Pleura	Effusion	HHC	22	Nil	2 yrs, AWD	No
10	66	M	Peritoneum	Abdominal pain	Shipyard welder	ND	INA	3 yrs, DOC	No
11	80	F	Pleura	Dyspnea, effusion	HHC	11+	INA	3 yrs, AWD	Yes
12	82	M	Pleura	Effusion	INA	ND	INA	6 mos, AWD	No
13	32	F	Peritoneum	Ascites	INA	ND	Chemo	INA	No
14	45	M	Peritoneum	Ascites	Maintenance worker	ND	INA	15 yrs, AWD	Yes

INA, information not available; ND, not determined; AWD, alive with disease; HHC, household contact; NED, no evidence of disease; DOD, dead of disease; DOC, dead of other cause.

and calcified pleural plaque were present in another case (case no. 1). Ascites was confirmed by computed tomographs of the abdomen in three peritoneal WDPMs (case nos. 3, 5, and 6). In the latter two cases bowel wall/mesentery thickening was also identified. In two peritoneal WDPMs thoracic imaging showed bilateral pleural thickening (case nos. 3 and 6). The case of WDPM originating in the tunica vaginalis demonstrated peritoneal thickening and minimal ascites (case no. 8).

Pathologic Findings

Gross Findings

Of the four cases in which gross descriptions were available, two were multifocal. Case no. 2 exhibited studding of the pleural cavity by <1 cm firm, white to tan lesions. Fine granular deposits were scattered throughout the peritoneum of case no. 5. In two other cases (case nos. 1 and 9) the tumors appeared as single fungating, arborescent masses (2 × 3 and 3 × 5 cm, respectively).

Microscopic Findings

The histologic appearance of tumors in the peritoneum, pleura, and tunica vaginalis was similar. All were well-differentiated papillary neoplasms. In the majority of cases a single layer of relatively uniform cuboidal mesothelial cells covered thin fibrovascular papillary cores. Individual tumor cells exhibited minimal cytologic atypia, with moderately abundant eosinophilic cytoplasm, central vesicular nuclei, and occasional single nucleoli (Fig. 1A, B). Broader, paucicellular papillary cores were observed in a few cases (Fig. 1C). In one case the fibrovascular cores appeared variably hyalinized and were lined by flattened or attenuated mesothelial cells (case no. 1) (Fig. 1D). Psammoma bodies were present in one case (case no. 9). Mitoses were absent. Focal invasion of the underlying stroma by tumor exhibiting a tubular configuration was identified in two cases (case nos. 1 and 2). Histochemical stains performed in one case (case no. 7) demonstrated focal alcian blue stain-positive

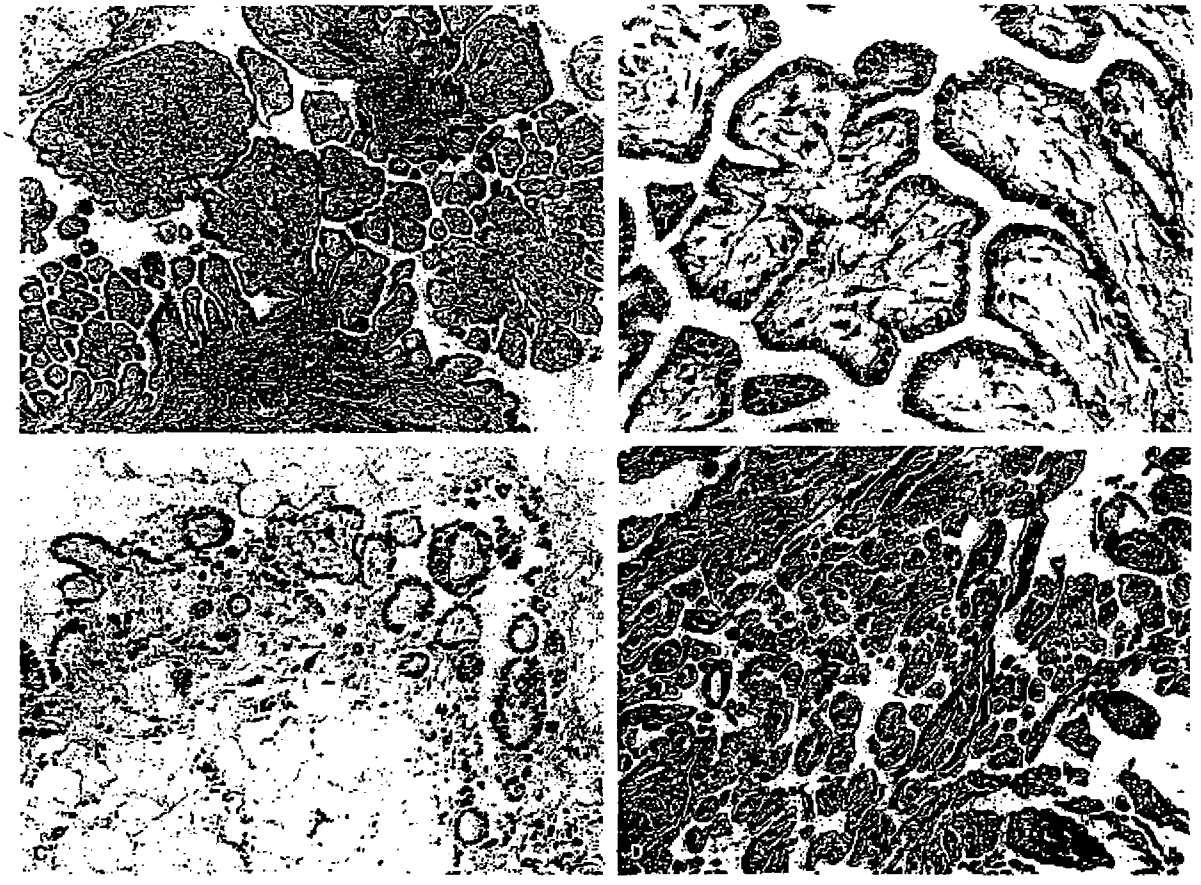


FIG. 1. (A) Well-differentiated papillary mesothelioma (WDPM) of the tunica vaginalis (case no. 8), characterized by slender fibrovascular papillae lined by uniform mesothelial cells. (B) Detail of fibrous papillae showing a single layer of cuboidal mesothelial cells with minimal cytologic atypia. (C) Stout, paucicellular papillary cores are occasionally observed, as in this WDPM of the peritoneum (case no. 6). (D) In one case of WDPM of the pleura (case no. 1), attenuated mesothelial cells cover variably hyalinized papillae.

intracytoplasmic material, which was negative for PAS with and without diastase predigestion.

Immunohistochemical Results

The staining results of the nine cases in which immunohistochemistry was performed are summarized in Table 2. All nine tumors showed strong reactivity for cytokeratin (AE1/AE3 and Cam 5.2). Six of six tumors reacted with calretinin, four of which exhibited staining in both a nuclear and cytoplasmic distribution. Thick membrane staining for HBME-1 was present in the three cases tested. Cytoplasmic membrane staining by EMA was observed in two of four cases. Reactions for CEA, B72.3, and CD15 were negative (Fig. 2).

TABLE 2. *Immunohistochemical results in well-differentiated papillary mesothelioma*

Case no.	CK	Cal	HBME-1	EMA	CEA	B72.3	Leu-M1
1	+	+	NP	NP	NP	NP	NP
3	+	+	NP	NP	–	–	NP
6	+	NP	NP	NP	–	NP	–
7	+	NP	NP	–	–	–	–
8	+	+	+	NP	NP	NP	NP
9	+	NP	NP	NP	–	NP	–
10	+	+	+	–	–	–	–
11	+	+	+	+	–	–	NP
13	+	+	+	+	–	–	–

CK, cytokeratins AE/AE3 and Cam 5.2; Cal, calretinin; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; NP, not performed.

Ultrastructural Findings

Transmission electron micrographs from one pleural (case no. 4) and one peritoneal (case no. 10) WPDM demonstrated tumor cells with long, slender microvilli with a length-to-diameter ratio in excess of 10, abundant cytoplasmic mitochondria and rough endoplasmic reticulum, and well-formed desmosomes. The papillary cores were composed of cells with the ultrastructural appearance of fibroblasts.

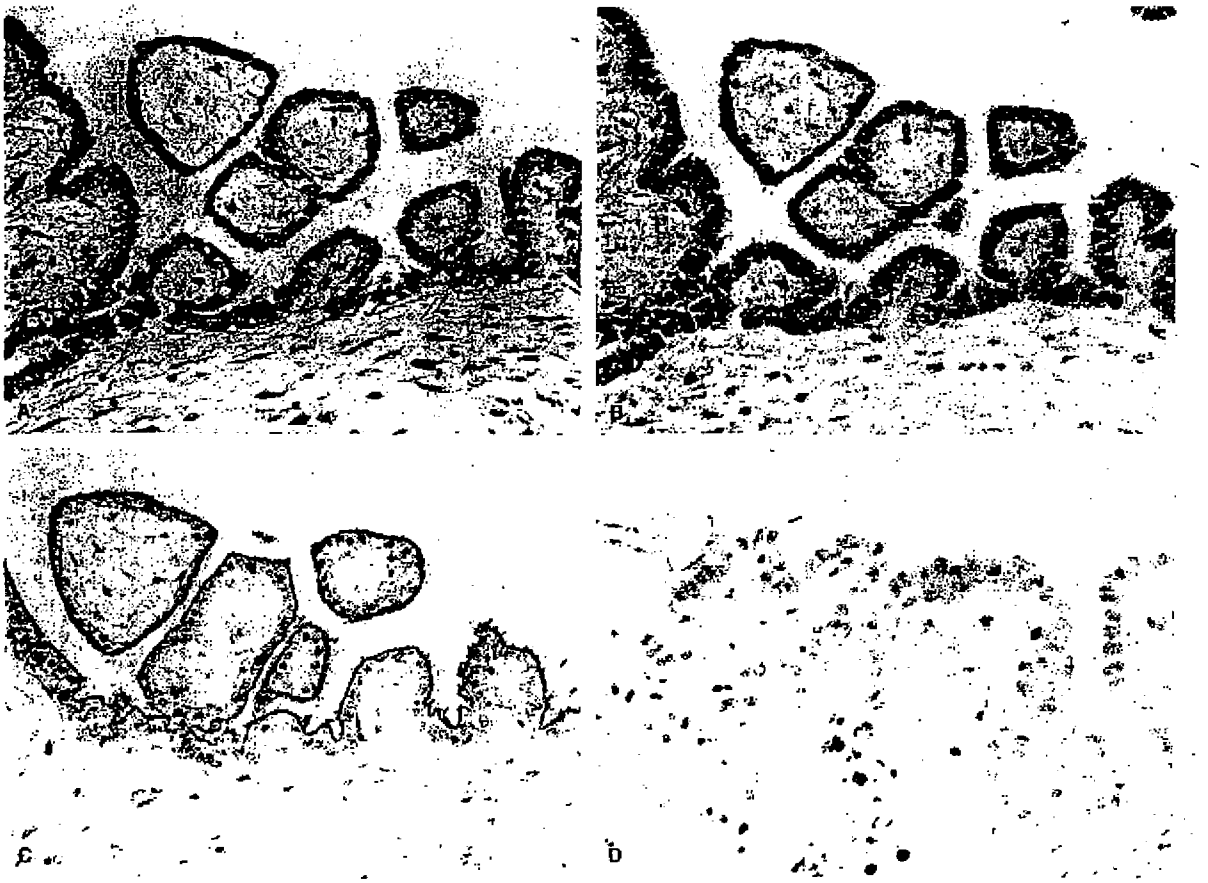


FIG. 2. **(A)** Neoplastic mesothelial cells show strong reactivity for cytokeratins (AE1/AE3 and Cam 5.2) (case no. 8). **(B)** Strong nuclear and cytoplasmic staining is present for calretinin (case no. 8). **(C)** HBME-1 produces thick membrane staining of tumor cells (case no. 8). **(D)** The tumor cells are negative for carcinoembryonic antigen (CEA) (case no. 6).



FIG. 3. Diffuse malignant mesothelioma (DMM) of the peritoneum with an abundant papillary pattern is reminiscent of WDPM (top). However, DMM demonstrates cytologic atypia and diffuse areas of invasion (bottom).

Asbestos Fiber Burden Analysis

Asbestos content was performed using light microscopy and a sodium hypochlorite digestion technique on lung tissue from case no. 10. There were 2000 asbestos bodies/gram of wet lung tissue, which greatly exceeds our normal value of 0–20 asbestos bodies/gram of wet lung tissue.[11]

Treatment and Follow-up

Detailed treatment information was available in seven cases, which is summarized in Table 1. Follow-up information for at least 1 year was available for nine patients. Four of the seven patients whose management was known did not receive postoperative adjuvant treatment (case nos. 2, 6, 8, and 9). All are alive with clinically stable disease 1–5 years (mean 2.5 years) after diagnosis. Three patients received postoperative chemotherapy. Two were treated with cisplatin and doxorubicin. One is free of clinical disease 3 years after treatment (case no. 3). The other died 3 years after diagnosis with radiographic evidence of disease progression (case no. 5). An autopsy was not performed. Another patient is alive with recurrent ascites after receiving Onconase (case no. 13). Of the four patients with detailed follow-up for whom treatment was not known, three are alive with clinically indolent disease 6 months to 15 years (mean 6 years) after diagnosis (case nos. 11, 12, and 14). The other died of lung cancer 3 years after diagnosis with no evidence of residual mesothelioma at autopsy (case no. 10).

DISCUSSION

WDPM is generally regarded as a tumor of low malignant potential, predominantly affecting the peritoneum of women in the third and fourth decade. To our knowledge, there are only 20 reports of WDPM in men in the English language literature.[2–4,6,8,14,16,17,22,28,29] These include the only two cases arising in the pleura.[14,29] Eleven of our 14 patients were men, five of whom had pleural tumors. The sixth and seventh pleural WDPMs in our series are the first to be documented in women.

As in earlier reports, the typical histologic appearance of WDPM in our series is of thin fibrovascular papillae lined by relatively uniform cuboidal mesothelial cells. Less commonly, the papillary cores of WDPM appear coarse and paucicellular.[6] In rare instances the dominant histologic pattern is of hyalinized fibrovascular fronds covered by flattened mesothelial cells.[28] Psammoma bodies are occasionally encountered.[5,6] Cells lining the papillae in each of these growth patterns are consistently immunoreactive for mesothelium-associated markers, such as calretinin and HBME-1. The mesothelial nature of the lining cells has been confirmed ultrastructurally in our series and by other investigators.[8]

A number of earlier studies on WDPM included cases with focal solid areas of tumor.[5,6,9] None of the cases in the current series exhibits this growth pattern. However, two of our cases exhibit focal areas of stromal invasion similar in appearance to the irregular "glandular" elements associated with extensive fibrosis and seedling foci of tumor illustrated in previous reports.[5,6] Follow-up in our two cases with focal invasion is relatively short. Radiographically, these two cases do not differ significantly from others in our series without invasion.

Recent reports on WDPM have purported a variable, rather than entirely benign, prognosis.[7,8,14] In our experience WDPM exhibits a spectrum of clinical behavior, ranging from complete resolution after adjuvant therapy to disseminated disease resulting in death. Based on our series, the prognostic variability of WDPMs of the pleura is not significantly different from tumors arising in the peritoneum. The prognostic significance of other factors, such as microscopic invasion, gender, and tumor multifocality, remains to be determined. Likewise, the role of chemotherapy in the treatment of WDPM requires further investigation, given the mixed response of WDPMs in our series.

Although possible exposure to asbestos has been noted in a few earlier reports of WDPM,[6,15] no clear link between WDPM and asbestos exposure has been established. Of our 14 patients, six (42%) had a quantifiable history of asbestos exposure, ranging from 2.5 to 35 years before diagnosis of mesothelioma. Pleural plaque, a well-established marker of asbestos exposure,[10] was histologically confirmed in three of our cases (case nos. 1, 11, and 14). In addition, asbestos burden analysis was performed in one case (case no. 10), which demonstrated a markedly elevated asbestos body content.

Despite their occasional abundant papillary pattern, DMMs are usually bulkier than WDPMs and demonstrate diffusely infiltrative cytologically atypical cells (Fig. 3).[5] However, the distinction between WDPM and DMM with a prominent papillary pattern can be difficult, particularly in small biopsy specimens, where a diffusely invasive component may not be adequately represented. Patients with WDPM generally have a far better prognosis than those with DMM. An unrecognized diffusely invasive component probably accounts for cases that are more aggressive and ultimately fatal.

WDPM must also be distinguished from hyperplastic mesothelial processes. Papillary structures may occur in mesothelial hyperplasia.[7,19] However, in contradistinction to the conspicuous papillary pattern of WDPM, such changes are rare in hyperplasia. The lack of inflammation and accompanying reactive changes in the adjacent serosal tissue also point to the diagnosis of WDPM.

Although WDPM may be confused with carcinomatosis of the peritoneum at surgery, in most cases these entities are readily distinguished microscopically. The absence of multilayering, cell stratification, cytologic atypia, as well as mitotic activity support a diagnosis of WPDM.[6] In difficult cases immunoreactivity for CEA and CD15, and other glycoproteins, such as Ber-EP4, TAG-72, and MOC-31, is useful in supporting a diagnosis of adenocarcinoma.[21]

In summary, WDPM is a variant of mesothelioma with a variable clinical behavior. WDPM occurs in both men and women and arises in both the peritoneum and pleura, as well as in the tunica vaginalis. It appears that, in at least some cases, WDPM is associated with asbestos exposure. □

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