Annals of Diagnostic Pathology 38 (2019) 43–50

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Well-differentiated papillary mesothelioma: A 17-year single institution experience with a series of 75 cases☆

Meng Sun, Lu Zhao, I Weng Lao, Lin Yu, Jian Wang*

Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China
Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

ARTICLE INFO

Keywords:
Well-differentiated papillary mesothelioma
adenomatoid tumor
multicystic mesothelioma
PAX8

ABSTRACT

We present our experience with 75 cases of well-differentiated papillary mesothelioma (WDPM) that were diagnosed at our institution between 2000 and 2017. The patients included 58 females and 17 males with age ranging from 18 to 69 years (mean, 42 years). Clinically, the vast majority of WDPMs were incidental findings during laparotomy or laparoscopic surgery for a variety of benign or malignant disease. The lesion manifested as either a small solitary nodule or multiple miliary nodules on the peritoneum or serosal surfaces of internal organs. Histologically, 67 cases were consistent with a classical WDPM, of which 6 cases contained microinvasive foci and 1 case had malignant transformation. Eight cases were hybrid tumors with variable combined component of adenomatoid tumor (n = 4), multicystic mesothelioma (n = 2), and both (n = 2). By immunohistochemistry, besides calretinin, D2-40, CK5/6 and WT1, 94% (29/31) of cases also showed immunostaining for PAX8. In comparison, PAX8 staining was only present in 12% (6/50) of epithelioid malignant mesothelioma selected as control cases. Follow-up information available in 46 cases revealed no signs of tumor progression or local recurrence except for the case that showed transformation to a fully malignant mesothelioma after a period of 15 years. Our comprehensive study further expanded the clinical and histopathological spectrum of WDPM. Compared with epithelioid malignant mesothelioma, PAX8 staining is highly sensitive and specific for WDPM ($P < 0.001$).

1. Introduction

Well-differentiated papillary mesothelioma (WDPM) is a very rare but distinct type of mesothelial neoplasm that predominantly occurs in the abdominal or pelvic peritoneum of women at reproductive ages [1-7]. Occasionally, it also arises in the pleura [5,6,8-11], testicular tunica vaginalis or epididymis [5,12-16], or more less frequently the pericardium [17]. In clinical settings, WDPM is usually an incidental finding during laparotomy or laparoscopic surgery for a wide variety of conditions. Histologically, WDPM is characterized by superficial spreading of well-formed papillary architecture lined by a single layer of bland, flattened or cuboidal mesothelial cells. However, with increasing recognition of this uncommon entity, a greater diversity of growth patterns in WDPM is appreciated than initially described, including hybrid tumors with variable component of adenomatoid tumor or multicystic mesothelioma [5], unusual multifocal glomeruloid pattern [18], and microinvasion of the submesothelial layer which may cause diagnostic confusion with frank malignant mesothelioma [6]. The goal of this study is to review a large series of WDPM with aim to further investigate its clinical and histopathological spectrum. The potential utility of PAX8 immunostaining as an auxiliary marker in WDPM is also evaluated.

2. Materials and methods

Seventy-five consecutive cases of WDPM were retrieved from the consultation files and surgical pathology files of the Department of Pathology, Fudan University Shanghai Cancer Center, between 2000 and 2017. Of this series, 18 cases had been reported in our previous study [5]. The clinical data and pathological information were taken from the clinicians and the pathology reports submitted by the referring pathologists. The follow-up information was obtained from the referring pathologists and clinicians, or by direct telephone communication with the patients or their relatives. The original hematoxylin and eosin-stained slides in all cases of WDPM were reviewed by a specialist (J. W.) to confirm the diagnosis. The following pathologic features were

☆ Meng Sun and Lu Zhao are the first authors who contributed equally in the study.

* Corresponding author at: Department of Pathology, Fudan University Shanghai Cancer Center, 270 Dong An Street, Shanghai 200032, China.
E-mail address: softtissuetumor@163.com (J. Wang).

https://doi.org/10.1016/j.anndiagpath.2018.10.012

evaluated for each case: the growth pattern of the tumor cells, nuclear grade, mitotic activity, the presence of submesothelial stromal invasion, and the presence of foamy macrophages or psammoma bodies, composite component of adenomatoid tumor or multicystic mesothelioma (mesothelial inclusion cyst) if there exits.

Immunohistochemical staining was performed on 4-μm thick unstained sections generated from paraffin-embedded blocks on Ventana Automated Immunostainer (BenchMarker Ultra, Ventana Medical System, Inc.) according to the manufacturer's manual. A wide panel of antibodies were used in this study, including calretinin (DAK-Calret 1, 1:200; Dako), D2-40 (1:300; Dako), WT1 (6F-H2, 1:100; Dako), cytokeratin 5/6 (D5/6 B4, 1:100; Dako), pancytokeratin (AE1/AE3, 1:50; Dako), HBME-1 (1:40; Dako), PAX8 (MRQ-50, 1:150; Cell Marque), BerEP4 (1:100; Dako), MOC31 (1:100; Dako), carcinoembryonic antigen (CEA) (II-7, 1:100; Dako), oestrogen receptor (PPG5/10, 1:35; Dako), progesterone receptor (PgR 636, 1:50; Dako), Leu M1 (MMA, ready-to-use; Roche), GLUT-1 (1:200; invitrogen), IMP3 (EP286, ready-to-use; LBP China), epithelial membrane antigen (EMA) (E29, 1:200; Dako), desmin (D33, 1:100; Dako), progesterone receptor (PgR 636, 1:50; Dako), and Ki67(MIB1, 1:150; Dako). Appropriate positive and negative controls were run concurrently with all antibodies tested. For PAX8 immunostaining, 50 cases of epithelioid malignant mesothelioma (EMM) were selected as control cases. The 50 cases of EMM consisted of 14 cases of pleural MM, 32 cases of peritoneal MM and 4 cases of MM involving the tunica vaginalis testis. Immunoreactivity was graded based on intensity (weak, moderate and strong) and extent as: 0, no cells staining; 1+, < 5% cells staining; 2+, 5% to 50% cells staining; and 3+, > 50% cells staining.

Interphase fluorescence in situ hybridization (FISH) study was carried out in 10 cases of WDPM for the deletion on 9p21 (p16 gene locus). 5-μm thick sections generated from formalin-fixed, paraffin embedded tissues were incubated in a humidified chamber (HYBrite™ system; Vysis, Abbott, Des Plaines, IL) using a Spectrum-Green-labeled chromosome 9 centromeric (CEP 9) probe and a p16 (CDKN2A) Spectrum-Orange-labeled probe (Abbott Molecular, Des Plaines, IL) according to the manufacturer's protocol. The fluorescence signals were analyzed using an Olympus BX51 fluorescence microscope (Olympus, Tokyo, Japan). A total of 100 nuclei were evaluated from each specimen.

The χ^2 test was used to assess the sensitivity and specificity of PAX8 immunostaining in WDPM and EMM. The P value of < 0.05 was considered significant with two-sided tests.

3. Results

3.1. Clinical features

The ages of 74 patients (one patient's age was not available) ranged from 18 to 69 years (mean, 42 years; median, 40 years). Approximately 56% of patients occurred between the age of 30 and 50 years, with age peak of incidence in the 4th decade (Fig. 1). There were 58 females and 17 males with a gender ratio of 3.4:1. Forty-nine cases had operation

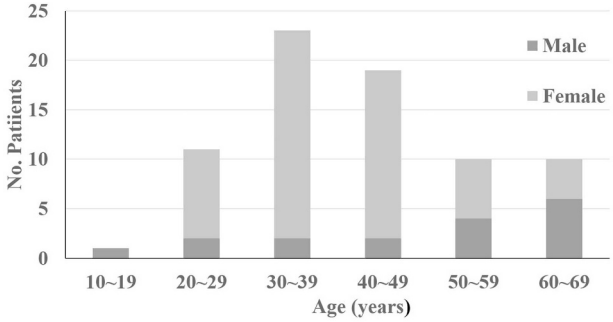

Fig. 1. Age and sex distribution in 75 patients with WDPM.

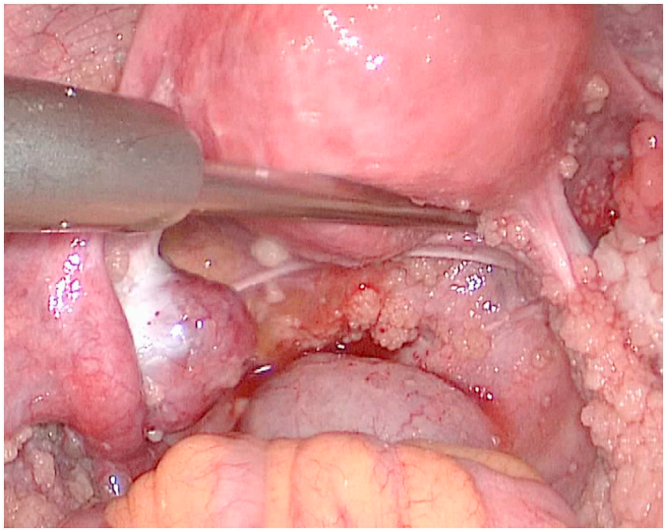

Fig. 2. Laparoscopy revealed multiple miliary nodules protruding from the peritoneum.

record, of which 20 cases (41%) presented with a solitary small nodular lesion and 29 cases (59%) were described as having multiple miliary nodules on the peritoneum or serosal surfaces of internal organs lesions (Fig. 2). In total, the tumor occurred in the abdominal or pelvic peritoneum (31 cases), omentum (12 cases), mesentery (7 cases), Douglas pouch (3 cases), ligament of the uterus (3 cases), serosal surfaces of the ovary (8 cases), fallopian tube (5 cases), uterus (4 cases), stomach (4 cases), intestines (4 cases), pleura (3 cases), testicular tunica vaginalis (2 cases) and inguinal hernia sac (1 case) respectively. Of 63 cases with recorded clinical data, the lesion of WDPM in 57 cases (90%) was an incidental finding during surgery for a wide variety of benign or malignant disease. Among these, 30 cases were found during the surgery or exploratory laparotomy of gynecological lesions, including uterine leiomyoma (12 cases), ovarian cyst (5 cases), endometriosis of ovary (chocolate cyst) (3 cases), cesarean delivery (3 cases), carcinoma of the uterine cervix (1case), endometrial carcinoma (1case), endometrioid adenocarcinoma (1 case), pelvic endometriosis (1 case), teratoma of ovary (1 case), laparoscopy for infertility (1case), and granulosa cell tumor of ovary (1case). The other 27 cases were found during surgery for nonspecific pelvic lesions (11 cases), gastrointestinal stromal tumor (11 cases), inguinal hernia (2 cases), scrotal nodule (2 cases) and lung cancer (1case). Six patients (4 with peritoneal WDPM and 2 with pleural WDPM) had clinical symptoms. The 4 patients with peritoneal WDPM presented with acute or chronic abdominal pain and 3 of them accompanied with ascites. The 2 patients with pleural WDPM complained of dyspnoea and cough accompanied by pleural effusions, one of whom had a history of asbestos exposure. The relevant clinical information in the remaining 12 cases was unavailable. Follow-up information was available in 46 cases, ranging from 5 months to 136 months (mean, 36.3 months; median, 29 months). Thirty-nine patients were alive with no evidence of recurrence or tumor progression. One case had a malignant transformation into a fully malignant mesothelioma 15 years after the initial diagnosis of a WDPM. The diagnosis of an EMM was verified by a recent laparoscopic biopsy. Considered being inoperable, the patient was administrated with cisplatin and pemetrexed. In this series, 6 patients died of associated carcinomas, 3 of whom died of pancreatic carcinoma at 6 months, 7 months and 23 months, and the other 3 patients died of gastric carcinoma, ovarian carcinoma and cervical carcinoma at 25 months, 21 months and 74 months, respectively.

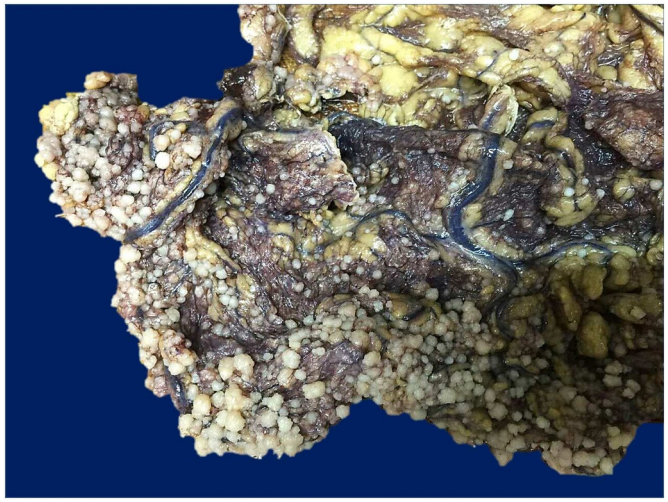

Fig. 3. Gross examination of the excised specimen showed multiple small nodules in the peritoneum.

3.2. Pathological features

The size of the lesion in 49 recorded cases ranged from 0.2 to 6.0 cm in maximum diameter (median, 1 cm; mean, 1.43 cm). Of note, the nodules in 40 cases of pure WDPM (80%) were < 2 cm. In typical cases with multiple lesions, the excised peritoneum and omentum were studded with numerous miliary nodules or papillary projections (Fig. 3). For those with size larger than 2 cm, 8 cases were hybrid tumors with combined component of adenomatoid tumor (n = 4), multicystic mesothelioma (n = 2) and both (n = 2), and 1 case was a WDPM with microinvasive foci.

Microscopically, the lesion in 67 cases was characterized by superficial spreading of well-formed papillary structures, either solitary (Fig. 4A) or multiple which may show crowding of the papillae in some cases (Fig. 4B, C). The papillae had broad fibrovascular cores (Fig. 4D). In one case, the fibrovascular core was filled with foamy histiocytes (Fig. 4E). At high magnification, the papillae were lined by a single layer of uniform flattened or cuboidal cells with bland cytomorphology (Fig. 4F). Small tubuloglandular or nest-like structures were presented in the cores or stalks of papillae in some cases. In addition, 6 of the 67 cases were found to have invasive foci described as sheet of compact small tubuloglandular structures, single row of cells or nests of mild atypical mesothelial cells, which were beyond the fibrovascular core of the papillae but limited to the submesothelial layers with no invasion to the surrounding tissues (Fig. 4G, H). One case showed malignant transformation with epithelioid malignant mesothelioma developing in WDPM after a 15-year interval (Fig. 4I, J). In this series, 4 cases also had a combined component of adenomatoid tumor (Fig. 4K), 2 cases contained multicystic areas consistent with multicystic mesothelioma (Fig. 4L), and 2 cases had both.

The immunohistochemical results are summarized in Table 1. Briefly, all tested cases showed strong and diffuse expression of calretinin (58/58) (Fig. 5A), D2-40 (59/59) (Fig. 5B) and HBME-1 (10/10). WT1 and CK5/6 immunostaining were noted in 98% (51/52) and 93% (42/45) of cases respectively. In addition, partial moderate (2+) to diffuse strong staining (3+) of PAX8 (Fig. 5C) and GLUT-1 (Fig. 5D) was observed in 94% (29/31) and 89% (16/18) of cases respectively. Focal weak expression (1+) of EMA was seen in 13 of 37 cases (35%). One case each showed focal staining (1+) of BerEP4 (1/24, 4.2%) and desmin (1/38, 2.6%). Ki-67 index was very low (< 1%~5%). Other markers, including MOC31, CEA, ER, PR, LeuM1 and IMP3, all rendered negative results. Of the 8 hybrid tumors, the components of adenomatoid tumor and multicystic mesothelioma showed the same immunophenotypes as those of WDPM. Of the 50 EMM, only 6 cases (12%) showed immunostaining of PAX8 (4 cases diffuse and strong, and 2 cases partial) (Fig. 6A, B) whereas the majority of cases (88%) were all negative. These 6 PAX8-positive EMMs included 3 peritoneal MMs, 2 pleural MMs and 1 MM of the tunica vaginalis testis. The χ^2 test showed significant difference of PAX8 expression between WDPM and EMM ($P < 0.001$) (Table 2).

By molecular analysis, none of the ten WDPMs tested by FISH showed p16 deletion.

4. Discussion

In the current study, we described the largest series of WDPM (75 cases) to further characterize its clinicopathologic and immunohistochemical features. Our patients ranged in age from 18 to 69 years with the mean age and median being 42 years and 40 years respectively. Approximately 56% of the patients were in their third to fourth decades. Interestingly, our findings were almost in line with some previous reports [2,3,6], but different from others of which occurred in patients older than those of ours [8,9]. This prompted us to summarize the clinical data of previously reported studies, which included 180 cases of WDPM to date, located in the peritoneum (135 cases), pleura (37 cases), testicular tunica vaginalis (6 cases) and inguinal hernia sac (2 cases) [2,3,6,8,9]. Of these 180 cases, peritoneal WDPM (135/180, 75%) and pleural WDPM (37/180, 21%) accounted for the vast majority. The 135 cases of peritoneal WDPM originated from 112 females and 22 males with an age range from 7 to 82 years (mean, 43 years; median, 41 years), and with an age peak of incidence between 30 and 50 years. Of note, only 2 (1%) of them had a history of asbestos exposure. Compared with peritoneal WDPM, the patients with pleural WDPM had no gender differences (19 females, 18 males) and had a higher age at onset, ranging in age from 22 to 80 years with a median and mean age of 64 years and 61.5 years respectively, and a peak prevalence of 50 to 70 years. Another noteworthy finding was that 16 (43%) of these cases had a history of asbestos exposure, which was much higher than peritoneal WDPM (1%).

As illustrated in the current study as well as previously reported case series, most of WDPM were incidentally detected during surgeries for a variety of benign or malignant lesions. Notably, over half of them were gynecological diseases. The most common disease in our study was uterine leiomyoma (12/30, 40%), whereas endometriosis comprised the main cause in the series reported by Malpica et al. [3]. Other uncommon conditions included ovarian cyst carcinoma of the uterine cervix, endometrial carcinoma, endometrioid adenocarcinoma, pelvic endometriosis, teratoma of ovary, granulosa cell tumor of ovary, cesarean delivery and laparoscopy for infertility. By contrast, symptomatic WDPM is very rare. In this study, 4 patients with peritoneal WDPM presented with acute or chronic abdominal pain as initial symptoms, and more notably, 3 of them were found to have ascites. Ascites as the presentation of WDPM was seldomly seen with only 3 cases had been reported so far. Two of them had a poorer prognosis, with one died of intestinal obstruction and the other one had persistent ascites [2]. Patients with pleural WDPM could present with dyspnoea and unilateral pleural effusion, but usually without chest pain [9]. Most patients of testicular WDPM suffered from scrotal pain or swelling, and hydrocele is the most common presenting symptom as being reported in 82% of the cases [16].

Clinically, WDPM can present either as a solitary small nodule or as multiple papillary formations on the peritoneum or pleura. With respect to the size of the tumor, approximately 40 (82%) of our cases were < 2 cm, and the remaining 9 cases were > 2 cm. Of the 9 cases with a larger size, 8 cases combined with adenomatoid tumor and/or multicystic mesothelioma, and the other presented with invasive foci. Therefore, we proposed that the tumor size should be considered when WDPM needs to be defined because WDPM is usually small, and larger WDPM may be associated with containing area of adenomatoid tumor and/or multicystic mesothelioma or invasive foci. In addition, Churg A.

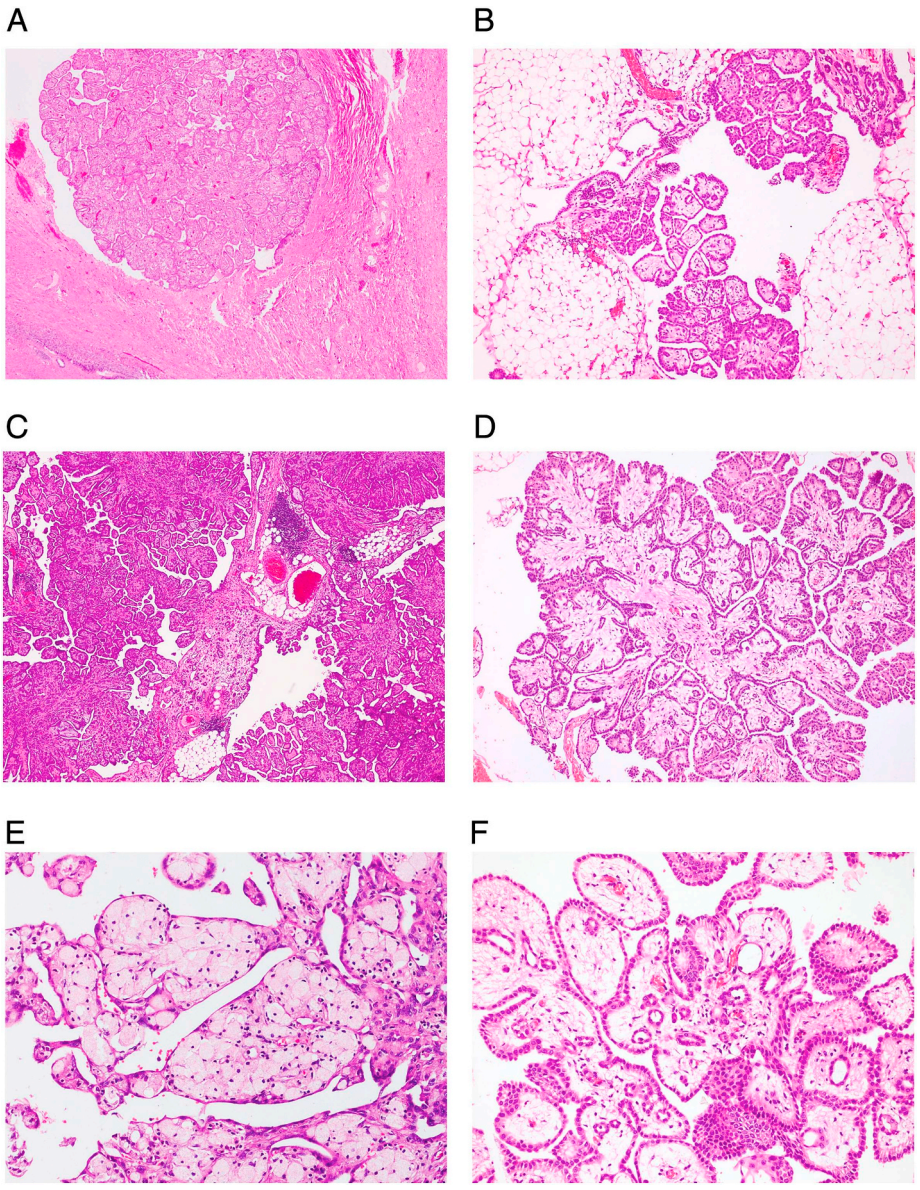

Fig. 4. A solitary WDPM arising on the surface of ovary which was initially misdiagnosed as serous borderline tumor (A), and multiple WDPMs arising in the omentum (B) with crowding of the papillae (C). The papillae have a broad fibrovascular core (D) filled with foamy histiocytes cells in occasional case (E), and frequent small tubuloglandular structures in the stalk (F). Microinvasive foci appeared as compact tubuloglandular structures, single row of cells or nests of mild atypical mesothelial cells that beyond the fibrovascular core of the papillae (G, H). Epithelioid malignant mesothelioma developing within a WDPM (I, J). WDPM with combined component of adenomatoid tumor (K) and multicystic mesothelioma (L).

et al. found that larger WDPM might present with compressive crowding papillae and prone to recurrence [6].

In this study, 6 of 64 cases of classic WDPM showed limited invasion, which appeared as sheet of small tubuloglandular structures, single row of cells solid nests of mild atypical mesothelial cells that grow in the submesothelial layers with no invasion to the surrounding tissues. Other invasive patterns were also seen in previously reported studies, including solid sheets of spindled cells, cytologically higher-grade lesions appearing as sheets of atypical mesothelial cells, or the tumor invading the surrounding tissues like the ovarian cortex [3], and the underlying fat [6]. It has been supposed that WDPM with invasive foci has a tendency to multifocality and recurrence. Whether the invasive foci in some cases of WDPM represents a potential connection to malignant transformation remains to be further clarified. Nevertheless, there were a few case reports of malignant mesothelioma developing within WDPM although some lacked convincing illustrations [9,19-23]. In this series, we illustrated an overt EMM developing within a WDPM after a 15-year interval, indicating that WDPM has a potential of malignant transformation although this condition is very rare. In a recent study, loss of BAP1 expression was found in WDPM with synchronous or metachronous MM [24]. It has been suggested that BAP1 loss in WDPM might predict development of MM.

In a previous report, we described two cases of WDPM containing a combined component of adenomatoid tumor and three cases of WDPM containing coexiting areas of multicystic mesothelioma [5]. Other studies also showed features of combined WDPM and adenomatoid tumor [25], as well as composite multicystic mesothelioma and adenomatoid tumor [26]. The simultaneous occurrence of WDPM, adenomatoid tumor and multicystic mesothelioma in some cases suggests histogenetic relationships between these three indolent mesothelial neoplasms. Most recently, it has been shown that all WDPM harbored somatic missense mutations of TRAF7 gene that drive aberrant NF-kB pathway activation [27]. Of note, somatic missense mutations in the TRAF7 gene was also identified in adenomatoid tumor of the genital tract [28],

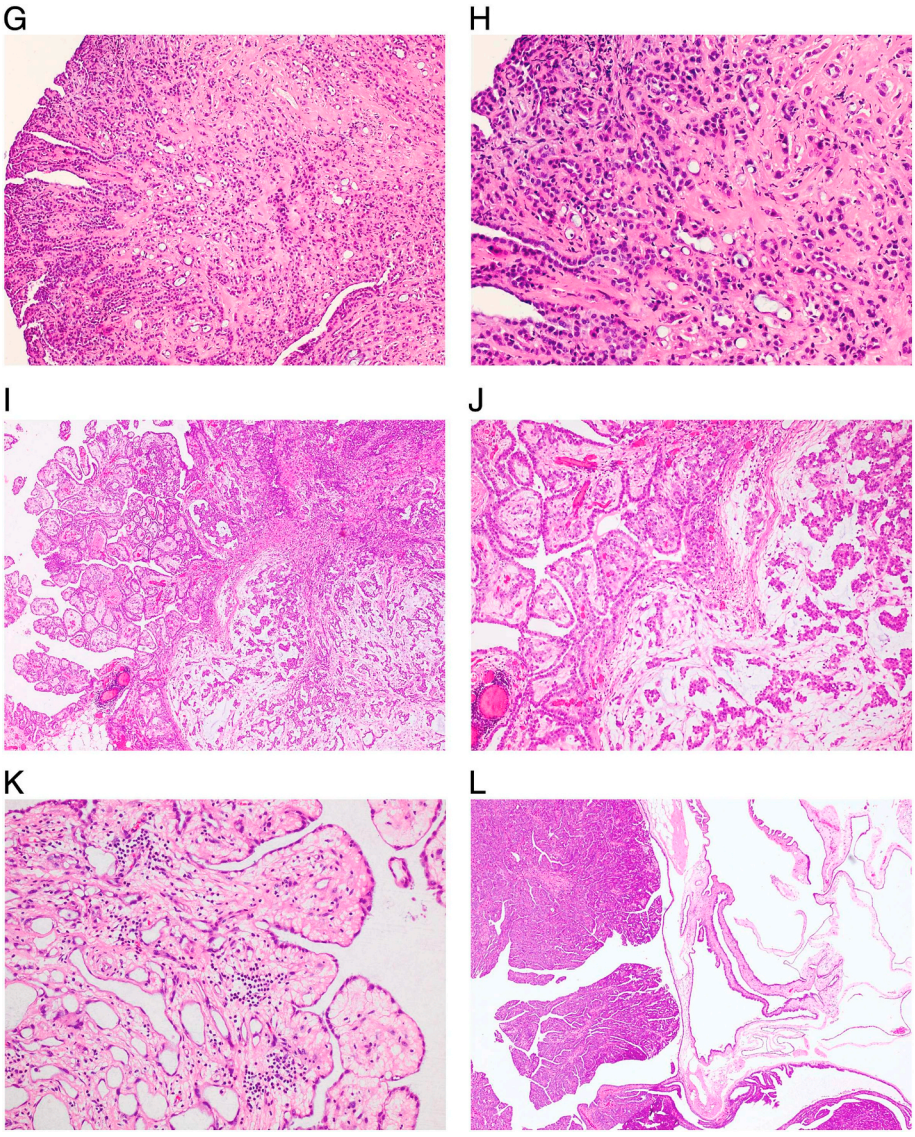

Fig. 4. (*continued*)

Table 1
Immunohistochemical results of well-differentiated papillary mesothelioma.

Antibody	Number of positive cases	Number of tested cases	Positive rate
AE1/AE3	10	10	100%
Calretinin	58	58	100%
D2-40	59	59	100%
HBME1	10	10	100%
WT1	51	52	98%
CK5/6	42	45	93%
PAX8	29	31	94%
GLUT1	16	18	89%
EMA	13	37	35%
BerEP4	1	24	4.2%
Desmin	1	38	2.6%
IMP3	0	2	0%

indicating a shared molecular pathogenesis between WDPM and adenomatoid tumors.

The main differential diagnosis of WDPM includes serous borderline tumor (SBT), reactive mesothelial hyperplasia (RMH) and epithelioid malignant mesothelioma. While the majority of SBT occur in the ovary, rare case of SBT can also present as a paratesticular lesion. It is not uncommon to misdiagnose WDPM as SBT in both sexes. However, the papillae in SBT are typically covered by columnar serous cells which are frequently immunoreactive to ER, PAX8, WT1 and CK7 with negative staining for calretinin. Because there are overlapping immunophenotypic patterns of PAX8, this marker is not reliable for distinguishing WDPM from SBT [29]. Compared with WDPM, reactive mesothelial hyperplasia is usually associated with a previous history of the cardiovascular, immune, inflammatory, or toxic disease and has reactive/inflammatory changes in the adjacent serosa. Previous studies suggested that reactive mesothelial hyperplasia was more often positive for desmin than malignant mesothelioma [30,31]. In the current study, only 1 case of WDPM showed focal staining of desmin. Therefore, desmin immunostaining may help distinguishing WDPM from RMH besides the morphology. Lastly, in terms of patient's therapy and prognosis, distinguishing WDPM from EMM is crucial. As WDPM may contain microinvasive foci and WDPM-like areas may be present in some cases of EMM, it is challenging to make a distinction between these two entities on histology alone especially in biopsy specimens. Recent studies suggested that PAX8, a member of the paired box (PAX) family of transcription factors which is important in organogenesis of the thyroid gland, kidney, and Müllerian system, might serve as a beneficial marker in separating WDPM from EMM. Several studies have showed that the expression of PAX8 in MM was either nil or critically low. In one series reported by Ordóñez, none of the 40 peritoneal

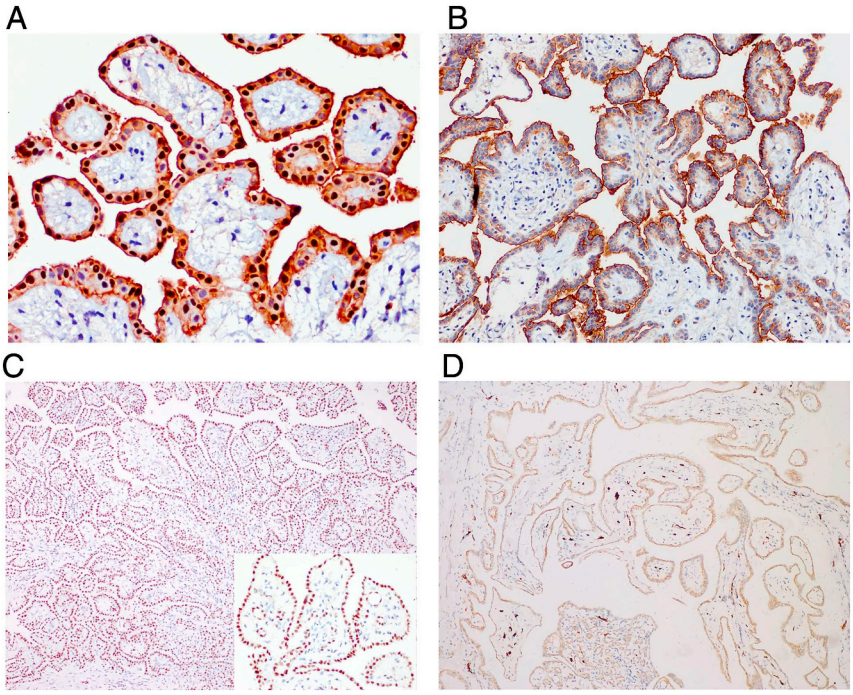

Fig. 5. Strong nuclear staining of calretinin (A) and membrane staining of D2-40 (B), strong and diffuse nuclear staining of PAX8 (C, and inset), and moderate cytoplasmic staining of GLUT1 (D).

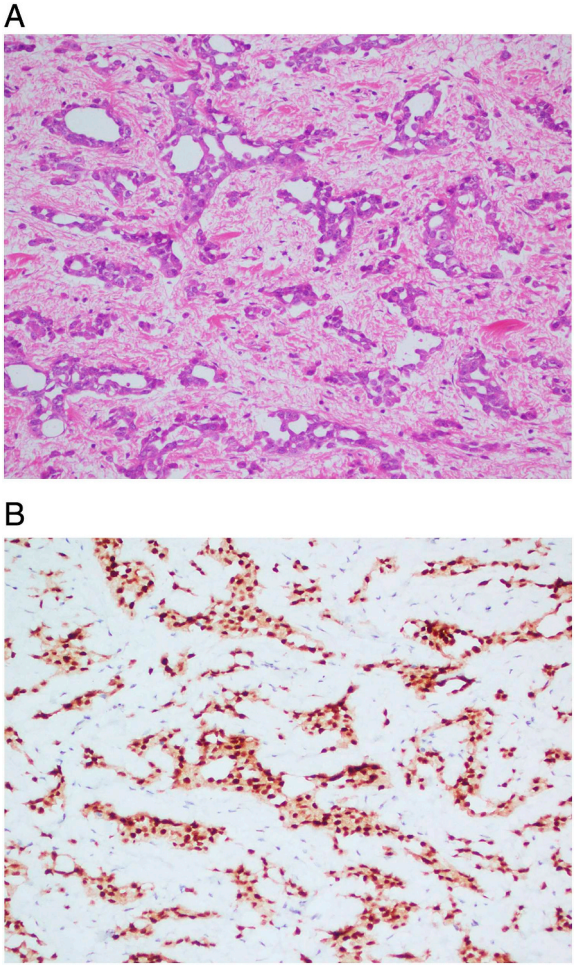

Fig. 6. Epithelioid malignant mesothelioma (A) showing strong and diffuse staining of PAX8 (B).

Table 2
Comparison of PAX8 immunostaining in well-differentiated papillary mesothelioma and epithelioid malignant mesothelioma.

Factors	PAX8 immunostaining
WDPM	29/31(94%)
EMM	6/50(12%)
Sensitivity	0.94
Specificity	0.88
PPV	0.83
NPV	0.94
P value	< 0.001

WDPM: well-differentiated papillary mesothelioma; EMM: epithelioid malignant mesothelioma; PPV: positive predictive value; NPV: negative predictive value.

mesotheliomas were positive for PAX8 [32]. In another series described by Lee et al., PAX8 was negative in all 22 tubulopapillary EMMs and 35 poorly differentiated EMMs with solid or sarcomatoid growth [33]. Nevertheless, a small subset of MM expressed PAX8, as in 2 of 47 (4%) MMs in the study by Laury et al. [34], 5 of 27 (18%) peritoneal MMs in the study by Chapel et al. [35], and 4 of 34 (12%) peritoneal MMs in a recent study by Xing et al. [29], ranging from focal to diffuse staining. Our study showed a similar result with PAX8 expression being identified in 6 of 50 (12%) EMMs, including 3 peritoneal MMs, 2 pleural MMs and 1 MM of the tunica vaginalis testis. Compared with MM, WDPM showed a relatively higher rate of PAX8 expression, ranging from 61% (20/33) in Xing et al.'s study to 94% (29/31) in the current study. By statistical analysis, PAX8 staining is highly sensitive (94%) and specific (88%) ($P < 0.001$) for WDPM when compared with EMM, suggesting that PAX8 is a useful marker in separating WDPM from EMM in most instances, but should be interpreted with caution as a small set of EMM may also express this marker. In the latter settings, combined BAP1 immunohistochemistry and p16 FISH will assist in the distinguishing as loss of BAP1 expression and p16 deletion have not been reported in WDPM to date.

In this study, we also investigated the expression of GLUT1 in

WDPM. GLUT1 was reported to be frequently expressed in MM with positive rate of 53% to 100% but less in benign mesothelial proliferation [36,37]. Lee et al. recommended the combination of GLUT-1 and IMP3 for distinguishing benign from malignant mesothelial proliferations [38]. To our knowledge, the study of GLUT-1 expression in WDPM is limited. Up to present, only 3 cases of WDPM were studied with GLUT1 immunohistochemistry, in which 2 cases were negative [11,36], the remaining one showed positive expression [14]. In this study, 89% (16/18) of WDPM were positive for GLUT-1, indicating that GLUT1 is not useful in the distinction between WDPM and MM. In our study, only 2 cases were stained with IMP3 and were both negative. The diagnostic value of IMP3 in WDPM remains to be further evaluated.

Up to present, the molecular genetic studies in WDPM are limited. Previous studies showed heterozygous loss of chromosomes 4 and 22 [6], loss of NF2 [39], harboring the somatic mutation of E2F1 [40], and germline BAP1 mutation [41]. In a most recent study, by performing genomic profiling, Stevers et al. identified that all 10 peritoneal WDPM harbored somatic missense mutations in either the TRAF7 or CDC42 genes and lacked alterations involving BAP1, NF2, CDKN2A, DDX3X, SETD2, and ALK which were frequent in malignant mesothelioma [27]. This novel finding demonstrates that WDPM is a genetically distinctive entity different from MM. The robust expression of L1 cell adhesion molecule (L1CAM) in WDPM, a marker of NF-kB pathway activation, might become an additional marker in distinguishing WDPM from MM.

WDPM is currently considered as a tumor of uncertain malignant potential or a tumor with an indolent behavior. Most patients with WDPM in this study presented with a favorable prognosis after tumor resection, as well as most of the previously reported cases. Churg et al. suggested that WDPM with invasive foci has a tendency toward multifocality and recurrence but without life-threatening [7]. However, very few patients pursued an aggressive course [8] or underwent malignant transformation [22-24]. There is no consensus about the therapeutic strategies of WDPM at present. Lee et al. suggested variable treatment strategies based on the disease status, including complete resection, close follow-up, and chemotherapy [42].

In summary, we described the largest series (75 cases) of WDPM and further investigated the clinical and pathological spectrum of this rare mesothelial neoplasm. Our study demonstrated more frequent expression of PAX8 in WDPM comparing with EMM, indicating its potential utility in the distinction between WDPM and EMM. However, in challenging cases with overlapping features, additional markers of BAP1 and the recently described L1CAM together with p16 FISH detection are recommended in the differential diagnosis.

Sources of funding

Supported by Grants from Shanghai Key Developing Disciplines (2015ZB0204) and Shanghai Hospital Development Center Emerging Advanced Technology Joint Research Project (SHDC12014105).

Declarations of interest

None.

Acknowledgements

The authors would like to thank Xue-Ke Zhou and Xu Cai for technical assistance and Qian-ming Bai for FISH analysis.

References

[1] Foyle A, Al-Jabi M, McCaughey WT. Papillary peritoneal tumors in women. Am J Surg Pathol 1981;5:241–9.
[2] Daya D, McCaughey WTE. Well-differentiated papillary mesothelioma of the peritoneum: a clinicopathologic study of 22 cases. Cancer 1990;65:292–6.
[3] Malpica A, Sant'Ambrogio S, Deavers MT, Silva EG. Well-differentiated papillary mesothelioma of the female peritoneum: a clinicopathologic study of 26 cases. Am J Surg Pathol 2012;36:117–27.
[4] Hoekstra AV, Riben MW, Frumovitz M, Liu J, Ramirez PT. Well-differentiated papillary mesothelioma of the peritoneum: a pathological analysis and review of the literature. Gynecol Oncol 2005;98:161–7.
[5] Chen X, Sheng W, Wang J. Well-differentiated papillary mesothelioma: a clinicopathological and immunohistochemical study of 18 cases with additional observation. Histopathology 2013;62:805–13.
[6] Churg A, Allen T, Borczuk AC, Cagle PT, Galateau-Sallé F, Hwang H, et al. Well-differentiated papillary mesothelioma with invasive foci. Am J Surg Pathol 2014;38:990–8.
[7] Jakobsen M, Engvad B, Jensen T, Marcussen N. Incidental finding of multiple well-differentiated papillary mesotheliomas in peritoneum. APMIS 2016;124:333–4.
[8] Butnor KJ, Sporn TA, Hammar SP, Roggli VL. Well-differentiated papillary mesothelioma. Am J Surg Pathol 2001;25:1304–9.
[9] Galateau-Salle F, Vignaud JM, Burke L, Gibbs A, Brambilla E, Attanoos R, et al. Well-differentiated papillary mesothelioma of the pleura: a series of 24 cases. Am J Surg Pathol 2004;28:534–40.
[10] Galateau-Salle F, Churg A, Roggli V, Travis WD, World Health Organization Committee for Tumors of the Pleura. The 2015 World Health Organization classification of tumors of the pleura: advances since the 2004 classification. J Thorac Oncol 2016;11(2):142–54.
[11] Shimizu S, Yoon H, Ito N, Tsuji T, Funakoshi Y, Utsumi T, et al. A case of solitary well-differentiated papillary mesothelioma with invasive foci in the pleura. Pathol Int 2017;67:45–9.
[12] Barbera V, Rubion M. Papillary mesothelioma of the tunica vaginalis. Cancer 1957;10:183–9.
[13] Chetty R. Well differentiated (benign) papillary mesothelioma of the tunica vaginalis. J Clin Pathol 1992;45:1029–30.
[14] Brimo F, Illei PB, Epstein JI. Mesothelioma of the tunica vaginalis: a series of eight cases with uncertain malignant potential. Mod Pathol 2010;23:1165–72.
[15] Bonetti LR, Schirosi L, Sartori G, Lupi M, Maiorana A. Well-differentiated papillary mesothelioma of the epididymis in a man with recurrent haematospermia. Andrologia 2012;44:285–7.
[16] Parcesepe P, Sina S, Zanella C, Pancione M, Giuliani J, Detogni P, et al. Case report of a well-differentiated papillary mesothelioma of the tunica vaginalis in an undescended testis with review of literature. Int J Surg Pathol 2016;24:443–7.
[17] Sane AC, Roggli VL. Curative resection of a well-differentiated papillary mesothelioma of the pericardium. Arch Pathol Lab Med 1995;119:266–7.
[18] Martínez-Consuegra N, Muñoz-Juárez M, Ortiz-Hidalgo C. Unusual multifocal glomeruloid pattern in a well-differentiated papillary mesothelioma of the peritoneum. Int J Surg Pathol 2008;16:426–7.
[19] Bürrig KF, Pfitzer P, Hort W. Well-differentiated papillary mesothelioma of the peritoneum: a borderline mesothelioma. Report of two cases and review of literature. Virchows Arch A Pathol Anat Histol 1990;417:443–7.
[20] Kim MJ, Moon EJ, Park YJ, Roh JW, Park YS, Park SY, et al. A case of well-differentiated papillary mesothelioma developing malignant mesothelioma with seeding mass on the trocar insertion site of diagnostic laparoscopy and malignant change. Cancer Res Treat 2001;33:357–61.
[21] Torii I, Hashimoto M, Terada T, Kondo N, Fushimi H, Shimazu K, et al. Well-differentiated papillary mesothelioma with invasion to the chest wall. Lung Cancer 2010;67:244–7.
[22] Washimi K, Yokose T, Amitani Y, Nakamura M, Osanai S, Noda H, et al. Well-differentiated papillary mesothelioma, possibly giving rise to diffuse malignant mesothelioma: a case report. Pathol Int 2013;63:220–5.
[23] Costanzo L, Scarlata S, Perrone G, Rossi L, Papa A, Di Matteo FM, et al. Malignant transformation of well-differentiated papillary mesothelioma 13 years after the diagnosis: a case report. Clin Respir J 2014;8:124–9.
[24] Lee HE, Molina JR, Sukov WR, Roden AC, Yi ES. BAP1 loss is unusual in well-differentiated papillary mesothelioma and may predict development of malignant mesothelioma. Hum Pathol 2018;79:168–76.
[25] Hatano Y, Hirose Y, Matsunaga K, Kito Y, Yasuda I, Moriwaki H, et al. Combined adenomatoid tumor and well differentiated papillary mesothelioma of the omentum. Pathol Int 2011;61:681–5.
[26] Chan JK, Fong MH. Composite multicystic mesothelioma and adenomatoid tumour of the uterus: different morphological manifestations of the same process? Histopathology 1996;29:375–7.
[27] Stevers M, Rabban JT, Garg K, Van Ziffle J, Onodera C, Grenert JP, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42. Mod Pathol 2018 Aug 31. https://doi.org/10.1038/s41379-018-0127-2. [Epub ahead of print].
[28] Goode B, Joseph NM, Stevers M, Van Ziffle J, Onodera C, Talevich E, et al. Adenomatoid tumors of the male and female genital tract are defined by TRAF7 mutations that drive aberrant NF-kB pathway activation. Mod Pathol 2018;31(4):660–73.
[29] Xing D, Banet N, Sharma R, Vang R, Ronnett BM, Illei PB. Aberrant Pax-8 expression in well-differentiated papillary mesothelioma and malignant mesothelioma of the peritoneum: a clinicopathologic study. Hum Pathol 2018;72:160–6.
[30] Attanoos RL, Griffin A, Gibbs AR. The use of immunohistochemistry in distinguishing reactive from neoplastic mesothelium. A novel use for desmin and comparative evaluation with epithelial membrane antigen, p53, platelet-derived growth factor-receptor, P-glycoprotein and Bcl-2. Histopathology 2003;43:231–8.
[31] Kawai T, Tominaga S, Hiroi S, Ogata S, Nakanishi K, Kawahara K, et al. Peritoneal malignant mesothelioma (PMM), and primary peritoneal serous carcinoma (PPSC) and reactive mesothelial hyperplasia (RMH) of the peritoneum. Immunohistochemical and fluorescence in situ hybridisation (FISH) analyses. J Clin Pathol 2016;69:706–12.

[32] Ordóñez NG. Value of PAX8, PAX2, claudin-4, and h-caldesmon immunostaining in distinguishing peritoneal epithelioid mesotheliomas from serous carcinomas. Mod Pathol 2013;26(4):553–62.
[33] Lee M, Alexander HR, Burke A. Diffuse mesothelioma of the peritoneum: a pathological study of 64 tumours treated with cytoreductive therapy. Pathology 2013;45(5):464–73.
[34] Laury AR, Hornick JL, Perets R, Krane JF, Corson J, Drapkin R, et al. PAX8 reliably distinguishes ovarian serous tumors from malignant mesothelioma. Am J Surg Pathol 2010;34(5):627–35.
[35] Chapel DB, Husain AN, Krausz T, McGregor SM. PAX8 expression in a subset of malignant peritoneal mesotheliomas and benign mesothelium has diagnostic implications in the differential diagnosis of ovarian serous carcinoma. Am J Surg Pathol 2017;41(12):1675–82.
[36] Val-Bernal JF, Mayorga M, Val D, Garijo MF. Well-differentiated papillary mesothelioma manifesting in a hernia sac. Pathol Res Pract 2014;210:609–12.
[37] Kato Y, Tsuta K, Seki K, Maeshima AM, Watanabe S, Suzuki K, et al. Immunohistochemical detection of GLUT-1 can discriminate between reactive mesothelium and malignant mesothelioma. Mod Pathol 2007;20(2):215–20.
[38] Lee AF, Gown AM, Churg A. IMP3 and GLUT-1 immunohistochemistry for distinguishing benign from malignant mesothelial proliferations. Am J Surg Pathol 2013;37(3):421–6.
[39] Nemoto H, Tate G, Kishimoto K, Saito M, Shirahata A, Umemoto T, et al. Heterozygous loss of NF2 is an early molecular alteration in well-differentiated papillary mesothelioma of the peritoneum. Cancer Gene Ther 2012;205(11):594–8.
[40] Yu W, Chan-On W, Teo M, Ong CK, Cutcutache I, Allen GE, et al. First somatic mutation of E2F1 in a critical DNA binding residue discovered in well-differentiated papillary mesothelioma of the peritoneum. Genome Biol 2011;12(9):R96.
[41] Ribeiro C, Campelos S, Moura CS, Machado JC, Justino A, Parente B. Well-differentiated papillary mesothelioma: clustering in a Portuguese family with a germline BAP1 mutation. Ann Oncol 2013;24(8):2147–50.
[42] Lee YK, Jun HJ, Nahm JH, Lim TS, Park JS, Ahn JB, et al. Therapeutic strategies for well-differentiated papillary mesothelioma of the peritoneum. Jpn J Clin Oncol 2013;43:996–1003.