The Korean Journal of Pathology 2009; 43: 583-8
DOI: 10.4132/KoreanJPathol.2009.43.6.583

Fine Needle Aspiration Cytologic Features of Well-Differentiated Papillary Mesothelioma in the Pleura
- A Case Report -

Han Suk Ryu · Min-Sun Jin
Hee-Seung Choi · HeeJong Baek[1]
Jae Soo Koh

Departments of Pathology and
[1]Thoracic Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

Received : July 13, 2009
Accepted : September 8, 2009

Corresponding Author
Jae Soo Koh, M.D.
Department of Pathology, Korea Cancer Center Hospital, 75 Nowon-gil, Nowon-gu, Seoul 139-706, Korea
Tel: 02-970-2545
Fax: 02-970-2430
E-mail: jskoh@kcch.re.kr

Well-differentiated papillary mesothelioma (WDPM) is a rare subtype of malignant mesothelioma, which is considered to have low malignant potential. Because of its rare occurrence in the pleura, cytopathologists are not familiar with the cytologic features of WDPM, and to date only one report regarding the cytomorphology of aspiration biopsies of WDPM in pleura has been released. The authors present the findings of fine needle aspiration cytology of WDPM in the pleura in a 53-year-old woman. Aspiration smears showed papillary clusters composed of one to three layers of surface tumor cells and a central hyalinized stromal core. Tumor cells were round, ovoid, and spindle like with minimally atypical nuclei and small conspicuous nucleoli. Mitotic activity was virtually absent. Excisional biopsy histologic and immunohistochemical findings were wholly compatible with WDPM findings. Knowledge of the specific cytologic findings of WDPM is crucial for accurate diagnosis and appropriate treatment.

Key Words : Well-differentiated papillary mesothelioma; Pleura; Cytology

Diffuse malignant mesotheliomas of the pleura are uncommon and are usually encountered in patients over 60 years of age. They are associated with a dismal prognosis and have an associated median survival of less than 1 year. On the other hand, well-differentiated papillary mesothelioma (WDPM), a distinct subtype of mesothelioma, is less aggressive than conventional malignant mesothelioma. A previous report by Galateau-Salle *et al.*[1] quoted an average survival period of 74 months for WDPM. A relationship with asbestos exposure has been reported in some cases,[1,2] but this has not been established by epidemiological studies. WDPMs predominantly occur in the female peritoneum.[3] By reason of a few reports of cytomorphologic analysis of the peritoneum[4-9] and of the tunica vaginalis[10] have been reported, cytologists are not familiar with the cytologic findings of WDPM. When WDPM is presented as solitary or multiple nodules along the pleural surface of lung, it may be difficult to suspect WDPM based on fine needle aspiration cytology (FNAC) findings. To date, only one case report has been issued that concisely describes the cytologic characteristics of WDPM of pleura fluid,[11] and no report has described the cytomorphologic features of fine needle aspiration biopsy of WDPM and describing cytologic characteristics as compared with other lesions in pleura. Here, we present a case of WDPM of the pleura in a 53-year-old woman and cytomorphologic features of FNAC and effusion cytology, and corresponding histologic and immunohistochemical analysis findings.

CASE REPORT

A 53-year-old woman presented with a right side chest pain in 2003. The patient had a 3-year history of mild chest pain with aggravation one month before admission. She had no history of occupational or residential asbestos exposure. Computed tomography (CT) of the chest revealed a 3 cm sized peripherally located mass in the right middle lobe of the lung without evidence of pleural effusion (Fig. 1), which was consistent with lung cancer, mesothelioma, or metastatic disease along the pleural sur-

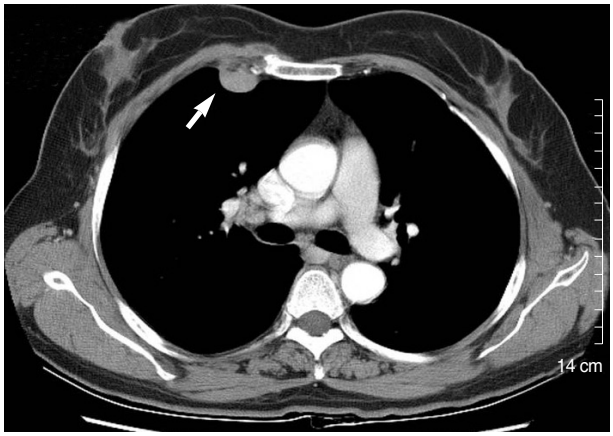

Fig. 1. CT scan of the chest. A 3 cm sized mass is present in right middle lobe of the lung (arrow) with an irregularly thickened adjacent pleural surface.

face from an extrathoracic malignant tumor. Fine needle aspiration biopsy (FNAB) of the mass was performed. Aspiration cytologic findings primarily indicated sclerosing hemangioma. She was recommended for follow-up on a biannual basis. After one year of surveillance, a CT scan showed a small amount of pleural effusion but without a mass size change. A cytologic examination of pleural fluid suggested mesothelial cell proliferation. Because previous cytologic examinations suggested a benign condition, the patient underwent a partial excisional biopsy for a confirmative diagnosis. Gross examination revealed a 1.1 × 1.0 cm grayish-white firm nodular mass, which was attached to the pleural surface of the partially excised lung. The confirmatory histologic diagnosis (supported by ancillary immunohistochemical analysis) was of well-differentiated papillary mesothelioma. She had not received adjuvant chemotherapy or radio-

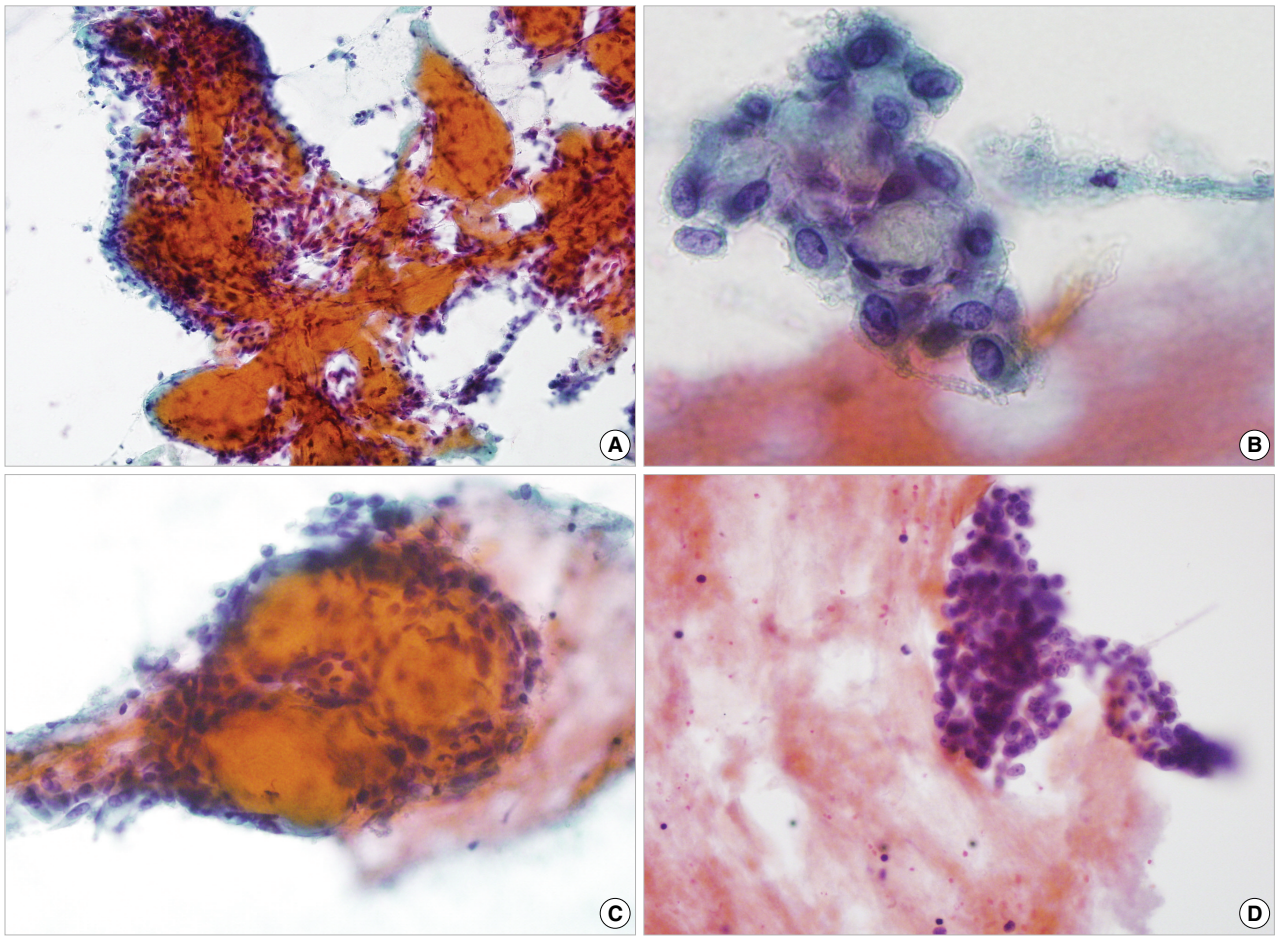

Fig. 2. Cytologic features of the FNA biopsy (A-C). (A) Syncytial papillary structures of a centrally hyalinized stromal core with surrounding tumor cells (Papnicolaou stain) are noted. (B) Small spherical forms are composed of a collagenous core and a lining of tumor cells (Papnicolaou stain). (C) Round to ovoid cells and vesicular nuclei with minimal nuclear atypia and small conspicuous nucleoli are observed (Papnicolaou stain). (D) Cytologic features of pleural fluid. Small groups of mesothelial cells with bland looking nuclei and prominent small nucleoli, similar to those of reactive mesothelial hyperplasia are observed (Papnicolaou stain).

therapy, and at the time of her last follow up, approximately 5 years after diagnosis, there had been no clinical or radiological evidence of the remnant tumor size change or recurrent disease.

FNAC was obtained by a radiologist under CT guidance using a 20-gauge needle. Material was fixed in 95% alcohol before Papanicolaou staining. Remaining FNAC material was centrifuged and the sediment was used to prepare a cell block. A sample of pleural fluid was also centrifuged and the sediment was smeared onto glass slides and Papanicolaou stained. The surgical specimen and the FNA biopsy cell block were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with H&E (hematoxylin and eosin). Immunohistochemistry was performed on the surgical specimen for cytokeratin (1:400, Biogenex, San Ramon, CA, USA), epithelial membrane antigen (1:100, Dako, Carpinteria, CA, USA), vimentin (1:1,000, Biogenex), thyroid transcription factor-1 (1:50, Labvision, Fremont, CA, USA), calretinin (predilution (1:100), Labvision), carcinoembryonic antigen (1:50, Dako), D2-40 (1:100, Invitrogen, Carlsbad, NM, USA), Ki-67 (1:50, Invitrogen), CK5/6 (1:100, Invitrogen) and p53 (1:200, Labvision) using a standard streptoavidin-Biotin complex technique.

Aspiration smears showed some amount of papillary clusters in a bloody background, but isolated epithelioid cells were scarce. Papillary structures varied in size and shaped from large syncytium to small spherical cores (Fig. 2A). Both were typically composed of a central hyalinized stromal core and a lining of single or multi-layered epithelioid cells with round, ovoid, and sometimes a spindle-shaped vesicular nucleus with a small conspicuous nucleolus (Fig. 2B). Nuclear membranes had smooth contours and showed minimal nuclear atypia with no mitosis or multinucleated forms (Fig. 2C). A few cells had intranuclear inclusions like those seen in papillary thyroid carcinoma. Effusion cytology revealed small amounts of cell clusters in a bloody background. Clusters showed flat sheets of orderly arranged reactive mesothelial cells, which had bland vesicular nuclei with centrally located small conspicuous nucleoli. The cells had polygonal cyanophilic cytoplasm with distinct cytoplasmic borders and slit like intercellular spaces (Fig. 2D). Some hyalinized papillary structures were also appreciated in both cell block sections of aspirate and effusion cytology. A single layer of surface lining cells with slight atypia covered. Occasional psammomatous calcified materials were noted, especially in hyalinized stromal cores.

Histologically, a relatively well-circumscribed exophytic nodular lesion was observed along the pleural surface that did not invade lung parenchyma (Fig. 3A). The tumor contained numerous complex papillary structures, which were composed of fibrous cores surrounded by a single to three layers of tumor cells. The fibrous cores displayed various structures from well-developed vascular cores with some activated fibroblasts to acellular sclerotic patterns without vessels. Surface lining tumor cells were uniformly cuboidal or polygonal. The cells had bland looking vesicular nuclei with a single small conspicuous nucleolus (Fig. 3B). No mitosis was observed, and psammoma bodies were infrequently observed in sclerotic fibrous cores.

Immunohistochemical analysis demonstrated that the tumor cells were positive for D2-40, calretinin, cytokeratin, vimentin, and epithelial membrane antigen (EMA), while on the other hand they were negative for thyroid transcription factor-1 (TTF-1), carcinoembryonic antigen (CEA), p53, cytokeratin 5/6, and cytokeratin 19. The Ki-67 labeling index was less than 1% of

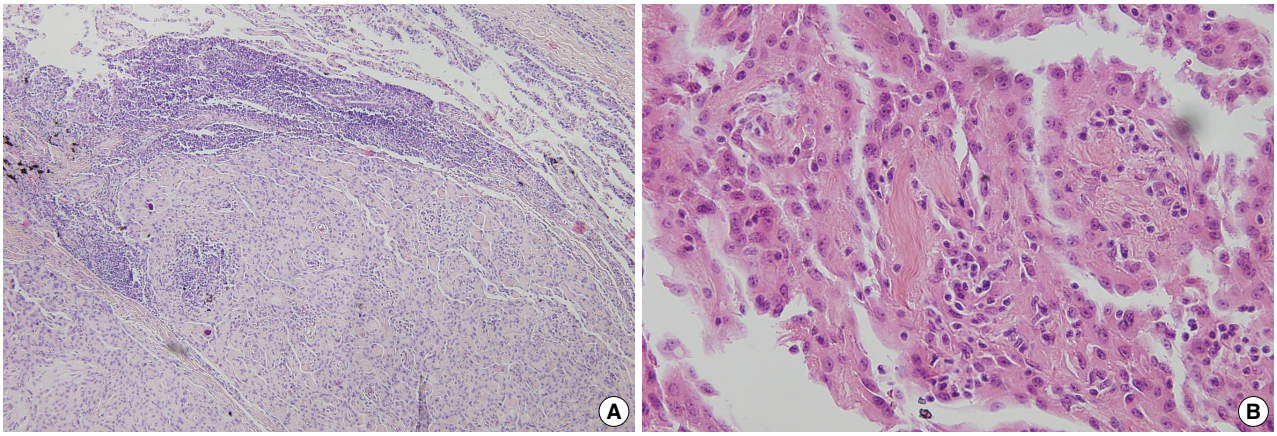

Fig. 3. Histologic features of the corresponding surgical specimen. (A) A low-power view shows a nodule along the pleural surface without lung parenchymal invasion, and papillary structures composed of a central hyalinized stromal core with surrounding minimally atypical tumor cells. (B) Cuboidal epithelioid cells are arragned along central hyalinized stromal cores. The tumor cells have bland vesicular nuclei with centrally located small conspicuous nucleoli.

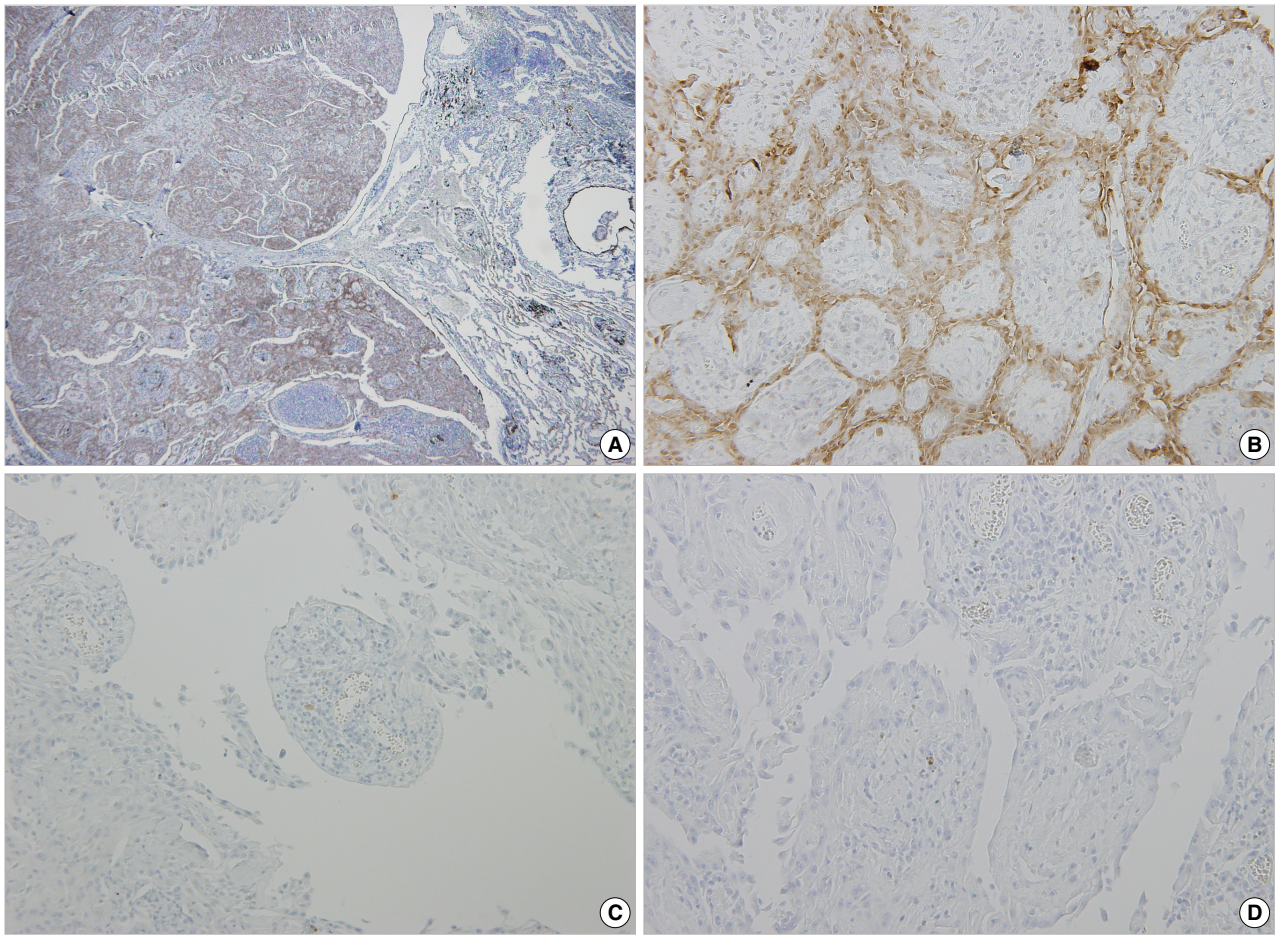

Fig. 4. Immunohistochemical stains. (A) The cytoplasm is positive for D2-40. (B) Strong nuclear and cytoplasmic stainings for calretinin are shown. Tumor cells are negative for thyroid transcription factor-1 (C) and carcinoembryonic antigen (D).

tumor cells (Fig. 4).

DISCUSSION

WDPM of the pleura is a rare disease, and fewer than 50 cases have been reported in the current literature.[1,12] It is important to differentiate WDPM from diffuse malignant mesothelioma during cytologic and histologic examinations because of the prognostic difference between the two. WDPM is considered to be of low malignant potential and is associated with prolonged survival, which is often over several years, whereas diffuse malignant mesothelioma is associated with dismal prognosis and has an average survival rate of less than 1 year from diagnosis.[1-3,12] As a result, the identification of the distinct cytologic and histologic characteristics of WDPM is critical to prevent misdiagnosis. In such cases, pleural WDPM must be differentiated from diseases, such as, conventional malignant mesothelioma, reactive mesothelial hyperplasia, and peripherally located pulmonary lesions, like sclerosing hemangioma and metastatic adenocarcinoma, during cytologic examinations. Malignant mesothelioma is typically characterized by a single cell population with appearances ranging from benign looking mesothelial cells to highly atypical cells.[12,13] Some cases of malignant mesothelioma of the epithelioid type with a prominent papillary pattern can be very difficult to distinguish from WDPM. However, the former usually shows an admixture of a solid sheet area and papillae of mesothelial cells that are atypical due to an enlarged nucleus, hyperchromasia, multinucleation, and prominent large nucleoli. Furthermore, background small clusters of atypical cells are present in three-dimensional groups with scalloped edges; cell-cell engulfment is also noted. WDPM usually exemplifies bland or minimally atypical nuclei characteristics with fine vesicular chromatin patterns and small conspicuous nucleoli. Cell-cell engulfment and three-dimensional clusters are extremely uncommon findings in WDPM.

Our case was primarily suggestive of sclerosing hemangioma by FNA biopsy analysis. This is the primary reason why the patient underwent partial resection for a further confirmative diagnosis rather than complete excision for treatment. There are some overlapped clinical and cytological findings between WDPM and sclerosing hemangioma. Most sclerosing hemangiomas are solitary and peripherally located in lung parenchyma, though sclerosing hemangioma may also involve visceral pleura in 4%.[14] These clinical situations tend to confuse cytologists attempting to differentiate the two. In the described case, the tumor was also mainly located along the pleural surface without involvement of lung parenchyma according to histologic findings. The aspiration of sclerosing hemangioma with a papillary pattern showed prominent papillary configurations with bland looking cuboidal cells around hyalinized fibrous cores, as are seen in WDPM. However, prominent hyalinized fibrous cores are less commonly found in sclerosing hemangioma than in WDPM. Tumor cells of sclerosing hemangioma occasionally have intranuclear inclusions but nucleoli are rarely detected. Also a dual cell population is much more a characteristic finding of sclerosing hemangioma.[15-17]

Metastatic adenocarcinoma to the pleural cavity can be easily differentiated from WDPM using cytologic features and clinical information.

Finally, it is necessary to differentiate WDPM from reactive mesothelial hyperplasia. Several authors have cautioned that their differentiation is difficult based on cytologic features alone.[4,5,8,9,13,18] The reason behind this is the hyalinized stromal core, which is a characteristic finding of WDPM, is also found in reactive mesothelial hyperplasia by washing cytologic examinations.[17] However, Ikeda *et al.*[8] described that the number of hyalinized stromal cores are more abundant in WDPM than in reactive mesothelial hyperplasia, and found that this was helpful for detecting WDPM. In the present case, reactive mesothelial hyperplasia was considered during the effusion cytology diagnostic study because only a small number of mesothelial cells showed prominent nucleoli and vesicular bland nucleic features.

Immunohistochemical studies are critical in obtaining a correct diagnosis. In our case, tumor cells were positive for specific mesothelial associated markers, including D2-40 and calretinin, and negative for TTF-1, which is positive in pulmonary originated tumors including pulmonary adenocarcinoma and sclerosing hemangioma. Other adenocarcinoma-associated markers, including CEA and cytokeratin 19 were immunonegative. In WDPM, most epithelial mesothelioma cells are strongly positive for EMA, and because WDPM is considered a distinct mesothelioma subtype, EMA expression provides supportive evidence for the diagnosis of WDPM. Butnor *et al.*[2] reported that EMA staining was observed in two of four cases of WDPM, and Henderson *et al.*[19] reported that 77% of malignant mesotheliomas showed EMA-positivity, whereas only 4% of reactive mesothelial proliferations were EMA positive. In our case, EMA positivity supported the neoplastic nature of the lesion. Our patient remains alive and has been well for about 5 years after diagnosis without any adjuvant therapy. Major reports advocate observation only without extensive debulking surgery, chemotherapy, or radiotherapy.[7] This is due to the fact that most cases of WDPM show prolonged survival as compared with malignant mesothelioma and because WDPM is considered a lesion of low malignant potential.[12] However, the occurrence of rapidly progressive disease suggests that the underlying disease is a diffuse malignant mesothelioma, and thus sampling adequacy and further evaluations are important to secure diagnostic accuracy.[12]

In conclusion, some pathologic conditions share clinical and cytologic features with WDPM in the pleura, and therefore, it is important that cytologists recognize the cytomorphologic features of WDPM to enable clinicians to be properly informed about possibility of a low grade mesothelial tumor.

REFERENCES

1. Galateau-Salle F, Vignaud JM, Burke L, *et al.* Well-differentiated papillary mesothelioma of the pleura: a series of 24 cases. Am J Surg Pathol 2004; 28: 534-40.
2. Butnor KJ, Sporn TA, Hammar SP, Roggli VL. Well-differentiated papillary mesothelioma. Am J Surg Pathol 2001; 25: 1304-9.
3. Daya D, McCaughey WT. Well-differentiated papillary mesothelioma of the peritoneum. A clinicopathologic study of 22 cases. Cancer 1990; 65: 292-6.
4. Gong Y, Ren R, Ordonez NG, Sun X, Sneige N. Fine needle aspiration cytology of well-differentiated papillary mesothelioma: a case report. Acta Cytol 2005; 49: 537-42.
5. Haba T, Wakasa K, Sasaki M. Well-differentiated papillary mesothelioma in the pelvic cavity. A case report. Acta Cytol 2003; 47: 88-92.
6. Hejmadi R, Ganesan R, Kamal NG. Malignant transformation of a well-differentiated peritoneal papillary mesothelioma. Acta Cytol 2003; 47: 517-8.
7. 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.

8. Ikeda K, Suzuki T, Tate G, Mitsuya T. Cytomorphologic features of well-differentiated papillary mesothelioma in peritoneal effusion: a case report. Diagn Cytopathol 2008; 36: 512-5.
9. Jayaram G, Ashok S. Fine needle aspiration cytology of well-differentiated papillary peritoneal mesothelioma. Report of a case. Acta Cytol 1988; 32: 563-6.
10. Tolhurst SR, Lotan T, Rapp DE, *et al.* Well-differentiated papillary mesothelioma occurring in the tunica vaginalis of the testis with contralateral atypical mesothelial hyperplasia. Urol Oncol 2006; 24: 36-9.
11. Kao S, Mahon K, Lin B, *et al.* Pleural well-differentiated papillary mesothelioma: a case report. J Thorac Oncol 2009; 4: 920-2.
12. Travis WD BE, Muller-Hermelink HK, editors. World Health Organization classification of tumors. Pathology and genetics of tumours of the lung, pleura, thymus and heart. IARC press; 2004: 135-6.
13. Kho-Duffin J, Tao LC, Cramer H, Catellier MJ, Irons D, Ng P. Cytologic diagnosis of malignant mesothelioma, with particular emphasis on the epithelial noncohesive cell type. Diagn Cytopathol 1999; 20: 57-62.
14. Travis WD BE, Muller-Hermelink HK, editors. World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC press; 2004: 115-6.
15. Gal AA, Nassar VH, Miller JI. Cytopathologic diagnosis of pulmonary sclerosing hemangioma. Diagn Cytopathol 2002; 26: 163-6.
16. Kaw YT, Nayak RN. Fine needle aspiration biopsy cytology of sclerosing hemangioma of the lung. A case report. Acta Cytol 1993; 37: 933-7.
17. Wojcik EM, Sneige N, Lawrence DD, Ordonez NG. Fine-needle aspiration cytology of sclerosing hemangioma of the lung: case report with immunohistochemical study. Diagn Cytopathol 1993; 9: 304-9.
18. Lee A, Baloch ZW, Yu G, Gupta PK. Mesothelial hyperplasia with reactive atypia: diagnostic pitfalls and role of immunohistochemical studies-a case report. Diagn Cytopathol 2000; 22: 113-6.
19. Henderson DW, Shilkin KB, Whitaker D. Reactive mesothelial hyperplasia vs mesothelioma, including mesothelioma in situ: a brief review. Am J Clin Pathol 1998; 110: 397-404.