Title: Well-differentiated papillary mesothelial tumor: a manifestation of mesothelioma in situ.

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Abstract

The nature and behavior of papillary lesions of the mesothelium have been uncertain. Indeed, the name has recently been changed from well-differentiated papillary mesothelioma to well- differentiated papillary mesothelial tumor to reflect this uncertainty. The development of BAP-1 immunostaining has been of great aid in confirming malignancy in those mesothelial proliferations in which BAP-1 expression is lost. In this case, the patient presented with a papillary tumor of the pleura in which there was loss of BAP-1 expression, in the papillary tumor, and also the adjacent flat mesothelium, allowing the diagnosis of mesothelioma in situ. The patient went on to develop invasive mesothelioma. This case demonstrates the utility of BAP-1 immunostaining in confirming the malignant nature of in situ mesothelial proliferations. The findings suggest that perhaps the former term of well-differentiated papillary mesothelioma is the more appropriate.

Keywords: Mesothelioma, Mesothelioma in situ, Well-differentiated papillary mesothelial tumor

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1. Introduction

In many organ systems, the existence of in situ neoplasm, prior to invasive neoplasm, is well-recognized. The identification and diagnosis of mesothelioma in situ have been challenging, prior to the application of BAP-1 immunostaining. Loss of expression of BAP-1 is recognized as a reliable indicator of

malignancy of mesothelial cells and now allows the histologic/immunohistochemical diagnosis of mesothelioma in situ (MIS) in the 50% or so of mesotheliomas that lose BAP-1 expression.

Another challenge in the interpretation of mesothelial lesions has been the interpretation of the nature of pleural papillary mesothelial proliferations. Indeed, in recent years the name has been changed from well-differentiated papillary mesothelioma to well-differentiated papillary mesothelial tumor (WDPMT), because of the uncertainty regarding the behavior of individual cases [1, 2] The application of BAP-1 immunostaining has made possible the recognition of malignancy in those lesions that have lost BAP-1 expression.

It has been suggested that WDPMT may be a marker of underlying mesothelioma in situ, although evidence for this association is sparse. In this case report, there are biopsies from regions of WDPMT and single-layer flat mesothelial cells, in which both lesions have lost BAP-1 expression. Additional biopsies from the patient also demonstrated mesothelioma in situ, as well as early invasive mesothelioma before any gross lesions were observed at surgery or by imaging. These findings add to the concept of WDPMT as a manifestation of malignant mesothelioma.

2. Case presentation

The patient is an 80-year-old female with a history of hypertension, atrial fibrillation, and prior smoking who developed a cough and dyspnea while vacationing which led to evaluation showing a left pleural effusion. She had a possible asbestos exposure as her father had worked in the industry. A chest CT scan showed a relatively limited left pleural effusion without pleural nodularity or adenopathy. Cytopathology from the effusion was felt to be suggestive of mesothelioma, so a formal thoracoscopic left pleural biopsy was performed. The biopsy revealed broad, arborescent papillary formations covered by a single layer of mesothelial cells (Figure 1). The tumor cells exhibited mildly atypia, with inconspicuous nuclei, rare mitotic figures, and no evidence of stromal invasion. Rare psammomatous

calcifications were also observed. The remaining sites obtained from various locations of the pleura, including the left pleura, did not show any significant abnormalities, with flat mesothelial cells arranged in a single layer with generally bland morphology and focal atypia (Figure 2). Immunohistochemical analysis for BRCA1 Associated Protein-1 (BAP-1) was performed on formalin-fixed, paraffin-embedded tissues from both the papillary tumor and flat mesothelial locations (Figure 1-2). The results showed loss of BAP-1 expression not only in the papillary lesion but also in the flat mesothelial lining in several locations away from the papillary lesion. Concurrent cytological examination of biopsy specimens reveal atypical mesothelial cell proliferation with some of the mesothelial cells showing BAP-1 loss of expression (Figure 3). Based on the pathologic and immunohistochemical findings, the diagnosis was well-differentiated papillary mesothelial tumor (WDPMT) with loss of BAP-1 expression, indicative of malignant mesothelioma, with regions of mesothelioma in situ. The findings suggested that the well-differentiated papillary mesothelial tumor in this patient was a focal manifestation of more diffuse mesothelioma in situ.

After further cardiopulmonary evaluation and a long discussion with the patient and her family, the patient ultimately underwent a left pleurectomy and pulmonary decortication, again with findings of minimal volume disease. The patient tolerated the procedure quite well and was discharged home after 11 days in the hospital. Histologic sections of the left pleura disclose a small focus of invasive malignant mesothelioma of epithelioid type. There was a 5 mm tumor invading the parietal pleural tissue. In addition, a focal 2 mm residual well-differentiated papillary mesothelial tumor was found in a different site apart from the invasive lesion, and multifocal mesothelioma in situ was also observed. BAP-1 loss of expression was observed in the invasive mesothelioma, residual papillary lesion, and mesothelioma in situ. Interestingly, two lymph nodes contained rare positive mesothelial cells that had lost BAP-1 expression and were considered isolated tumor cells (Figure 4).

3. Molecular study

The FISH studies for CDKN2A (p16) 9p21.3 (Abbott Molecular LSI 9p21 9p16)/CEP9 Dual Color Probe was performed. FISH analysis utilizing the Chromosome 9 dual color (centromere 9/9p21-CDKN2A) probe did not reveal any abnormalities in the 200 nuclei/probe assessed. Thus, the results indicate the absence of homozygous CDKN2A loss.

4. Discussion

According to recent studies, well-differentiated papillary mesothelial tumors (WDPMTs) generally exhibit a benign clinical course and a more favorable prognosis compared to malignant mesothelioma [3]. Malignant mesothelioma, on the other hand, typically has a poor long-term survival rate. The majority of WDPMT cases progress slowly with a common recurrent course. Complete excision can result in a cure for a minority of cases [1]. Similar to mesothelioma in situ, WDPMTs are characterized by the presence of bland mesothelial cells without invasion.

In our case, the initial presentation revealed a well-differentiated papillary mesothelial tumor with bland mesothelial cells and no evidence of invasion. Notably, we observed the loss of BAP-1 nuclear expression not only in WDPMT but also in concurrent multifocal mesothelioma in situ located elsewhere. While it has been reported that WDPMTs typically exhibit retained BAP-1 expression, a single case report documented a BAP1 germline mutation in WDPMT [4]. A case series demonstrated that certain cases exhibited both the pathologic features of mesothelioma in situ, with a single layer of mesothelial cells losing BAP1, as well as areas of WDPMT also showing BAP1 loss. The presence of BAP1 loss in papillary areas suggests that, at least in this case, the WDPMT truly represented mesothelioma in situ [5]. Additionally, a study indicated that combined cases of WDPMTs and malignant mesothelioma demonstrate loss of BAP1 expression, suggesting a potential clonal relationship between these two

entities [4]. Thus, the loss of BAP-1 expression, especially in the presence of multifocal mesothelioma in situ in our case, represents an exceptionally unusual scenario.

After a 3-month follow-up, the observed lesion progressed to a malignant mesothelioma with small areas of invasion. Some residual papillary mesothelial lesions were still present, and loss of BAP-1 expression was detected in all invasive, in situ, and residual papillary components. Recent studies indicate that the progression of WDPMTs to malignant mesothelioma is uncertain, with only a few reported cases [5, 6]. The progression from WDPMT to early invasive mesothelioma in our case, accompanied by the loss of BAP-1 stain in the WDPMT lesion, strongly supports the hypothesis that WDPMT may sometimes act as a manifestation of mesothelioma in situ and carries a risk of progression to invasive mesothelioma.

Molecular data on WDPMTs is limited. Pleural WDPMTs have not shown CDKN2A homozygous deletion, which has been observed in a minority of mesothelioma in situ cases [5, 7].

5. Abbreviations

BAP-1, BRCA1 Associated Protein-1; WDPMT, well-differentiated papillary mesothelial tumor; MIS, mesothelioma in situ; FISH, fluorescence in situ hybridization; CDKN2A, Cyclin Dependent Kinase Inhibitor 2A; CEP, C -terminally encoded peptide

6. Funding

None.

7. Patient consent statement

The author can attest that in the submitted case report no identifying information or patient health information is included. Only non-identifiable images are depicted.

8. Declaration of Competing Interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

9. Authors' contributions

None.

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None.

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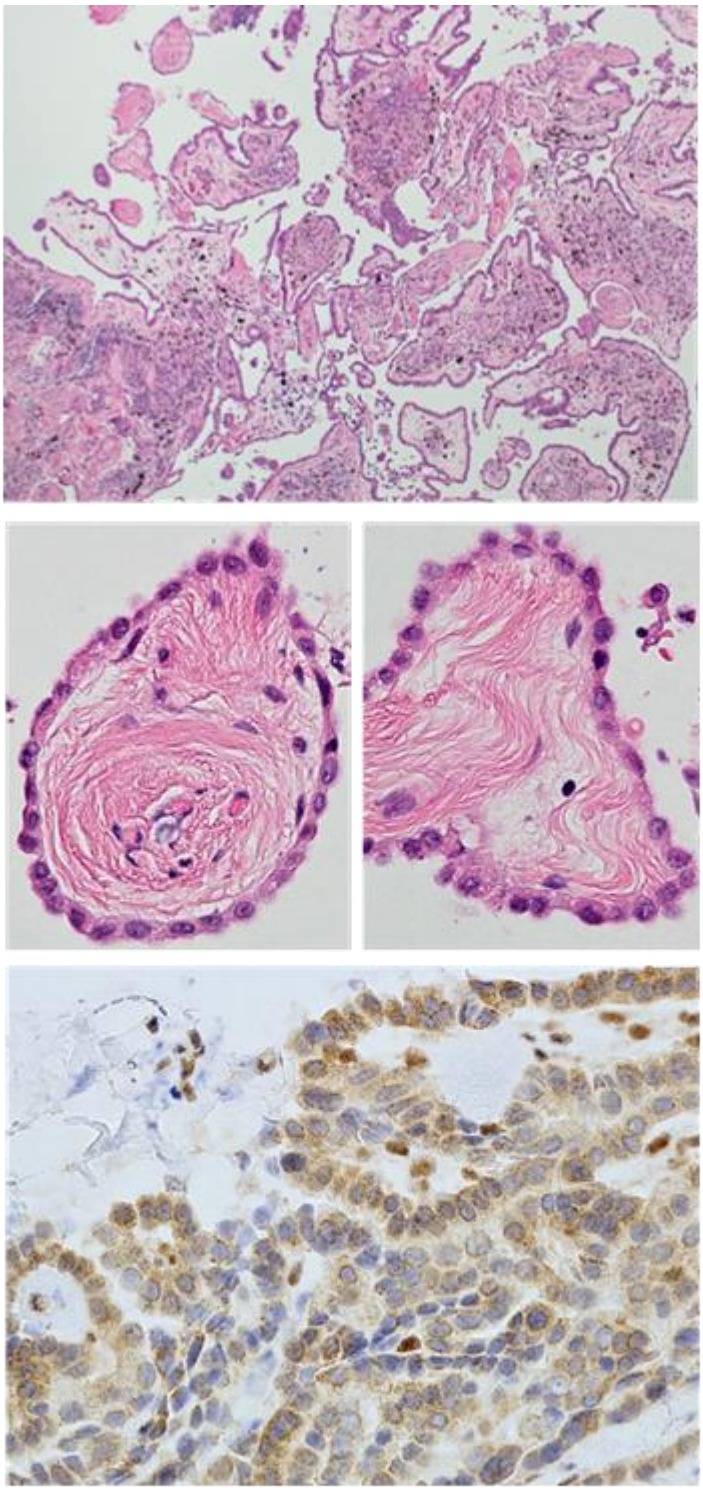
1. Figure1.TIF; Well-differentiated papillary mesothelial tumor: A) note papillary configuration (H&E stain, x40, B) individual papillae with only mildly atypical mesothelial cells on the surface, and C) BAP-1 immunostain with brown chromogen, showing absence of nuclear staining indicating loss of BAP-1 expression (x400)

2. Figure2.TIF; Random biopsies at time of re-exploration for persistent pleural effusion with no gross lesions noted; A) multiple flat areas of atypical mesothelial cells that were BAP-1 negative were present, consistent with mesothelioma in situ (H&E, x400; B) focus of superficially-invasive malignant mesothelioma (H&E, x200), with C) showing loss of BAP-1 expression (no red staining of nuclei) (x200).

3. Figure3.TIF; Cytopathology of pleural fluid: A) Pap stain showing clusters of atypical mesothelial cells; B) smear showing similar findings, and C) BAP-1 immunostain showing loss of expression in some

of the mesothelial cells, probably reflection a mixture of benign and malignant mesothelial cells (B & C H&E stain, all x400)

4. Figure4.TIF; Positive lymph node: A) epithelioid cells in a mediastinal lymph node (H&E, x400; B) cells are calretinin positive, but could represent benign mesothelial inclusions (x40), and C) however, epithelioid cells show loss of BAP-1 immunostaining (no red nuclear staining, x400) indicating these are malignant mesothelial cells.



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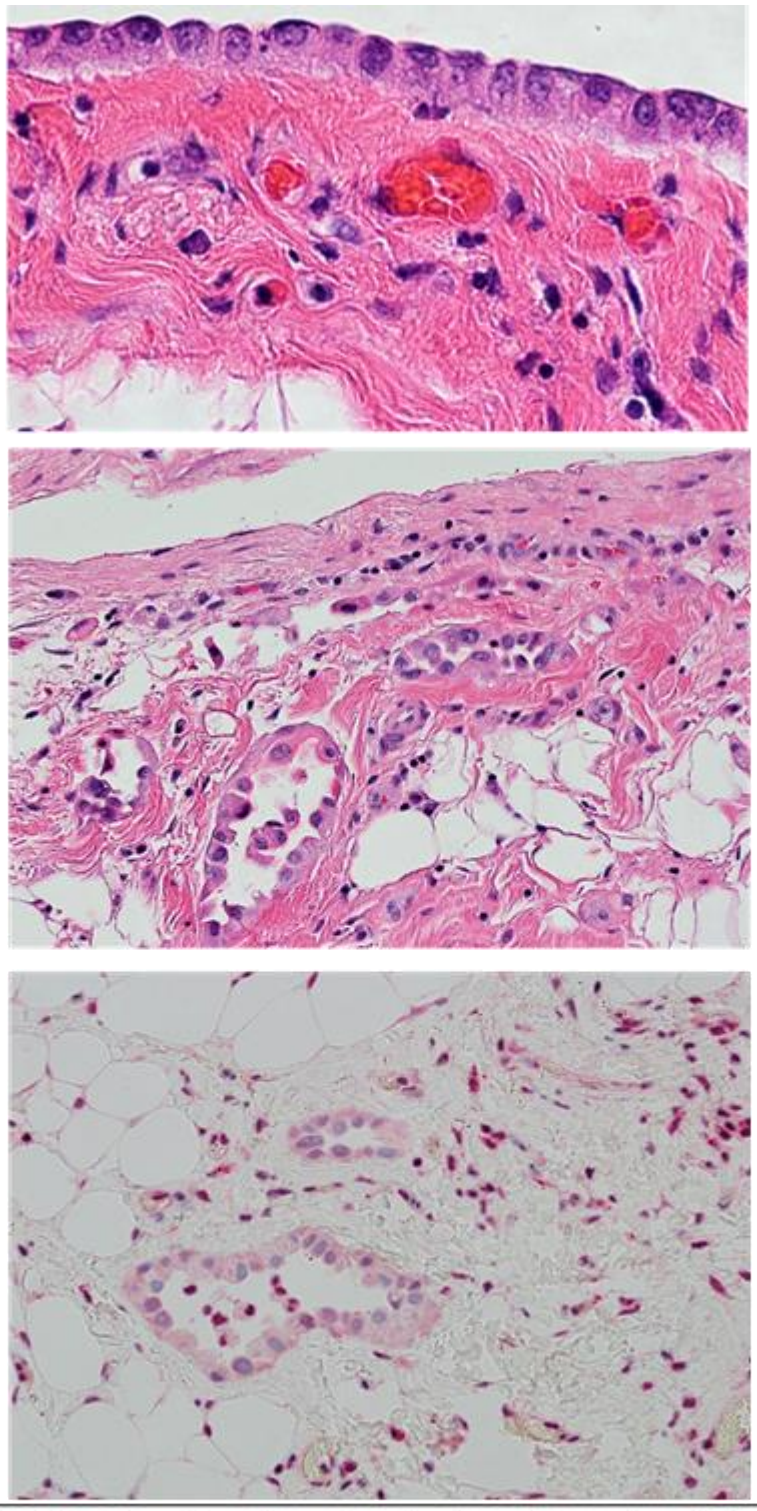

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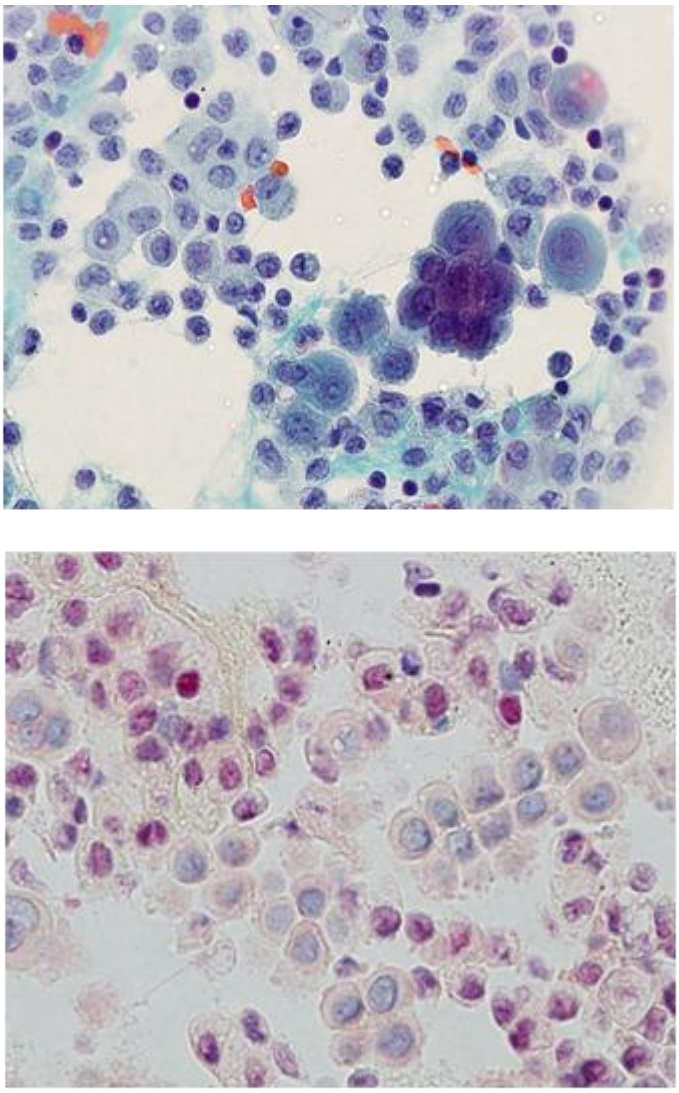

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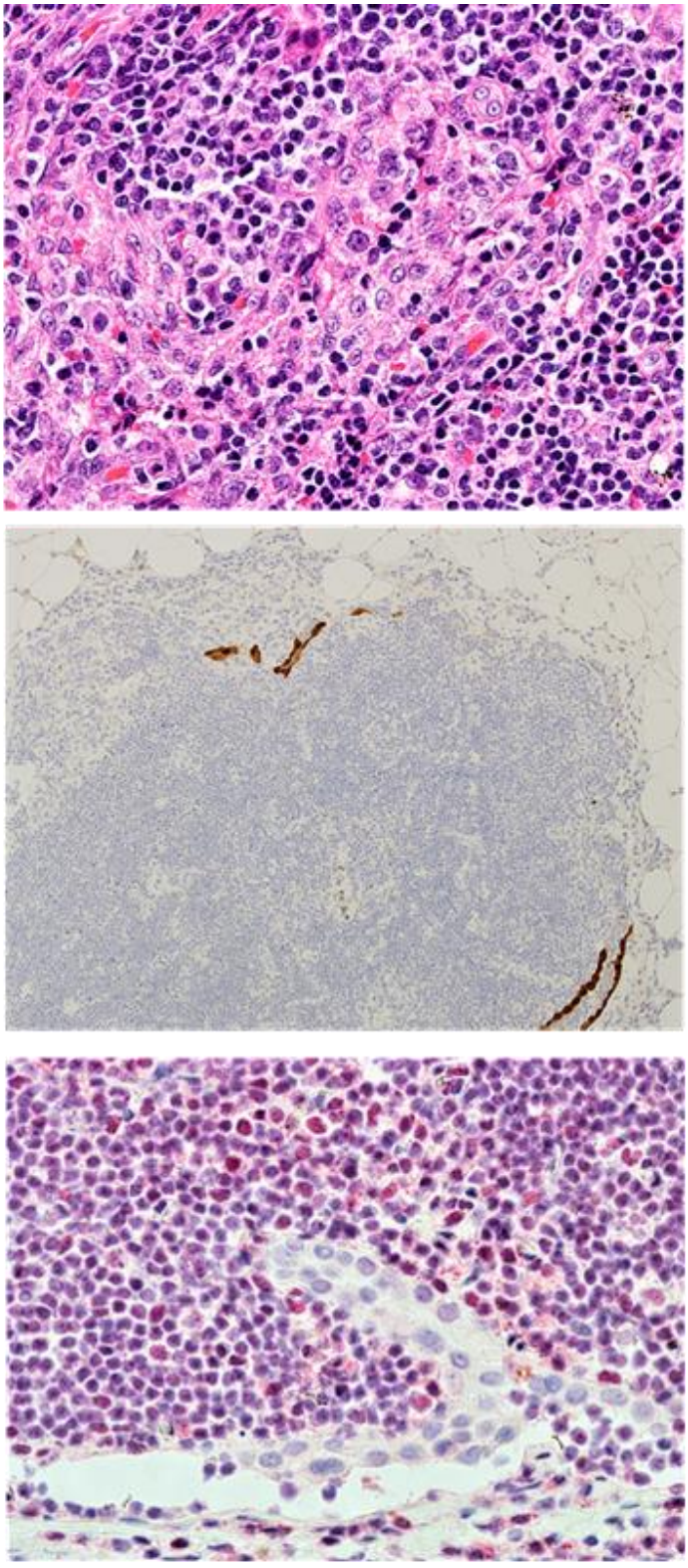

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