

Progression from Malignant Mesothelioma in Situ to Malignant Mesothelioma: A Case Report Spanning 13 Years

Nurfiza Ladak¹; Pratibha Sharma Shukla^{2*}

¹NYU Langone Medical Center, New York, NY 10016.

²NYU Langone Medical Center/Bellevue Hospital 462 First Avenue, Rm 4W35B New York, NY 10016.

Received Date : July 15, 2022
Accepted Date : Aug 10, 2022
Published Date : Sep 02, 2022
Archived : www.jcmimagescasereports.org
Copyright : © Pratibha Sharma Shukla 2022

***Corresponding Author:** Pratibha Sharma Shukla, NYU Langone Medical Center/Bellevue Hospital 462 First Avenue, Rm 4W35B New York, NY 10016.
Tel: 212-562-7892
Email: pratibha.shukla@nyulangone.org

Abstract

Malignant mesothelioma is an aggressive neoplasm associated with poor prognosis. Identification of in-situ phase of malignant mesothelioma can help detect disease at an earlier stage and potentially improve outcome by early therapeutic intervention. The concept of malignant mesothelioma in-situ (MIS) has re-emerged, diagnostic criteria based on use of immunohistochemistry and molecular techniques have been described recently and the latest WHO classification of lung tumors includes MIS as a distinct diagnostic entity. Here we present morphologic and immunohistochemical findings from a patient presenting with multiple peritoneal and pleural in-situ malignant mesothelioma lesions with eventual progression to pleural invasive malignant mesothelioma over a protracted period of 13 years. There are very few well documented cases of malignant mesothelioma in-situ and this unique case provides insight into the morphologic variants and natural behavior of malignant mesothelioma in-situ over an extended period of time.

Introduction

The progression from an in situ lesion to invasive cancer is widely recognized in many different forms of malignancies. Mesothelioma in situ (MIS) although having existed as a concept for many decades has only recently emerged as a distinct diagnostic entity. This is primarily due to the historical controversy surrounding its existence, as many early descriptions came from cases that also harbored foci of invasive disease, which led to the belief that the in situ component did not represent true in situ disease but rather spread of the invasive cancer along a mesothelial lined surface [1,2]. Furthermore, based on morphology alone, mesothelioma in situ cannot be reliably distinguished from reactive atypia [3]. However, advances in molecular techniques and our understanding of the genetic alterations driving mesothelioma now offer new diagnostic modalities, which has renewed interest in this area.

The lack of standardized diagnostic criteria was historically a further hindrance to the routine diagnosis of mesothelioma in situ in everyday practice. Recently, Churg et. al [4] presented a retrospective series of 10 cases of mesothelioma in situ with the following definition: a single layer of surface mesothelial cells showing loss of BRCA Associated Protein 1 (BAP1) nuclear immunostaining and/or CDKN2A homozygous deletion, no evidence of tumor by imaging and/or by direct examination of

the pleura/ peritoneum, and no invasive mesothelioma developing for at least 1 year. They showed that mesothelioma in situ is associated with a high risk of developing invasive mesothelioma over a protracted time. Here we report a unique case of recurrent peritoneal and pleural mesothelioma in situ lesions in a patient with eventual progression to pleural malignant mesothelioma over a period of 13 years.

Clinical Course

A nulliparous, never smoker woman in her thirties, with no history of asbestos exposure or family history of mesothelioma, initially presented with persistent cough and progressive shortness of breath, unresponsive to antibiotics and steroids. Subsequent chest x-ray and CT displayed a right sided pleural effusion and scattered small cystic nodules on the pleural surface. Right thoracoscopy and excisional biopsies of the pleural nodules led to the diagnosis of multicystic mesothelioma after pathologic examination. Eighteen months later, persistent dull pelvic pain led to a pelvic ultrasound and pelvic CT, which revealed ascites and a cystic right adnexal mass. Laparoscopic right salpingo-oophorectomy resulted in the diagnosis of well-differentiated papillary mesothelioma) and multicystic mesothelioma involving the ovarian surface and pelvic peritoneum. She subsequently had a hysterectomy and left salpingo-oophorectomy for debulking of peritoneal cystic masses six

Citation: Pratibha Sharma Shukla. Progression from Malignant Mesothelioma in Situ to Malignant Mesothelioma: A Case Report Spanning 13 Years. J Clin Med Img Case Rep. 2022; 2(5): 1232.

months after the diagnosis of peritoneal well-differentiated papillary mesothelioma.

The patient continued to suffer from recurrent pleural effusions requiring thoracentesis and drainage of pleural fluid two to three times a year leading to placement of dual pleurex catheter. Recurrent hydropneumothorax and pleural cystic nodules associated with atelectasis required several thoracotomy and sternotomy procedures for pleural decortication and debulking with wedge resections of underlying lung parenchyma. Thirteen years after her initial presentation, she underwent yet another pleural decortication and was diagnosed with invasive epithelioid mesothelioma after pathologic examination. At the time of her last follow up, she was suffering from severe shortness of breath due to persistent hydropneumothorax and significant atelectasis of lung parenchyma. She also had extensive peritoneal cystic nodules.

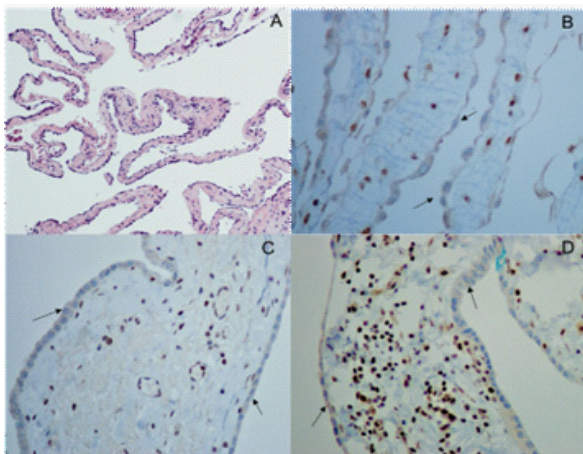


Figure 1: A,B) Pleural lesion from the first presentation. A) Cystic spaces lined by flat mesothelial lining, H&E, 10x. B) Loss of BAP1 expression in mesothelial lining (arrows) while stromal nuclei show retained expression, 40x. C) Loss of BAP1 expression in flat mesothelial lining of pleural lesion from 4 years prior to the diagnosis of invasive mesothelioma, 40x. D) Pleural lesion closer to the diagnosis of invasive mesothelioma with loss of nuclear BAP1 expression in flat mesothelial lining as well as in foci of mildly atypical mesothelium (arrows), 40x.

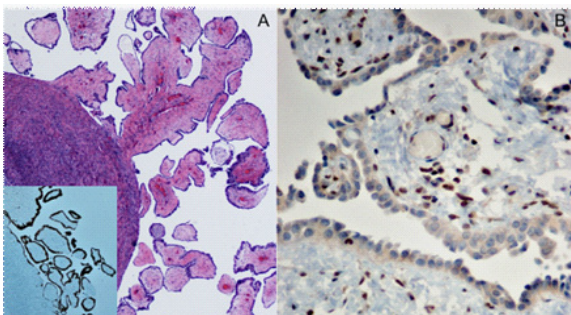


Figure 2: A-B) Peritoneal lesion from the first presentation. Papillary proliferation on an ovarian surface. Inset: Calretinin stains the mesothelial cells lining the papillary proliferations B) Loss of BAP1 nuclear expression in mesothelial cells lining the papillae while stromal nuclei show retained BAP1 expression, 40x.

Histopathologic and Immunohistochemical Features

Hematoxylin and eosin (H&E) stained and immune-stained slides from all surgical procedures performed on the patient from the time of initial presentation to the diagnosis of invasive epithelioid mesothelioma (a total of 9 surgical proce-

dures) were reviewed. Sections from pleural cystic nodules excised at initial presentation showed multiple multi-loculated cystic structures lined by a layer of bland flat to cuboidal cells that stained positive for calretinin, pan-keratin and vimentin. No evidence of invasion into surrounding tissue was seen, and a diagnosis of multicystic mesothelioma was rendered (**Figure 1A**). The right and left salpingo-oophorectomy and hysterectomy specimens from 18 and 24 months after the initial presentation, macroscopically showed normal sized ovaries and uterus covered with fine papillary excrescences and thin walled cystic structures up to 7 cm in diameter. Microscopically, the papillary excrescences showed fibrous cores covered with one layer of bland mesothelial cells that stained positive with calretinin (**Figure 2A**). The cystic structures were similar to the previously seen pleural multicystic mesothelioma. No mitotic activity or foci of microinvasion were found, resulting in a diagnosis of mixed well-differentiated papillary mesothelioma and multicystic mesothelioma.

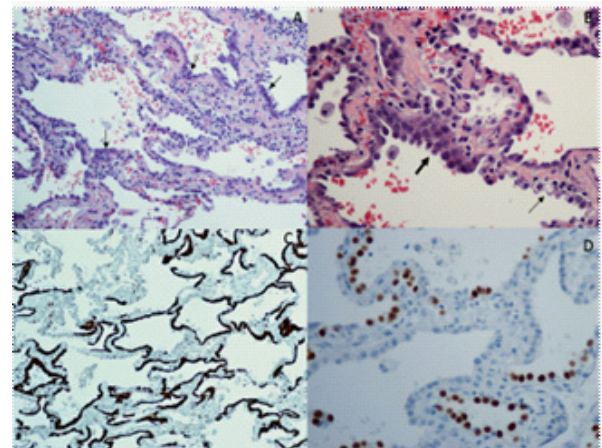


Figure 3: A-D) Invasive mesothelioma: A) Lepidic involvement of lung parenchyma by mesothelioma. (arrows, 20x). B) Atypical mesothelial cells lining alveolar spaces (thick arrow), residual alveolar epithelium (thin arrow), 40x. C) Calretinin stain highlights the lepidic growth pattern of malignant mesothelioma. D) TTF-1 stain is negative in mesothelioma cells and highlights the residual alveolar epithelium.

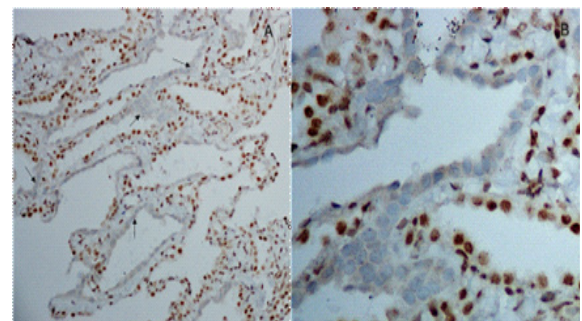


Figure 4: Invasive mesothelioma. BAP1 stain shows loss of nuclear expression in malignant mesothelial cells lining alveolar spaces (arrows) while residual alveolar epithelium and stromal cells have retained expression of nuclear BAP1, A: 20x, B: 40x.

Five subsequent excisions of pleural surface nodules had similar microscopic features without evidence of infiltration of subpleural connective tissue or of underlying lung parenchyma in entirely submitted specimens, and were diagnosed as recurrent mixed well-differentiated papillary mesothelioma

and multicystic mesothelioma. Rare foci of atypia with enlarged and crowded mesothelial cells displaying minor papillary tufting were noted in the last 2 specimens, without evidence of invasion. Pleural nodules and lung wedge resection thirteen years following initial presentation revealed similar cystic and papillary lesions, however with multiple foci of infiltration of sub-pleural connective tissue as well as extensive involvement of underlying lung parenchyma with lepidic growth pattern highlighted by calretinin stain and loss of nuclear BAP1 expression (**Figure 3 & 4**), resulting in the diagnosis of invasive epithelioid mesothelioma. Significant nuclear atypia was also noted, specifically in the invasive component. Scattered areas with microscopic features of well-differentiated papillary mesothelioma and multicystic mesothelioma were present, also exhibiting BAP1 loss. Retrospective immunohistochemistry for BAP-1 performed on the initial pleural and peritoneal lesions from 13 and 11 years prior and also on intervening pleural lesions from 4 and 2 years prior to the diagnosis of invasive epithelioid mesothelioma revealed loss of nuclear BAP1 expression, confirming the diagnosis of mesothelioma in situ in these specimens (**Figs. 1B-D, 2B**).

Discussion

The clinical implications and relevance of the diagnosis of mesothelioma in situ are unclear. However, with the advent of relevant diagnostic criteria and the retrospective analysis of identified cases, it has been shown that patients with mesothelioma in situ do better than patients with malignant mesothelioma, consistent with the notion that mesothelioma in situ represents earlier stage disease. Churg et al [4] found that 7 of their 10 mesothelioma in situ patients subsequently developed invasive mesothelioma, with a median time to progression of 60 months. Pulford et al [5] found in a retrospective analysis that mesothelioma in situ associated with minimal invasion conferred a survival advantage over patients with frankly invasive malignant mesothelioma (8 months vs 22 months). BAP1 is a tumor suppressor gene with de-ubiquitinase activity required to suppress cell growth [6,7]. Over 60% of malignant mesothelioma cases harbor exonic deletions or somatic mutations of the BAP1 gene, with loss of immunohistochemical expression of BAP1 being highly specific for differentiating malignant mesothelioma from benign mesothelial proliferations [8-10]. Simon et al [11] found in comparative genomic hybridization studies that on a chromosomal level, similar alterations exist across both the in situ component and invasive mesothelioma. Loss of BAP1 expression in mesothelioma in situ that precedes malignant mesothelioma demonstrates that it is an early event in the pathogenesis of malignant mesothelioma and BAP1 loss by immunohistochemistry is considered a reliable marker for mesothelioma in situ.

We have documented a case of peritoneal and pleural mesothelioma in situ lesions confirmed by loss of BAP1 expression by immunohistochemistry (IHC). The pleural lesion progressed to invasive epithelioid mesothelioma after several recurrences over a protracted time. Multiple recurrences of pleural surface lesions had histologic features that were diagnosed as well-differentiated papillary mesothelioma and multicystic mesothelioma. Although retrospective review revealed foci of mild stratification and nuclear atypia in some of the pleural lesions closer to the diagnosis of invasive mesothelioma, no evidence of stromal invasion was seen in any of them (all pleural speci-

mens prior to the diagnosis of invasive mesothelioma were entirely submitted for microscopic examination). Most significantly, retrospectively identified loss of BAP1 expression in the neoplastic mesothelial cells of both pleural and peritoneal lesions with morphologic features of multicystic mesothelioma and well-differentiated papillary mesothelioma in specimens from 13 and 11 years prior respectively, provides strong evidence that these recurrent mesothelial proliferations represented mesothelioma in situ all along, rather than the benign mesothelial entities reflected in the original diagnoses. Lee et al [12] have shown that pure cases of well-differentiated papillary mesothelioma retain IHC expression of BAP1, whereas BAP1 loss in well-differentiated papillary mesothelioma is associated with synchronous or metachronous malignant mesothelioma. These findings align with our case and support the concept of progression from mesothelioma in situ to malignant mesothelioma. We have documented progression of pleural in-situ mesothelioma to invasive epithelioid mesothelioma by confirming loss of BAP1 nuclear expression in surface mesothelial flat and papillary lesions at the time of initial presentation, 13 years prior to the diagnosis of invasive pleural mesothelioma. Loss of nuclear BAP1 expression was also seen in the initial peritoneal lesions that showed morphologic features of well differentiated papillary mesothelioma without any evidence of invasive mesothelioma in thoroughly sampled specimens. The peritoneal lesions have stayed relatively stable on imaging with persistent cystic nodules and mild ascites without requiring additional surgery. This case is also unique in having multifocal (pleural and peritoneal) in-situ mesothelioma and documented progression of pleural lesions to invasive mesothelioma.

As mentioned earlier, the definition of mesothelioma in situ by Churg et al. [4] includes only a flat or slightly papillary single layer of surface mesothelial proliferation with loss of BAP1 nuclear immunostaining and/or CDKN2A homozygous deletion excludes cases with any evidence of tumor by imaging or direct examination. However, we feel this definition should include cystic and papillary surface mesothelial proliferations, as well as macroscopic evidence of tumor, as surface nodules were present in our case. We are in agreement with Pulford et al. [5] who utilize a broader definition of mesothelioma in situ. They state that BAP1 deletion in any non-invasive architectural pattern should be classified as mesothelioma in situ, as studies have shown that these cells have the molecular alterations of malignancy [11]. The 2021WHO classification of lung tumors includes mesothelioma in situ as a distinct diagnostic entity [13]. Although no specific therapy for mesothelioma in situ is currently available, the diagnosis of mesothelioma in situ can result in close monitoring of patients for disease progression, and may help us better understand the biological behavior of this disease entity.

Conclusion

We have documented a case of unequivocal gradual progression of pleural mesothelioma in situ to epithelioid malignant mesothelioma confirmed by nuclear BAP1 loss by immunohistochemistry. With close management and surgical intervention in the form of debulking procedures, the patient did not progress to invasive disease for a period of thirteen years. This case is therefore unique in that it provides insight into potential clinical management and outcomes in these patients.

References

1. Whitaker D, Henderson DW, Shilkin KB. The concept of mesothelioma in situ: implications for diagnosis and histogenesis. *Semin Diagn Pathol.* 1992; 9(2): 151-61
2. Bono F, Lombardi M. Prominent in situ component in a pleural malignant mesothelioma. *Int J Surg Pathol.* 2015; 23(2): 127-9
3. Henderson DW, Shilkin KB, Whitaker D. Reactive Mesothelial Hyperplasia vs Mesothelioma, Including Mesothelioma In Situ: A Brief Review, *American Journal of Clinical Pathology.* 1998; 110(3): 397-404
4. Churg A, Galateau-Salle F, Roden, A.C. et al. Malignant mesothelioma in situ: morphologic features and clinical outcome. *Mod Pathol.* 2020; 33: 297-302
5. Pulford E, Douglas W. Henderson, SK. Malignant mesothelioma in situ: diagnostic and clinical considerations. *Pathology.* 2020; 52(6): 635-642
6. Jensen D Proctor M, Marquis S, et al. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. *Oncogene.* 1998; 16: 1097-1112.
7. Cheung M, Testa JR. BAP1, a tumor suppressor gene driving malignant mesothelioma. *Transl Lung Cancer Res.* 2017; 6(3): 270-278.
8. Churg A, SheffieldBS, Galateau-Salle F. New markers for separating benign from malignant mesothelial proliferations: are we there yet?. *Arch Pathol. Lab. Med.* 2016; 140: 318-321
9. Churg A, Hwang H, Tan L et al. Malignant Mesothelioma in situ. *Histopathology.* 2018; 72: 1033-1038
- 10 Integrative molecular characterization of malignant pleural mesothelioma. Hmeljak J, Sanchez-Vega F, Hoadley KA et al. *Cancer Discov.* 2018; 8(12): 1548-1565
11. Simon F, Johnen G, Krismann M, Müller KM. Chromosomal alterations in early stages of malignant mesotheliomas. *Virchows Arch.* 2005 Oct; 447(4): 762-7. [PMID: 16012846 DOI: 10.1007/s00428-005-0005-4] [Epub 2005 Oct 19].
12. Lee HE, Molina JR, Sukov WR, Roden A, Yi ES. BAP1 loss is unusual in well-differentiated papillary mesothelioma and may predict development of malignant mesothelioma. *Human Pathology.* 2018; 79: 168-176.
13. Tsao M. PL01.05. The New WHO Classification of Lung Tumors. *Journal of Thoracic Oncology.* 2021; 16(3): S63