



Bilateral Pleural Mesothelioma In Situ and Peritoneal Mesothelioma In Situ Associated With *BAP1* Germline Mutation: A Case Report

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ABSTRACT

Mesothelioma in situ is a recently described precursor to invasive mesothelioma. Thus far, all cases in the literature have involved one pleural cavity or the peritoneal cavity. We describe a patient with biopsy-proven mesothelioma in situ involving both pleural cavities and the peritoneal cavity. Genetic analysis results revealed that the patient had a *BAP1* germline mutation. This is the first report of mesothelioma in situ involving multiple body cavities and raises a question of whether such patients will all have *BAP1* germline mutations.

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Introduction

Mesothelioma in situ, defined by immunohistochemical loss of *BAP1*, but without evidence of invasion, has recently been accepted as a precursor to invasive mesothelioma.^{1,2} *BAP1* is a known tumor suppressor gene with a variety of functions, including protein deubiquitination, cell cycle control, and apoptosis. Germline mutations in the *BAP1* gene have been correlated with a tumor predisposition syndrome.³ Here, we describe a unique case of synchronous bilateral pleural mesothelioma in situ and metachronous peritoneal mesothelioma

in situ in the same patient found to have an underlying *BAP1* germline mutation.

Case Presentation

Informed consent to report this case was provided by the patient, a 43-year-old woman who was found to have a pT4aN1M0 ER and PR-positive, HER-2 negative multifocal left breast invasive ductal carcinoma in 2015. She received adjuvant chemotherapy and radiotherapy to the left side of chest wall. In November 2019, she presented with a symptomatic right pleural effusion. There was no known history of asbestos exposure.

Ultrasound-guided right thoracentesis provided pleural fluid for cytology which revealed atypical mesothelial cells. The patient was referred to thoracic surgery and underwent video-assisted thoracoscopic surgery pleural biopsy in March 2020. Subtle nodularity of the pleura was noted. Pathologic examination revealed

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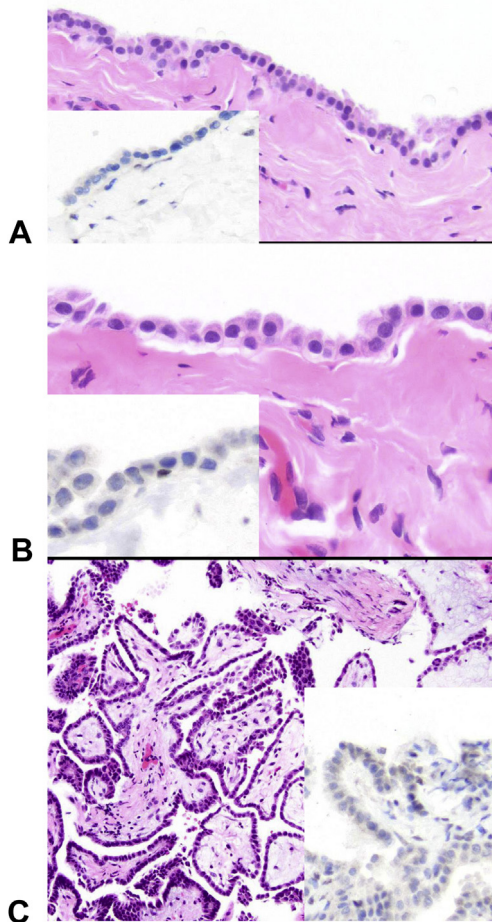


Figure 1. (A) Pleural biopsy result from the right side from a single layer of cuboidal mesothelial cells which have lost *BAP1* (inset). (B) Pleural biopsy result on the left side revealing a process morphologically identical to that in the right side (inset: *BAP1* stain). (C) Peritoneal biopsy result revealing a papillary proliferation with loss of *BAP1* (inset). Areas of flat mesothelioma in situ similar to panels A and B were also present.

a single layer of cuboidal mildly atypical mesothelial cells along with simple papillary structures covered by a single layer of mesothelial cells (Fig. 1A), with no evidence of invasion into underlying tissues. Immunohistochemical staining for *BAP1* revealed nuclear loss, whereas MTAP staining (a surrogate test for *CDKN2A* deletion) was retained. A diagnosis of mesothelioma in situ was made. Before making a decision on therapy, a left thoracoscopic examination and biopsy were performed for a small left effusion. The pleura was visually normal. Pathologic examination noted a microscopic picture identical to that on the right side, with a single layer of flat mesothelial cells and occasional papillary structures, all of which had lost *BAP1* (Fig. 1B). A diagnosis of mesothelioma in situ was made.

The patient represented to hospital in October 2020 with a small bowel obstruction. At laparoscopy, ascites

and what seemed to be peritoneal carcinomatosis were encountered. Biopsy results revealed an extensive papillary mesothelial proliferation and a flat proliferation of mesothelial cells with loss of *BAP1* nuclear staining (Fig. 1C), consistent with peritoneal mesothelioma in situ. No invasive mesothelioma was identified.

Because of the presence of bilateral pleural disease, no therapeutic intervention was recommended in March 2020, but the patient was referred for genetic analysis, which revealed a germline two-base pair frameshift deletion (c.458_459delCT) in *BAP1*.

After multidisciplinary discussion, the patient was referred to medical oncology and started on nivolumab and ipilimumab. She has intermittent drainage of her right pleural effusion for symptomatic relief. Follow-up computed tomography of the chest and magnetic resonance imaging of the abdomen have not revealed any evidence of invasive disease.

Discussion

Mesothelioma in situ is a rare diagnosis, but one which is being made with increasing frequency. The importance of this diagnosis is that, when confined to one pleural cavity, the patient can be treated for cure, something that is not possible with invasive pleural mesothelioma. This case is remarkable in that mesothelioma in situ was diagnosed synchronously in both pleural cavities, and this was followed by the development of the same process in the peritoneal cavity. *BAP1* mutations are known to be associated with the development of invasive mesothelioma and, it has been noted that some patients with *BAP1* germline mutations develop synchronous pleural and peritoneal mesotheliomas.⁴ Here, we reveal for the first time that germline *BAP1* mutations can lead to mesothelioma in situ in multiple serosal cavities, and this is presumably the mechanism by which the invasive tumors develop.

In this case, the peritoneal mesothelioma in situ seemed microscopically not only as flat mesothelium that had lost *BAP1* but also as a papillary process that mimics well-differentiated papillary mesothelial tumor, a lesion that is generally benign. Nevertheless, we have recently reported that some examples of well-differentiated papillary mesothelial tumor actually represent mesothelioma in situ as defined by loss of *BAP1* staining.⁵

It has been suggested that in patients with *BAP1* germline mutations, the germline mutation initially involves only one allele and that a second hit is required to trigger the development of mesothelioma, and this phenomenon has been reported in preclinical models using radiation exposure to *BAP1*^{+/-} mice.⁴ It is possible, but

speculative, that in this patient therapeutic radiation, which is known to induce mesotheliomas in patients without *BAP1* mutations, provided the second hit. Nevertheless, that theory assumes that there was sufficient scatter of radiation to affect both the contralateral pleural cavity and the abdominal cavity.

Conclusion

BAP1 mutations can lead to mesothelioma in situ in multiple serosal cavities.

CRediT Authorship Contribution Statement

Alyssa Maclean: Conceptualization, Writing - original draft.

Andrew Churg: Writing - review & editing, Visualization, Supervision.

Scott Johnson: Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

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