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Meningiomas in Patients With Malignant Pleural Mesothelioma Harboring Germline *BAP1* Mutations

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Abstract

BAP1 is a tumor suppressor gene implicated in DNA repair and cell growth. Individuals with germline BAP1 mutations are at a significantly increased risk for developing many different cancers including malignant mesothelioma, uveal melanomas, cutaneous melanomas and renal clear cell carcinomas. Meningiomas with absent BAP1 expression have been reported to be more aggressive and present often with rhabdoid features. Here, we report the co-occurrence of pleural mesotheliomas and meningiomas in patients with germline BAP1 mutations. We describe the cancer history, family pedigrees, clinical management, and outcomes of four BAP1 germline mutation carrier families with a history of malignant mesothelioma and meningioma.

Keywords

Meningioma; BAP1; Mesothelioma; Germline

Introduction

BAP1 is a tumor suppressor gene located on chromosome 3p21 implicated in DNA repair and cell growth.[1-3] Individuals with germline *BAP1* mutations are at a significantly increased risk for developing many different cancers, including malignant mesothelioma, uveal melanomas, cutaneous melanomas, meningiomas, and renal clear cell carcinomas.[4-8]

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These germline *BAP1* mutations are inherited in an autosomal dominant pattern, increasing the risk of developing *BAP1*-associated cancers through multiple generations of an affected family.

Meningiomas with absent *BAP1* expression have been reported to be more aggressive and present often with rhabdoid features.[6] Shankar et al.[6] reported in their study of four sporadic and two germline *BAP1*-mutant meningiomas that all the cases met the criteria for at least a WHO grade II atypical meningioma designation. Patients with *BAP1*-mutant meningiomas tend to have worse clinical outcome, with multiple recurrences and shortened overall survival.

Here, we report the co-occurrence of pleural mesotheliomas and meningiomas in patients with germline *BAP1* mutations. We describe the cancer history, family pedigrees, clinical management, and outcomes of four *BAP1* germline mutation carrier families with a history of malignant mesothelioma and meningioma.

Case 1

A 64-year-old woman presented to the National Cancer Institute for enrollment into NCT03830229, a natural history study of patients with germline *BAP1* mutations in August 2019. Genetic testing in 2015 revealed that she tested positive for a familial germline *BAP1* nonsense mutation, c.778C>T, which causes a premature translational stop signal in the gene. She had a strong family history of *BAP1*-associated cancers, which includes the following: three maternal uncles and a first cousin with mesothelioma, mother and first cousin with renal cancer, brother with bladder cancer, and a sister with melanoma (Fig. 1A). At the time of enrollment into the study, the patient had a history of more than 20 basal cell carcinomas and melanomas in situ that were resected, and three episodes of spontaneous pneumothoraxes. Two months after enrollment into the study, the patient presented with dyspnea on exertion. Result from a computed tomography chest imaging revealed a large right pleural effusion. Results of biopsies obtained through thoracentesis and video-assisted thoracoscopic surgery confirmed the diagnosis of malignant mesothelioma with loss of *BAP1* expression in the tumor. Result of a brain magnetic resonance imaging (MRI) performed in October 2019 as part of the protocol was unremarkable and revealed no intracranial metastases. The patient subsequently underwent right thoracotomy with pleurectomy, decortication, and diaphragm plication. After 4 months in March 2020, she presented to her local emergency department for increasing confusion, dyspnea, right arm spasm, and photophobia. Further workup revealed a new hilar mass and hyponatremia at 113 mmol/liter. Brain MRI result also revealed a 2-cm homogeneous mass with a dual tail overlying the left frontoparietal convexity with subjacent mass effect on the brain and localized parenchymal edema involving the pre- and postcentral gyri with effacement of the central sulcus (Fig. 2A). The patient subsequently passed away owing to progression of her thoracic disease before pathologic confirmation of her meningioma could be performed; however, the radiological assessment was consistent with meningioma.

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Case 2

A 42-year-old woman who was initially diagnosed with having pleural mesothelioma in 2014 presented for consultation. She is the daughter of case 1. Genetic testing results revealed a concordant familial germline *BAP1* nonsense mutation c.778C>T. She underwent right-sided pleurectomy with decortication in November 2014. One month after surgery, she experienced a nonmechanical fall and underwent neurologic assessment with brain imaging. MRI result revealed a nonspecific lesion in the right sphenoid sinus; subsequently, biopsy was performed which confirmed the lesion to be a meningioma. In March 2016, the patient noted increasing headaches, diplopia, blurred vision, and epistaxis. Follow-up brain MRI result revealed that the meningioma had enlarged markedly, extending intra-cranially and laterally into the cavernous sinus, affecting her optic nerve and encasing her right carotid artery (Fig. 2B). She subsequently underwent a subtotal resection. Pathologic result revealed a grade 3 papillary meningioma. She also received 60 Gy in 30 fractions of radiation therapy. Nevertheless, she passed away from complications related to her meningioma surgery in 2018.

Case 3

A 70-year-old woman was diagnosed with having pleural mesothelioma in September 2017. She had a family history of mesothelioma, multiple basal cell carcinomas, breast cancer, colon cancer, and lung cancer (Fig. 1B). Genetic testing revealed a germline *BAP1* frameshift mutation, c.1717delC. The frameshift mutation in this case leads to a truncated protein lacking the nuclear localization signal required for BAP1 to function as a tumor suppressor. She underwent right pleurectomy and decortication in November 2017 with prolonged postsurgical recovery. The patient refused adjuvant chemotherapy. In December 2018, she was found to have recurrent left pleural disease and received six cycles of palliative systemic chemotherapy with carboplatin and pemetrexed. In June 2019, she experienced a neurologic deficit with a right fourth nerve palsy, and MRI scan result at the time revealed a 1.4-cm dural-based enhancing mass adjacent to the right sylvian fissure (Fig. 2C) and progression of her mesothelioma. The patient was enrolled in a clinical study investigating the combination of the mesothelin-targeting immunotoxin LMB100 and the immune checkpoint inhibitor pembrolizumab from July 2019 to October 2019.

In October 2019, she underwent surgical resection of the brain mass owing to its continued growth. Pathologic result revealed a rhabdoid meningioma, WHO grade III (Fig. 3A-C). In addition, immunohistochemical stain for BAP1 revealed nuclear loss of expression in the tumor cells. The patient subsequently passed away in 2020 owing to disease progression from pleural mesothelioma.

Case 4

A 33-year-old woman presented after genetic testing revealed that she had a germline *BAP1* nonsense mutation termed c.1777C>T. This is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. Notably, she has a strong family history of *BAP1*-associated malignancies and meningiomas (Fig.

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1C). Her grandmother died of mesothelioma. Both her mother and maternal cousin were found to carry germline *BAP1* mutations. The patient herself was diagnosed with having a meningioma at the age of 24 years after she presented with jaw pain and frequent severe migraines. In 2013, the headaches evolved to left jaw pain and intermittent blurred vision from the left eye and left-sided facial tingling and numbness. MRI result of the brain revealed a 3.8 × 2.9 cm × 2.8 cm mass in the left temporal lobe encroaching into the prepontine cistern, resulting in effacement of the pons and abutment of the basilar artery and left carotid cavernous artery with compression of the left trigeminal nerve. She underwent a full surgical resection and radiation therapy. Pathologic result revealed a grade 2 atypical meningioma with rhabdoid features with a Ki-67 of 15%. The meningioma subsequently recurred in 2020 and was treated with gamma knife radiation. To date, she has not had a recurrence. Her mother was also diagnosed with having a meningioma at age 58 years after presenting with hearing loss. This tumor, categorized as a grade 2 meningioma, was subsequently resected and treated with 6 weeks of radiation.

Discussion

We have described three patients with germline *BAP1* mutations who concomitantly had both malignant mesothelioma and meningiomas and one patient with a germline *BAP1* mutation who had meningioma with a strong family history of malignant mesotheliomas and meningiomas. A previous report had described co-occurrence of malignant mesothelioma and meningioma in patients with germline *BAP1* mutations.[9] Cheung et al.[9] described two sisters from a family carrying a germline *BAP1* c.1938T>A mutation who developed both malignant mesothelioma and meningioma.

Our experience with these cases highlights several points on the diagnosis and management of meningiomas in patients with mesothelioma. If a patient with malignant mesothelioma also presents with a meningioma, there should be a high index of suspicion that the patient may have a germline *BAP1* mutation and should seek genetic testing. Notably, we have not found any uveal melanoma or renal cell carcinomas co-developing with meningiomas in patients with germline *BAP1*. Meningiomas have been identified in 8.5% of probands with *BAP1*-tumor predisposition syndrome and 2.2% of relatives with the *BAP1* pathogenic variant.[10] Alternatively, if an individual with a known germline *BAP1* mutation presents with new neurologic symptoms, a high index of suspicion for meningioma should be maintained. In cases 2 and 3, both patients had grade 3 rhabdoid and papillary meningiomas, respectively. Meningiomas associated with germline *BAP1* mutations have been noted to have a diverse histologic spectrum, with reported rhabdoid, papillary, and anaplastic features.[11-13]

Although meningiomas are a rare co-occurrence in patients with malignant mesothelioma with germline *BAP1* mutations, these meningiomas are of high grade with an aggressive clinical course. Hence, we recommend baseline central nervous system imaging with MRI for patients with germline *BAP1*. Onset of any neurologic symptom should warrant prompt MRI imaging. Lesions suggestive of meningioma should involve a multidisciplinary team involving neurosurgeons, neuroradiologists, radiation oncologists, and neuropathologists to discuss further interventional options. Currently, there are no standard guidelines for

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central nervous system imaging surveillance for patients with *BAP1*. We recommend active surveillance with brain MRI for individuals carrying a germline *BAP1* mutation every 2 years, starting from 5 to 10 years before the youngest affected relative or by age 30 years.

Currently, there is limited information on the prevalence, genotype-phenotype correlations, penetrance, frequency of cancers, diagnostic criteria, and established consensus management recommendations for germline *BAP1* carriers. Given this highly penetrant syndrome and the increased risk for multiple malignancies, more evidence-based surveillance guidelines are needed for families with germline *BAP1* mutations.

To obtain more information on germline *BAP1* mutations in patients with malignant mesothelioma and other *BAP1*-associated malignancies, we have a prospective natural history study at the National Cancer Institute (NCT03830229) providing long term follow-up and surveillance for patients with mesothelioma and their family members with germline *BAP1* mutations. Patients undergo surveillance imaging with MRI of the chest, abdomen, pelvis, brain, and breast (in women more than age 30 y) every 2 years and annual ophthalmology and dermatology examination, to screen for the development of *BAP1*-associated cancers. All enrolled patients undergo genetic counseling, and abnormal findings are clinically managed. Under this protocol, cascade testing is available to extend genetic testing to biological relatives.[14] Findings from this study will characterize *BAP1* cancers and importantly outline the clinical management.

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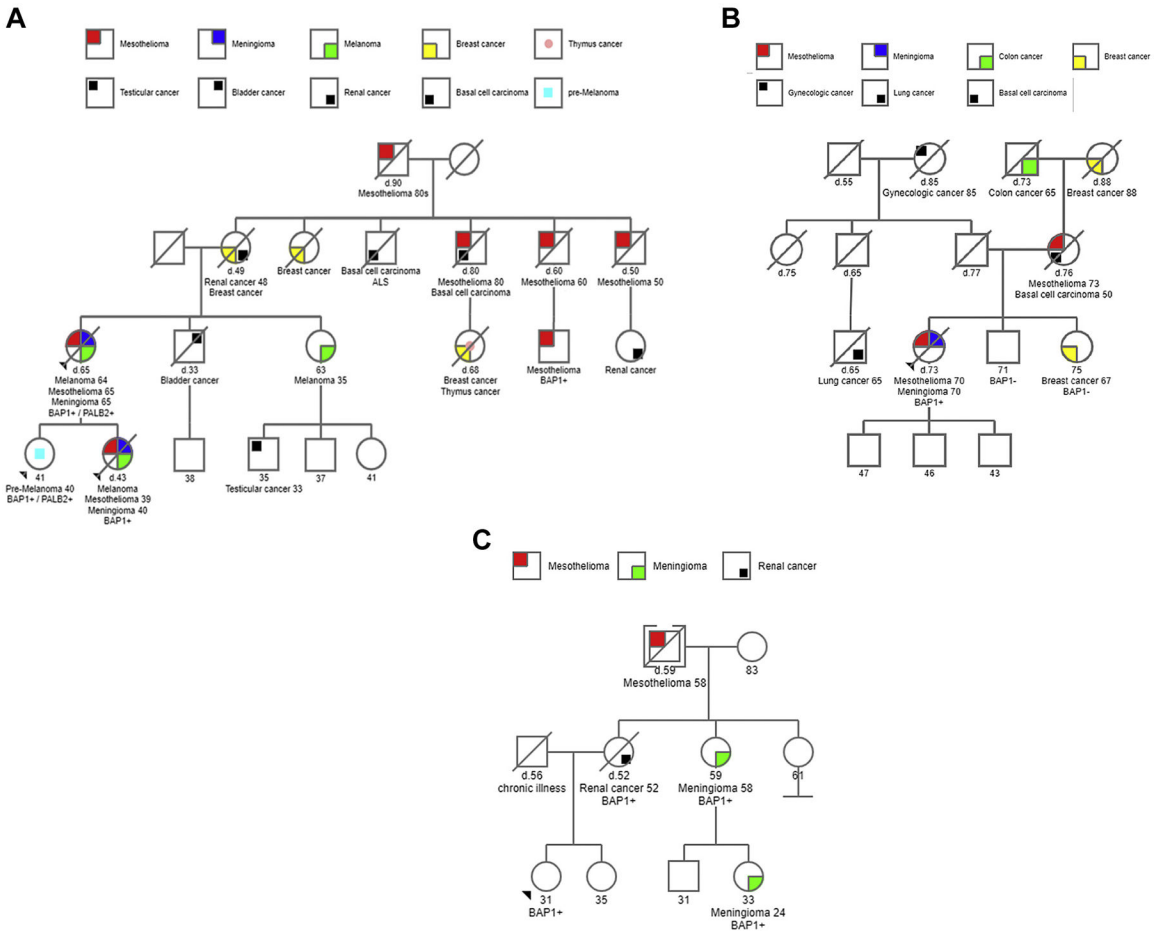

Figure 1.

Pedigrees of the cases. (*A*) Cases 1 and 2, (*B*) case 3, and (*C*) case 4.

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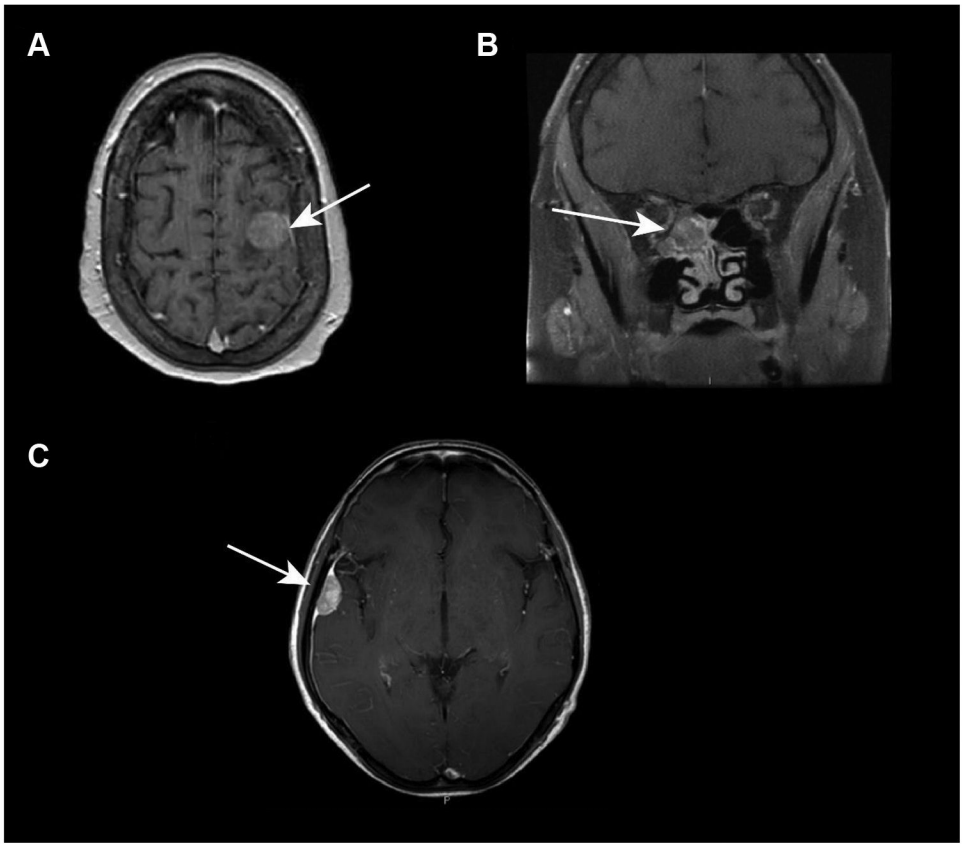

Figure 2.

MRI results of cases 1, 2, and 3. (*A*) T_1-weighted MRI of the brain of case 1 revealing meningioma overlying the left frontoparietal convexity (white arrow). (*B*) T_1-weighted MRI of the brain of case 2 revealing meningioma extending intra-cranially and laterally into the cavernous sinus (white arrow). (*C*) T_1-weighted MRI of the brain of case 3 revealing meningioma adjacent to the right sylvian fissure (white arrow). MRI, magnetic resonance imaging.

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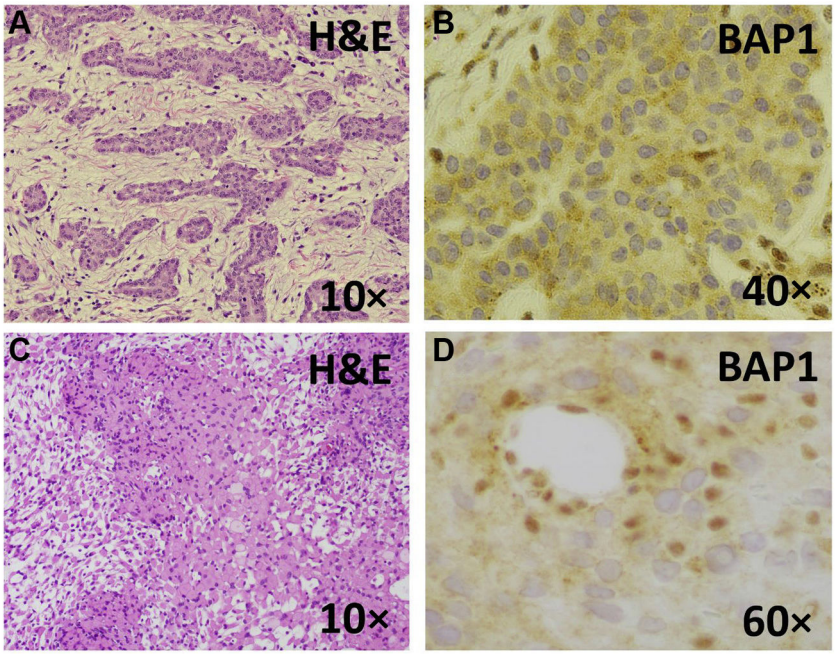

Figure 3.

Histologic features of the mesothelioma and meningioma of case 3. (*A*) 10× H&E stain mesothelioma. (*B*) 40× BAP1 immunostain in epithelioid mesothelioma reveal loss of BAP1 nuclear expression in tumor cells. (*C*) 10× H&E stain of meningioma reveal sheets of rhabdoid cells with eccentric, mildly pleomorphic nuclei, and abundant eosinophilic cytoplasm. (*D*) 60× BAP1 immunostain in meningioma reveal loss of BAP1 nuclear expression in tumor cells. H&E, hematoxylin and eosin.