Case Report

A Case Report of BAP1-inactivated Melanocytoma with Discussion of Possible Dual Roles of BAP1 Loss in Tumorigenesis

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BRCA1-associated protein (BAP1) is a tumor suppressor involved in a myriad of cellular processes. BAP1-inactivated melanocytomas (BIMs) are rare melanocytic tumors characterized by the loss of nuclear expression of BAP1. Here, we report a case of a 33-year-old female presenting with a cutaneous macule on the left lateral nasal wall. Histopathological examination revealed a dermal-based melanocytic neoplasm comprised of large epithelioid melanocytes with pleomorphic nuclei, some with multinucleation. Due to the morphology atypia, melanoma was suspected. However, PRAME (PReferentially expressed Antigen in MElanoma) immunohistochemical staining was negative, and further BAP1 staining showed loss of nucleus expression. Chromosomal microarray confirmed the loss of chromosome 3 (including BAP1) and chromosome X. Compared with malignant melanoma, most BIMs follow indolent courses. We further discussed the possible molecular pathogenesis of BIMs and propose that although the loss of BAP1 predisposes melanocytes to form tumor, it may hinder the development of more malignant forms. Hence, BAP1 may emerge as an interesting target for exploring synthetic lethality to better understand melanoma pathogenesis. *[N A J Med Sci. 2025;18(1):009-012. DOI: 10.7156/najms.2025.1801009]*

Key Words: *BRCA1-associated protein (BAP1), BAP1-inactivated melanocytomas (BIMs), tumorigenesis*

INTRODUCTION

BRCA1-associated protein (BAP1), discovered in 1998,[1] is recognized as a tumor suppressor with deubiquitinating activity. It is intricately involved in a variety of cellular processes, such as DNA damage repair and transcription in the nucleus, cell death and mitochondrial metabolism in the cytoplasm. BAP1-inactivated melanocytomas (BIMs) can manifest as sporadic lesions or, less commonly, as early manifestations of the BAP1 tumor predisposition syndrome (BAP1-TPDS) - a rare autosomal dominant condition caused by germline mutations in the BAP1 gene. BIMs are rare with unknown prevalence. BAP1-TPDS has been reported to affect around 200 families in the literature and one report shows that about 12% of BIMs are associated with germline mutations.

The 2018 WHO classification of melanoma separated BIMs into two categories: BAP1-inactivated nevus, characterized by low to intermediate dysplasia, and the BAP1-inactivated melanocytoma/melanocytic tumor of uncertain malignant potential, marked by intermediate to high-grade dysplasia. The rarity of high-grade BIMs and their morphological similarities with malignant melanoma often led to diagnostic challenges.

In this report, we describe a case mimicking melanoma and later confirmed to be a BAP1-inactivated melanocytoma. BIMs and melanoma differ in their mutation pathways, highlighting the importance of auxiliary diagnostic techniques such as gene mutation detection.

In addition, BAP1 loss involved in different tumors such as uveal melanoma and melanoma arising from blue nevus and have prognosis value on some. We discuss an intriguing role of BAP1 in tumor pathogenesis in BIMs comparing other melanocyte related tumors with BAP1 loss.

Received: 01/03/2025; Revised: 03/26/2025; Accepted: 04/30/2025
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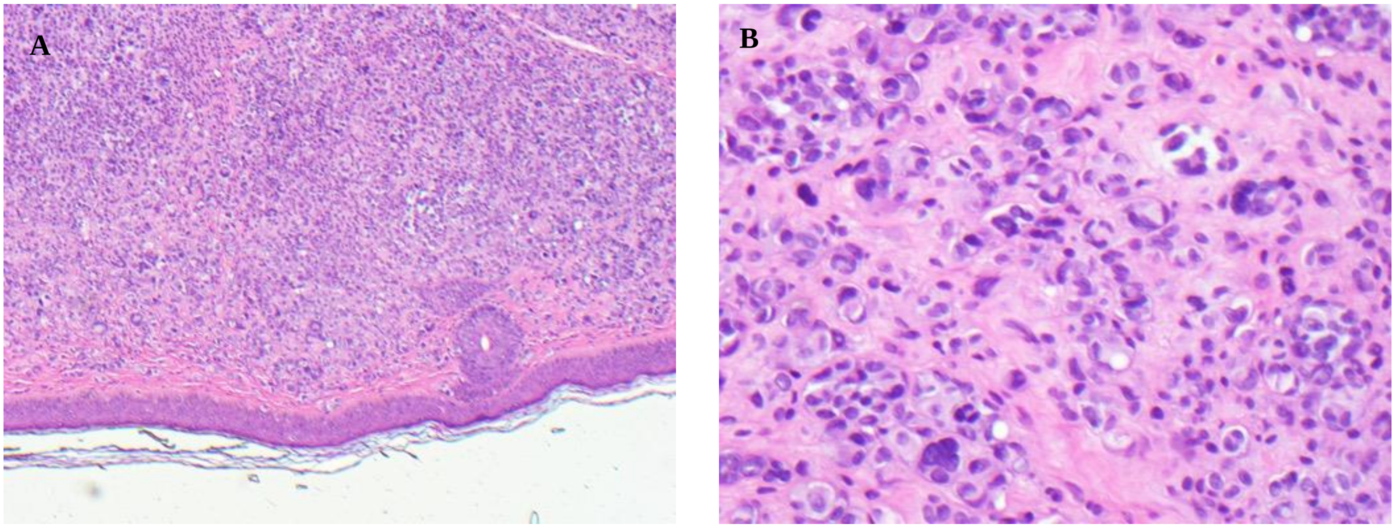

Figure 1. Hematoxylin and eosin stain of the BIM. (**A**) Lesion is primarily located in the dermis (40x). (**B**) The lesion shows epithelioid cells with marked variability in cell size and nuclear pleomorphism (400x).

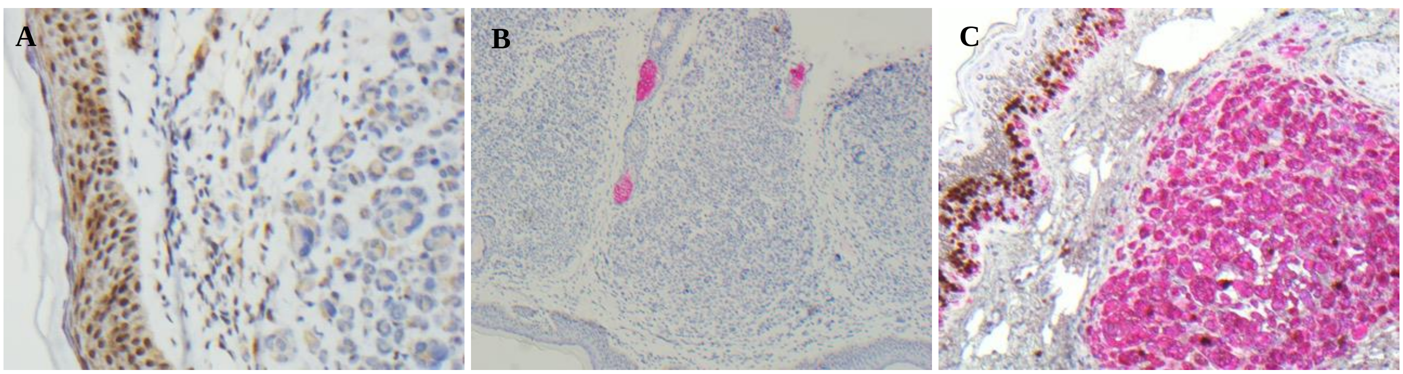

Figure 2. IHC staining of related marker proteins. (**A**) The tumor cells lost BAP1 nuclear staining (400x). See the cells in epidermal as internal positive control. (**B**) The tumor cells are negative for PRAME (40x) and sebaceous glands are known for positive for PRAME and as an internal positive control. (**C**) The tumor cells are positive for Melan-A (red) with low Ki67 (brown) (400x).

CASE REPORT

The case was sent to the Roswell Park Comprehensive Cancer Center as a consultation case and had previously been diagnosed as melanoma externally. A 33-year-old female with a history of hypertension presented with a cutaneous amelanotic papule located on the left lateral nasal wall. The lesion measured 2 x 7 mm and was situated approximately 5 mm from the medial canthus. The adjacent skin was mobile.

A shave biopsy was performed, and histopathological evaluation revealed a dermal-based melanocytic neoplasm. The lesion was composed of large epithelioid melanocytes with significant nuclear pleomorphism (**Figure 1**). The nuclei exhibited marked variability in size and shape, ranging from oval to irregularly contoured forms. Multinucleated cells were observed, characterized by nuclei of varying sizes within a shared cytoplasm. The cytoplasm was abundant, and nucleoli were small and inconspicuous.

Dermal mitotic figures were present, however, confined to the upper third of the lesion. The Ki-67 proliferative index was estimated to be less than 10%. Due to its nuclear pleomorphism, abundant cytoplasm, and low proliferative activity, BIM was suspected. Immunohistochemical studies revealed loss of nuclear BAP-1 nucleus expression (**Figure 2**), which is characteristic of BIMs. PRAME immunostaining was negative and Melan-A immunohistochemical stain confirms the absence of intraepidermal component (**Figure 2**). To support the diagnosis, chromosomal microarray using formalin-fixed paraffin-embedded tissue (FFPE) was performed. The results confirmed the heterogeneous loss of chromosome 3 (including BAP1) and chromosome X (**Table 1**). A diagnosis of BAP1-inactivated melanocytoma was made. It is noteworthy that the patient also had a similar lesion on the abdomen. However, due to the consultative nature of the case, the abdominal lesion was not biopsied.

Table 1. Chromosomal microarray result.

CHANGE	GE(CN)	REGION	GENOME COORDINATES	SIZE (Mb)
LOSS	(1)	Chromosome 3	Chr3:63410-97852564	197.8
LOSS	(1)	Chromosome X	Chr3:63410-97852564	155.0

Chromosomal Microarray, Tumor, FFPE, GE = Gene Expression, CN = Copy Number, **Nomenclature,** Arr(X)x1, (3)x1

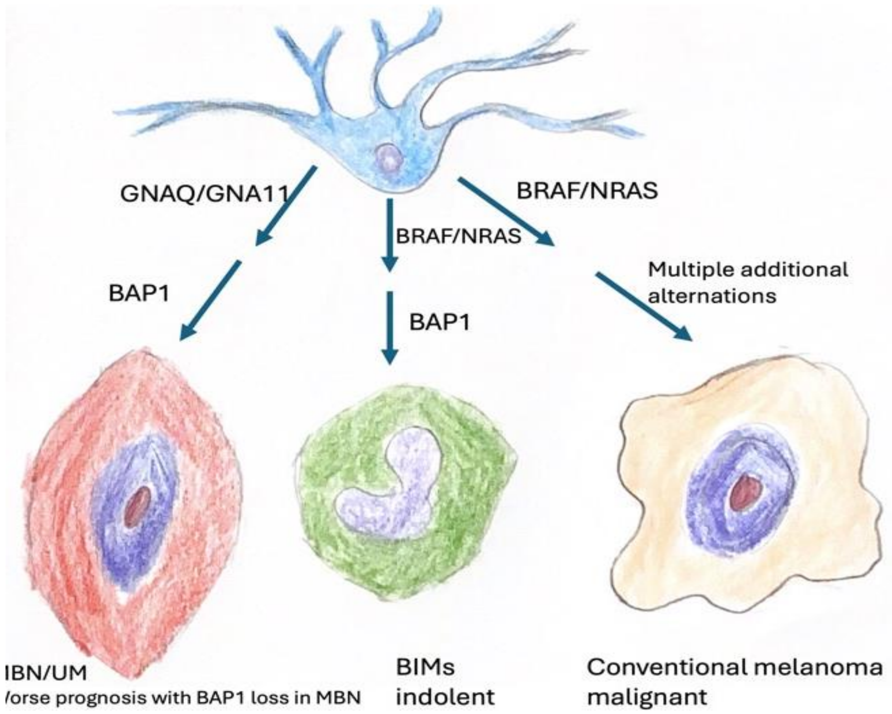

Figure 3. Cartoon illustration of the mutation pathways in BIMs, conventional melanoma, MBN, and UM. BIMs follow an indolent course compared to conventional melanoma, even though both harboring BRAF mutations. BAP1 plays an important role in proper mitotic division, and its loss slows proliferation, potentially preventing BIMs progressing to a more malignant state. However, when BAP1 loss is combined with mutations in G-protein coupled signal pathway, as observed in UM and MBN, the tumor either exhibits poor prognosis or acquires high metastatic potential.

DISCUSSION

The case we presented was initially misdiagnosed as malignant melanoma before a correct diagnosis of BAP1-inactivated melanocytoma was established. This underscores the critical role of accurate diagnostic practices, as the lesion's specific location significantly influenced patient management strategies. BIMs typically display notable variability in cellular size and morphologic heterogeneity, yet they often follow an indolent clinical course.[2] Our case mirrored this trend, exhibiting high morphological heterogeneity and cellular pleomorphism, while maintaining a low mitotic index. Research has indicated that BIMs with polyploidy alterations, with 14%[3] and 24%[2] of tetraploid being reported, commonly present with low mitotic figures. This suggests that mitotic anomalies may entrap cells, impeding further divisions.[2] Corresponding this, studies utilizing mesothelial tumor cells have demonstrated that BAP1 loss leads to a variety of mitotic irregularities, including multipolar and elongated spindles, misaligned chromosomes via BRCA1-dependent and independent mechanisms.[4] Similar mechanisms may occur in melanocytes, contributing to the morphological diversity observed in BIMs. Indeed, BIMs were reported having decreased ciliation and increased centrosome amplification compared with nearby benign nevi,[5] which disrupt the normal mitotic process.

BIMs typically possess driving mutations, most frequently BRAF, and to a lesser extent: NRAS, BRAF fusion,[6] and RAF fusions.[7] Compared to BIMs, conventional melanomas have similar initial mutations like BRAF mutation but acquire other mutations instead of BAP1 mutation. Giving the benign courses of BIMs than conventional melanoma, we are tempted to think that the presence of BAP1 loss in BIMs may impede their progression to more malignant behavior (**Figure 3**). In this theory, we think the loss of BAP1 paralyzed the cell from division driven by BRAF mutation, thus creating the abundant cytoplasm, multiple nuclei, and nucleus polymorphism phenotypes. It may cause confusing since BAP1 is considered as a tumor suppressor. However, it has been reported that either overexpression of BAP1 in BAP1-null cancer cell lines or depletion of BAP1 reduces cell proliferation and delays cell cycle transition.[8] This suggests that BAP1 has functions beyond its role as a tumor suppressor. The disrupted mitotic process induced by BAP1 loss slows the proliferation rate. The slowed proliferation may limit tumor cells from acquiring additional mutations over time and reducing the likelihood of malignant transformation. How BAP1 loss, together with BRAF mutation, keeps the proliferation pace from either diminishing or malignant transformation is a complex process. BIMs are reported to gradually replace the original nevus,[2] reflecting a slow, steady growing pattern that may enhance their resilience to environmental stress.

The story of BAP1 in uveal melanoma (UM), and melanoma arising from blue nevus (MBN) is different from in BIMs. In the context of UM, BAP1 loss has been strongly correlated with metastasis,[9,10] and for MBN, BAP1 loss related to poor prognosis. The difference is possibly attributable to distinct mutational backgrounds compared to BIMs. Both UM and MBN frequently harbors mutations in the G protein-coupled receptor signal pathway, such as GNAQ and GNA11, whereas cutaneous melanomas and BIMs commonly exhibit mutations in the protein tyrosine kinase pathway like BRAF or NRAS. Considering the ligands and downstream target varieties between protein tyrosine kinase pathway and G protein-coupled receptor signal pathways, it is reasonable that in combination with the loss of BAP1, outcomes are different (**Figure 3**). A recent study found that BAP1-deficient UM cells exhibit slowed proliferation but increased resistance to nutritional stress, which facilitate metastasis.[11] This indicates the slowed proliferation associated with BAP1 loss is a universal phenomenon, irrespective of mutation background. However, tumors use this feature differently. In UM, instead of becoming indolent, slowed growth corresponds to enhanced metastatic potential.

Furthermore, the co-occurrence of loss of BAP1 and SF3B1(involving in pre-mRNA splicing) mutation has been linked to cellular senescence in human UM cells.[9] Interestingly, loss of BAP1 and SF3B1 mutation individually correspond to high and intermediate metastatic risks. This may explain the mutually exclusive mutation of BAP1 and SP3B1 in UM, and more importantly, underscores the intricate interplay of BAP1 with other mutations during tumorigenesis.

The case also highlights the loss of chromosome X, a phenomenon previously reported in BIMs,[12] suggesting the association between BAP1 and chromosomal instability. Other reported chromosome loss in BIMs including loss of chromosome 9. Additional research is warranted to delineate the specific chromosomal losses linked to loss of BAP1 in BIMs.

Our findings emphasize the diagnostic value of BAP1 staining in differentiating BIMs from conventional melanomas. In addition, PRAME staining, which is usually positive in malignant melanoma and tends to be absent or weak in BIMs,[13] further aids in this distinction, as evidenced by our case and supported by others.[7]

In summary, we reported a rare case of BIMs and discussed the mechanisms causing the morphological heterogeneity in BIMs and the multifaceted role of BAP1 in tumorigenesis.

CONFLICTS OF INTEREST
None

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