BAP-1 inactivated tumors: a still unclear spectrum of melanocytic lesions P306

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Background

BAP1-inactivated melanocytic tumors (BIMTs) are melanocytic lesions characterized by loss of BAP1, a gene located on the short (p)arm of chromosome 3 (3p21.1).

BAP1 is a 90kDa nuclear-localised deubiquitinating enzyme, with ubiquitin carboxyl hydrolase (UCH) activity and two nuclear localization signal (NLS) motifs (figure 1). It is a multifunctional tumor suppressor involved in chromatin remodeling, DNA damage response through its relationship with BRCA1, cell cycle control, regulated cell death, and the immune response (1).

Uveal Melanoma
Malignant Mesothelioma
Cutaneous Melanoma and Basal Cell Carcinoma
Clear Cell Renal Cell Carcinoma
Hepatocellular carcinoma
Cholangiocarcinoma
Meningioma

Table 1: BAP1-TPDS, cancers in descending order of frequency

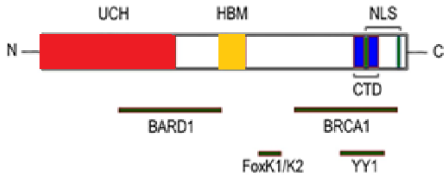


Figura 1: Ubiquitin carboxyl-terminal hydrolase BAP1

Cutaneous BIMTs are frequently sporadic but some occur in a BAP1 autosomal dominant tumor syndrome (BAP1-TPDS) (1).

BAP1-TPDS should be suspected in an individual who has *(Table 1)* : BAP1-inactivated melanocytic tumors (BIMT), usually presenting somatic BRAF V600E mutation; Uveal (eye) melanoma (UM); Malignant mesothelioma (MMe); Cutaneous melanoma (CM); Renal cell carcinoma (RCC); Basal cell carcinoma (BCC); Hepatocellular carcinoma; cholangiocarcinoma and meningioma.

In 2018 WHO classified BIMTs, including combined BAP1-inactivated naevus/melanocytoma, in Combined Naevi, considering that many BIMTs are combined neoplasms, with a BAP1-inactivated clone developing within a common or a dermal naevus.

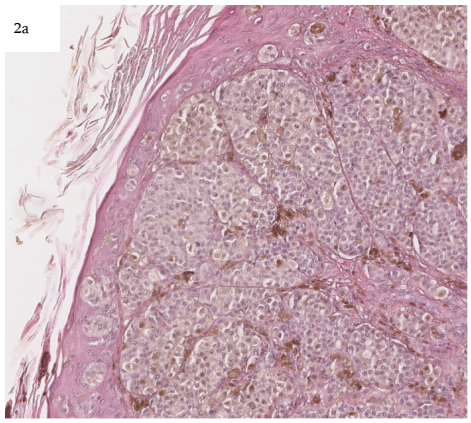
BAP1-inactivated naevus (BIN) is composed by nevoid cells with minimal atypia, while BAP1-inactived melanocytoma (BIM) is an atypical tumor characterized by large epithelioid cells with pleomorphic vesicular nuclei and prominent nucleoli (2). The term BAP1 inactivated melanoma should be used for *bona fide* melanoma with BAP1 loss.

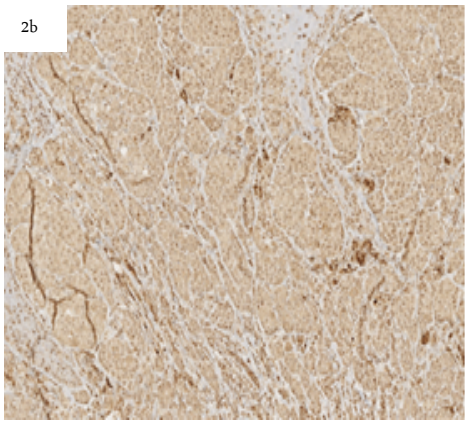
Case Presentation

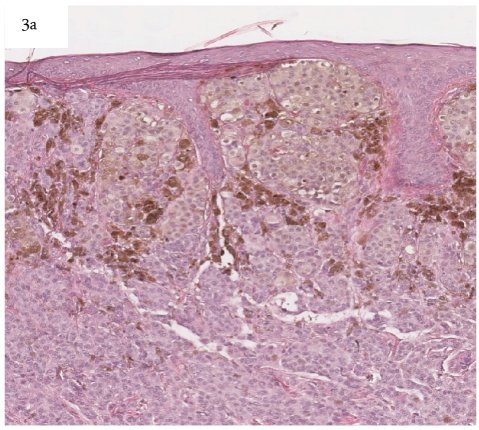
A 62-year-old man without family history of cancer presented in March 2022 with two suspicious brown papules on the right thigh and abdominal region. Both lesions were removed, and histological examination was performed. A diagnosis of melanoma and cutaneous metastasis from melanoma, respectively, was made (Figure 2a- 3a). Both lesions were composed by epithelioid and nevoid tumor cells with loss of nuclear expression of BAP1 in the epithelioid component (Figure 2b-3b). One month later the patient underwent excision of three more nodular lesions, two of which presented histological features similar to previous melanomas, including BAP1 loss of expression (Figure 4a-4b-5a-5b) and BRAF V600E mutation . After three months the patient discovered a pancreatic mass, which is still under evaluation.

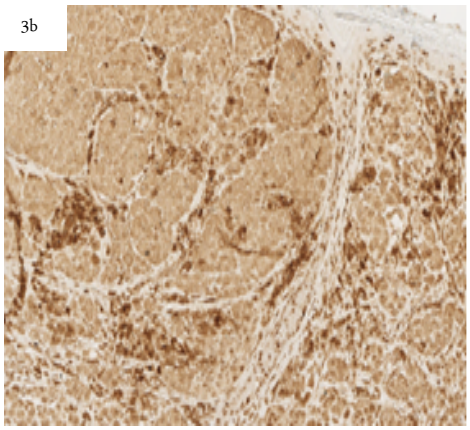
Conclusions

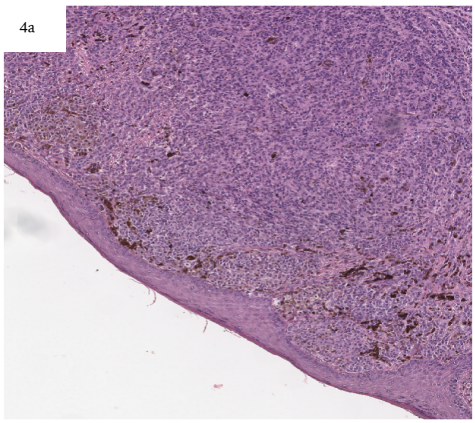
The clinicopathologic spectrum of BIMTs (characterized by loss of BAP1 protein), includes BIN, BIM and BAP1 inactivated melanoma. BIMTs can be sporadic or associated to a germline mutation and a BAP1 tumor predisposition syndrome. To date, the boundary between melanoma and melanocytoma is unclear. The determination of precise histological criteria to subclassify these tumors is fundamental for a better definition and for an appropriate therapeutic approach.

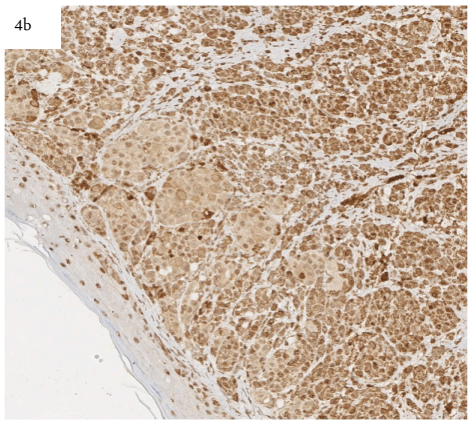


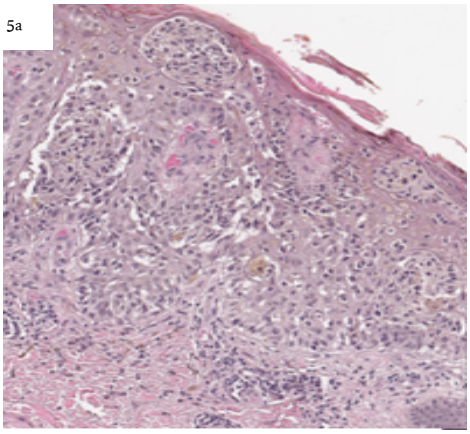


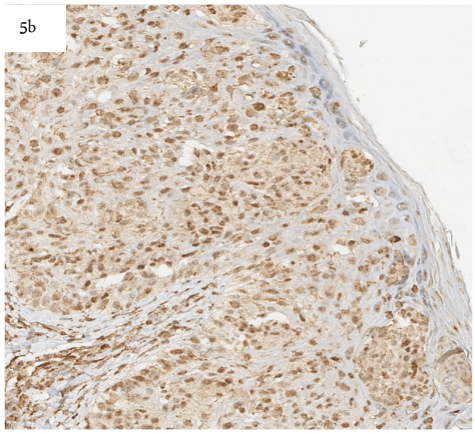












Figures 2a, 2b, 2c, 3a and 3b: the first two melanomas diagnosed in March 2022. Both tumours were composed by epithelioid and nevoid cells (figure 2a and 3a, H&E 20x) and presented loss of BAP1 nuclear staining in large epithelioid melanocytes (figure 2b and 3b 20x). Note the pagetoid spreading of melanocytes in figure 2a that characterizes the primary melanoma. Figures 4a, 4b, 5a, 5b: the two lesions diagnosed in April 2022 (4a and 5a H&E 20x and BAP1 immunohistochemical staining,20x).

References

(1) David E.Elder et al. WHO Classification of Skin Tumours, 4th ed., 2018; 393–4.

(2) Ferrara G. et al. BAP1-inactivated melanocytic tumour with borderline histopathological features (BAP1-inactivated melanocytoma): A case report and a reappraisal. Australas J Dermatol. 2021 Feb;62(1):e88-e91.

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