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CASE REPORT

Loss of BAP1 Protein Expression by Immunohistochemistry in the Salivary Duct Carcinoma Component of an Intracapsular Carcinoma ex Pleomorphic Adenoma of the Parotid Gland

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Abstract

Background *BRCA1-associated protein 1* (*BAP1*) is a tumor suppressor gene that is altered in a variety of neoplasms as well as in BAP1 tumor predisposition syndrome. *BAP1* alterations are associated with aggressive behavior in some malignancies and may have treatment implications in future. We present the first documented case of loss of BAP1 protein expression by immunohistochemistry in the salivary duct carcinoma (SDC) component of an intracapsular carcinoma ex pleomorphic adenoma (CXPA) in the context of molecular loss of function of *BAP1* in the neoplasm.

Methods A woman of approximately 55 years of age presented with a deep parotid lobe mass, which was resected and found to be CXPA. BAP1 immunohistochemistry and next-generation sequencing was performed to further characterize the neoplasm.

Results The neoplasm showed loss of BAP1 protein expression in the SDC component but retention in the residual pleomorphic adenoma (PA). Next-generation sequencing confirmed a *BAP1* loss of function alteration in the neoplasm.

Conclusion This is the first documented case report of BAP1 protein expression loss in the SDC component of a CXPA. Future studies are needed to investigate the relevance of *BAP1* alterations in SDC and CXPA, which may have prognostic and treatment implications.

Keywords *BAP1* · Salivary duct carcinoma · Carcinoma ex pleomorphic adenoma · Salivary gland neoplasm

Introduction

Carcinoma ex pleomorphic adenoma (CXPA) represents the malignant transformation of a pleomorphic adenoma (PA), demonstrates predilection for the major salivary glands [1], and can further be classified as intracapsular, minimally invasive, or invasive based on the extent of invasion into surrounding tissues. Carcinomatous components most commonly include salivary duct carcinoma (SDC), myoepithelial carcinoma, and epithelial–myoepithelial carcinoma (EMC), among others [10, 25].

Reported molecular alterations in CXPA are varied. In addition to those alterations common to PA, such as rearrangements of *PLAG1* and *HMGA2*, other molecular alterations include *TP53, BRCA1*, *BRCA2*, and *EGFR* [1, 5, 25]. However, to date there have been no reported cases of *BRCA1-associated protein 1* (*BAP1*) in CXPA or SDC.

We present the first documented case of loss of BAP1 protein expression in a CXPA, which was limited to the SDC component of the neoplasm. A loss of function alteration

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of *BAP1* was additionally demonstrated by next-generation sequencing, which has not been reported before in CXPA.

Case Report

The patient was a woman of approximately 55 years with no relevant past medical history who was found to have a rapidly enlarging mass of the deep parotid lobe. Resection of the lesion yielded a 4.5-cm, well-circumscribed, solid and cystic mass.

Histologic examination revealed an encapsulated, pleomorphic adenoma with a SDC that was positive for androgen receptor (AR, anti-androgen receptor, SP107, Rabbit monoclonal primary antibody, Cell Marque) (Fig. 1). No capsular, lymphovascular, or perineural invasion were present.

BAP1 immunohistochemistry (BAP1, anti-Bap1 mouse monoclonal antibody, sc-28283, Mayo Clinic Laboratories, Santa Cruz Biotechnology) showed BAP1 protein expression loss in the SDC portion of the neoplasm but retention in the residual PA (Fig. 2).

Next-generation sequencing (Tempus Laboratories, 648 gene panel) revealed a c.37+1G>A splice region variant loss of function alteration. Additionally present were the following alterations: *PIK3CA* gain of function, *BRCA2* loss of function, *NF1* loss of function, *FANCA* loss of function, androgen receptor overexpression, and *FBXO32::PLAG1*

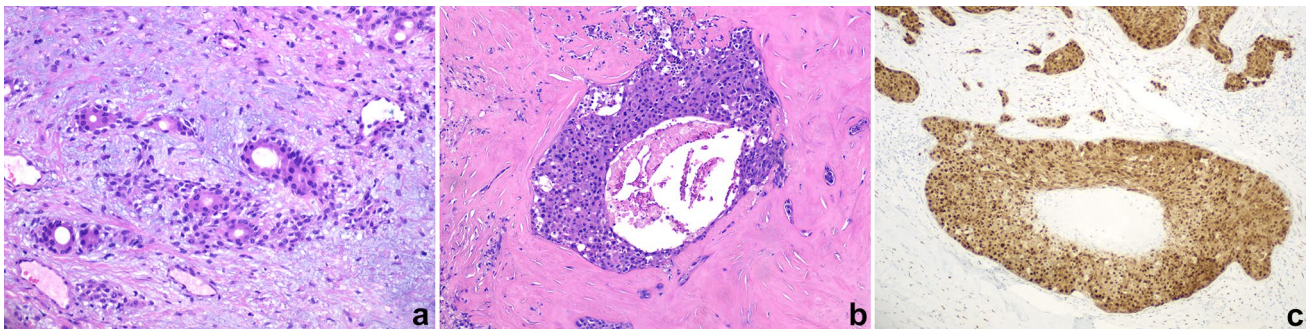

Fig. 1 Resection of the neoplasm revealed residual PA (**a**) and SDC (**b**) with AR positivity (**c**)

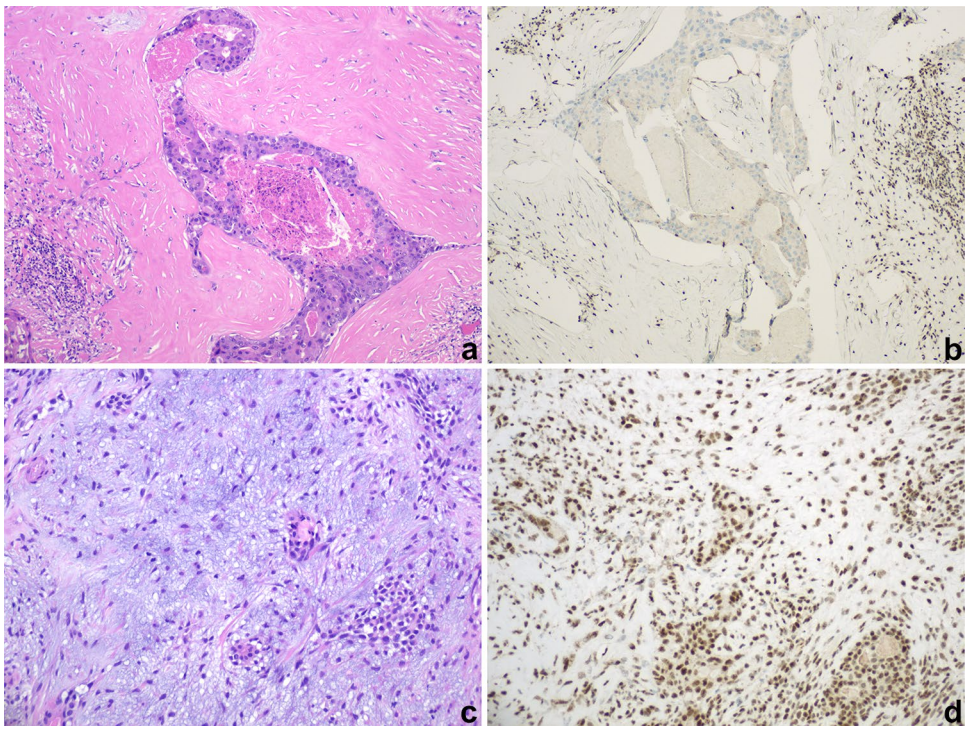

Fig. 2 The SDC component **a** showed loss of BAP1 by immunohistochemistry, **b** while the residual PA **c** showed retention **d** of BAP1

chromosomal rearrangement. Material for germline testing was not available.

Due to the presence of intracapsular CXPA, a subsequent lymph node dissection was performed, and there were no lymph node metastases. The patient was referred to radiation oncology for additional treatment and has had no recurrence or disease progression at over one-year post-resection.

Discussion

BAP1 is a tumor suppressor gene located on chromosome 3p21.3 that functions as a deubiquitinating enzyme that interacts with the *BRCA1* RING finger domain, among other proteins, and has roles in cell growth as well as genomic maintenance and stability [6, 7, 15, 17, 19, 22, 28]. *BAP1* alterations are represented among many human neoplasms, including mesothelioma, cholangiocarcinoma, renal cell carcinoma, and melanoma [18]. A recent query of The Foundation Medicine database performed by Laitman and colleagues found *BAP1* alterations in adenoid cystic carcinoma as well as 6.18% of salivary gland adenocarcinoma; however, the specific diagnostic type of salivary gland malignancy remained unspecified in the report [18]. One study found *BAP1* alterations in 20.8% of mucoepidermoid carcinomas studied ($n=48$) [26]; however, a second study of mucoepidermoid carcinomas found no such alterations ($n=40$) [16].

The findings in the current case are unique because of the well-delineated loss of BAP1 protein expression by immunohistochemistry in the SDC component of the neoplasm with retention in the PA component of the neoplasm, a finding that suggests that BAP1 alterations may be relevant to SDCs arising in the setting of CXPA.

The identification of *BAP1* alterations in other tumors has both prognostic and treatment implications. For example, somatic *BAP1* inactivation has been implicated in metastatic potential in uveal melanoma [11] and is associated with an aggressive clinical course in high-grade meningiomas [24]. Germline *BAP1* alterations cause BAP1 tumor predisposition syndrome, which predisposes patients to uveal and cutaneous melanomas, renal cell carcinoma, and mesothelioma [3, 20]; however, such a syndromic association with salivary gland neoplasms has not been reported. Finally, emerging studies suggest therapeutic strategies in *BAP1*-altered tumors, including platinum-based chemotherapies, such as cisplatin [13], and poly(ADP-ribose) polymerase (PARPI) inhibitors, such as niraparib and Olaparib [8, 12, 19].

Other alterations in this intracapsular CXPA are discussed as follows: *PIK3CA* alterations are reported in SDC [9, 23]. *BRCA2* alterations are identified in a substantial number of PAs and CXPAs [14]. *NF1* alterations are identified in SDC and adenocarcinoma, not otherwise specified, but not in CXPA in one study [27]. A *FANCA* mutation is reported in a SDC in a patient with a germline *BRCA1* mutation [4]. AR expression is reported in many CXPA cases as well as approximately one-third of PAs in one limited study [21]. *FBXO32::PLAG1* rearrangements are reported in both PA and CXPA [2].

Though the finding of immunohistochemical loss of BAP1 expression in the SDC component of a CXPA is novel and unique, it is limited by the nature of this being a single case report rather than a larger series. An additional limitation is that microdissection of different neoplastic components was not able to be performed to verify if the *BAP1* alteration was limited to the SDC component. Though protein expression loss is well delineated by immunohistochemistry in the context of whole-tumor *BAP1* loss of function, future studies will be needed to further parse the genetic landscape of SDC in CXPA in regard to *BAP1*.

In conclusion, we report the first documented case of BAP1 protein expression loss by immunohistochemistry in the SDC component of an intracapsular CXPA in the context of a *BAP1* loss of function alteration by next-generation sequencing. Future studies will be needed to further investigate *BAP1* alterations in CXPA, which may have prognostic and treatment implications.

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Declarations

Competing Interests The authors have no competing interests or funding and declare that they have no conflicts of interest.

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Informed Consent For this type of study (case report), informed consent is not required (IRB approved, UAMS).

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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