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An atypical presentation of renal mass associated with BAP-1 tumor predisposition syndrome: Case report and review of literature

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ABSTRACT

BCRA-associated protein-1 (BAP-1) mutation has been associated with the development of a familiar syndrome that predisposes to tumors with a higher incidence than in general population, including melanoma and renal carcinoma.

We report a 47-year-old woman diagnosed with a BAPoma (melanocytic tumor characterized by the loss of BAP-1). Due to her extensive family history with multiple neoplasms, a FDG PET-CT was performed. Consequently, she was diagnosed with an atypical renal mass, which is rarely linked to this syndrome.

We review and discuss the available literature on the screening, diagnosis and treatment of renal tumors associated with BAP-1 tumor predisposition syndrome.

1. Introduction

The BCRA-associated protein-1 (BAP-1) is a tumor suppressor gene located on the human chromosome 3p.[1] The negative germline mutation of this gen has been associated with the development of a familiar syndrome that predisposes to different tumors, including cutaneous melanoma and renal carcinoma.[2,3]

Clear cell carcinoma is the most frequently subtype associated with this syndrome, and it shows worse prognosis than renal tumors without BAP-1 mutation.[4] However, the role of BAP-1

alterations in non-clear cell renal cell carcinoma is much less studied due to the lower prevalence of this tumor subtype.[4,5]

Our aim is to report the case of a 47-year-old patient diagnosed with a renal oncocytoma in the context of BAP-1 tumor predisposition syndrome, an exceptional situation poorly described in the literature before. In addition, we review the literature regarding renal tumors with BAP-1 mutation and we highlight the importance of global diagnosis in our patients.

2. Case presentation

We present the case of a 47-year-old woman followed up in dermatology for a scalp lesion, stable since childhood, with progressive growth in the last six months. She had no history of previous diseases, but she had an important family history of different malignancies: her father was diagnosed with leukemia, her mother and aunt were diagnosed with non-melanoma skin cancer, several uncles were diagnosed with lung and breast cancer and her grandparents were diagnosed pancreatic and lung cancer.

Physical examination of the scalp showed a 2 cm pink pedunculated hyperkeratotic lesion in the interparietal region, with multiple smaller erythematous papules around it (Fig. 1a).

The lesions were excised. Histopathology showed cells in the dermis with a nevus-like appearance and epithelioid morphology occasionally pigmented, and extended deep surrounding the adnexal structures, with no tendency to maturation. They presented well-defined borders, wide eosinophilic cytoplasm with prominent nucleoli and pseudoinclusions (Fig. 1b).

Immunohistochemistry was positive for melan-A in the whole sample. BAP-1 expression was lost (Fig. 1c), so she finally was diagnosed with (MBAITs, BAP-1-inactivated melanocytic tumor).

She subsequently presented several skin recurrences, all of them with the same histopathological and immunohistochemical findings previously described. Due to the high association between the loss of BAP-1 expression and other concomitant neoplasms, the case was presented to the Tumor Committee where they decided to perform PET-CT as a

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screening for other tumors.

FDG PET-CT showed (Fig. 2).

- On the one hand, a large tumor dependent on the lower pole of the right kidney with a maximum diameter of 16cm, with no evidence of local invasionIn addition, there were suspicious left infrarenal para-aortic retroperitoneal lymphadenopathies (SULpeak 1.6), at least a cT2b N1, Stage III. The lesion had heterogeneous contrast enhancement and large regions of necrosis and cystic degeneration. Renal vessels were not involved.
- On the other hand, a large uterus with multiple myomas was observed, measuring 17 x 16 × 12cm. It presented two areas of hypermetabolism, in the cranial pole and left posterior region, with no other associated lesions.

According to these findings, the patient was referred to our urology consultation. At the time of diagnosis, the patient was asymptomatic, with no lumbar pain, hematuria, urinary tract infections or other urological symptoms.

On physical examination, we could palpate an abdominal mass dependent on the right kidney which continued into a large pelvic mass (corresponding to the uterus).

Due to high suspicion of renal carcinoma, it was decided to perform a coordinated surgical procedure with the Gynecology department. First of all, hysterectomy and bilateral salpingectomy were performed (Fig. 3a).

Subsequently, a radical right nephrectomy and para-aortic lymphadenectomy was performed by transperitoneal anterior approach (suprainfraumbilical median laparotomy). A suspicious left adenopathy of 2cm in diameter was found and removed (Fig. 3b and c). Surgical time was 4h 30 min, with an estimated bleeding of 800 cc. The patient stayed stable during the surgery and did not require blood transfusion. The postoperative period was uneventful and the patient was discharged from the hospital on the seventh day.

The nephrectomy sample was compatible with a renal oncocytoma of 17.5 x 14.5 × 8 cm, with no evidence of BAP-1 loss. Three lymph nodes were analyzed without signs of malignancy.

The hysterectomy and double adnexectomy sample showed diffuse myometrial thickening, with intramural uterine leiomyomas and other findings with no malignancy. Ascitic fluid cytology and peritoneal lavage cytology were also negative.

3. Discussion

The BCRA-associated protein-1 (BAP-1) gene, located on chromosome 3p21.1, was discovered by Jensen and colleagues in 1998. It encodes an enzyme, BAP-1, which works as a tumor suppressor protein through its deubiquitinase activity, regulating target genes in cell cycle control and DNA damage repair.[1]

The negative germline mutation of BAP-1 has been associated with the development of a familiar syndrome that predisposes to tumors with a higher incidence than in general population, including uveal melanoma, mesothelioma, cutaneous melanoma and renal carcinoma.[2,3] Less frequently, it has been also described the association with cholangiocarcinoma, multiple myeloma, lung cancer, paraganglioma, meningioma, breast and ovarian carcinoma.[3]

In addition, a melanocytic proliferation with its own clinical and histological characteristics has been described in this context. It is known as BAPoma, Wiesner's nevus or atypical intradermal melanocytic tumor with mutated BAP-1 (MBAITs). BAPoma is considered an intermediate type of melanocytic tumor. It appears as a single, reddish-brown single papule, less than 1cm in diameter.[3] Its diagnosis is confirmed by immunohistochemistry, which shows loss of nuclear expression of BAP-1 in the affected melanocytes. Our patient showed multiple circumscribed lesions surrounding a larger lesion of 2cm, which is an atypical presentation of MBAITs, different to other cases previously described in the literature.

The biological behavior of BAP-1 associated tumors is variable. Uveal melanoma and primary cutaneous malignant melanoma appear at younger ages and with higher aggressiveness than in cases with unmutated BAP-1. Mesothelioma also appears in younger patients, but it has 7 times longer survival.[3]

Regarding renal tumors with BAP-1 loss expression, multiple investigations have demonstrated their appearance at earlier ages and their correlation with a higher tumor grade, larger size and the presence of necrosis, which leads to a worse prognosis, regardless of the treatment

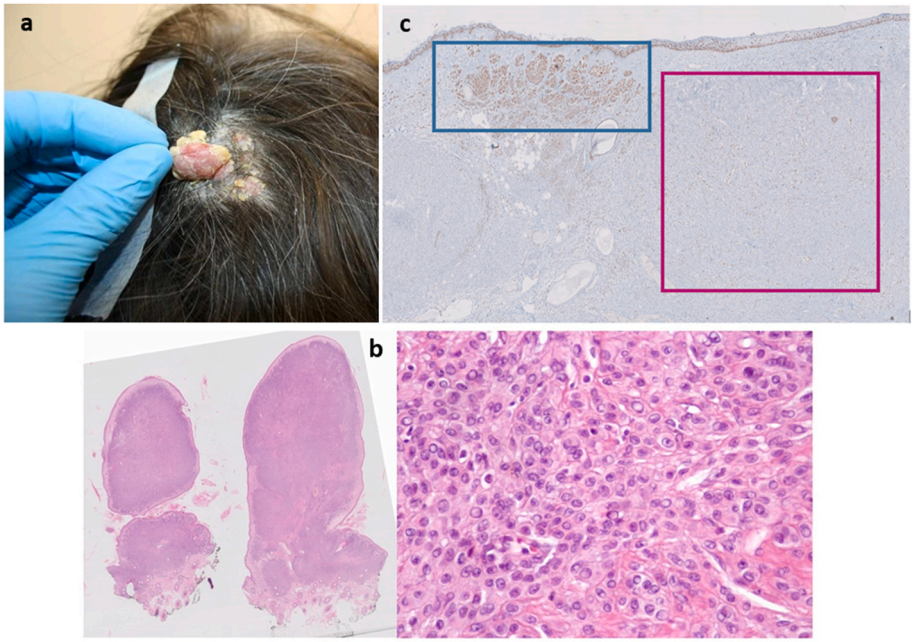

Fig. 1. a. Main lesion in scalp of 2cm with several satellite lesions. Fig. 1b. Histopathological findings of scalp lesions. Fig. 1c. Immunohistochemical study of BAP-1. On the left, highlighted in blue, nevus with preserved BAP-1. On the right, nevus with loss of BAP-1 expression (in red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

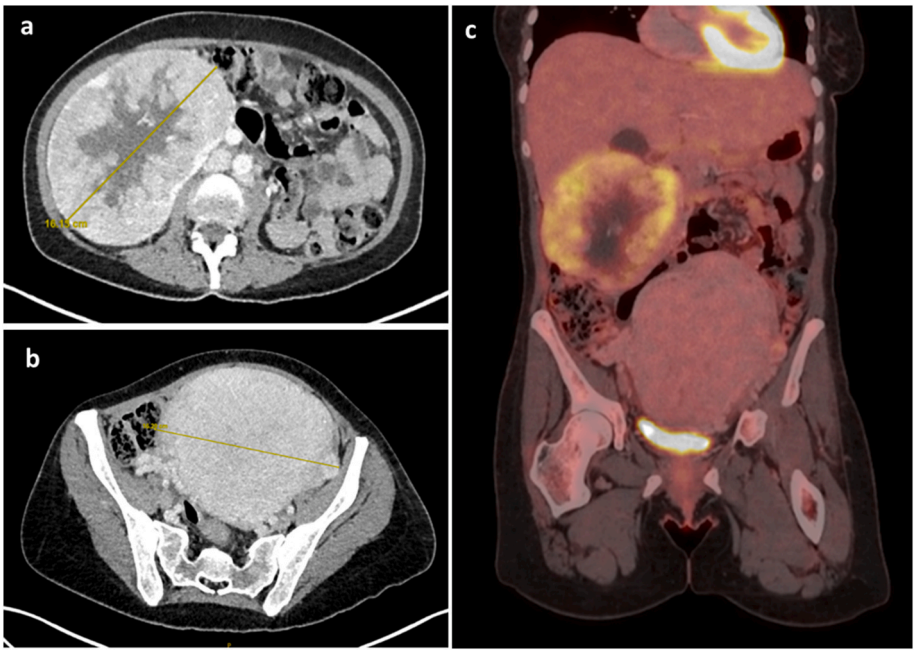

Fig. 2. Abdominal CT. 2a. Right renal lesion of 16 cm with necrotic areas and cystic degeneration. 2b. Large myomatous uterus with a diameter of 17 cm. Fig. 2c. FDG PET-CT coronal plane with enhancement of the renal mass.

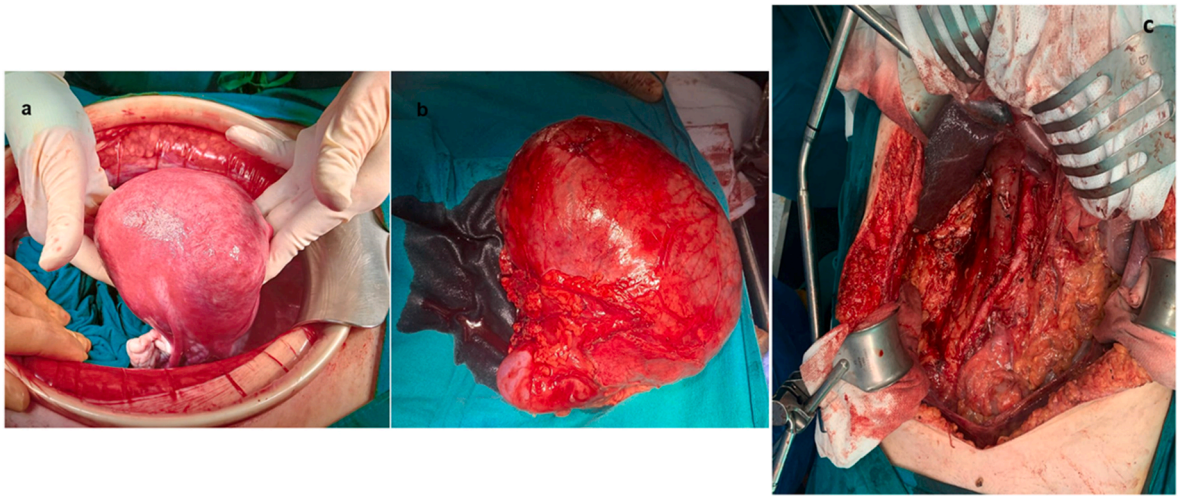

Fig. 3. a. Hysterectomy sample. Fig. 3b. Right radical nephrectomy sample. Fig. 3c. Para-aortic lymphadenectomy.

used.[1,2,4]

The histological subtype which more frequently presents BAP-1 mutations is ccCRC (clear cell renal carcinoma), with a prevalence of mutated BAP-1 of 10–14%.[4,5] However, the role of BAP-1 alterations in non-clear cell RCC is much less studied due to the lower prevalence of this tumor subtype.

In a cohort of patients with 186 ccCRC and 79 non-clear cell RCC, loss of BAP-1 expression was detected in 9% (17/186) of ccCRC tumors, but only in 1% (1/79) of non-clear cell RCC tumors ($p = 0.016$).[5]

Thai H. Ho et al.[4] evaluated BAP-1 expression in 458 patients undergoing nephrectomy for ccCRC and non-clear cell RCC (papillary variant, chromophobe and oncocytoma). Loss of BAP-1 occurred in 10% (18/187) of the ccCRC cases. However, this mutation was not observed in any of the papillary ($n = 61$), chromophobe ($n = 17$) or oncocytoma ($n = 34$) tumors, p 0.00021.

High clinical suspicion is essential in the management of BAP-1 tumor predisposition syndrome. It should be established upon histological diagnosis of BAPoma, or any other tumor with loss of BAP-1 expression. In this way, dermatologists can play, as in our case, an important role in early diagnosis of associated tumors.

It is also recommended to perform a genetic study of BAP-1 loss in the patient and their first-degree relatives, justified by the autosomal dominant inheritance pattern that follows this syndrome.[1,3]

There is no consensus on the image tests that should be performed in the follow-up of those patients. One of the proposals recommends biannual dermatologic screening for nevi in all patients and their relatives over 22 years of age, as well as annual eye screening for all patients and their relatives over 11 years of age.[3] Screening for pleural mesothelioma is complex, and an annual CT scan can be performed, although with the inherent risk of irradiation. For the screening of renal carcinoma, biannual abdominal MRI has been proposed, which also evaluates peritoneum (potential focus of mesothelioma). Thorax can be included in the study to evaluate the pleura. Another possibility is to perform abdominal ultrasound annually, which is more accessible, cheaper and

harmless for the patient. In general, it is recommended to start follow-up in family members 5 years before the first case of cancer diagnosed in the family.[3]

In our case, the patient continues her follow-up by Dermatology service in order to control the appearance of new skin lesions and by us, with renal ultrasound every 6 months. In addition, the subsequent study and follow-up of her relatives will be determined by the results of the genetic study of the mutation in the BAP-1, which is still pending.

4. Conclusions

BAPoma is an intermediate type of melanocytic tumor whose diagnosis is confirmed by immunohistochemistry, which shows loss of nuclear expression of BAP-1. It may appear as part of a familiar syndrome that predisposes to tumors with a higher incidence than in general population, including renal carcinomas. High clinical suspicion is important to search for other associated neoplasms.

Clear cell carcinoma is the most frequently subtype associated with this syndrome, showing worse prognosis than renal tumors without BAP-1 mutation. However, as we described above, benign masses such as renal oncocytomas may also appear as part of this syndrome. It is necessary to establish a standardized protocol for the screening and follow-up of these patients and their relatives.

5. Section headings

Urology – oncology.

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Statement of ethics

The authors are accountable for all aspects of this work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures were performed in accordance with the Declaration of Helsinki (revised in 2013). Written informed consent was obtained from the patient for the publication of anonymized details in this case report.

CRediT authorship contribution statement

M. Alonso Grandes: Writing – review & editing, Writing – original draft, Conceptualization. **R. Roldán Testillano:** Writing – review & editing, Visualization, Conceptualization. **A.M. Márquez Negro:** Validation, Investigation. **C. Cernuda Pereira:** Writing – review & editing, Visualization, Validation, Conceptualization. **M. Dorado Valentín:** Writing – review & editing, Validation, Supervision. **R. Khedaoui:** Supervision, Methodology, Investigation, Conceptualization. **A. Páez Borda:** Writing – review & editing, Visualization, Validation, Supervision.

Declaration of competing interest

No conflict of interest has been declared by the authors.

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None.

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ABBREVIATIONS:

BCRA: Breast cancer gene
BAP-1: BCRA-associated protein-1
MBAITs: BAP-1-inactivated melanocytic tumor
ccCRC: Clear cell renal carcinoma
RCC: Renal cell carcinoma
CT: Computed tomography
MRI: Magnetic Resonance Imaging