

CASE REPORT

Early onset of a nasal perivascular epithelioid cell neoplasm not related to tuberous sclerosis complex

Esordio precoce di una neoplasia nasale a cellule epitelioidi perivascolari non associata a sclerosi tuberosa

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SUMMARY

Perivascular epithelioid cell neoplasms are a group of rare tumours reported in various organs under a variety of designations. Such tumours are of interest primarily because of the distinctive morphology of their cell population and their immunoreactivity with melanocytic and myoid markers. There is a strong association between perivascular epithelioid cell neoplasms and tuberous sclerosis complex. Perivascular epithelioid cell neoplasms very rarely occur in the upper aero-digestive tract. To date only three cases of nasal perivascular epithelioid cell neoplasms have been reported in the literature. The present report refers to a 22-year old woman, without any stigmata of tuberous sclerosis complex, with early onset of a polypoid nasal mass with pathological and immunohistochemical features entirely compatible with those of a perivascular epithelioid cell neoplasm.

KEY WORDS: Perivascular epithelioid cell neoplasm • Immunohistochemistry • Nasal cavity • Tuberous sclerosis complex • Rare disease

RIASSUNTO

Le neoplasie a cellule epitelioidi perivascolari sono un gruppo di tumori rari che possono coinvolgere diversi organi. Questi tumori sono di particolare interesse per la peculiare morfologia delle cellule neoplastiche e per la loro immunoreattività per marcatori melanocitari e mioidi. È stata dimostrata una chiara associazione fra le neoplasie a cellule epitelioidi perivascolari e la sclerosi tuberosa. Le neoplasie a cellule epitelioidi perivascolari molto raramente si manifestano nelle vie superiori. Al momento sono stati riportati solo tre casi di neoplasia a cellule epitelioidi perivascolari a livello nasale. Nel presente lavoro presentiamo un caso di neoplasia nasale a cellule epitelioidi perivascolari non associata a sclerosi tuberosa.

PAROLE CHIAVE: Neoplasia a cellule epitelioidi perivascolari • Immunoistochimica • Cavità nasale • Sclerosi tuberosa • Malattia rara

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Introduction

Perivascular epithelioid cell neoplasms (PEComas) are a group of rare mesenchymal tumours sharing unusual histological, immunohistochemical and ultrastructural features¹. Such tumours are composed of a distinctive cell population defined as perivascular epithelioid cells (PECs), characterized by acidophilic or clear cytoplasm, which typically coexpress smooth muscle and melanogenesis markers¹. The PEComa family includes different entities, reported in different organs and include angiomyolipoma (AML), clear-cell "sugar" tumour of the lung (CCST), lymphangiomyomatosis (LAM), and other

more uncommon clear cell tumours arising at a variety of visceral, bone and soft tissue sites, such as the clear cell myomelanocytic tumour of the falciform ligament/ligamentum teres¹.

AML and LAM are strictly associated to tuberous sclerosis complex (TSC)¹. TSC (OMIM 191100) is an autosomal dominant inherited condition characterized by hamartomas in the brain, skin, eyes, heart, lungs and kidneys. Moreover, epilepsy, mental retardation and autism are often present. The disorder is caused by inactivating mutations in either the TSC1 (9q34) or TSC2 (16p13.3) genes which seem to play a role in the regulation of the Rheb/mTOR/p70S6K pathway. Activation of this pathway has

been observed both in TSC-related and non-TSC-related PEComas¹.

Generally, PEComas are considered benign tumours, however, in some cases, a malignant potential has also been observed¹. The mainstay of treatment is wide excision although some current clinical trials are examining the benefit of mTORC1 inhibitors, such as rapamycin²⁻⁴.

PEComas are rare tumours and their occurrence in the upper aero-digestive tract is even more rare. In fact, a thorough search on several databases disclosed that, to date, only three cases of PEComa, arising in the nasal cavity, have been reported³⁻⁵. Herewith a fourth case is reported with early onset, histological features of spindle-cell tumour and typical immunohistochemical features.

Case report

The patient, a 22-year-old female, was born to unrelated parents after 3 spontaneous abortions by the mother. Pregnancy and delivery were uneventful and the infant's psychomotor development was normal. There was no family history of TSC, hamartomas or epilepsy. Her parents suffered from renal calculosis.

The patient's clinical history was otherwise unremarkable until the age of 22 years when she presented epistaxis and respiratory difficulties due to a left nasal obstruction.

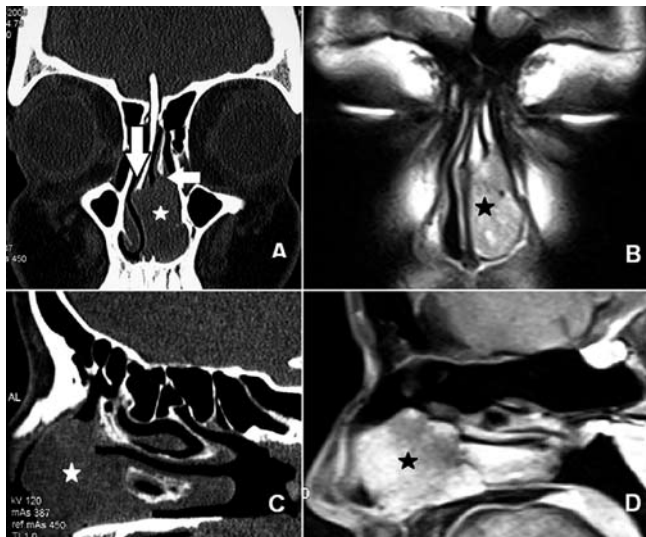


Fig. 1. A. Coronal CT image. Polypoid formation (star) occupying anterior part of left nasal fossae and inferior meatus, reaching cranially the anterior margin of the middle turbinate (horizontal arrow). There are no signs of infiltration or bony destruction but a nasal septum deviation (vertical arrow). B. Coronal T1 (post-contrast) MRI. The mass (star) shows a homogeneous signal after gadolinium administration. The bony framework and septal cartilage show no signs of infiltration. C. Sagittal CT image. Evaluation of both sagittal and antero-posterior extension of the polypoid formation (star) with preservation of bony framework. D. Sagittal T1 (post-contrast) MRI. Homogeneous signal of the polyp (star) following gadolinium administration.

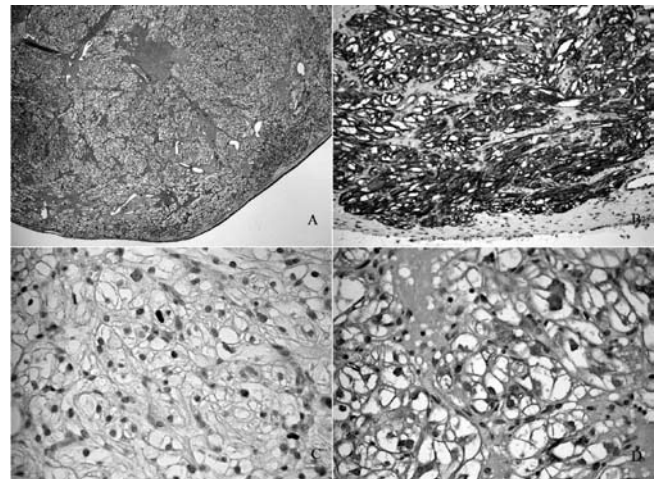


Fig. 2. A. Low power view of surgical sample from the polypoid endo-nasal mass. On haematoxylin-eosin stain, clear cells are organized in nests with interposed connective stroma. Respiratory epithelium covers surface of lesion (10x). B. Immunohistochemical reaction with antibodies directed against muscle actin staining diffusely PEComa cells (20x). C. Immunohistochemical reaction with antibodies directed against progesterone receptor staining only part of the nuclei in the lesion (40x). D. Immunohistochemical reaction with antibodies directed against HMB45 staining the cytoplasm of sparse PEComa cells (40x).

Clinical otorhinolaryngologic examination, computed tomography (CT) and magnetic resonance imaging (MRI) scans revealed a left nasal polypoid mass, 1.5 cm in diameter, with deviation of the septum to the right (Fig. 1). Therefore, an endoscopic anterior turbinectomy with a diode laser was performed, permitting en-bloc removal of the tumour; the post-operative course was uneventful. Histological examination showed proliferation of epithelioid or spindle cells with wide, clear or eosinophilic cytoplasm, organized in large bundles around ectatic blood vessels. Neoplastic cells showed mild atypia (oval nuclei and small nucleoli). There was no significant mitosis or necrosis. The immunohistochemical study demonstrated coexpression of myogenic and melanocytic markers such as actin, muscle actin, desmin, melan A, and HMB45 (Fig. 2). Progesterone receptor expression was observed in a limited number of nuclei (Fig. 2). Immunoreactions for cytokeratins, EMA, vimentin, myogenin, S100 protein, CD56/N-CAM, CD10, oestrogen receptor and CD34 gave negative results. The histological and immunohistochemical features were consistent with a diagnosis of PEComa¹.

At clinical re-evaluation, the patient presented no clinical findings suggestive of TSC: skin examination revealed only one hypopigmented macula on the left thigh and two café-au-lait spots > 1.5 cm in diameter on the left thigh and the right thigh, respectively, no other cutaneous signs of TSC were observed. Finally, it should also be pointed out that ophthalmologic assessment, cardiological evaluation, including echocardi-

gram, abdomen and renal ultrasound, and brain MRI, were normal.

The patient underwent a further endonasal surgery for the removal of residual neoplastic tissue one month after the first polypectomy. Recurrence of the nasal lesion has not been observed over a 13-month follow-up.

Discussion

In this report, a PEComa is described occurring in the upper respiratory tract presenting as an endo-nasal polypoid mass.

PEComas of the nasal cavity are extremely rare and a total of four cases (including the present case) have been reported in the literature to date, all in females³⁻⁵. The age of the three previously reported cases ranged from 34 to 79 years, with a mean age 54.3 years. The age of our patient (22 years) was younger than in the previously reported cases, and also younger than the median age recorded for visceral and mucocutaneous PEComas¹. The left nasal cavity was involved in 3 cases, and the nasal septum in one case. All the cases were histologically benign and presented slight differences in terms of immuno-staining for melanocytic and muscular markers. Concerning follow-up, in one case no recurrence was observed after long-term follow-up⁵, while in the remaining 3 cases the clinical follow-up was too short for evaluation. Progesterone receptor expression (observed in our case), although limited, is an unusual finding in extra-renal PEComas and to our knowledge has never been reported in a nasal lesion¹. The young age and the sex of the patient could account for this unusual feature.

In the whole PEComa family, AML and LAM are more strongly associated with the tuberous sclerosis complex (TSC). Approximately 60-80% of adult TSC patients present AML and 25-40% of adult female TSC patients present LAM. Conversely, about 80% of patients with AML do not have TSC. Other PEComas, although very rare and with a less strong association with TSC, however occur at a much higher frequency in patients with TSC than in the general population¹.

None of the patients affected by PEComa of the nasal cavity, reported in the literature, have any stigmata or family history of TSC. However, as early onset of tumours is often associated with germline mutations, our patient was scrupulously evaluated from a clinical point of view to verify if any sign of TSC could be observed. She presented only one hypopigmented macula and two café-au-lait spots in the absence of other cutaneous signs of TSC. Furthermore, all the other clinical and radiological investigations showed negative results. In conclusion, our patient did not fit the clinical criteria typical of a clinical

diagnosis of TSC, and thus no molecular testing was performed.

Clinically, PEComa of the nasal cavity can be mistaken for any other benign or malignant primary or metastatic exophytic tumour occurring in the region³, and, in the absence of any particular clinical feature, only histological examination of the tissue removed can provide a correct diagnosis. While the distinction from the most common inflammatory or Schneiderian nasal polyp is straightforward, on routine histological slides, a range of neoplastic lesions can be more difficult to differentiate on pure morphological grounds. Frequent clear cell features raise the possibility of a clear cell neoplasm, including metastatic renal cell carcinoma, adrenocortical carcinoma, paraganglioma. Renal cell carcinoma, in particular, frequently localized to the upper aerodigestive tract, needs to be excluded, in older patients. Negative staining for cytokeratins and CD10 are the key diagnostic feature. The immunohistochemical coexpression of a muscle marker (such as smooth-muscle actin) with HMB45, in combination with negative staining for S100 protein, allows a malignant melanoma to be excluded, which shows, however, greater cellular atypia. Other important differential diagnoses of PEComa include smooth-muscle tumours, which are negative for melanocytic markers and have a more eosinophilic cytoplasm, and angiomyolipomas. The latter have occasionally been described in the nasal cavity but seem to differ from the classic renal AML.

Although the number of single case reports and small series is rapidly increasing¹, there is no general agreement regarding the cell from which PEComas originate, and no normal counterpart has been recognized. The presence of PEComas in different areas of the human body, although with an increased frequency in the uterus/pelvic area, favours a direct or indirect origin from ubiquitous cells, such as undifferentiated cells from the neural crests, pericytes or mutated precursors of smooth muscle cells.

In our opinion, this description of a further case of PEComa of the nasal cavity is worthwhile, because of the rarity of the disorder, and because the present case is the first one to be reported in which an early onset was discovered. Although nasal PEComa is a very uncommon lesion, it should be considered in the differential diagnosis of polypoid nasal masses, especially when the mass occurs unilaterally. To date, including our case, a total of four cases have been reported. Therefore, further reports on additional cases might help to better understand the link between this tumour and TSC and to predict the biological behaviour of these very rare and distinctive tumours in terms of recurrence and malignancy.

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