PEComa of the Nose: Report of a Case with Immunohistochemical and Ultrastructural Studies and a Review of the Literature

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Abstract PEComas are a family of mesenchymal neoplasms that have in common the presence of a unique cell type, the perivascular epithelioid cell (PEC). PECs uniquely exhibit a distinct immunophenotype with expression of both melanocytic, particularly HMB-45, and myogenic markers. Nasal PEComas are exceedingly rare. To date, 14 cases have been described in the literature and with the exception of 6 cases, the rest consistently lack epithelioid cells and HMB-45 expression and are best classified as nasal hamartomas or angioleiomyomas with an adipocytic component. Nasal PEComas may closely resemble malignant melanomas since both entities share many morphologic, immunohistochemical, ultrastructural and clinical features. The distinction is of paramount importance as melanomas tend to display an aggressive behaviour with associated poor outcome. Herein, we report a case of nasal PEComa in a 19 year girl, focusing on the importance of light microscopic, immunohistochemical and ultrastructural features in accurately establishing the diagnosis.

Keywords PEComa · Nasal cavity · Immunohistochemistry · HMB-45 · Electron microscopy · MUM-1 · Angiomyolipoma

Case Report

A 19 year female presented with a history of right-sided nasal obstruction. The patient reported that a year earlier she was punched in the nose, which resulted in profuse bleeding. At the time she was seen by her physician who controlled the bleeding, however, over time she started to have a blocked nose and subsequently noted a growth in the right nostril. Her medical history was unremarkable and the patient had no personal or familial history of tuberous sclerosis. Clinical examination revealed a fleshy polypoid soft tissue mass in the right nasal cavity pushing the nasal septum to the left.

Computerized tomographic (CT) scans revealed a homogeneous, avidly enhancing, soft tissue mass expanding the right nasal cavity with bone thinning and remodelling but no destruction (Fig. 1). Two months later the lesion was excised under general anaesthesia, resulting in profuse bleeding, which required firm nasal packing. The excised mass was polypoid in nature, soft in consistency and had a solid haemorrhagic cut surface. It measured 4 × 2.3 cm.

Histological examination revealed a polyp lined by respiratory-type epithelium, with the connective tissue core of the lesion containing nests of epithelioid cells in a perivascular arrangement (Fig. 2a, b). The tumour cells had well defined cell borders, abundant eosinophilic to clear cytoplasm and centrally located round to oval nuclei with small but prominent nucleoli (Fig. 2c). No pleomorphism, spindled or adipocyte-like cells were observed. Mitoses, necrosis, lymphovascular and perineural invasion were not detectable. Focally, there was evidence of surface ulceration, myxoid change and mild chronic

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Fig. 1 A coronal CT shows a homogeneous, avidly enhancing, soft tissue mass expanding the right nasal cavity with bone thinning and remodelling but no destruction

inflammation. The tumour cells were diffusely immunoreactive for HMB-45 and faintly, but focally positive for SMA (Fig. 2d). The tumour cells were negative for MNF-116, EMA, S100 protein, Melan-A, desmin, vimentin, MUM-1 and chromogranin. Formalin-fixed tissue was used for electron microscopy and ultrastructural examination revealed moderate

amounts of stacked rough endoplasmic reticulum, mitochondria, lysosomes and oval cytoplasmic melanosome-like electron dense granules, 248.10–593.83 nm in diameter, lacking internal periodic filaments (Fig. 3a, b). Sparse but well developed actin myofilaments were seen in the peripheral cytoplasm (Fig. 3c). Based on the microscopic features, immunohistochemical profile and electron microscopic findings the diagnosis of an epithelioid nasal PEComa was established. The post-surgical period was uneventful and follow up at 6 and 17 months showed no evidence of recurrence.

Discussion

PEComas are a family of mesenchymal neoplasms that have in common the presence of a unique cell type, the perivascular epithelioid cell (PEC). PEComas include angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), clear cell ‘sugar’ tumour of the lung and extra-pulmonary sites, clear cell myomelanocytic tumour of the falciform ligament/ligamentum teres and rare clear cell tumours of other sites [1].

Perivascular epithelioid cells uniquely exhibit a distinct immunophenotype with expression of both melanocytic,

Fig. 2 Light microscopic features of the nasal PEComa, **a** the lesion is a polyp lined by respiratory epithelium, $\times 10$; **b** nests of epithelioid cells seen in a perivascular arrangement, $\times 20$; **c** epithelioid cells

possess abundant eosinophilic to clear cytoplasm and centrally located round to oval nuclei with small but prominent nucleoli, $\times 40$; **d** the epithelioid cells are positive for HMB-45, $\times 40$

Fig. 3 Ultrastructural features, **a** stacked rough endoplasmic reticulum, $\times 15,000$; **b** an oval electron dense melanosome-like granule, 248.10 nm in diameter, $\times 30,000$; **c** peripheral well developed actin myofilaments, $\times 15,000$

particularly HMB-45, and myogenic markers, such as SMA. Just as the name implies they have an epithelioid appearance and a typical perivascular arrangement. However, not all PECs are epithelioid and it is believed that PECs have the ability to modulate their morphology. They can become spindled or

accumulate cytoplasmic vacuoles, the so called “adipocyte-like” cells [2]. The classic AML of the kidney is the prototype of a PEComa in which all three cell types are found.

The PECs’ change in shape strongly influences their immunophenotype. Spindled PECs display strong expression of myogenic markers while epithelioid PECs demonstrate pronounced expression of HMB-45 and mild if any reaction for SMA. Ultrastructurally, PECs possess cytoplasmic melanosome/melanosome-like granules and actin myofilaments. The PEC has no normal cellular counterpart and its histogenesis remains to be elucidated. One plausible theory is that PECs originate from the neural crest undifferentiated stem cells and as such can coexpress smooth muscle and melanocytic markers [3]. Another theory is that their perivascular location suggests a pericytic origin, while others believe that PECs are indeed smooth muscle cells with aberrant expression of melanocytic markers [4].

Recent molecular studies have shown that PEComas are linked to tuberous sclerosis, an autosomal dominant disease characterized by mutations or losses of TSC1 or TSC2 genes. This association is significantly stronger for the two members of the family AML and LAM. Kenerson et al. [5] using western blotting and immunohistochemistry demonstrated upregulation of the mTOR signalling pathway with negative feedback inhibition of AKT, consistent with functional loss of TSC1/2 in sporadic renal AMLs and non-renal PEComas.

In total, 14 cases of nasal AMLs/PEComas have been described in the literature (Table 1) and with the exception of 6 cases, the rest consistently lack epithelioid cells and HMB-45 expression and consist of well differentiated mature fat, smooth muscle and blood vessels; and are best classified as nasal hamartomas or angioleiomyomas with an adipocytic component [6–17]. We fully agree with Tosios et al. [18] in that the term ‘angiomyolipoma’ should be discouraged for angiomyomatous lesions with mature adipocytes, including terms such as ‘mucocutaneous’ AML coined by Watanabe and Suzuki [8].

The differential diagnosis of an epithelioid PEComa includes malignant melanoma, clear cell sarcoma, paraganglioma, alveolar soft part sarcoma (ASPS) and clear cell carcinoma [19]. The nasal cavity is the most common site for head and neck mucosal melanomas [20]. Since many PEComas pursue a benign clinical behaviour, it is important to differentiate them from malignant melanomas and clear cell sarcomas, which demonstrate an aggressive behaviour with associated poor outcome.

Malignant melanoma may cause considerable diagnostic difficulty since it shares many morphologic, immunohistochemical, ultrastructural and clinical features with PEComas at this site. These include epithelioid morphology, the expression of melanocytic markers, the ultrastructural presence of melanosome-like granules and the clinical findings of a nasal, polypoid haemorrhagic mass with nasal obstruction and epistaxis. In fact in the first report of a

Table 1 Clinicopathological features of nasal PEComas/AMLs reported in the literature

References	Age and sex	Site	Clinical findings	Histology	HMB-45	Follow up
[6]	52 M	Right nasal cavity	Type II diabetes and high blood pressure	Fat, smooth muscle and blood vessels	Negative	6–12 months with no recurrence
[7]	64 M	Right nasal cavity	Allergic rhinitis and healed TB	Fat, smooth muscle and blood vessels	Negative	2 years with no recurrence
[8]	66 M	Right nasal cavity	Chemotherapy for non-Hodgkin's lymphoma	Fat, smooth muscle and blood vessels and lymphocytes	Negative	6 months with no recurrence
[8]	88 F	Left nasal cavity	Clear	Fat, smooth muscle and blood vessels	Negative	6 months with no recurrence
[9]	34 F	Left nasal cavity	Clear	Epithelioid and spindled cells with focal adipocytes	Positive	12 months with no recurrence
[10]	45 M	Right nasal cavity	Type II diabetes	Fat, smooth muscle and blood vessels	Negative	1 month with no recurrence
[11]	52 M	Left nasal cavity	Clear	Fat, smooth muscle and blood vessels	Negative	No follow up
[12]	44 M	Right nasal cavity	Clear	Fat, smooth muscle and blood vessels	Negative	2 months with no recurrence
[13]	50 F	Anterior nasal septum	Clear	Epithelioid and spindled cells	Positive	6 years with no recurrence
[14]	79 M	Left nasal cavity	Not known	Epithelioid cells	Positive	No follow up
[15]	18 F	Left nasal cavity	Clear	Epithelioid cells	Positive	26 months with no recurrence
[15]	71 F	Nasal cavity	Not known	Epithelioid cells	Positive	No follow up
[16]	54 ??	Left nose	Clear	Fat, smooth muscle and blood vessels	Negative	No follow up
[17]	22 F	Left nasal cavity	Clear	Epithelioid and spindled cells	Positive	13 months with no recurrence

nasal PEComa by Banerjee et al. [9], the lesion was initially diagnosed as malignant melanoma on biopsy.

The diffuse and strong expression of S100 protein and lack of SMA immunoreactivity is indicative of melanoma/clear cell sarcoma in most cases. However, the expression of S100 protein does not entirely rule out the possibility of a PEComa, since S100 expression has been reported in up to 33 % of PEComas [21]. In addition, S100 negative melanomas are known to exist and epithelioid PEComas usually exhibit weak if any staining for SMA.

In doubtful cases where light microscopic features and melanocytic/smooth muscle markers are not sufficient to reach a final diagnosis, addition of MUM-1 to the panel of immunohistochemical markers may prove invaluable. A fairly recent study showed that MUM-1 is usually negative or weakly positive (25 % of cases) in PEComas versus the strong expression of MUM-1 seen in malignant melanomas [22]. Molecular studies are of value in diagnosis of clear cell sarcoma, since most cases harbour the t (12; 22) (q13, q13) (EWS-ATF1) gene fusion.

Epithelioid PEComas may be confused with carcinomas, especially clear cell carcinoma. The strong expression of

melanocytic markers and SMA immunoreactivity separate a carcinoma from PEComa. Although rare PEComas show focal expression of cytokeratins, a diffuse staining pattern characteristic of a carcinoma is not seen.

A nested growth pattern and a vascular stroma may closely resemble a paraganglioma, however, the lack of expression of neuroendocrine markers (e.g., chromogranin and synaptophysin) and the absence of S100 positive sustentacular cells, reliably separate a paraganglioma from a PEComa. In addition paragangliomas do not exhibit the characteristic myomelanocytic immunophenotype of PEComas.

ASPSs have been reported in the nasal cavity and may be indistinguishable from PEComas on light microscopy; with the exception that vascular or lymphatic invasion is commonly seen in ASPS. Argani et al. [23] by way of standard immunohistochemistry, FISH and RT-PCR demonstrated that a distinctive subset of PEComas harbour TFE3 gene fusions, thus sharing a common genetic trait with ASPS. These PEComas exhibit distinct morphological and immunohistochemical features. They are purely epithelioid in nature, have a nested growth pattern and are negative for SMA, similar to the PEComa in the present

case. However, ASPS does not show expression of SMA and melanocytic markers, although occasional S100 positivity in ASPS has been reported.

An epithelioid smooth muscle neoplasm may mimic an epithelioid PEComa but careful examination will reveal spindled areas with characteristic light microscopic features, suggestive of smooth muscle differentiation, such as intense cytoplasmic eosinophilia, fibrillar cytoplasm, perinuclear vacuoles and ‘cigar-shaped’ nuclei.

A significant proportion of PEComas appear to be clinically benign with a favourable outcome. This is further substantiated by the lack of recurrence reported in cases of nasal PEComas with follow up (Table 1). However, given the rarity of PEComas and the paucity of the reported cases in the literature, it is not clear whether any of these tumours can be definitely labeled benign or should be considered to be of uncertain malignant potential.

A subset of PEComas have been reported to exhibit a malignant behaviour and pursue an aggressive clinical course [24, 25]. Provisional criteria for malignancy have been proposed based on worrisome features of large size (>5 cm), high nuclear grade and cellularity, necrosis and >1 mitotic figures/50 HPF [19]. The development of solid criteria for malignancy may require evaluation of a reasonable number of cases with adequate follow up information.

Conflict of interest The authors declare that they have no conflict of interest.

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