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ORIGINAL PAPER

Perivascular Epithelioid Cell Tumors (PEComas) of the Head and Neck: Report of Three Cases and Review of the Literature

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Abstract PEComas are a family of neoplastic lesions that share overlapping morphology, immunohistochemistry, and ultrastructure that include angiomyolipoma, lymphangioleiomyomatosis, clear cell "sugar" tumor of the lung as well as similar tumors occurring in a variety of visceral, cutaneous and soft tissue sites throughout the body. The defining histopathological features are epithelioid cells with a perivascular distribution containing clear to pale eosinophilic granular cytoplasm and a round-to-oval centrally located nucleus with an inconspicuous nucleolus. Immunohistochemically, coexpression of melanocytic (HMB-45 and/or Melan-A) and myoid markers are characteristic. In the present study, we describe three PEComas occurring in the head and neck (nasal cavity and larynx) and discuss the behavior of these distinctive tumors and review the literature of head and neck PEComas. The importance of recognizing this entity will ensure its consideration in the differential diagnosis of tumors of the head and neck with a similar morphology. The histogenesis of PEComas still remains elusive and additional cases with a prolonged follow up remain important to accurately determine the behavior of these distinctive tumors. Complete surgical excision still remains the treatment of choice for histologically benign PEComas.

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Introduction

The term perivascular epithelioid cell tumor (PEComa), first coined by Bonetti et al. [1], is currently defined as a mesenchymal tumor composed of distinctive perivascular myoid cells. PEComas are a family of neoplastic lesions that share overlapping morphology, immunohistochemistry, and ultrastructure and includes angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), clear cell "sugar" tumor (CCST) of the lung, as well as similar tumors occurring in a variety of visceral, cutaneous, and soft tissue sites throughout the body. PEComas may be associated with the tuberous sclerosis complex (TSC), particularly AML and LAM [2–4], or represent a *forme fruste* of the disease [1]. Notably, non-AML and non-LAM PEComas are only rarely associated with TSC. In general, PEComas are characterized by a female predominance (with a female to male ratio of 7:1) and wide age distribution. In recent decades, these tumors have been described in virtually all body sites. The defining histopathological features are epithelioid cells with a perivascular distribution containing clear to pale eosinophilic granular cytoplasm and a round-to-oval centrally located nucleus with an inconspicuous nucleolus [5]. While the perivascular distribution of tumor cells is characteristic, it may not be seen in all PEComas, which most typically have a delicate vascular stroma surrounding tumor nests. Immunohistochemically, coexpression of melanocytic (HMB-45 and/or Melan-A) and myoid markers is characteristic [6]. The growing interest in PEComas has led to an increasing number of reports demonstrating different anatomic locations of these

lesions, including several case reports involving various head and neck sites. In the present study, we describe three PEComas occurring in the head and neck (nasal cavity and larynx) and discuss the behavior of these distinctive tumors, plus review previously recorded cases at this anatomic site.

Case Histories

Case 1

An 18-year-old woman presented with a mass in the left nasal cavity. The mass had been progressively increasing in size over a period of 1 year, resulting in complete obstruction of the left nasal cavity. Magnetic resonance imaging (MRI) revealed a smoothly demarcated 2.9 cm soft tissue mass located in the anterior left nasal cavity arising from the inferior turbinate. The cribriform plate was not involved and there was no intracranial extension. Imaging studies favored a vascular tumor but also included schwannoma, inverted papilloma, and paraganglioma in the differential, although the lesion was not typical for any of these latter entities. The patient underwent tumor embolization followed by surgical resection. One month after the primary excision (debulking), a complete re-excision was performed to obtain clear margins. No residual tumor was identified. Twenty-six months after primary surgery the patient was alive and asymptomatic without evidence of disease. No personal or family history of tuberous sclerosis was reported.

Microscopically, the tumor showed extensive surface ulceration and effacement of the submucosal structures with a narrow zone of subepithelial sparing in the areas with an intact surface. The tumor was predominantly composed of uniform epithelioid clear cells arranged in nests and trabeculae and intimately associated with a uniform delicate vascular stroma (Fig. 1) but no perivascular growth was identified. There was no cytological atypia, mitotic activity, or necrosis. Patchy perivascular chronic inflammation, resembling dysgerminoma/seminoma, was present toward the surface. Diastase-sensitive PAS positive cytoplasmic granules were present, consistent with glycogen. Immunohistochemical stains demonstrated cytoplasmic calponin, HMB45 and Melan-A positivity. The cells were negative for S-100 protein, smooth muscle actin (SMA), desmin, synaptophysin, cytokeratin CAM 5.2, and pancytokeratin. Ki-67 (MIB1) revealed a very low (<5%) proliferation index.

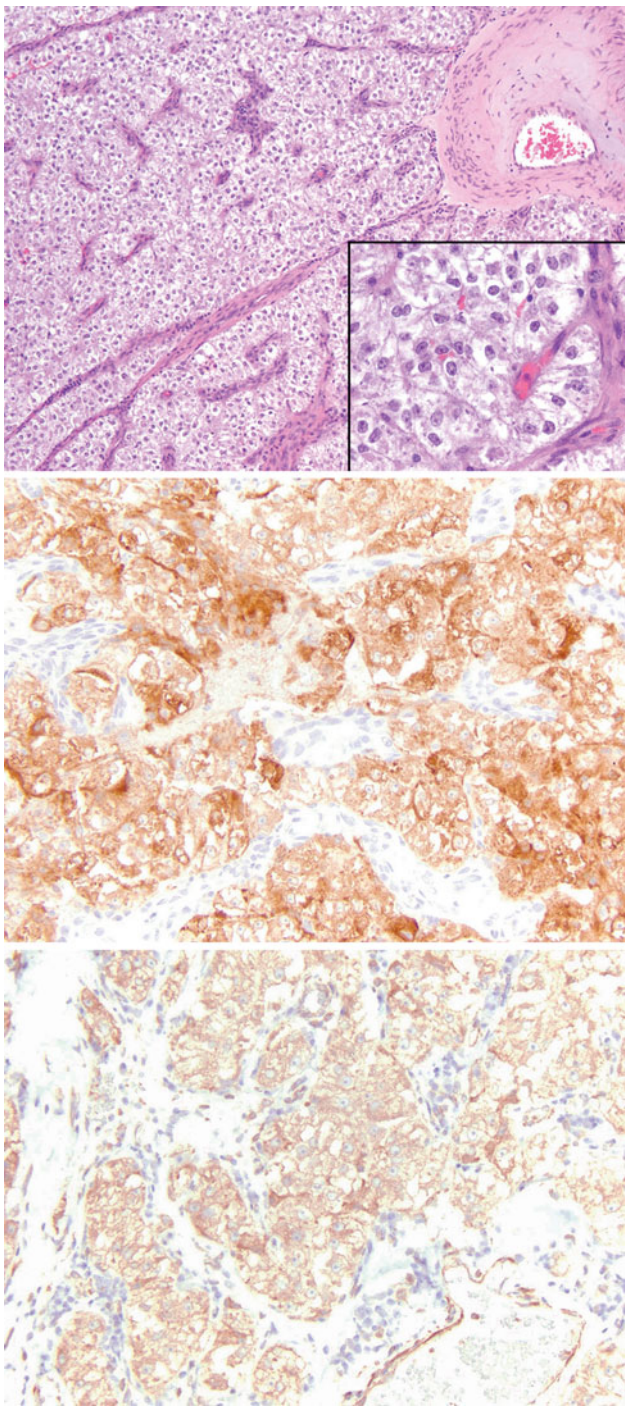

Fig. 1 Nasal PEComa (Case 1) comprised of sheets and nests of polygonal cells associated with a prominent vascular stroma. The cells are cytologically bland with abundant clear to eosinophilic granular cytoplasm (*top*; H&E 100×; *inset* 400×). The tumor was strongly positive for Melan-A (*middle*; 200×) and calponin (*bottom*; 200×)

Case 2

A 71-year-old woman presented with a polypoid lesion of the nasal cavity of unknown duration and symptoms of nasal obstruction. No additional history or follow-up information was available. Microscopically, the lesion was composed of large polygonal cells arranged in sheets and nests and associated with a delicate vascular stroma. The tumor effaced the

submucosal structures with a narrow zone of subepithelial sparing and an intact surface. The vessels were variable in size with many larger thin-walled ectatic vascular channels and scattered small capillary-sized vessels. No areas of distinct perivascular distribution of tumor cells were identified. The cells had clear to pale eosinophilic, granular to vacuolated cytoplasm with central nuclei and small nucleoli (Fig. 2). Some cells also contained a brown cytoplasmic pigment consistent with melanin. The proliferation was intimately arranged around the different types of blood vessels and there was no evidence of mitotic activity, atypia, or necrosis. A mucicarmine stain was negative and diastase-sensitive PAS positive cytoplasmic granules were present, consistent with glycogen. Immunohistochemical stains demonstrated cytoplasmic positivity for HMB45, SMA, vimentin, and focally for synaptophysin. The cells were negative for S-100 protein, pancytokeratin, and desmin.

Case 3

A 26-year-old woman presented with hoarseness of unknown duration and workup revealed a mass involving the left glottis but sparing the anterior commissure. Initial biopsy of the tumor was interpreted as a paraganglioma and the patient subsequently underwent left partial vertical laryngectomy with negative margins. On further review of the morphology and immunohistochemistry, a diagnosis of PEComa was rendered. There was no evidence of a personal or family history of tuberous sclerosis. Eight years after surgery the patient was alive and disease-free. During follow up the patient has only been treated for recurrent upper respiratory tract infections.

Microscopically, the tumor was composed primarily of epithelioid clear cells arranged in nests. Like Cases 1 and 2, there was a zone of subepithelial sparing with an intact overlying surface. The periphery demonstrated separate tumor lobules ("islands") including involvement of the vocalis muscle but no destructive infiltrative growth was identified. The tumor cells were intimately associated with a uniform delicate vascular stroma (Fig. 3) and focal areas showed a perivascular subendothelial distribution of tumor cells. There was no cytological atypia, mitotic activity, or necrosis. The cells contained abundant cytoplasmic glycogen (PAS positive, diastase sensitive). Immunohistochemical stains demonstrated cytoplasmic positivity for HMB45 and SMA, and were negative for synaptophysin, pancytokeratin, S-100 protein, and vimentin.

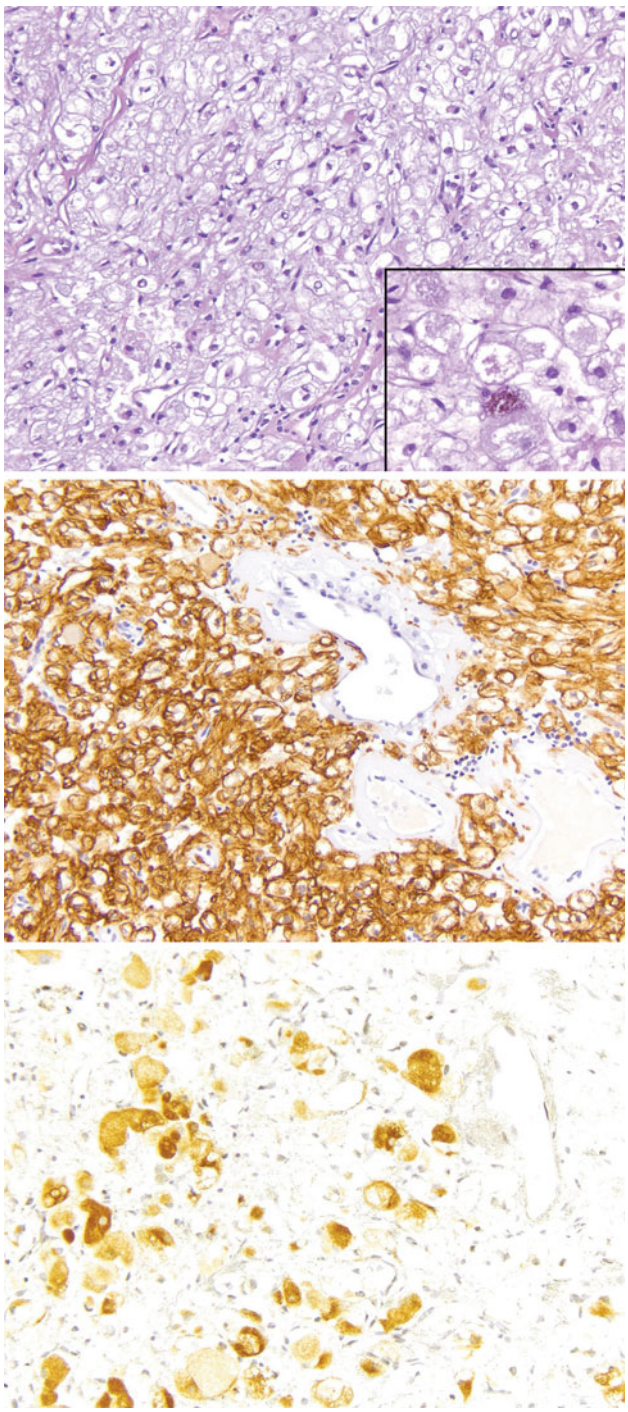

Fig. 2 The other nasal PEComa (Case 2) had slightly larger cells with more cytoplasmic clearing and a delicate vascular stroma (*top*; H&E 100×). In this example, scattered cells with finely granular brown melanin pigment were present (*top*; *inset* 400×). The tumor was strongly positive for SMA (*middle*; 200×) and patchy HMB45 staining (*bottom*; 200×)

Discussion

Herein, we describe three PEComas of the nasal cavity (two cases) and larynx (one case) all of which occurred in females, consistent with the sex predilection of all PEComas, who ranged from 18 to 71 years of age. Other than a mass effect, no other specific signs or symptoms were noted. PEComas are rare in the head and neck [7–17], and

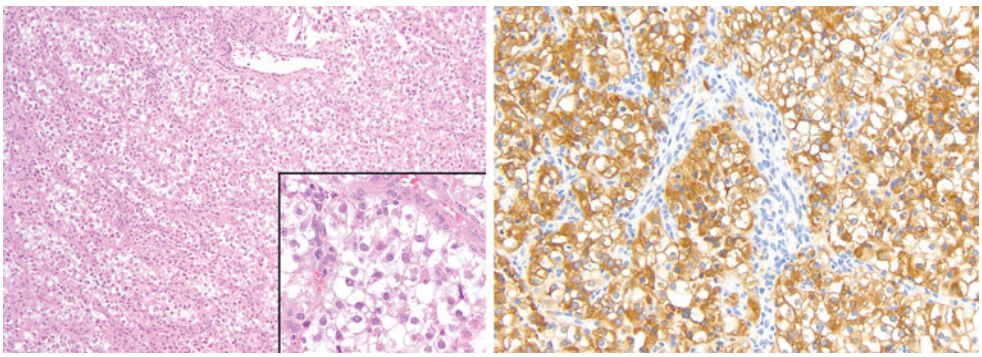

Fig. 3 The laryngeal PEComa (Case 3) was histologically identical to Case 1, with characteristic polygonal cells and a delicate vascular stroma (*inset*), but showed foci with the characteristic perivascular distribution of tumor cells as seen in the upper field (*left*; H&E 100×; *inset* 400×). The tumor was strongly positive for HMB45 (*right*; 200×) and patchy SMA staining

those arising in the nasal cavity and larynx are even more unusual [7, 12]. The common morphologic features observed in all three tumors included: large polygonal to epithelioid cells with clear or eosinophilic granular cytoplasm, centrally located nuclei with vesicular chromatin, and occasional nucleoli; a predominantly nested growth pattern associated with a delicate vascular stroma, similar to the vessels seen in clear cell renal cell carcinomas and paragangliomas; and a zone of subepithelial sparing. Except for Case 1, which showed extensive surface ulceration, the other two cases had an intact overlying surface. In Case 2, the vessels were more variable and a subpopulation of tumor cells demonstrated a faint brown cytoplasmic melanin pigment. Only Case 3 had the characteristic perivascular distribution of tumor cells, although only focally present. In addition, no case revealed significant cytological atypia, necrosis, infiltrative growth, vascular invasion, or mitotic activity. Moreover, by immunohistochemistry, all three cases reacted positively with melanocytic markers (HMB45 and/or Melan-A) and myoid markers (SMA or calponin).

The two patients with nasal PEComas were women 18 and 71 years of age, respectively. Not surprisingly, given the strong uniform expression of the melanocytic markers HMB45 and/or Melan-A, a differential of sinonasal melanoma was considered in both cases. Only two previous cases of nasal PEComas have been reported, expressing characteristic histologic and immunophenotypic features diagnostic of this tumor [7, 12]. The first case, reported in 2001 by Banerjee et al. [7], presented as a polyp in the left nasal cavity of a 34-year-old woman who complained of nasal obstruction and occasional epistaxis. There was no personal or family history of tuberous sclerosis. Twelve months after an intranasal polypectomy, the patient was well without evidence of disease. In 2009, Kuroda et al. [12] reported the second case of nasal PEComa in a 79-year-old Japanese woman who presented with a firm polypoidal mass in the nasal cavity. Notably, this was the first case of nasal PEComa expressing TFE3 protein. Follow-up information was not available for this patient, thus the prognosis could not be assessed.

In Case 3, the PEComa was originally misdiagnosed as paraganglioma and only correctly diagnosed as PEComa after subtotal laryngectomy. To our knowledge, this is the first reported case of PEComa of the larynx, although case reports of AML arising in the larynx and the epiglottis have been reported previously by Stodulski et al. [18] and Zhang et al. [19], respectively.

The descriptive term perivascular epithelioid cell (PEC) was proposed by Bonetti et al. [1, 20] to describe a novel cell type demonstrating HMB45 immunoreactivity and the presence of premelanosomes ultrastructurally, and which morphologically resembled the CCST of lung, AML of the kidney and liver, and LAM [21–26]. They hypothesized that the PEC may originate from the walls of blood vessels, given the perivascular association and the fact that there is no known normal cellular counterpart to the PEC. The PEComa family of tumors has grown to include AML (renal and extrarenal variants), LAM, CCST of the lung, clear cell myomelanocytic tumor (CCMMT) of the falciform ligament/ligamentum teres, primary extrapulmonary "sugar" tumor and clear cell tumors of diverse sites [10].

Epidemiologically, this tumor has a distinct female predominance, as observed in our three cases. Although most cases occur in middle aged patients [10], two of our three patients were under the age of 30. The role of sex hormones has been speculated in the pathogenesis of some PEComas since estrogen or progesterone receptors have been found in renal AML and LAM [5]. However, the absence of estrogen and progesterone receptor expression in other PEComas could not confirm this hypothesis [10]. Although there is an association of AML and LAM with tuberous sclerosis complex, this association has been documented in less than 10% of patients with PEComas of soft tissue and gynecologic origin [10].

Histologically, PEComas are characterized by predominantly epithelioid and/or spindled cells. Tumor cell nuclei range from round or ovoid in epithelioid cells to more elongated in the spindle cells. PEComa cells have a characteristic glycogen-rich, clear to lightly eosinophilic granular cytoplasm with vesicular nuclei and inconspicuous nucleoli. The nuclei are generally uniform with occasional cells exhibiting striking degenerative-type nuclear hyperchromasia and pleomorphism. Multinucleated giant cells may also be focally present and variable degrees of melanin pigmentation can be seen (as in Case 2). Mitotic figures are rare, though abundant and atypical mitotic figures can be seen in malignant examples. The cells have a focally nested, trabecular, or sheet-like growth pattern and may be intimately arranged around and within blood vessel walls. The vasculature ranges from a delicate capillary network to hyalinized arterioles and small arteries, best demonstrated in Case 2. At scanning magnification, the lesions may be well circumscribed or infiltrative.

Immunohistochemically, PEComas characteristically coexpress melanocytic and myoid markers [10]. Folpe et al. [10] evaluated 26 PEComas of soft tissue and gynecologic origin, and identified expression of melanocytic markers in all cases, with HMB45 being the most sensitive (92%) followed by Melan-A (72%). SMA was seen in 80% and desmin positivity in 8 (36%). Calponin was not used in this study but one case did express caldesmon. Case 1 was unusual in that there was no expression of SMA, but myoid differentiation was confirmed by immunoreactivity with calponin, another myoid marker; otherwise, this was a histologically typical PEComa with melanocytic differentiation (both HMB45 and Melan-A positive). Calponin has not been very well studied in PEComas but there are reports of calponin positive and SMA negative PEComas [11].

Based on the review by Hornick et al. [6] PEComas (excluding renal AML, LAM, and CCST of lung) most commonly involve the retroperitoneal, visceral, abdominal, and pelvic sites. The gastrointestinal tract and the uterus are the most common extrarenal organs involved with soft tissue and skin being less frequently involved. Case reports and small series have also described PEComas in unusual sites including the vulva, heart, breast, common bile duct, urinary bladder, and a variety of head and neck sites.

Based on our review of the English literature, we identified 13 cases [7–17] of primary head and neck PEComas (excluding examples described as AML). Including our three cases, this number now consists of 16 tumors (Table 1). There is less of a female predilection among this series (F: M = 10:6), compared to non-head and neck PEComas, and patients ranged in age from 7 to 80 years with both a mean and median of 48 years. The nasal cavity and ocular sites accounted for four cases each, representing half of the head and neck sites. The next most frequent sites

Table 1 Clinicopathologic findings of previously reported head and neck PEComas

Author	Gender/ age(years)	Size/location	Giant cells	Mitoses/10HPF	Necrosis	Follow-up
Banerjee	Female/39	2.0 cm/Nasal cavity	Absent	Very few	Absent	12 months/ANED
Lehman	Female/49	5.0 × 3.8 × 3.5 cm/ Skull base	Absent	3 per HPF	Absent	Spine, lung met, DOD,3 months
Folpe	Male/80	2.0 cm/Scalp	Present	Greater than 10 per 50 HPF	Absent	Lost to follow up
Folpe	Female/77	2.6 cm/Neck soft tissue	Present	1 per 50 HPF	Absent	6 months/ANED
Iyengar	Female/9	1.2 × 1.0 × 0.8 cm/Orbit	Absent	Very few	Absent	7 months/ANED
Koutlas	Female/46	4.0 × 2.0 cm/Hard palate	Absent	Absent	Present	20 months,/ANED
Kuroda	Male/79	Nasal cavity	Absent	Absent	Absent	Follow up too short
Furusato	Female/26	2.0 × 1.7 × 1.4 cm/Eyelid	Absent	Very few	Absent	24 months/ANED
Furusato	Male/7	1.3 cm/Ciliary body	Absent	Very few	Absent	24 months/ANED
Guthoff	Male/54	1.5 × 1.0 × 1.0 cm/Eyelid	Absent	Very few	Absent	17 months/ANED
Calder	Male/76	1.6 × 1.3 × 1.0 cm/Scalp	Absent	2 per 10 HPF	Absent	5 years,Cervical node met/ANED
Ghazali	Female/32	2 cm/Cheek	Present	2 per 10 HPF	Absent	years/ANED
Argani	Male/80	2 cm/Scalp	Absent	Absent	Absent	NA
Bandhlish	Female/18	2.9 cm/Left nasal	Absent	Absent	Absent	26 months/ANED
Bandhlish	Female/71	Nasal cavity	Absent	Absent	Absent	Lost to follow-up
Bandhlish	Female/26	Glottic larynx	Absent	Absent	Absent	8 years/ANED

HPF high power field, *met* metastases, *DOD* dead of disease, *ANED* alive with no evidence of disease

of occurrence were scalp (three), intraoral (two), and one case each in cervical soft tissue, skull base, and larynx, respectively. Similar to PEComas at other body sites, these tumors tend to behave in an indolent fashion. Adequate follow-up was reported in 14 patients. Two patients (one skull base and one scalp) behaved in an aggressive fashion with distant or loco-regional metastases and one patient (skull base) died of disease-related causes [8, 16]. Therefore, 14% of head and neck PEComas, with available follow-up, behaved aggressively with loco-regional or distant metastases and only 7% died of disease. The patient with cervical lymph node metastasis was alive and disease-free at last follow-up. The remaining twelve patients were all reported as alive and free of disease following surgical resection.

The malignant potential of PEComas remains unknown. A vast majority of reported PEComas seem to behave in a benign fashion, although a malignant course with local recurrences and distant metastases has been reported [8, 10, 16, 27, 28]. Predicting the behavior of PEComas based on histology alone is challenging. However, criteria for risk classification of non-AML PEComas based on histopathologic features have recently been proposed [10]. Tumors with two or more of the following atypical features are considered malignant: size >5 cm, infiltrative growth, high nuclear grade, necrosis, mitotic rate ≥1/50 hpf and vascular invasion. Tumors with nuclear pleomorphism or multinucleated giant cells only, or those >5 cm are considered to be of uncertain malignant potential. All other tumors can be considered benign. However, this study was based on tumors of gynecologic origin and soft tissue (including two head and neck tumors), so application to all head and neck sites may not be appropriate.

Although size was known in only one of our cases (Case 1), all seemed to be much smaller than 5 cm based on review of the tumor dimensions on the glass slides (all tumor tissue was submitted in each case). None of our cases demonstrated an infiltrative growth pattern, vascular invasion, high nuclear grade, necrosis or mitotic activity. Twenty-six months (Case 1) and 8 years (Case 3) into follow-up, both patients are alive with no evidence of recurrence and/or metastases; the other patient (Case 2) was lost to follow up. These observations are consistent with the finding reported by Folpe et al. [10] regarding the benign clinical behavior of these tumors. Still, the prognostic features of these tumors are largely unpredictable since occasional cases have demonstrated metastatic potential even though malignant histopathological features of the tumor were not observed [10].

The differential diagnosis for head and neck PEComas is broad and somewhat site dependent. The differential diagnosis may include primary or metastatic melanoma, paraganglioma, clear cell sarcoma (malignant melanoma of soft parts), clear cell carcinoma, clear cell variants of salivary gland carcinomas, alveolar soft part sarcoma, granular cell tumor, clear cell oncocytoma, metastatic renal cell carcinoma and rhabdomyoma. By immunohistochemistry, negative S-100 staining and positive myoid marker expression are useful in differentiating PEComas from melanomas (primary and secondary). It must be noted, however, that some studies have shown that up to 33% of PEComas demonstrate S-100 positivity [10], although most studies indicate positivity rates of about 10%, and characterized by only focal and usually cytoplasmic (not nuclear) staining. Furthermore, these S-100 positive PEComas typically also express myoid markers, a finding not generally seen in true melanocytic lesions [10]. Spindle cell variant of melanoma may show limited SMA expression [29]. Malignant melanomas generally tend to have more significant nuclear pleomorphism and increased mitotic activity which was not seen in any of our cases. In addition, prior history of melanoma or an in situ component would support this diagnosis.

Few PEComas (13%) of the soft tissue and gynecologic origin may show focal cytokeratin expression [10] but the lack of diffuse cytokeratin expression combined with the coexpression of melanocytic and myoid markers should help to exclude the differential of clear cell carcinoma, clear cell oncocytoma, clear cell variants of salivary gland carcinoma, and metastatic renal cell carcinoma. A "Zellballen" architecture and a vascular stroma may resemble a paraganglioma, as seen in Case 3 which was initially misdiagnosed as such on incisional biopsy. But the lack of staining for chromogranin, synaptophysin, and S-100 (sustentacular distribution), as well as the expression of melanocytic and myoid markers makes this distinction straightforward. Alveolar soft part sarcoma (especially the solid type) may resemble PEComas and often show TFE3 nuclear expression. Although they may show positivity for muscle markers, they will lack expression of melanocytic markers. In addition, characteristic cytoplasmic PAS positive (diastase resistant) crystals may be identified and a recurring t(X;17) translocation resulting in a *ASPL-TFE3* fusion protein can be demonstrated. However, use of TFE3 immunostaining to separate these two neoplasms may not be helpful since nearly one-third of PEComas also express nuclear TFE3 [17]. Moreover, this same study showed that five of 29 (17%) PEComas also had *TFE3* gene rearrangements (four) or *TFE3* amplification (one), thus limiting the utility of molecular testing in this differential diagnosis. Granular cell tumors have more abundant and granular cytoplasm coupled with characteristic positivity for S-100 and negativity for muscle markers thereby excluding this diagnosis. Clear cell sarcoma (also known as malignant melanoma of soft parts) has a nested growth pattern with clear cells and stains positively with

melanocytic markers, but the cells do not express myoid markers, which can help distinguish them from PEComas. However, it may be difficult to distinguish them from the rare PEComas that are SMA negative and S-100 positive. As reported by Folpe et al. [10] not all PEComas express smooth muscle markers: 80% of PEComas of soft tissue were SMA positive in their study. Therefore, the most specific test to distinguish these two entities in challenging cases is cytogenetic and/or molecular genetic confirmation of the characteristic t(12;22) seen in clear cell sarcoma that results in *EWS-ATF1* fusion protein [10]. Finally, adult rhabdomyoma can be excluded based on strong desmin reactivity, lack of melanocytic markers and characteristic large cells with, at least occasional, foci of cytoplasmic striation.

The pathogenesis of PEComas is still not completely understood and is being explored owing to their rarity. However inactivation of *TSC1* and/or *TSC2* genes, [30, 31] with subsequent activation of mammalian target of rapamycin (mTOR) pathway has been associated with the pathogenesis of both syndromic and sporadic PEComas [32]. Recent studies highlighting genetic events, including chromosome losses (1p, 17p, 18p, 19p) and gains (2q, 3q, 5q, 12q and X) have been indicated in the development of some PEComas [32].

The optimal treatment for this group of tumors is not well established, but surgical resection with adequate margins seems to be the gold standard. The role for adjuvant radiation is not fully appreciated but may be indicated for those tumors that qualify as histologically malignant or of uncertain malignant potential. Given the role of mTOR pathway activation, inhibitors of this pathway (such as sirolimus) may prove helpful in treating malignant PEComas, as well as unresectable, histologically benign PEComas. In our cases, surgical excision with negative margins resulted in adequate treatment in the two cases with follow-up.

Conclusion

In this study we report three PEComas arising in the larynx and the nasal cavity, which are rare sites of involvement. All with follow-up had a clinically benign course. The importance of recognizing this entity will ensure its consideration in the differential diagnosis of tumors of the head and neck with a similar morphology. The histogenesis of PEComas still remains elusive and additional cases with prolonged follow up remain important to accurately determine the behavior of these distinctive tumors. Complete surgical excision still remains the treatment of choice for histologically benign PEComas.

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