Unusual PEComa With *PRCC*::*TFE3* Fusion Mimicking Sinonasal Tract Melanoma

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Background: We report a nasal cavity unusual perivascular epithelioid cell tumor (PEComa) mimicking mucosal melanoma.

Methods: Immunohistochemistry was performed using BenchMark Ultra and panel of antibodies. The Ion Torrent platform and Ion AmpliSeq cancer hotspot panel were utilized for DNA genotyping. Target-specific RNA libraries for the detection of fusion transcripts were constructed using Archer Universal RNA Reagent Kit v2 and Archer FusionPlex Solid Tumor panel and sequenced on the MiSeqDx instrument.

Results: The tumor, diagnosed in 46-year-old female, was composed of spindle cells, and lacked pigmentation. Immunohistochemically, it showed a patchy HMB-45 positivity. Other melanocytic markers (S100 protein, Melan-A, SOX10) were negative. The tumor cells were weakly positive for KIT (CD117) while negative for smooth muscle actin, pancytokeratin cocktail (AE1/AE3), and synaptophysin. Diagnosis of primary sinonasal tract mucosal melanoma was favored. Additional molecular studies detected *PRCC*::*TFE3* fusion as the sole genetic change, and suggested the diagnosis of unusual PEComa. Previously, *TFE3* fusions were reported in a subset of PEComas but not in melanomas, while *PRCC* involvement has only been documented once in an ocular PEComa. Immunohistochemistry revealed strong nuclear TFE3 expression concordant with the molecular findings.

Conclusions: This report emphasis the importance of molecular testing in the differential diagnosis between PEComa and melanoma, especially when the tumor arises in a site typical of melanoma but showing an unusual morphology and immunophenotype. The detection of *TFE3* fusion transcripts suggested the diagnosis of SNT PEComa, although it cannot be excluded that this and similar tumors represent a distinct diagnostic category.

Key Words: PEComa, sinonasal tract, melanoma, immunohistochemistry, HMB45, KIT, TEF3, genotyping, next-generation sequencing, PRCC::TFE3 fusion, gene fusion transcripts

(*Appl Immunohistochem Mol Morphol* 2024;32:322–325)

Perivascular epithelioid cell tumor (PEComa) is an umbrella name for a family of related mesenchymal neoplasms involving various anatomic sites and composed of perivascular epithelioid cells with markers of both melanocytic and smooth muscle differentiation. Tumors may develop in individuals with tuberous sclerosis, a rare inherited condition.[1] Most PEComas harbor loss of function alterations of tuberous sclerosis complex genes *TSC1*/*TSC2*.[2] However, a subset of tumors is characterized by the transcription factor E3 (*TFE3*) rearrangement and presence of *TFE3* fusion transcripts.[3,4]

The differential diagnosis between PEComa and melanoma can be challenging especially when tumors arise in a site more typical of mucosal melanoma (MM) and demonstrates an unusual morphology and immunophenotype. This report presents a case of PEComa mimicking a primary sinonasal tract (SNT) MM.

CASE REPORT

A 46-year-old female presented with a history of recurrent sinusitis not improving on medical therapy. There was no associated rhinorrhea or change in smell. By computed tomography there was a 5 cm high density, diffusely enhancing mass involving the right nasal cavity, ethmoid sinus, and the pterygopalatine fossa. Bone remodeling was observed without true bone destruction. By nasal endoscopy, there was a soft tissue mass primarily arising from the inferior turbinate, obstructing ∽80% of the nasal passage. She was treated by wide exenteration including right medial maxillectomy, septal resection, total ethmoidectomy, and sphenoidectomy. No radiation,

Received for publication February 5, 2024; accepted June 5, 2024.

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J.L.: conception and design. L.D.R.T.: case selection, acquisition of clinical data. J.L., L.D.R.T., and M.M.: histopathology/immunohistochemistry. M.Ch. and A.K.: molecular genetics. J.L., L.D.R.T., M.Ch., A.K., and M.M.: writing, review, and/or revision of the manuscript.

Data/specimen used in this study have been de-identified by contributor before the investigation. Data available upon request subjected to NIH policies and procedures.

This study was funded by the US federal government (National Cancer Institute, Bethesda, Maryland).

The authors declare no conflict of interest.

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DOI: 10.1097/PAI.0000000000001211

chemotherapy, or immunotherapy was accepted by the patient. Three years later, she developed a right ovarian clear cell carcinoma (tumor size 30 cm). Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) with lymph node dissection was performed. There were no peritoneal deposits intraoperatively and lymph nodes were negative. Epithelial markers were used to confirm the diagnosis, along with PAX8. She was managed with postoperative chemotherapy. She is alive without evidence of disease (sinonasal tract or ovary) 4 years after TAH-BSO and 7 years after SNT surgery.

The sinonasal tumor was composed of spindle cells with mild pleomorphism, pale eosinophilic cytoplasm, and indistinct cell borders. Staghorn vessels were present (Fig. 1A). Pigmentation and necrosis were absent. There were 4 mitoses/2 mm^2. Immunohistochemistry (IHC) was performed using BenchMark Ultra (Ventana Medical Systems-Roche Group, Tucson, AZ). The IHC panel included antibodies to human melanoma black (HMB)-45, Melan-A, S100 protein, sex determining region Y-box transcription factor 10 (SOX10), PReferentially expressed Antigen in MElanoma (PRAME), KIT (CD117), smooth muscle actin (SMA), desmin (DES), pancytokeratin cocktail (AE1/AE3), TFE3, synaptophysin (SYN), tumor protein P53 (TP53), Mouse Double Minute 2 (MDM2), ß-catenin, and c-Myc. The tumor showed a patchy, moderate to strong HMB45 reactivity (Fig. 1B). There was no expression of other melanocytic differentiation markers (S100 protein, Melan-A, SOX10). Diffuse but weak KIT immunoreactivity was noticed (Fig. 1C). Furthermore, there was no expression of SMA, DES, SYN nor pancytokeratin. Prominent nuclear accumulation of p53 was seen in tumor cells but MDM2 IHC was negative. Also, c-Myc IHC was negative, while ß-catenin showed membranous and weak cytoplasmic staining.

Nucleic acids were extracted from formalin fixed paraffin embedded (FFPE) tumor tissue using Maxwell RSC DNA or RNA FFPE Kit and Maxwell RSC instrument (Promega, Madison, WI). Targeted-DNA next-generation sequencing (NGS) was performed using the Ion Torrent platform (Life Technologies/Thermo Fisher Scientific, Waltham, MA) and Ion AmpliSeq cancer hotspot

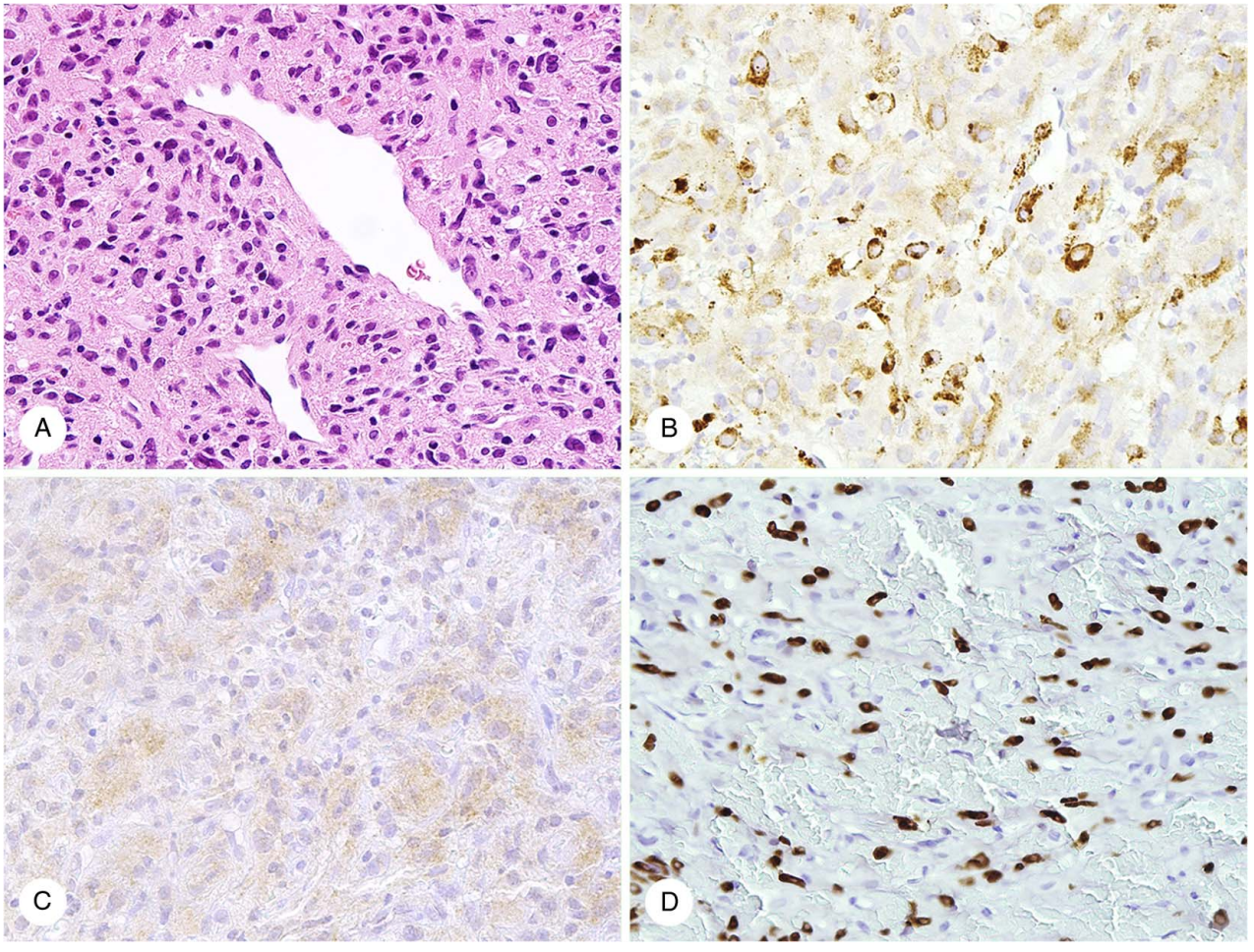

FIGURE 1. Histology and immunohistochemistry of sinonasal tract PEComa. A, Tumor composed of spindle cells with mild pleomorphism, pale eosinophilic cytoplasm, and indistinct cell borders. Staghorn vessels were present. B, A patchy, moderate to strong HMB45 positivity. C, Diffuse but weak KIT (CD117) immunoreactivity. D, Strong nuclear TFE3 expression.

TABLE 1. Clinicopathologic Characteristic of Primary Sinonasal Tract PEComas

	Case [Reference No.]								
Characteristics	1 [8]	2 [10]	3 [9]	4 [this study]	5 [7]	6 [11]	7 [8]	8 [12]	9 [6]
Sex	Female	Female	Female	Female	Female	Female	Female	Male	Male
Age (y)	18	19	22	46	50	54 y	71 y	39 y	79 y
Lesion	Nonpolypoid	Polypoid	Polypoid	Polypoid	Exophytic	Polypoid	Polypoid	Polypoid	Polypoid
Size	2.9 cm	4×2.3 cm	1.5 cm	5 cm	NA	2×1 cm	NA	2.5 cm	NA
Follow-up	ANED 26 mo	ANED 17 mo	ANED 13 mo	ANED 84 mo	ANED 72 mo	ANED 9 mo	NA	ANED 24 mo	NA
Cell morphology	Epithelioid	Epithelioid	Epithelioid/ spindle	Spindle	Epithelioid/ spindle	Epithelioid/ Spindle (F)	Epithelioid	Epithelioid	Epithelioid
Atypia	Not present	Not present	Present (M)	Present (M)	NA	Not present	Not present	Present	NA
Cytoplasm	Clear	Clear eosinophilic	Clear eosinophilic	Granular eosinophilic (P)	Clear/ granular eosinophilic (P)	Granular eosinophilic	Clear/ granular eosinophilic	Clear/granular	Clear/ granular eosinophilic
Pigment	NA	NA	NA	Not present	NA	Present	Present	Present	NA
Mitosis	0	0	Rare	4/2 mm^2	Rare	0	0	0	NA
Ki67	< 5%	ND	ND	ND	3%	ND	ND	5%	ND
Necrosis	Not present	Not present	Not present	Not present	Not present	NA	Not present	Not present	NA
SOX10	ND	ND	ND	Not present	ND	Negative	ND	Negative	ND
HMB45	Positive	Positive	Positive	Positive (F)	Positive (F)	Positive	Positive	Positive	Positive (F)
S100	Negative	Negative	Negative	Not present	Negative	ND	Negative	Negative	Positive (F)
MELAN A	Positive	Negative	Positive	Not present	Negative	Positive	ND	Negative	ND
MITF	ND	ND	ND	ND	ND	Negative	ND	Negative	Negative
PRAME	ND	ND	ND	Negative	ND	ND	ND	ND	ND
SMA	Negative	Positive (F)	Positive (F)	Negative	Positive	Negative	Positive	Negative	Positive
DES	Negative	Negative	Positive	Negative	Positive (F)	ND	Negative	Negative	ND
KIT (CD117)	ND	ND	ND	Positive (W)	ND	ND	ND	ND	ND
SYP	Negative	ND	ND	Negative	ND	ND	Positive (F)	ND	ND
CHG	ND	Negative	ND	ND	ND	ND	ND	ND	ND
CK	Negative	ND	ND	Negative	Negative	ND	Negative	Negative	ND
TFE3	ND	ND	ND	Positive	ND	Positive	ND	Positive	Positive
TFE3 fusion	ND	ND	ND	*PRCC*:: *TFE3*	ND	*NONO*:: *TFE3*	ND	*NONO*::*TFE3*	ND

ANED indicates alive no evidence of disease; CHG, chromogranin; CK, cytokeratins; F, focal; M, mild; MITF, microphthalmia-associated transcription factor; NA, not available; ND, not done; P, pale.

panel. Target-specific RNA libraries for the detection of fusion gene transcripts were constructed using Archer Universal RNA Reagent Kit v2 (ArcherDx, Boulder, CO) and Archer FusionPlex Solid Tumor panel (ArcherDx). Libraries were sequenced using the MiSeqDx instrument (Illumina, San Diego, CA). DNA and RNA NGS data were analyzed as previously reported.[5] Target-specific DNA NGS genotyping revealed no mutations in SNT tumor. However, gene transcripts derived from papillary renal cell carcinoma translocation-associated gene (*PRCC*) and *TFE3* fusion (*PRCC*::*TFE3*) were detected by the target-specific RNA assay. Fusion breakpoints in *PRCC* and *TFE3* were mapped to the exon 1 (chr1:156738031) and exon 6 (chrX:48891766), respectively (NG 008138.1 and NG 016297.2). To exclude the remote possibility of a metastatic deposit or a related fusion, testing was performed on the ovarian tumor, but no fusion gene transcripts were detected, while DNA genotyping revealed a *KRAS* p.Gly12Asp-driver mutation.

Following molecular genetic studies, PRAME and TFE3 IHC was performed. SNT tumor lacked PRAME immunoreactivity but showed strong, nuclear TFE3 expression (Fig. 1D).

DISCUSSION

PEComas in the sinonasal tract are exceptionally rare with only few well-documented cases reported in the literature (Table 1).[6–12] Moreover, molecular genetic studies are limited to only 2 recent reports.[11,12] In both cases, *NONO*::*TFE3* fusion transcripts, a result of subtle intrachromosomal Xp11.2 inversion, were found. In the current study, *PRCC*::*TFE3* fusion transcripts, a result of a t(X;1)(p11.2;q21) translocation, commonly seen in Xp11 translocation renal carcinomas, were detected.[13] In PEComa, *PRCC*::*TFE3* fusion appears to be a rare event with only a single case reported in an ocular tumor.[14] However, *NONO*::*TFE3* fusion transcripts were also found in 2 other ocular PEComas.[3,14] Thus, *NONO* and *PRCC* might be the main *TFE3* partners in PEComas arising in head and neck sites, although additional cases must be evaluated to confirm such a hypothesis.[12] Besides PEComas, *TFE3* fusions involving several different partners have been reported in mesenchymal and epithelial neoplasms, including alveolar soft part sarcoma, renal cell carcinoma, and epithelioid hemangioendothelioma.[13,15–17] TFE3 is a member of closely related transcription factors of the microphthalmia (MiT) family.[18] DNA damage activates TFE3 in a p53 and mTORC1 dependent manner resulting in the increase of p53

stability and protein level, leading to the increased expression of other transcription factors involved in DNA damage response and repair.[19]

PEComas harboring a *TFE3* fusion have a propensity to occur in younger patients, show epithelioid cell morphology, predominantly alveolar architecture, and limited expression of melanocytic and muscle differentiation markers.[3] Tumors ≥ 5 cm with a mitotic rate of ≥ 1/HPF and *TP53* mutations are associated with potential malignant behavior and recurrence.[20,21] The *PRCC*::*TFE3* fusion-positive tumor reported in this study was diagnosed in a 46-year-old female, showed spindle-cell morphology, patchy HMB45 positivity and lacked smooth muscle actin and desmin expression. Also, this tumor revealed high-risk features such as a size of 5 cm, 4 mitoses/2 mm^2 and nuclear accumulation of p53 which might indicate TP53 alteration. Nevertheless, a clinical outcome was favorable with no evidence of disease 7 years after surgery.

A lack of smooth muscle markers suggested mucosal melanoma diagnosis, although absence of smooth muscle differentiation has been reported in PEComas harboring *TFE3* rearrangements including *NONO*::*TFE3* fusion.[11–13] A lack of other melanocytic differentiation markers, such as S100 protein, Melan-A, and SOX10, argue against a melanoma diagnosis, although diffuse, or focal KIT expression has been reported in a fraction of SNT melanomas.[22] Also, dedifferentiated melanomas lacking all melanoma immunophenotypic markers have been described.[23] A recent study documented consistent PRAME expression in SNT melanomas (78/79; 99%) and lack of TFE3 reactivity.[24]

CONCLUSION

In this unusual case, a PEComa diagnosis was not established based on histology and immunohistochemistry. The tumor lacked typical PEComa features, such as epithelioid cell morphology, alveolar or nested architecture, and showed an uncommon immunophenotype. The detection of *TFE3* fusion transcripts suggested the diagnosis of SNT PEComa, although it cannot be excluded that this and similar tumors represent a distinct diagnostic category.

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