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TFE3-rearranged perivascular epithelioid cell tumors of the head and neck with rare fusion partners: clues to the differential diagnosis between benign and malignant tumors

Yuka Takahashi[1], Akihiko Yoshida[1], Seiichi Yoshimoto[2], Shigenobu Suzuki[3], Satsuki Kishikawa[1], Ayaka Mitsui[1], Eijitsu Ryo[5], Yuki Kojima[4], Kan Yonemori[4], Yasushi Yatabe[1,5] and Taisuke Mori[1,5*]

Abstract

Background Perivascular epithelioid cell tumors (PEComas) rarely appear in the head and neck region. This case report describes two transcription factor E3 (*TFE3*)-rearranged PEComa cases, consisting of one in the orbit and one in the nasal cavity.

Case presentation Both cases demonstrated sheet-like or focal nested architecture and comprised epithelioid cells with abundant clear to eosinophilic cytoplasm and vascular stroma. The first case exhibited partial pleomorphism, a small necrosis area, and slightly increased mitosis and was classified as malignant. The second case demonstrated mild atypia and no mitosis or necrosis and was categorized as benign. The nasal tumor was initially considered a *TFE3*-rearranged renal cell carcinoma metastasis. However, a subsequent renal tumor biopsy revealed angiomyolipoma. The RNA sequence revealed *ZC3H4::TFE3* and *PRCC::TFE3* fusions in the first and second cases, respectively.

Conclusion The fusion partner gene *ZC3H4* is uncommon, and this is the third reported PEComa case. The fusion partner gene *PRCC* is often reported in *TFE3*-rearranged renal cell carcinoma, and this PEComa case is the second reported in the head and neck region. The initially reported cases with the fusion partner genes *ZC3H4* and *PRCC* were categorized as malignant. These cases were discussed with a literature review.

Keywords Perivascular epithelioid cell tumor, Transcription factor E3, Head and neck, ZC3H4, PRCC

*Correspondence:
Taisuke Mori
tamori@ncc.go.jp
[1]Department of Diagnostic Pathology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
[2]Department of Head and Neck Surgery, National Cancer Center Hospital, Tokyo, Japan
[3]Department of Ophthalmic Oncology, National Cancer Center Hospital, Tokyo, Japan
[4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
[5]Division of Molecular Pathology, National Cancer Center Research Institute, Tokyo, Japan

Background

Perivascular epithelioid cell tumors (PEComas) are mesenchymal neoplasms composed of perivascular epithelioid cells, which exhibit characteristics of both melanocytic and smooth muscle differentiation. Histologically, the tumor includes epithelioid and/or spindle cells with granular clear to eosinophilic cytoplasm with nested, trabecular, or sheet-like architecture [1]. Most sporadic and tuberous sclerosis-associated PEComas are caused by loss of heterozygosity of tuberous sclerosis complex 2 (TSC2) locus that activates the mammalian target of rapamycin pathway [2]. A small PEComa subset expresses transcription factor E3 (*TFE3*) gene fusions [3]. *SFPQ* [4–6], *DVL2*, and *NONO* genes in soft tissue are the common fusion partners with *TFE3* [7]. Assessing the clinical behavior of PEComa according to histological findings is challenging. The generally used classification proposed by Folpe et al. [8] considered tumors with two or more worrisome features, including size of > 5 cm, infiltrative growth, high nuclear grade and cellularity, mitotic rate of ≥ 1/50 high-power fields, necrosis, and vascular invasion, as malignant. PEComas demonstrate a wide anatomical distribution, but a few cases in the head and neck region have been reported. This case report aimed to present two clinicopathologically interesting *TFE3*-rearranged PEComa cases with a rare fusion partner gene in the head and neck region. Distinguishing *TFE3*-rearranged PEComas from other tumors and differentiating between benign and malignant tumors is sometimes challenging. Therefore, we reviewed previous reports of *TFE3*-positive head and neck PEComas and *TFE3*-rearranged PEComas in other sites and conducted a comparison.

Materials and methods

Histopathologic and immunohistochemical analyses

The samples obtained by biopsy or surgery were fixed in 10% neutral-buffered formalin, embedded in paraffin, cut into 4-μm-thick sections, and stained with hematoxylin and eosin (H&E) for histologic assessment. Antibodies against the following antigens were utilizes for diagnoses: TFE3 (MRQ-37, 1:400, JAPAN TANNER), HMB-45 (HMB-45, ready to use, DAKO), PAX8 (PAX8R1 1:25, Abcam), PAX2 (EPR8586, 1:200, abcam), SOX10 (A-2, 1:500, SANTA CRUZ), and Ki67 (MIB-1, 1:100; Dako).

Fluorescence in situ hybridization (FISH)

FISH was performed on 4-μm-thick FFPE tumor sections, using the *TFE3* Spit (GSP Laboratory) dual-color FISH probes. FISH images were captured with the Metafer Slide Scanning Platform (Metasystem, Altlußheim, Germany), and at least 60 nonoverlapping tumor cells were assessed. Tumors in which > 20% of the cells demonstrated break-apart signals were considered positive for rearrangement.

RNA sequencing

FFPE sample sections from both cases 1 and 2 were deparaffinized and subjected to RNA extraction with an RNeasy FFPE kit (Qiagen, Hilden, Germany). RNA sequencing was performed with the TruSight Pan-Cancer panel (Illumina, San Diego, CA, USA), which targets 1385 cancer-related genes, following the manufacturer's instruction. Sequencing was conducted on a MiSeq instrument (Illumina) with MiSeq Reagent Kit version 3 (Illumina) with 150 cycles. The fusion gene was identified using the RNA-Seq alignment applications DRAGEN RNA, STAR, and Top-Hat2 (Illumina).

Statistical analysis

The Mann-Whitney U test was used to assess the correlation between the two parameters, which was then used to compare tumor age and size. Statistical significance was set at a *P*-value of < 0.05.

Case presentation

Figure 1(a, b, and c) illustrates the clinicopathological features of the two PEComa cases.

Case 1

A 35-year-old male patient presented with left eye pain and double vision. Magnetic resonance imaging T1-weighted images revealed a 10-mm tumor with a high signal in the left orbit, pushing up from below the inferior rectus muscle (Fig. 2a). Tumor enucleation demonstrated a dark reddish-red, full, hard-mass tumor. The boundary with the surrounding tissue was clear although the capsule was not well defined. Histologically, the tumor demonstrated a sheet-like growth pattern with abundant clear to eosinophilic cytoplasm and enlarged nuclei (Fig. 2b). Prominent thin-walled blood vessels were found.

The tumor was considered malignant due to meeting two criteria based on the proposed PEComa classification: 6 mitoses per 50 high-power fields and small necrosis. Additionally, partial pleomorphism was revealed. Immunohistochemically, TFE3 demonstrated diffuse nuclear positivity (Fig. 2c), HMB-45 exhibited focal cytoplasmic positivity (Fig. 2d), and Melan-A showed diffuse cytoplasmic positivity (Fig. 2e). Further, Ki67 positivity was low (Fig. 2f). FISH with the *TFE3* break-apart probes revealed separation of the 3' and 5' probes in both signals, indicating the presence of *TFE3* translocation (Fig. 2c, inset). An in-frame *ZC3H4::TFE3* fusion joining the 3' end of exon 13 of the *ZC3H4* gene (NM_015168.1) with the 5' end of exon 7 of the *TFE3* gene (NM_ 006521.6) was observed (Fig. 1b).

a

			Histology						IHC			FISH	RNA sequencing			Clinical feature	
Case	Site	Size	Architecture	Cell morphology	vascular invasion	Atypia	Necrosis	Mitoses (/50HPF)	TFE3	αSMA	Ki-67 (%)	TFE3	#Fusion Gene	Left Breakpoint	Right Breakpoint	Outcome	Metastasis
Case 1	ocular	10mm	Sheet-like	Epithelioid	(-)	(+)	(+)	6	(+)	NA	11	(+)	ZC3H4--TFE3	chr19:47575035:-EX13	chrX:48891300:-EX7	Alive with disease	None
Case 2	nasal	25mm	Nested/ alveolar	Epithelioid	(-)	None	None	1>	(+)	(+)	10	NA	PRCC--TFE3	chr1:156738031:+EX1	chrX:48891766:-EX6	5 m, No recurrence	None

Abbreviation; NA, not available

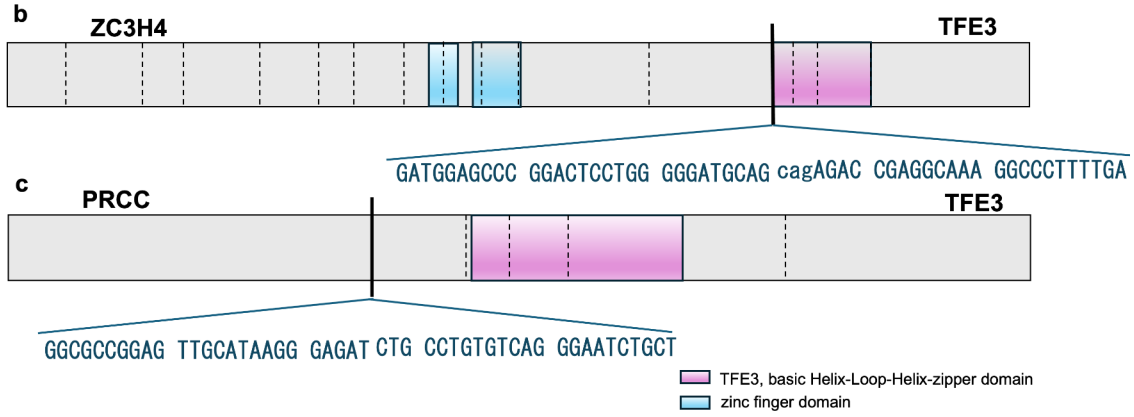

Fig. 1 Summary of the two cases. **a** Clinical, histological, and molecular features of the cases. **b** Schematic diagram of *ZC3H4::TFE3* and **c***PRCC::TFE3* fusions from cases 1 and 2, respectively

The patient's symptoms improved postoperatively. However, imaging studies 1 month post-enucleation revealed a residual or recurrent tumor within the inferior rectus muscle. Considering the malignant diagnosis, the ocular oncology department of the hospital proposed ocular content removal as the optimal course of action. The recommended course of action in the event of metastasis was chemotherapy with sirolimus.

Case 2

A 50-year-old female patient presented with left nasal obstruction. Contrast-enhanced computed tomography revealed a 25-mm high-density mass in the left nasal cavity (Fig. 3a). Concurrently, two masses were observed in the left kidney, with was 2 cm and the other was 0.5 cm in size (Fig. 4a). The nasal tumor was initially biopsied and suspected to be a renal carcinoma metastasis, but 2 cm-sized renal tumor was diagnosed as angiomyolipoma (Fig. 4b). The radiologist reads 0.5-cm renal fat-containing tumor as the 2-cm angiomyolipoma although 0.5-cm-sized renal tumor was not biopsied. Histologically, the nasal tumor demonstrated a nested growth pattern with abundant clear to eosinophilic cytoplasm and enlarged nuclei (Fig. 3b). Immunohistochemical assessment revealed TFE3 positivity and negativity in nasal cavity (Fig. 3c) and renal tumors, respectively. Additional immunohistochemistry diagnosed the nasal cavity tumor as PEComa, with positive HMB-45 andαSMA (Fig. 3d and f) and negative Melan-A, SOX10, PAX2, and PAX8. No mitosis or necrosis was observed in PEComa from the nasal cavity, and it was categorized as benign because it did not meet any of the malignant criteria. An in-frame *PRCC::TFE3* fusion joining the 3' end of exon 1 of the *PRCC* gene (NM_005973.4) with the 5' end of exon 6 of the *TFE3* gene (NM_ 006521.6) was found (Fig. 1c). *TFE3* break-apart FISH was conducted on the renal tumor diagnosed as AML, but no rearrangement was observed (Fig. 4c). Therefore, these two tumors were not pathogenetically related. The nasal tumor was endoscopically resected. No evidence of recurrence was observed 5 months postoperatively.

Review of previous PEComa cases

Kuroda et al. reported PEComa of the nasal cavity expressing TFE3 [9]. Since then, approximately 21 cases of *TFE3*-positive head and neck PEComa have been presented (Table 1) [3, 9–22].

Table 1 presents the clinicopathological characteristics of previously reported head and neck PEComa cases. The median age of the patients was 40 (range: 4–80) years. Of the 21 patients, 11 were males and 10 were females. The median tumor size was 2 (range: 1–7.2) cm. The tumors prevalently occurred in the orbital (11/21, 52%) and nasal regions (6/21, 29%). Follow-up data were available in 13 patients (2–120 months), and all were alive during the last follow-up. Two of the patients had residual or recurrent diseases but with no metastatic event. Histologically, the cell morphology was generally epithelioid, and one

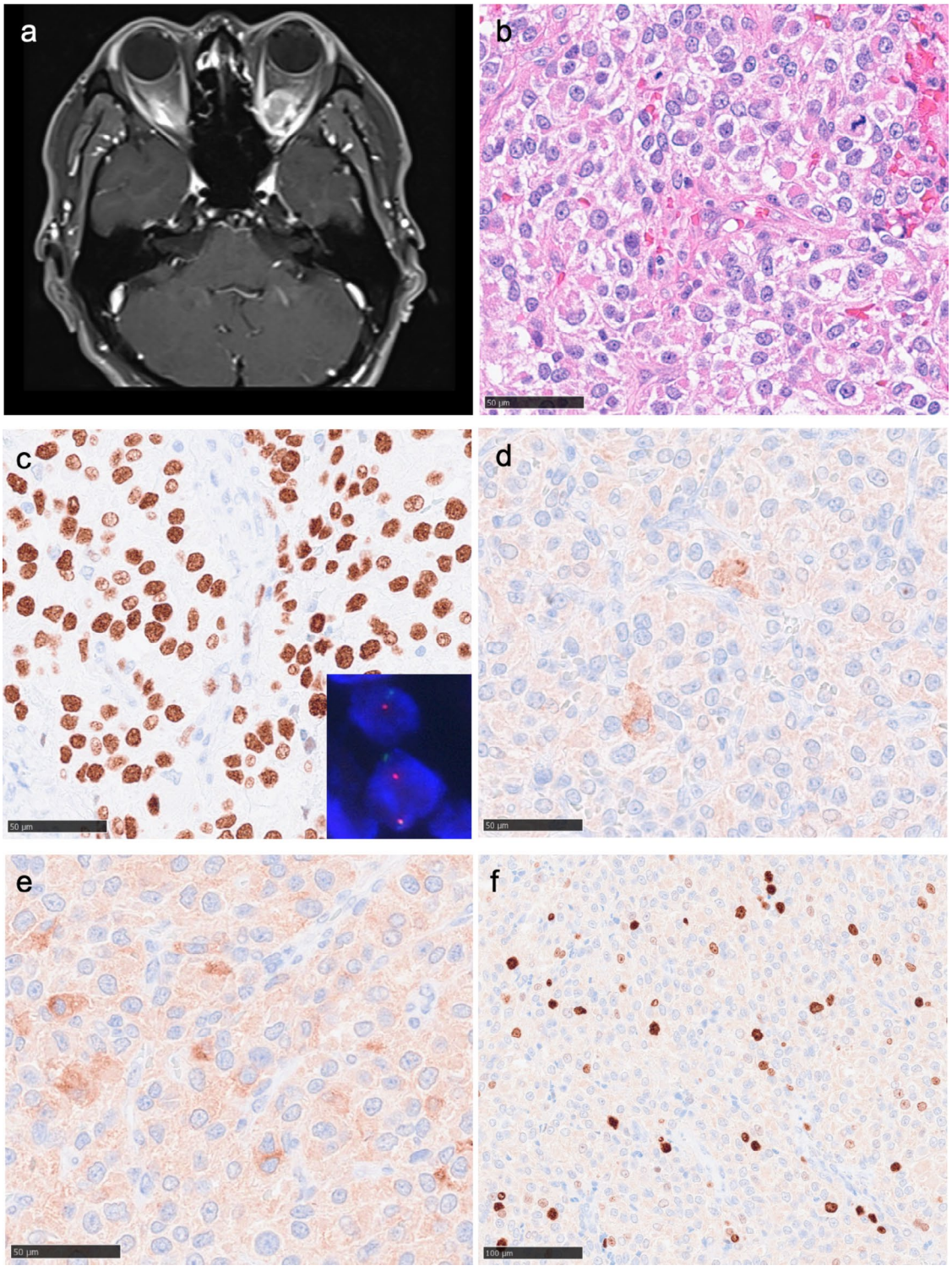

Fig. 2 Imaging and histological results of case 1. **a** Magnetic resonance imaging T1-weighted image demonstrating a 10-mm tumor with a high signal in the left orbit. **b** Tumor exhibiting a nested and sheet-like growth pattern mediated by connective tissue, including blood vessels. The tumor cells demonstrate epithelial-like morphology with nucleoli, coarse granular chromatin, and clear cytoplasm with acidophilic granules. Some mitotic figures are present (×400). **c** TFE3 demonstrating diffuse nuclear positivity (×400). Break-apart signals were observed in the tumor cells using *TFE3* FISH dual-color break-apart probes (inset). **d** HMB-45 exhibiting focal cytoplasmic positivity (×400). **e** Melan-A presenting diffuse cytoplasmic positivity (x400). **f** Ki67 labeling index of 11% (×200)

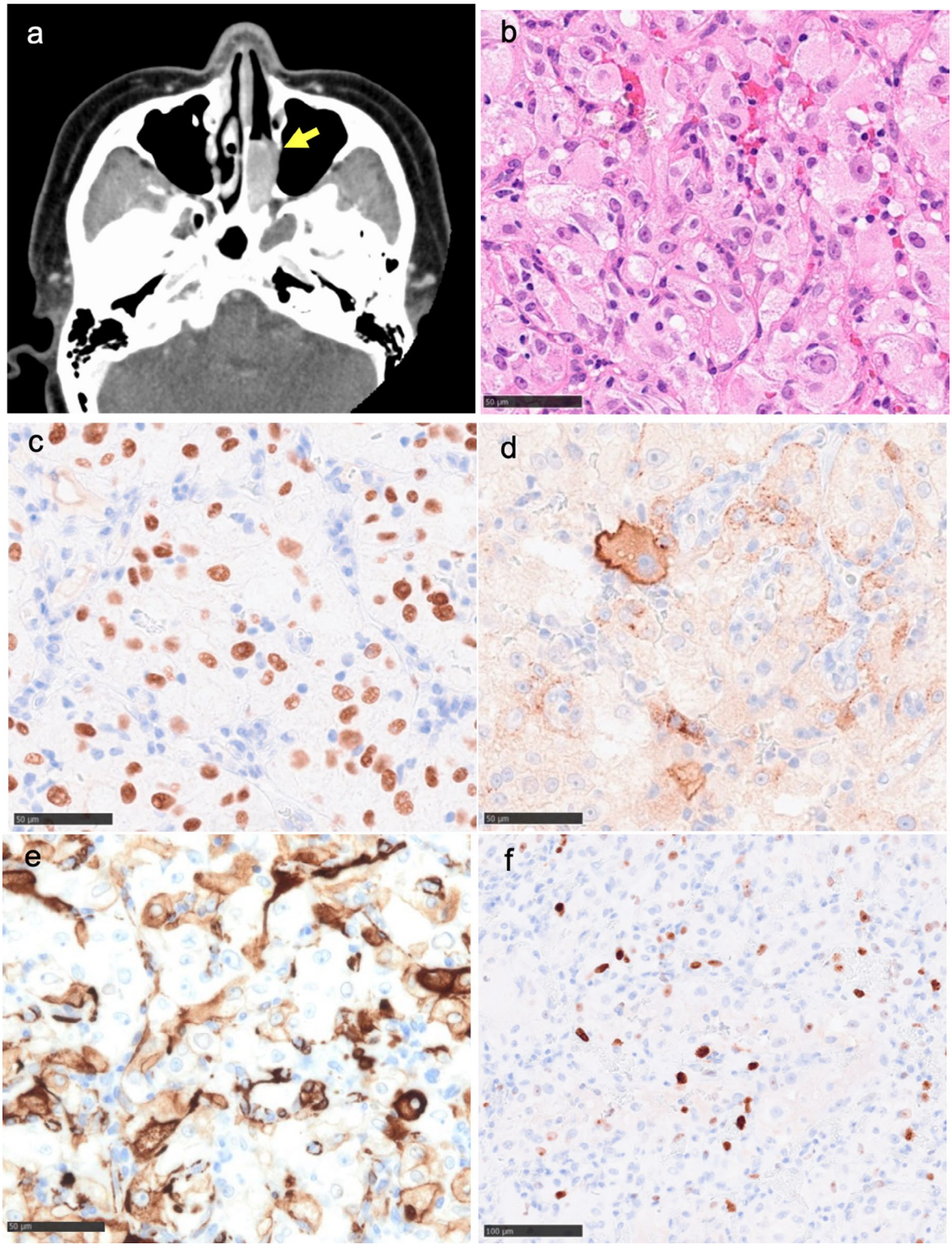

Fig. 3 Imaging and histological results of case 2 nasal tumor. **a** Contrast-enhanced computed tomography (CT) revealing a 25-mm high-density mass filling the left nasal cavity. **b** Tumor demonstrating a sheet-like architecture beneath the nonneoplastic stratified squamous epithelium. The tumor cells contain abundant eosinophilic cytoplasm and nuclei with distinct nucleoli and fine granular chromatin, accompanied by thin-walled blood vessels. No mitotic figures or necrosis were found (×400). **c***TFE3* revealing diffuse nuclear positivity (×400). **d** HMB-45 demonstrating diffuse cytoplasmic positivity (x400). **e** αSMA positive (x400). **f** Ki67 labeling index of 10% (×200)

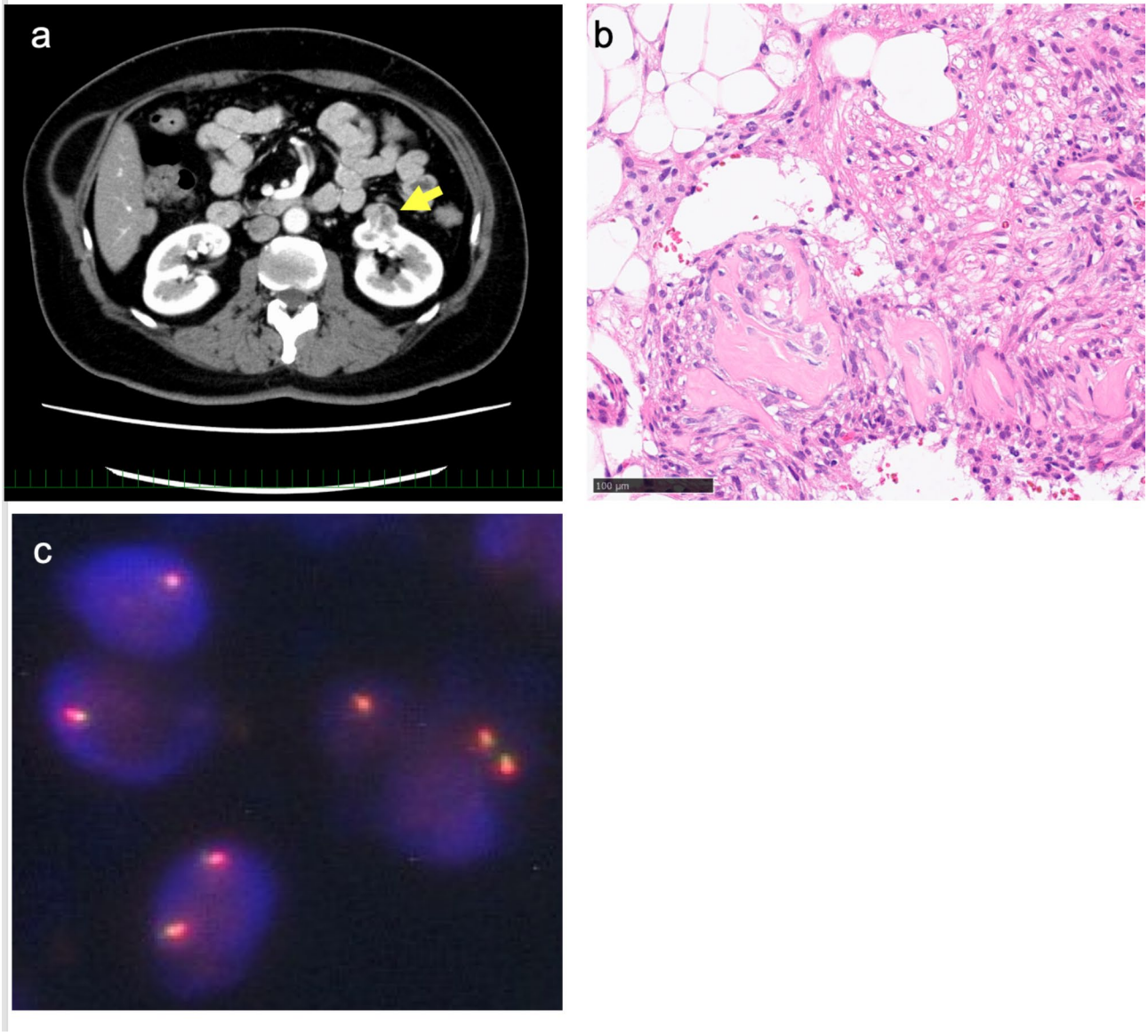

Fig. 4 Imaging and histological results of case 2 renal tumors. **a** CT image of the 2-cm mass in the left kidney. **b** Mixture of mature adipose tissue, thick-walled blood vessels, and smooth muscle cells, which was observed to be angiomyolipoma. **c***TFE3* FISH detecting no break-apart signals in the renal tumor (angiomyolipoma) cells

case demonstrated spindle cells. The architectural pattern was solid and nested with a sheet-like structure. Melanin pigment in the tumor cells was present in 9 (9/18, 50%), some atypia was observed in 8 (8/16, 50%), necrosis was found in 5 (5/14, 36%), and no or rare mitosis was revealed in 10 (11/16, 69%) patients. HMB-45 positivity was high (20/21, 95%), whereas Melan-A positivity was low (8/18, 44%). *TFE3* rearrangement was observed in 14 patients. FISH analysis revealed that five patients have *TFE3* rearrangement. *NONO* was the common fusion partner (6/12, 50%). McGregor et al. reported one patient to be technically FISH negative because of intrachromosomal translocation but proved to be rearranged with *NONO* by NGS [14]. The other two negative cases were proven to have NONO for the partner gene [16, 19] for the same reasons.

The literature reported 31 *TFE3*-rearranged PEComa cases from other sites (Suupplemental Table 1) [3, 5–7, 16, 20, 23–25]. The tumor sites include the kidney, colorectum, uterus, pelvic cavity, soft tissue of the lower extremity, and other less predominant sites and central nervous system. The median age of the patients was 37 (range: 4–69) years. Among the patients, 11 were males, 19 were females, and 1 was unknown. The median tumor size was 5 (range: 1–27) cm. Of the 31 patients, 30 demonstrated epithelioid cell morphology. One was admixed

Table 1 Pevious PEComa cases with TFE3 expression and/or TFE3 rearrangement of head and neck region

		Clincial data				Histology						IHC		Molecular	
		Age/ Gender	Location	Size (cm)	Outcome	cell morphology	architecture	melanin	atypia	necrosis	mitosis	TFE3	HMB45/ Melan A	TFE3 FISH	RNA-seq (fusion partner)
1	Present case	35/M	Left orbital mass	1	AWD, 3 m	Epithelioid	Nests and sheets	-	+	+	6/50HPF	+	+/+	+	ZC3H4
2	Present case	50/F	Left nasal cavity	2.5	NED, 1 m	Epithelioid	Nests	-	-	-	-	+	+/-	NA	PRCC
3	Kuroda et al. (2009) [9]	79/M	Left nasal cavity	NA	NA	Epithelioid	Nest	+	-	NA	NA	+	+/NA	NA	NA
4	Furusato et al. (2010) [11]	26/F	Left upper eyelid	2	NED, 24 m	Epithelioid	Nest and sheets	+	-	-	rare	+	+/+	NA	NA
5	Furusato et al. (2010) [11]	7/M	Left inferior ciliary body	1.33	NED, 24 m	Epithelioid	Nest and sheets	+	-	-	rare	+	+/-	NA	NA
6	Argani et al. (2010)[3]	80/M	Scalp	2	NA	Epithelioid	NA	NA	+	NA	NA	+	+/-	-	-
7	Lu et al. (2014)/Gao et al.(2021) [10]	20/M	Right Medial canthal mass	1	NED, 120 m	Epithelioid	Solid and nest	+	NA	NA	NA	+	+/-	NA	NONO
8	Goto et al. (2015) [12]	13/F	Right ciliary Body	1.1	NED, 48 m	Epithelioid	Solid and nest	-	-	NA	-	+	+/+	NA	NA
9	Argani et al. (2016) [7]	20/M	Orbital mass	NA	NA	Epithelioid	Nested and alveolar	+	NA	NA	NA	+	+/+	NA	NONO
10	Varan et al. (2017) [13]	7/M	Orbital mass	3.4	AWD, 6 m	Epithelioid	Nests and trabeculae	-	+	+	-	+	-/+	NA	NA
11	McGregor et al. (2017) [14]	54/M	Inferior turbinate	2	NED, 9 m	Epithelioid/spindle	Nests and broad cords	+	NA	NA	-	+	+/+	1 pair	NONO
12	Saluja et al. (2018) [15]	28/F	oropharynx	7.2	NED, 6 m	Epithelioid	Nest and sheets	-	+	+	6/10	+	+/-	+	-
13	Utpatel et al. (2020) [16]	39/M	Left middle nasal concha	2.5	NED, 24 m	Epithelioid	Nested and alveolar	+	+	-	-	+	+/-	-	NONO
14	Gao et al. (2021) [10]	17/F	Left choroidal/ ciliary mass	1.1	NED, 24 m	Epithelioid	sheet-like growth	-	+	-	3/10	+	+/-	+	PRCC
15	Feu-Basilio et al. (2021) [17]	28/M	Left orbital mass	1.6	NA	Epithelioid	Nests	-	-	-	-	+	+/NA	+	NONO
16	Lin et al. (2023) [18]	4/M	Right infero-medial orbit	1.5	NA	Epithelioid	sheet-like growth	-	+	+	+	+	+/+	NA (No ASPL-TFE3)	NA
17	Shah et al. (2024) [18]	32/F	Right inferior turbinate	2.9	NA	Epithelioid	Nested	+	-	-	-	NA	+/+	-	NONO
18	Fouchardiere et al. (2024) [20]	21/F	Right lower eyelid	NA	NED, 78 m	Epithelioid	sheet-like growth	+	-	-	-	+	+/-	+	NA
19	Lasota et al. (2024) [21]	46/F	Nasal cavity	5	NED,84 m	Spindle	Nests	-	+	-	4/2mm^2	+	+/-	NA	PRCC

Table 1 (continued)

		Clincial data				Histology				IHC		Molecular	
20	Argani et al. (2024) [22]	23/F	Occipital brain	NA	NA	Epithelioid	Nests	NA	NA	NA	+/NA	NA	PRCC
21	Argani et al. (2024) [22]	25/M	Floor of mouth	6.5	NA	Epithelioid/spindle	Nests	NA	-	< 1/10	NA	+/-	NA	ASPSCR1

Abbreviations: F, female; M, male; NA, not applicable; NED, no evidence of disease; AWD, alive with disease; m, month; HPF, high power field

with spindle cells and one with spindle and ovoid cells. Immunohistochemical assessment revealed *TFE3* positivity in all 31 cases. HMB-45 was positive in 27 (27/30, 90%) patients, whereas Melan-A was positive in 6 (6/20, 30%) patients. *TFE3* FISH was positive in 30 (30/31, 97%) cases. Finally, the fusion partners were *SFPQ* (14), *NONO* (1), ASPSCR1(1), ZC3H4(1), MED15(1), RBMX(1), PRCC(1), and *DVL2* (1).

The comparison of PEComas in the head and neck region with those in other sites revealed a smaller tumor size in the head and neck region than that in other sites ($p = 0.01$). This may be because the covered soft tissue is less than that of other sites and may be recognized earlier in the head and neck, particularly in the ocular region. No significant difference in age was found ($p = 0.33$). Cases matching malignant PEComas were 5 (5/15, 33%) in the head and neck region and 4 (4/17, 24%) in other sites based on the criteria of Folpe et al.

Discussion and conclusion

A variety of tumors may be found in the head and neck region, which poses a challenge in terms of diagnosis. H&E images demonstrating epithelioid-like cells, such as in this case, may indicate metastatic carcinoma (predominantly renal carcinoma in this instance), paraganglioma, melanoma, PEComa, rhabdomyosarcoma, and alveolar soft part tumor. The differential diagnosis may still include PEComa, alveolar soft part sarcoma, and renal cancer metastases if TFE3 rearrangements are determined. Furthermore, predicting the benign or malignant nature of PEComa is challenging based on histology alone. The histological classification proposed by Folpe et al. [8] categorized case 1 as malignant. Similarly, the initially reported case of PEComa with ZC3H4::TFE3 fusion was malignant, extracted from a metastatic PEComa case [26]. The second reported case of renal PEComa with the same fusion partner demonstrated no mention of malignancy, yet displayed a few mitotic Fig. [25]. The FISH analysis confirmed interchromosomal translocation in the present case, although it appeared narrower than other tumors with TFE3 sequences.

Case 2 also has a renal tumor, and the possibility of *TFE3*-rearranged renal cell carcinoma metastasis was suspected because a nasal biopsy was performed first. However, the nasal biopsy specimen was immunostained positive for HMB-45 and negative for PAX2 and PAX8. Subsequent renal biopsy demonstrated angiomyolipoma, which was immunohistochemically and molecularly TFE3 negative. Additionally, a history of tuberculosis sclerosis was not documented. In this case, the *PRCC::TFE3* fusion gene was observed in the nasal tumor, which is one of the most prevalent fusion genes in *TFE3*-rearranged renal cell carcinoma [26]. This fusion partner gene was reported in

three PEComa cases in the head and neck region [10]. Confirming the types of tumors by biopsy from every site is crucial because the clinical effect may vary based on whether the tumor is metastatic carcinoma or primary PEComa.

The cases reported with the fusion partner genes *ZC3H4* [27] and *PRCC* [10, 22] were histologically or clinically malignant tumors. In our cases, case 1 with the fusion partner gene *ZC3H4* was categorized as malignant, and case 2 with the fusion partner gene of *PRCC* was classified as benign, which is inconsistent with previously reported cases to some extent. Our review includes *TFE3* immunostaining-positive head and neck PEComa and nonhead and neck PEComa with *TFE3* rearrangement. The low specificity of TFE3 positivity as a surrogate for TFE3 fusion was considered, but all TFE3 positive cases were included because not many head and neck PEComa cases have been examined for TFE3 rearrangements. *SFPQ* is generally a predominant partner gene for *TFE3*, whereas *NONO* is more prevalent in the head and neck region. However, clinical and histological data are insufficient in some cases to identify the benign or malignant status of these tumors. Further, the current case reports have limited scope due to the inclusion of only those cases with a brief postoperative follow-up period. An increasing number of *TFE3* partner gene searches have been conducted, but the fusion partners and prognosis remain unknown. Therefore, further cases are anticipated to accumulate in the future.

In conclusion, we reported two head and neck *TFE3*-rearranged PEComa cases. The first is a malignant tumor in the orbit, with the rare fusion partner gene *ZC3H4*, and the second is a benign tumor in the nasal cavity, with the fusion partner gene *PRCC*, which is prevalent in *TFE3*-rearranged renal cell carcinoma. Interestingly, case 2 had renal angiomyolipoma, which was not related to a *TFE3*-rearranged tumor. A literature review revealed that *TFE3*-rearranged tumors exhibit similar histological features. Within *TFE3*-rearranged PEComas, there may be some differences between PEComas in the head and neck and those in other sites in terms of partner gene type.

Abbreviations

TFE3	Transcription factor E3
PEComa	Perivascular epithelioid cell tumors
FISH	Fluorescence in situ hybridization

Supplementary Information

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Supplementary Material 1

Author contributions

Conceived and designed the work: Y.T. and T.M. Provision of study material or patients: S.Y., S.S., Y.K., K.Y. Pathological analysis and FISH probe preparation: Y.T., A.M., A.Y., S.K, T.M. Y.Y. Data analysis and interpretation: Y.T. E.R., T.M Manuscript writing: Y.T. and T.M. Revised the manuscript: Y.Y., S.Y., S.S., Y.K., K.Y. Approved final version: T.M. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This was a case report and retrospective study that fulfilled the ethical requirements.

Consent for publication

Informed consent was obtained from the patients.

Competing interests

The authors declare no competing interests.

Declarations

Not applicable.

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