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TFE3-Rearranged PEComa/PEComa-like Neoplasms

Report of 25 New Cases Expanding the Clinicopathologic Spectrum and Highlighting its Association With Prior Exposure to Chemotherapy

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Abstract: Since their original description as a distinctive neoplastic entity, ~50 *TFE3*-rearranged perivascular epithelioid cell tumors (PEComas) have been reported. We herein report 25 new *TFE3*-rearranged PEComas and review the published literature to further investigate their clinicopathologic spectrum. Notably, 5 of the 25 cases were associated with a prior history of chemotherapy treatment for cancer. This is in keeping with prior reports, based mainly on small case series, with overall 11% of *TFE3*-rearranged PEComas being diagnosed postchemotherapy. The median age of our cohort was 38 years. Most neoplasms demonstrated characteristic features such as nested architecture, epithelioid cytology, HMB45 positive, and muscle marker negative immunophenotype. *SFPQ* was the most common *TFE3* fusion partner present in half of the cases, followed by *ASPSCR1* and *NONO* genes. Four of 7 cases in our cohort with meaningful follow-up presented with or developed systemic metastasis, while over half of the reported cases either recurred locally, metastasized, or caused patient death. Follow-up for the remaining cases was limited (median 18.5 months), suggesting that the prognosis may be worse. Size, mitotic activity, and necrosis were correlated with aggressive behavior. There is little evidence that treatment with MTOR inhibitors, which are beneficial against *TSC*-mutated PEComas, is effective against *TFE3*-rearranged PEComas: only one of 6 reported cases demonstrated disease stabilization. As co-expression of melanocytic and muscle markers, a hallmark of conventional *TSC*-mutated PEComa is uncommon in the spectrum of *TFE3*-rearranged PEComa, an alternative terminology may be more appropriate, such as "*TFE3*-rearranged PEComa-like neoplasms," highlighting their distinctive morphologic features and therapeutic implications.

Key Words: PEComa, *TFE3*, translocation, post-treatment

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Gene fusions involving the transcription factor E3 (*TFE3*) gene on chromosome Xp11.2 have been identified in a wide range of mesenchymal and epithelial neoplasms. The *ASPSCR1* (formerly *ASPL*)::*TFE3* fusion was discovered as the main driver alteration of alveolar soft part sarcoma[1] in 2001. Later that year, the *ASPSCR1*::*TFE3* fusion was identified in a subset of distinctive renal cell carcinomas with a predilection for young patients that are now recognized as the Xp11 translocation (*TFE3*-rearranged) renal cell carcinomas.[2] Numerous *TFE3* fusion partners in Xp11 translocation renal cell carcinoma have now been identified and characterized, including *PRCC*,[3] *SFPQ* (formerly *PSF*),[4] *NONO*,[4] *RBM10*,[5] *PARP14*,[6] *NEAT1*,[7] *KAT6A*,[7] *EWSR1*,[8] *MED15*,[9] *DVL2*,[10] *CLTC*,[11] *MATR3*,[12] and *FUBP1*.[12] In 2009-2010, recurrent *TFE3* gene fusions were identified in a distinctive subset of perivascular epithelioid cell tumors (PEComas),[13] which have predilection for young patients and are not associated with tuberous sclerosis complex. These lesions often display epithelioid clear cell morphology and express melanocytic markers, but (unlike typical PEComa) show minimal immunoreactivity for muscle markers.[14–16] Morphologically similar *TFE3*-rearranged neoplasms, which did not label for melanocytic markers have subsequently been reported.[17] *TFE3*-related fusions have also been identified in a distinctive subset of epithelioid hemangioendothelio-

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mas characterized by vasoformative features with plump endothelial cells showing abundant pale eosinophilic cytoplasm,[18] a subset of ossifying fibromyxoid tumors,[19,20] clear cell stromal tumor of the lung,[21] and cutaneous microcystic reticulated schwannoma.[22]

Since its original description, a total of ~50 cases of *TFE3*-rearranged PEComa have been reported in the literature, mostly as isolated case reports or small series.[10,13,15,16,23–51] A systematic review of the published literature, examining the validity of originally reported associations and potentially identifying new ones, has not been performed. In this study, we report 25 previously unpublished cases of *TFE3*-rearranged PEComa and review the published literature. Our findings expand the clinicopathologic spectrum of these distinctive neoplasms, identify a previously underappreciated association with prior exposure to chemotherapy, and review the limited available information on treatment and outcome.

MATERIALS AND METHODS

IRB Approval

This study was approved by the Institutional Review Boards at our respective institutions.

Cases

The new cases reported derive from the consultation files of the authors (P.A., J.M.G., L.M.R., E.B., A.A., and C.R.A.). All cases were confirmed by *TFE3* break-apart fluorescence in situ hybridization (FISH) and/or next-generation sequencing (NGS). The cases were identified during review of *TFE3*-rearranged neoplasms.

Immunohistochemistry

Immunohistochemistry for epithelial markers (cytokeratins AE1/3 and Cam5.2, epithelial membrane antigen), melanocytic markers (S100 protein, HMB45, and melan A), muscle markers (desmin, smooth muscle actin, and caldesmon), vascular markers (CD34), PAX8, Cathepsin K, and TFE3 were performed as previously described.[52]

Fluorescence in Situ Hybridization (FISH)

FISH on interphase nuclei from paraffin-embedded 4-μ sections was performed applying custom probes using bacterial artificial chromosomes (BAC). BAC clones were chosen according to UCSC genome browser (http://genome.ucsc.edu). The BAC clones were obtained from BACPAC sources of Children's Hospital of Oakland Research Institute (CHORI) (http://bacpacresources.org) and Life Technologies Corporation. BAC clones were chosen according to UCSC genome browser (http://genome.ucsc.edu).[10] DNA from individual BACs was isolated according to the manufacturer's instructions, labeled with different fluorochromes in a nick translation reaction, denatured, and hybridized to pretreated slides. Slides were then incubated, washed, and mounted with DAPI in an antifade solution, as previously described.[53] The genomic location of each BAC set was verified by hybridizing them to normal metaphase chromosomes. Two hundred successive nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems, Newton, MA). A positive score was interpreted when at least 20% of the nuclei showed a break-apart signal. Nuclei with an incomplete set of signals were omitted from the score.

Next Generation Sequencing (NGS)

NGS on case 2 was performed using an internal panel to cover full coding regions of ~450 cancer-related genes for clinical reporting of solid tumors as described previously.[54] Additional Integrated DNA Technologies probes (IDT Inc.) were also included to cover intron regions for detection of translocation. These include introns 1 to 4 and part of intron 5 of the *TFE3* gene. All variants, including translocations, were reviewed using the Integrated Genomics Viewer (Broad Institute). Case 5 was studied for RNA fusions using the Illumina Trusight 507 gene RNA panel.

RESULTS

Clinical History

Twenty-five new cases of *TFE3*-rearranged PEComas were selected, having material available for review and confirmation of diagnosis. The patients' ages ranged from 13 to 82 years (mean 40.3 years, median 38 years) (Table 1) and showed a near equal gender distribution (12 males, 13 females). Of note, at least 5 of the 25 cases (25%) were associated with prior exposure to chemotherapy for cancer. Their clinical histories are summarized below.

Case 1 was a 9-year-old male who developed Burkitt lymphoma and received chemotherapy regimen AHNL1131 (DA-EPOCH, or dose adjusted, etoposide, prednisone, vincristine [oncovin], cyclophosphamide, doxorubicin [hydroxydaunorubicin], and rituximab). Five years later, he developed hematuria and imaging studies (ultrasound, CT scan, and MRI) revealed a 2 cm renal hilar mass. The patient underwent an incisional biopsy of the lesion, which revealed a *TFE3*-rearranged PEComa. Although the lesion appeared likely incompletely excised, the patient and family elected close surveillance over nephrectomy. One year later, imaging showed no residual lesion within the kidney.

Case 2 was an 18-year-old female who developed Hodgkin lymphoma treated with chemotherapy and radiation. She was then in her usual state of health until age 38, when she developed right hip pain. MRI revealed an aggressive 5 cm T1 hypointense marrow-replacing lesion within the proximal femoral diaphysis, extending into the lesser trochanter with cortical breakthrough and extraosseous extension. The patient underwent biopsy of the lesion, which revealed a *TFE3*-rearranged PEComa, followed by a brief course of radiation which was terminated prematurely due to disease progression (the patient received 3800 cGy delivered in 19/25 fractions). She ultimately underwent radical femoral resection, which showed that the tumor had grown to 9.7 cm and did not show histologic evidence of treatment response. The patient shows no evidence of disease at 8 months.

TABLE 1. *TFE3*-Rearranged PEComa/PEComa-like Neoplasms in this Study

Case	Age/ sex	Site/size	Morphology	IHC+	IHC−	Fusion	Clinical/Outcome
1	13/M	Kidney/2 cm	Nested epithelioid	HMB45, TFE3, Cathepsin K+	AE1/3, S100-		History of Burkitts Lymphoma NED 1 y
2	38/F	Femur bone	Nested epithelioid	HMB45, TFE3, cathepsin K +; SMA, melan A focal+	Desmin, S100, AE1/3-	*SFPQ::TFE3*	s/p chemotherapy for Hodgkin's disease. NED 8 mo
3	27/M	Bladder/3 cm	Nested epithelioid	HMB45+; SMA focal+	Calponin, melan A, S100, CD34, PAX8, GATA3-	*SFPQ::TFE3*	Hematuria: s/p chemotherapy for relapsed Acute Lymphoblastic Leukemia 17 and 14 y previously
4	82/F	Bladder/2.5 cm	Nested epithelioid	HMB45, TFE3+	Melan A, actin, desmin, S100-	*NONO::TFE3*	s/p chemotherapy for Follicular Lymphoma 14 y ago. NED 3 y
5	27/M	Kidney/ 2.0 cm	Nested epithelioid	HMB45+	PAX8, CK7, CD117, cathepsin K-	*ASPSCR1::TFE3*	s/p chemotherapy for Neuroblastoma
6	27/F	Kidney/8 cm, pT2NX	Nested epithelioid	HMB45, TFE3, cathepsin K +; CD10 patchy weak;	SMA, desmin, melan A, PAX8-	*SFPQ::TFE3*	
7	7/F	Kidney/ 13.5 cm, pT3 (vascular invasion)	Nested epithelioid	HMB45+	Melan A, SMA, desmin, S100-	*DVL2::TFE3*	
8	50/M	Kidney/ 12.5 cm, sinus and adrenal invasion	Nested epithelioid	HMB45+	SMA, melan A-	*NONO::TFE3*	
9	17/F	Perivaginal/ 5 cm	Nested epithelioid	HMB45+; cytokeratin AE1/3 patchy	SMA, desmin, S100-	*SFPQ::TFE3*	
10	23/M	Intranasal	Solid epithelioid clear cell	TFE3, desmin, SMA, cathepsin K, GPNMB+	HMB45, melan A, S100, SOX10, AE1/3		
11	21/M	Bladder	Nested spindled and epithelioid	SMA, cathepsin K, GPNMB	HMB45, melan A, desmin, PAX8, AE1/3, S100, SOX10-		Hematuria and bladder mass.
12	46/F	Skin of back	Nested epithelioid	HMB45+	Melan A, SMA, desmin, S100-		Clinical "pilar cyst"
13	25/M	Colon Polyp/3.4 cm	Nested epithelioid	HMB45+	Melan A, S100, PAX8, AE1/3, chromogranin, synaptophysin-	*SFPQ::TFE3*	
14	60/F	Thigh/17 cm	Nested epithelioid	TFE3+	HMB45, desmin, S100, SOX10, CD34, cytokeratin-		NED 39 mo
15	66/F	Colon/6.6 cm	Nested epithelioid, pigment	HMB45+; melan A weak +	Actin, desmin, S100, CD34, PAX8, cytokeratin-.	*SFPQ::TFE3*	s/p 4 mo Sirolimus, only 10% necrosis
16	26/M	Kidney/7 cm	Nested epithelioid	HMB45+; SMA, melan A patchy +	Desmin, SOX10, PAX8, cytokeratin-	*NONO::TFE3*	
17	43/M	Kidney/ 17 cm	Nested epithelioid	HMB45+; SMA focal +	Desmin, melan A, S100, PAX8, cytokeratin, GATA3-	*PRCC::TFE3.*	Lung metastases→ palliative care at 2 y.
18	23/F	Occipital brain	Nested epithelioid	HMB45	PAX8-	*PRCC::TFE3*	
19	61/F	Endometrium	Nested epithelioid, pleomorphic	HMB45, Melan A+	Actin, desmin, S100, SOX10-		Sigmoid colon metastasis. Vaginal bleeding→debulking. Recurrent x2 over 2 y. Tumor grew on Everolimus 10 mg.
20	74/F	Thigh/7.5 cm	Xanthomatous, pseudolipoblastic, High grade	Cathepsin K+	HMB45, Melan A, actin, desmin, S100, SOX10, PAX8-.	*TFE3* FISH+ but *ASPSCR1::TFE3* negative.	Lung metastases at 14 mo.
21	55/F	Arm/6.7 cm (biopsy only)	Nested Epithelioid	HMB45, TFE3+	Melan A, actin, desmin, S100, SOX10, PAX8, Cam5.2-		Lung metastasis at diagnosis. History of polycystic kidney disease
22	54/M	Lung/1.3 cm	Inflammatory myofibroblastic tumor-like	HMB45+; actin weak+	Melan A, desmin, SOX10, S100, CD34-		PET positive
23	63/F	Mediastinum	Nested epithelioid	HMB45, cathepsin K+	Melan A, actin, S100, PAX8-.	*ASPSCR1::TFE3*	cT2N2 Breast Carcinoma, Developed New Mediastinal mass on dd-AC, Taxol after 2.5 mo.
24	25/M	Floor of mouth/6.5 cm	Nested epithelioid and spindled	SMA+; HMB45 patchy+	Melan A, Desmin, AE1/3, S100, SOX10-.	*ASPSCR1::TFE3*	
25	54/M	Kidney	Nested epithelioid	HMB45, TFE3, cathepsin K, melan A+	SMA-		Metastasis to brain at diagnosis

DOD indicates died of disease; IHC, immunohistochemistry; NED, no evidence of disease; s/*P*, status post; SMA, smooth muscle actin.

Case 3 was a 3 cm *TFE3*-rearranged PEComa of the bladder which developed in a 27-year-old male who had received chemotherapy for acute lymphoblastic leukemia and its relapse 17 and 14 years previously. No follow-up is available.

Case 4 was a 68-year-old female who developed stage 3 grade 1 follicular lymphoma and received chemotherapy including rituximab, cyclophosphamide, vincristine, and prednisone. Fifteen years later, at age of 82, the patient developed abdominal pain and had a CT scan, which revealed a 2.5 cm solid tumor in the right lateral bladder wall. Following transurethral resection, which was thought to remove most of the *TFE3*-rearranged PEComa, the patient was followed and showed no evidence of residual disease at 3 years follow-up.

Case 5 was a 27-year-old male who developed a *TFE3*-rearranged PEComa of the kidney over 20 years after having received chemotherapy for neuroblastoma. No follow-up is available.

Of note, case 23 was a 63-year-old female who received 2 months of intensive chemotherapy for breast cancer before a mediastinal *TFE3*-rearranged PEComa was detected. However, we did not consider this case to be chemotherapy related given the short interval from chemotherapy exposure to diagnosis.

Morphologic and Immunohistochemical Features

The majority of the current *TFE3*-rearranged PEComa cohort demonstrated the typical morphology and immunophenotype as originally described as characteristic of these neoplasms, and therefore they are discussed together. The neoplasms consisted of solid nests of epithelioid cells with abundant clear to pale eosinophilic cytoplasm, separated by a prominent fibrovascular stroma (Figs. 1–3). Nuclei were generally uniform and round with vesicular chromatin and variably prominent nucleoli. Mitotic activity was typically low ($<1/10$ high power fields). A minority of evaluable cases (6 of 17, 35%) demonstrated necrosis.

By immunohistochemistry, all 8 cases tested showed strong nuclear labeling for TFE3 protein. Twenty of 25 neoplasms demonstrated diffuse cytoplasmic labeling for HMB45, while 1 was focally positive and 4 were negative. In contrast, only 5 of 20 tested cases was positive for Melan A (3 only focally). Twelve of 20 cases were negative for actin, with 5 of the 8 positive cases demonstrating only focal labeling. Only one of 17 tested cases were positive for desmin. Cathepsin K labeled 8 of 9 tested cases.

However, several cases demonstrated variant morphology and immunoprofile. Case 10 was an intranasal epithelioid neoplasm with abundant clear glycogen-rich cytoplasm (PAS-positive, diastase sensitive), which labeled for muscle markers desmin and actin, but not for melanocytic markers HMB45 and melan A (Fig. 4). Case 22, a lung nodule, was spindled and associated with prominent chronic inflammation, yielding an inflammatory myofibroblastic tumor-like morphology (Fig. 5). Case 20 was a pleomorphic spindled and epithelioid neoplasm with atypical mitotic figures and abundant xanthomatous or pseudolipoblast cells (Fig. 6). The prominent vasculature in the limited material of case 1 raised the possibility of a primary vascular neoplasm.

Molecular Pathology

Among the 15 new cases with a defined *TFE3* fusion partner, 6 were *SFPQ*, 3 *ASPSCR1,* 3 *NONO*, 2 *PRCC*, and 1 *DVL2*. All fusions were detected by break-apart FISH with the exception of case 2, in which a *SFPQ* exon9::*TFE3* exon5 fusion was detected by NGS, and case 5 in which an *ASPSCR1* exon 7*:TFE3* exon 6 fusion was detected by NGS.

Clinical Outcome

As most of our cases are recent, clinical follow-up was overall limited. However, among the 7 with follow-up of at least 1 year, 2 developed lung metastases. Two other cases presented with distant metastasis at diagnosis. Two of the patients received treatment with an MTOR (mammalian target of rapamycin) inhibitor, but there was little evidence of therapeutic efficacy. One tumor (case 19) grew in size while on treatment with everolimus. An additional case (case 15) received 4 months of neoadjuvant sirolimus; however, the treated tumor demonstrated only minimal (10%) necrosis on microscopic examination.

DISCUSSION

The results of our study presenting 25 new cases, corroborated with the findings from the literature (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PAS/B798), highlight the distinctive features of *TFE3*-rearranged PEComas compared with conventional *TSC*-mutated PEComas. First, there is a trend toward young patient age, with the mean age in our *TFE3*-rearranged PEComa cohort of 38 years (38.9 years in overall literature review), while that of PEComas overall is 45 years.[55] Second, there is no association of *TFE3*-rearranged PEComa with tuberous sclerosis complex, as distinct and likely mutually exclusive genetic mechanisms are involved. In contrast, conventional PEComas (particularly those occurring in young patients) are more likely to be associated with germline *TSC1/2* mutations, which cause tuberous sclerosis complex. Third, their typical morphology is that of a neoplasm with nested architecture and epithelioid clear cell cytology, resembling an alveolar soft part sarcoma with clear cytoplasm. Fourth, these neoplasms most often lack muscle marker expression, like desmin and actin. Review of the literature indicates that 42 (59%) of 71 *TFE3*-rearranged PEComa cases tested showed no muscle marker expression, whereas actin or desmin expression was present in 29 (41%) of 71 tested cases and was only focal in most of these (16). In contrast, melanocytic and muscle marker co-expression is a defining hallmark of conventional PEComa. Fifth, the intriguing observation that *TFE3*-rearranged PEComas typically demonstrate diffuse HMB45 immunoreactivity and minimal to no reactivity for the melanocytic marker melan A holds up on review of the literature. While 69 (84%) of 82

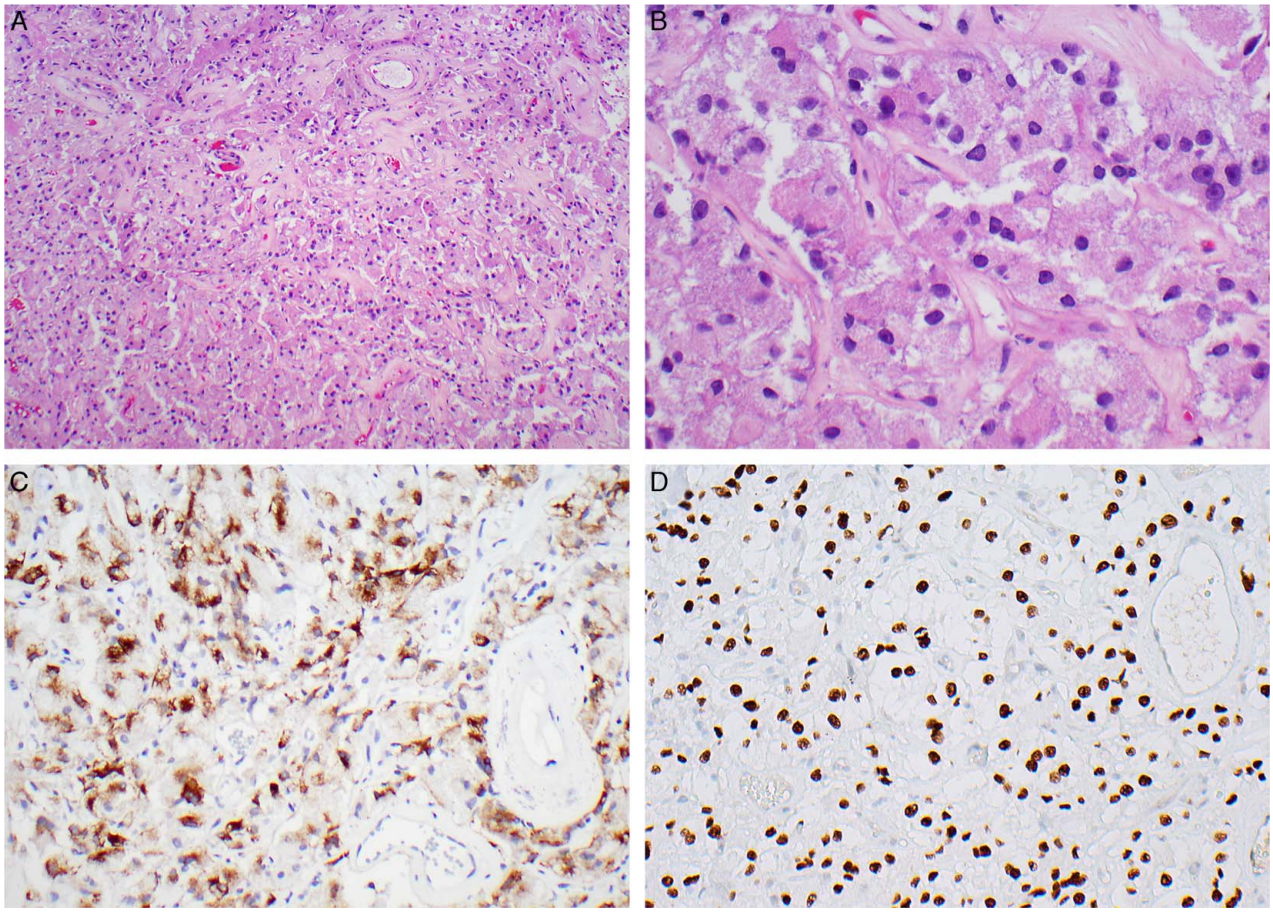

FIGURE 1. (case 4): This bladder biopsy reveals an epithelioid cell lesion with pale eosinophilic cytoplasm arranged in sheets and cords within hyalinized stroma (A). At higher power, the neoplastic cells have bland round nuclei and granular eosinophilic cytoplasm, resembling histiocytes (B). The neoplastic cells demonstrate diffuse cytoplasmic labeling for HMB45 (C) and strong diffuse nuclear labeling for TFE3 (D).

TFE3-rearranged PEComas reported in the literature have been positive for HMB45 (61 diffusely), only 23 (37%) of 63 cases tested labeled for melan A/Mart1, slightly more than half of these (12) in a patchy/focal fashion. Sixth, our results also confirm prior observations that *SFPQ* is the most common *TFE3* fusion partner in *TFE3*-rearranged PEComa. On review of the literature, 25 (51%) of 49 cases with known fusion partners demonstrated the *SFPQ::TFE3* fusion, followed by *ASPSCR1:TFE3* (10 cases) and *NONO:TFE3* (6 cases), while other partners such as *PRCC* (3 cases), *DVL2* (2 cases), *RBM10* (2 cases), and *RBMX* (1 case) are uncommon. Our series demonstrated only a slight female gender predilection, however, evaluating the published literature, there is a female predominance for *TFE3*-rearranged PEComa of nearly 3 females: 1 male (60 females: 23 males). This is not entirely unexpected given the involvement of the *TFE3* gene, which resides on the X chromosome. Of note, while PEComa overall has a female predominance of 5:1, alveolar soft part sarcoma is associated with a less impressive female predominance (58% of cases).[56]

Our study expands the clinicopathologic spectrum of *TFE3*-rearranged PEComas to include primary osseous presentation in the long bones (femur). Skeletal PEComas are extremely uncommon, limited to small case series.[57–59] Only one of the ~20 previously published intraosseous cases, a facial bone tumor in a 3-year-old (case 55 in literature review, Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PAS/B798), was associated with a documented *TFE3* gene fusion. The epithelioid clear cell morphology of *TFE3*-rearranged PEComa in bone raises the differential diagnosis of metastatic clear cell renal cell carcinoma. Absence of immunoreactivity for epithelial markers or PAX8 along with diffuse labeling for HMB45 helps make this distinction.

Moreover, the findings of our current cohort highlight a previously underappreciated association of *TFE3*-rearranged PEComa with prior exposure to chemotherapy. It should be noted that Vannucchi et al[43] documented that their case of a *TFE3*-rearranged bladder PEComa in a 66-year-old female was associated with prior exposure to chemotherapy for chronic lymphoblastic leukemia and noted two other similar cases in the literature, but did not explore this potential association further. Considering all

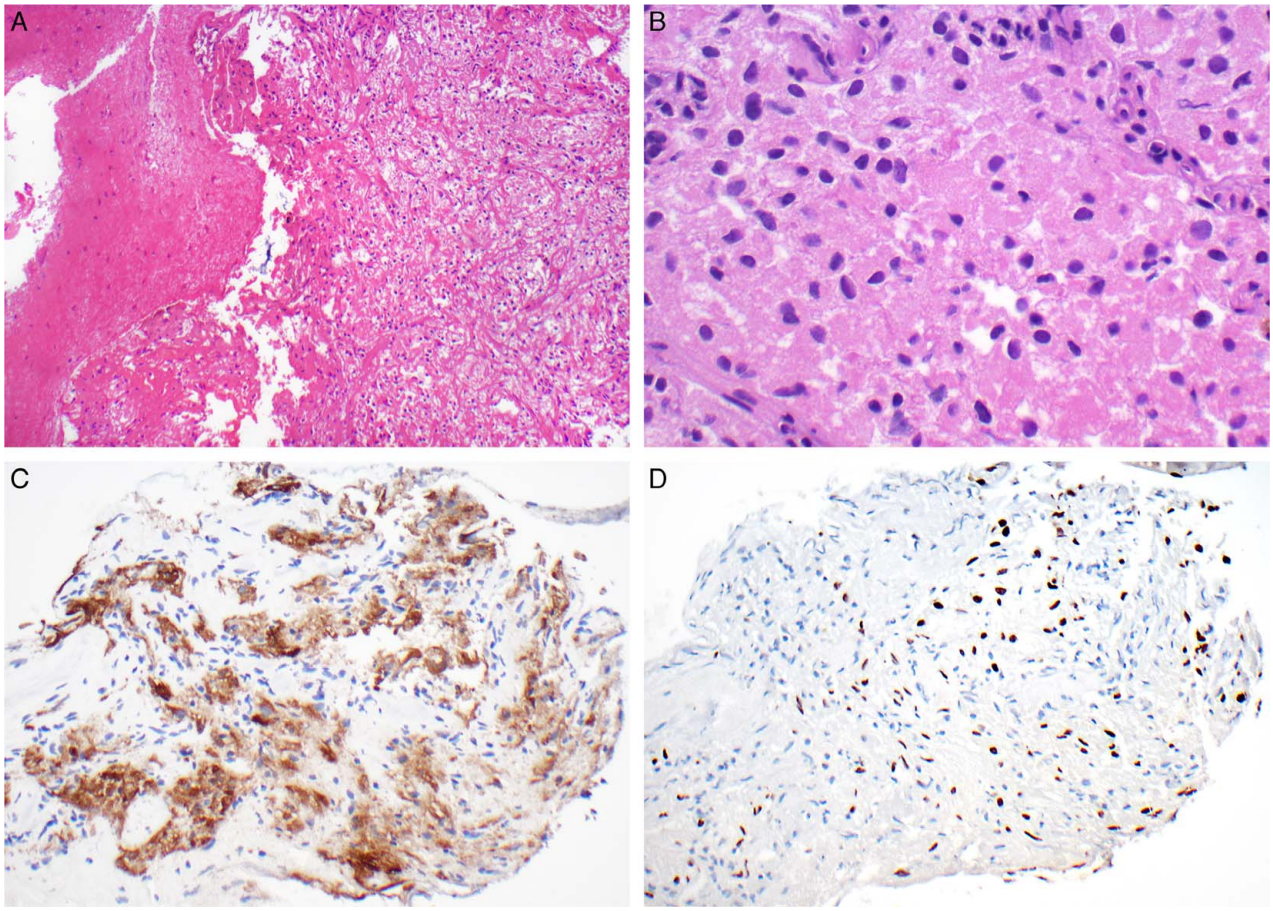

FIGURE 2. (case 1): This renal biopsy reveals an epithelioid cell lesion (right) associated with abundant hemorrhage (left). At high power, the epithelioid cells have round nuclei and pale granular eosinophilic cytoplasm, resembling histocytes (B). The neoplastic cells label diffusely for HMB45 (C) and strong diffuse nuclear labeling for TFE3 (D).

cases in the literature, 9 (11%) of 83 genetically confirmed *TFE3*-rearranged PEComa have documented prior exposure to chemotherapy. This does not include our case 23, in which the PEComa diagnosis occurred only 2 months after the patient began chemotherapy for breast cancer. We note several additional cases in the literature which seem likely to represent *TFE3*-rearranged PEComas that occurred following chemotherapy but lack molecular confirmation (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/PAS/B799).[69–72] Our group previously reported an association of *TFE3*-rearranged renal cell carcinomas with prior exposure to chemotherapy.[66] On review of the cases within our files, ~15% of Xp11 translocation renal cell carcinoma occurred in patients who received chemotherapy for prior cancer or in the setting of immunosuppression. Interestingly, 6 of the 9 (67%) reported cases of post-chemotherapy TFE3-rearranged PEComa have arisen in the genitourinary tract, while 29 of 83 (35%) reported cases of TFE3-rearranged PEComa overall have arisen in the genitourinary tract. Of note, an association with prior chemotherapy exposure has not been established in alveolar soft part sarcoma (with a pathognomonic *ASPSCR1::TFE3* gene fusion).

While data in the literature are limited, *TFE3*-rearranged PEComa appears to be aggressive. Out of 42 cases in the literature with clinical follow-up of 1 year or more, 13 (31%) have metastasized systemically and 5 (12%) others have caused patient death. Five (12%) others have recurred locally or metastasized to regional lymph nodes. Of note, of the 19 cases, which are reported to be disease free at 1 year or more follow-up, median follow-up is only 18.5 months, which is woefully inadequate for slowly growing tumors such as *TFE3*-rearranged neoplasms, which can recur long after initial presentation. The nonuniform reporting of potential prognostic factors (size, vascular invasion, mitotic rate, necrosis, atypia, etc.) hinders determination of their significance. However, there appears to be an association of recurrence with large size: with a mean tumor size of 3.0 cm in patients who have not recurred; 8.4 cm in those who developed or presented with systemic metastasis; and 11.4 cm in patients who succumbed of disease. Using 5 cm as the cutoff, only 1 of 17 cases less than 5 cm in greatest dimension recurred, while 17 of 20 cases, which were 5 cm or more metastasized or caused patient death (Fisher exact test, $P < 0.00001$) Necrosis also correlates with aggressive

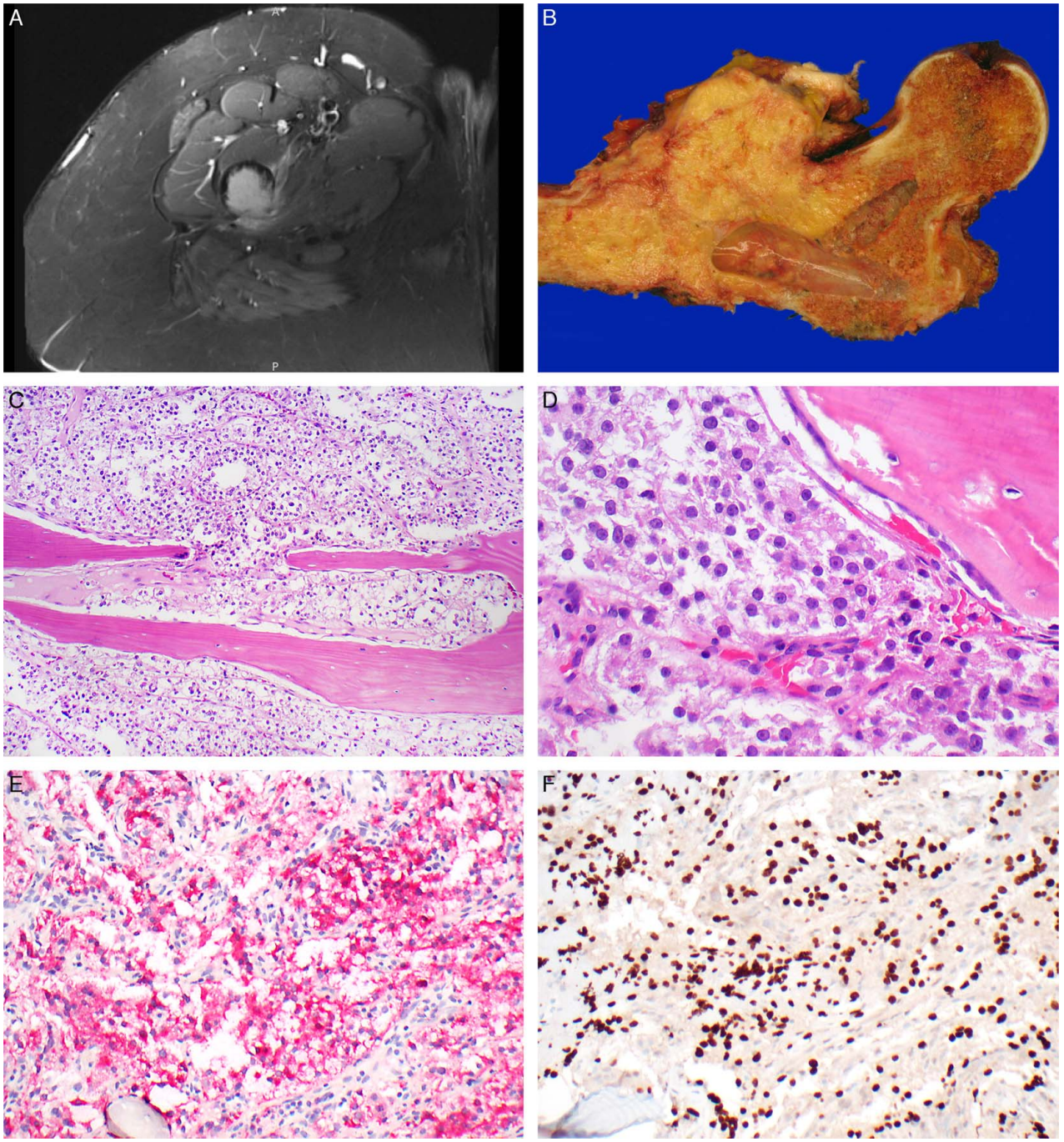

FIGURE 3. (case 2): MRI STIR images reveal an aggressive lesion in the proximal femur showing cortical breakthrough and extension into adjacent soft tissue (A). On gross examination, the fleshy tumor involves the femoral neck and breaks through the cortex to extend into soft tissue. Defects consistent with prior rod placement are also evident (B). The epithelioid neoplastic cells are arranged in nests, and permeate into existing lamellar bony trabeculae (C). At high power, the neoplastic cells abut bone lined by osteoblasts. The neoplastic cells have round nuclei with pinpoint nucleoli and granular eosinophilic to pale cytoplasm (D). The neoplastic cells demonstrate diffuse cytoplasmic labeling for HMB45 (red chromogen, E) and diffuse strong nuclear labeling for TFE3 (F).

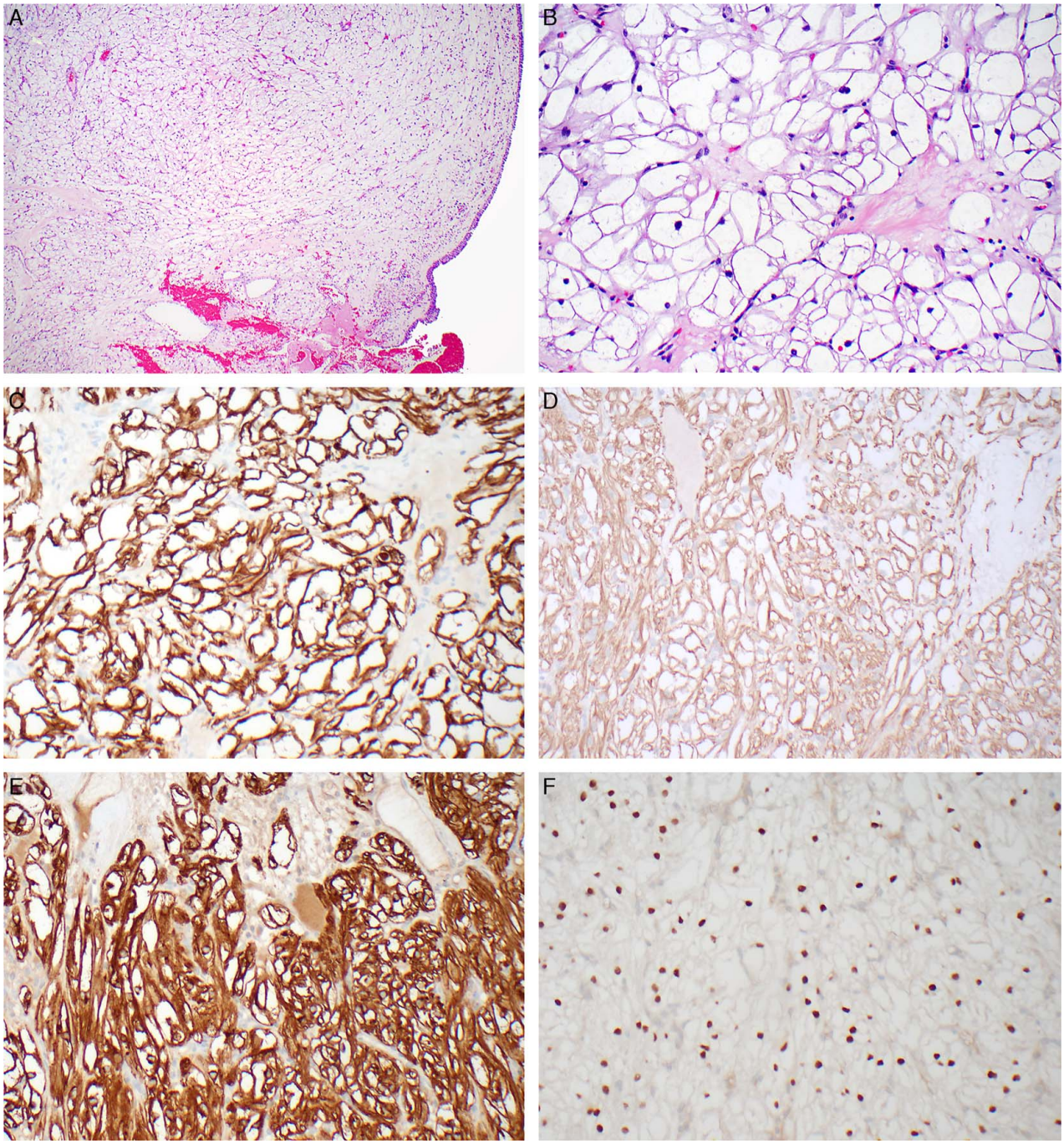

FIGURE 4. (case 10): This polypoid nasal lesion undermines the respiratory epithelium (right), which is focally ulcerated (bottom) (A). High-power view demonstrates an epithelioid cell lesion with voluminous, water clear cytoplasm, and hyalinized stroma (B). The neoplastic cells are negative for melanocytic markers but instead are diffusely immunoreactive for muscle markers desmin (C) and smooth muscle actin (D). They are diffusely immunoreactive for the downstream marker of TFE3 signaling, glycoprotein nonmetastatic B (GPNMB) (E) and demonstrate diffuse strong nuclear labeling for TFE3 (F).

behavior; of those neoplasms which metastasized or caused patient death, 14 of 16 had necrosis, while only 4 of 18 tumors in patients who did not recur had necrosis (Fisher exact test statistic value $P = 0.0002$). Increased mitotic rate also correlated with aggressive behavior: 14 of 17 cases which did not recur had mitotic rates of 1 or lower per 10 high power fields, while 12 of 15 cases which metastasized or caused death had mitotic rates of more

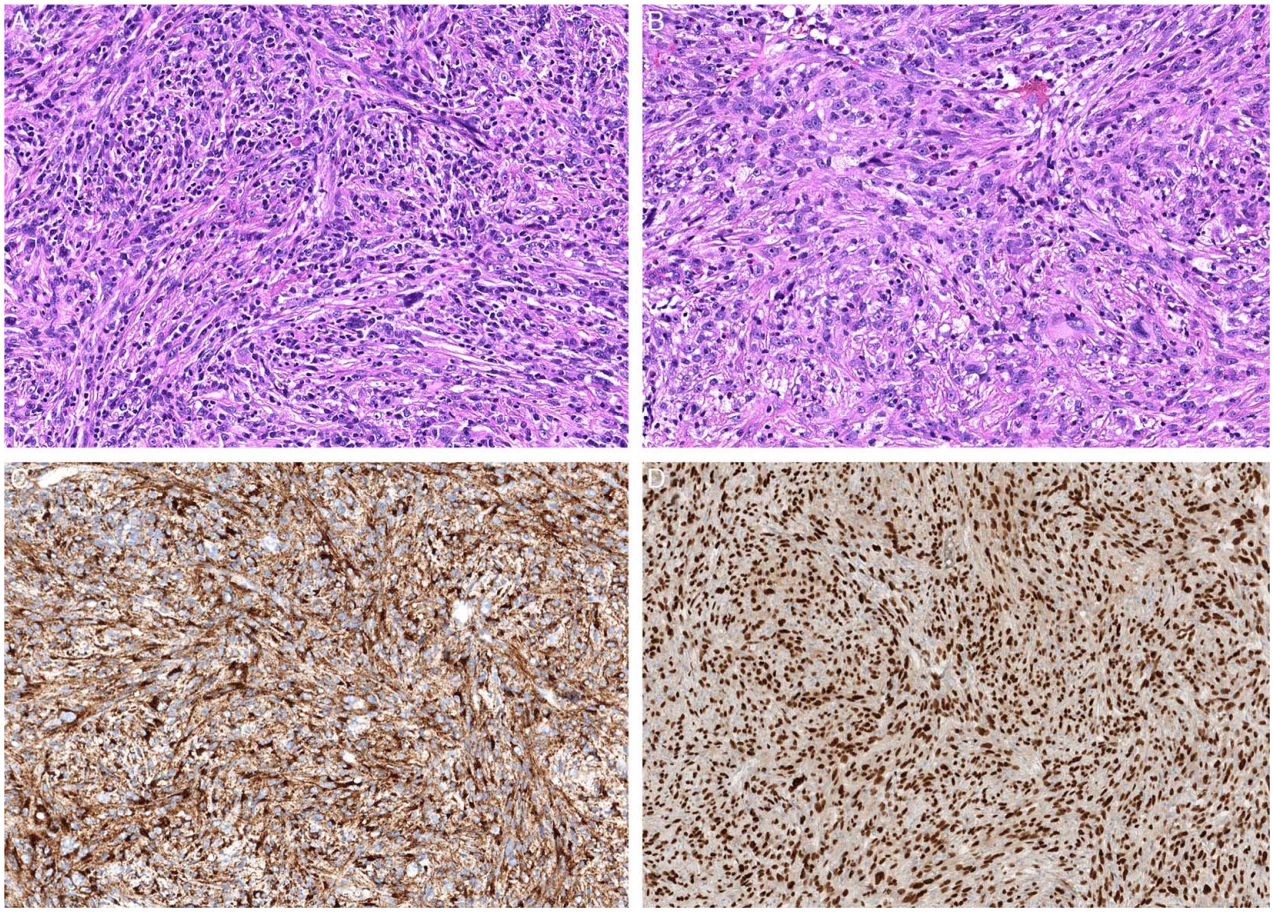

FIGURE 5. (case 22): This lung nodule is composed of neoplastic spindle cells with moderate atypia associated with a prominent chronic lymphoplasmacytic inflammatory infiltrate, reminiscent of an inflammatory myofibroblastic tumor (A). At higher magnification, some of the neoplastic cells have a more epithelioid appearance with a syncytial growth pattern with associated inflammatory infiltrate (B). The neoplastic cells label diffusely for HMB45, highlighting their spindled morphology (C) and demonstrate diffuse nuclear labeling for TFE3 (D).

than 1 per 10 high power fields ($P = 0.001$). However, even cases without aggressive features may progress late. This is exemplified by case 51 in our review, a 5 cm renal tumor that lacked atypia, mitotic activity or necrosis but metastasized to the liver 7 years after diagnosis. Hence, regardless of histology, these patients require long-term follow-up.

There are extremely limited data available on treatment for these neoplasms. One might predict that *TFE3*-rearranged PEComa would not respond to the MTOR inhibitors characteristically used in the treatment of conventional *TSC*-mutated PEComas. However, based on recent experimental data, it seemed possible that cross talk between the TSC/MTOR signaling pathways and TFE3 might allow for some therapeutic effect of MTOR inhibitors in *TFE3*-rearranged PEComas. Inactivation of *TSC* genes upregulates MTOR signaling and results in increased TFE3/TFEB levels and activity, which is reversible with rapalogs.[67–69] Conversely, TFE3 activity upregulates RagD expression which activates the MTOR pathway, creating a potential positive feedback loop.[70] Blocking MTOR signaling with rapalogs could thus in theory feedback to diminish TFE3 signaling in these neoplasms, thereby diminishing downstream growth promotion. However, review of the available clinical data provides little support for this hypothesis *in vivo*. On review of the literature of well documented cases (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PAS/B798), only 1 of 6 cases of genetically confirmed *TFE3*-rearranged PEComas treated with an MTOR inhibitor (case 36) demonstrated some evidence of treatment effect, in that there was a short period of disease stabilization, though the patient did progress on treatment after 5 months.[35] Analysis of the oncology literature is difficult as *TFE3* status of individual PEComa cases treated with MTOR inhibitors is not consistently reported. However, in one study, 8 of 9 patients with *TSC2*-mutated PEComa responded to nab-Sirolimus while 2 patients with *TFE3*-rearranged PEComa had stable disease but no response in limited follow-up.[71] Whether varying the specific MTOR inhibitor used or its dosage can impact outcome in *TFE3*-rearranged PEComa merits further study.

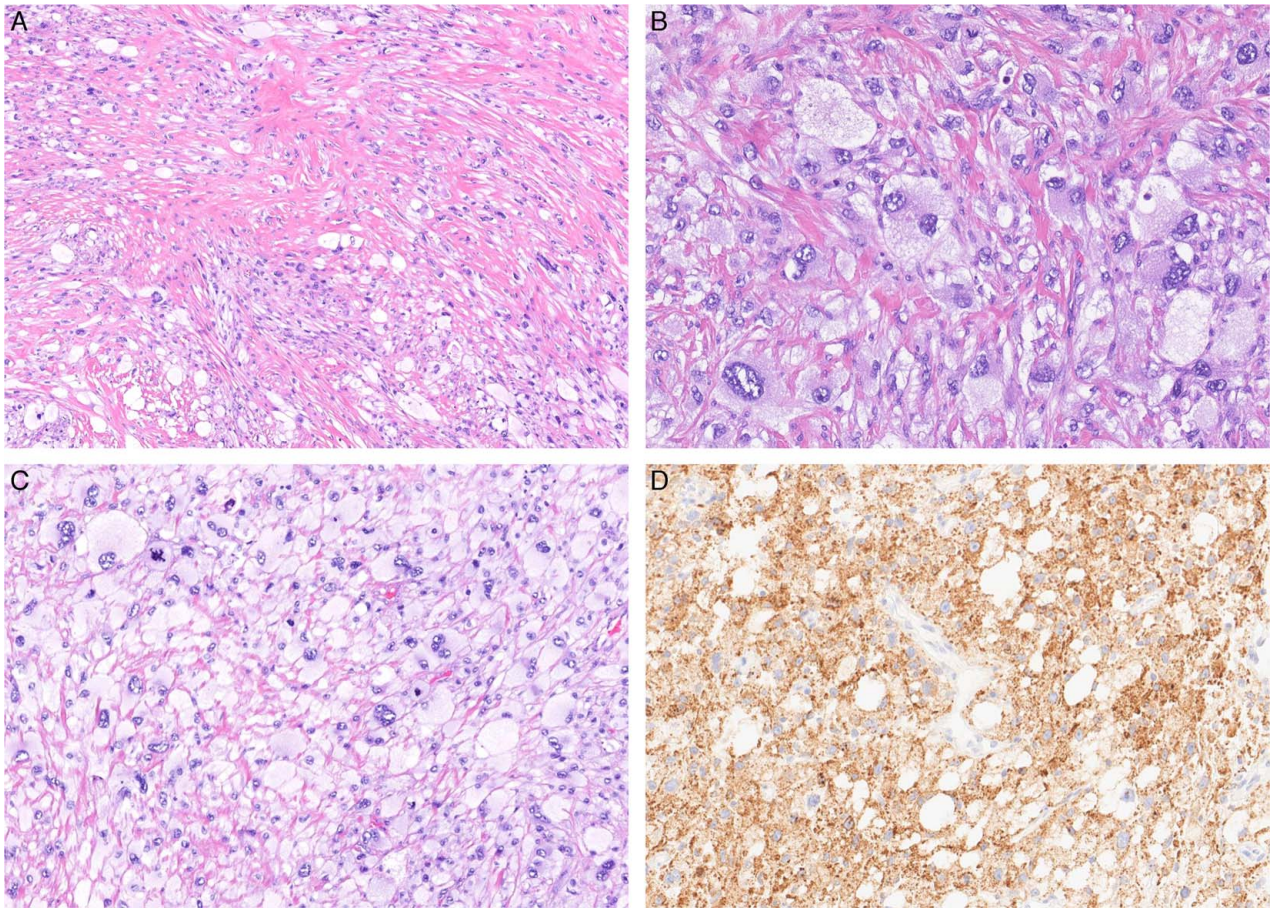

FIGURE 6. (case 20): This thigh mass demonstrated pleomorphic spindled to epithelioid morphology, with dense collagen (A). The pleomorphic epithelioid cells have voluminous xanthomatous cytoplasm, mimicking lipoblasts (B). The xanthomatous cells have areas of sheet-like growth with high mitotic activity including atypical forms (C). The neoplastic cells demonstrate diffuse cytoplasmic labeling for cathepsin K (D) but an absence of melanocytic or muscle marker expression.

As noted above, while our review demonstrates that most *TFE3*-rearranged PEComas have the characteristic morphology originally described (nested epithelioid cells reminiscent of alveolar soft part sarcoma, immunoreactivity for HMB45 but not muscle markers), we expand the morphologic spectrum to include variant morphologies. These include epithelioid clear cell neoplasms expressing muscle markers but not HMB45, pleomorphic xanthomatous neoplasms, and inflammatory myofibroblastic tumor-like neoplasms. It is possible that variant fusion partners contribute to these unusual morphologies in *TFE3*-rearranged neoplasms. This appears to be the case among *TFE3*-rearranged renal cell carcinomas, where for example the RCC with the *MED15-TFE3* fusion are frequently extensively cystic and mimic multilocular clear renal neoplasm of low malignant potential.[60,72] Along these lines, we recently described PEComa-like neoplasms with the *ASPSCR1::TFE3* gene fusion (typically found in alveolar soft part sarcoma) with predominant spindle cell morphology and immunoreactivity for smooth muscle actin but not HMB45 (the reverse of the typical phenotype of *TFE3*-rearranged PEComa).[17] Similar *ASPSCR1::TFE3* fusion positive cases have subsequently been reported by others.[49] Overall, two thirds of these *ASPSCR1::TFE3* neoplasms have labeled for smooth muscle actin, while only half label for melanocytic markers HMB45 and melan A. We previously noted that such cases were difficult to diagnose outright as PEComa given their absence of melanocytic marker expression.[17] Conversely, one could also have argued at the time of their original description in 2009-2010 that the HMB45 positive, muscle marker-negative immunophenotype of typical *TFE3*-rearranged PEComa is inconsistent with PEComa, since the latter is characterized as having a myomelanocytic immunophenotype with co-expression of melanocytic and muscle markers.[55] Since PEComa is the closest but not a perfect description for any of these neoplasms, it may be more appropriate to henceforth refer to *TFE3*-rearranged PEComas as "*TFE3*-rearranged *PEComa-like* neoplasms," particularly given the fact that they appear from our review to be less responsive to MTOR inhibitor therapy and thus their morphologic separation from typical PEComa correlates with distinctive therapeutic implications. A similar argument has recently been

made for separating *TFE3*-rearranged epithelioid hemangioendothelioma from typical *WWTR1::CAMTA1* fusion positive epithelioid hemangioendothelioma.[61]

As originally noted, typical *TFE3*-rearranged PEComas overlap morphologically with alveolar soft part sarcoma and share a *TFE3*-driven genetic program. The presence of *ASPSCR1::TFE3* gene fusion in both neoplasms (typical in alveolar soft part sarcoma, rare in *TFE3*-rearranged PEComa) furthers this overlap. Nonetheless, the distinctive morphologic (less discohesion, tighter nests, more frequent spindling, and more frequent pleomorphism) and immunophenotypic (near consistent HMB45 immunoreactivity and frequent melan A negativity) features of *TFE3*-rearranged PEComas argue against simply lumping them (and/or their melanotic counterparts) with alveolar soft part sarcoma. The *TFE3*-rearranged PEComa cases with variant morphology reported herein (exemplified in Figs. 5 and 6) are even further beyond the spectrum of alveolar soft part sarcoma.

For purposes of this review, we excluded the extensively melanotic pigmented *TFE3*-rearranged PEComas originally described as "melanotic Xp11 translocation renal cancer." These neoplasms exist on the spectrum of *TFE3*-rearranged PEComa; in fact, some cases in our cohort and literature contained rare cells, which contained pigment that may have represented melanin rather than hemosiderin. However, it remains possible that some of the clinicopathologic features of the melanotic *TFE3*-rearranged PEComas may differ from their nonpigmented counterparts. For example, we have not observed a strong association of melanotic *TFE3*-rearranged melanotic neoplasms with prior chemotherapy (unpublished observations). Moreover, their strong predilection to arise within the kidney (~50% of reported cases compared to 10% of *TFE3*-rearranged PEComa) raises the possibility that, at least in some cases, they may derive from a different cell of origin. Indeed, one of us (T.L.) has recently demonstrated in a mouse model that overexpression of the *SFPQ::TFE3* gene fusion within renal tubular cells results in loss of all the epithelial markers and conversion to a PEComa-like phenotype (TL, unpublished observations). This suggests that some *TFE3*-rearranged renal PEComas (melanotic or not) may derive from a renal tubular cell even though their phenotype is nonepithelial. Further studies in this area are in progress.

In summary, *TFE3*-rearranged PEComa have a broader morphologic and immunohistochemical spectrum than previously reported. The term "*TFE3*-rearranged PEComa like neoplasm" may be more suitable. There is an association with prior exposure to chemotherapy, and little evidence of response to MTOR pathway inhibition in limited experience. These neoplasms are often aggressive, as predicted by size, mitotic activity and necrosis. However, even benign-appearing lesions may metastasize late, mandating long-term follow-up.

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