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CASE REPORT

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TFE3-rearranged PEComa-like neoplasm of the kidney with carcinoma-like morphology and rapid progression: a case report

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Abstract

Background TFE3-rearranged perivascular epithelioid cell tumor (PEComa)-like neoplasm is a recently recognized mesenchymal tumor with melanocytic immunophenotype and TFE3 gene rearrangement, but often lacking smooth muscle differentiation. Herein, we present a case of TFE3-rearranged PEComa-like neoplasm of the kidney to expand its clinicopathological characteristics and biological behavior.

Case presentation A 22-year-old female presented with left lumbago for more than 20 days. Abdominal computed tomography (CT) scan revealed a heterogeneous mass in the upper pole of the left kidney. Nephron-sparing surgery for renal neoplasia was performed. Histology showed carcinoma-like morphology, characterized by nests of large eosinophilic cells with prominent nucleoli and a rich capillary network. Immunohistochemistry demonstrated HMB45, melan-A, and cathepsin K positivity, focal SMA reactivity, and negativity for Pan-CK and PAX8, prompting an initial diagnosis of epithelioid angiomyolipoma/PEComa. Seventeen months post-surgery, rapid recurrence and multiple metastases occurred. A CT-guided needle biopsy revealed similar histological and immunohistochemical characteristics but with increased mitotic activity and necrosis. Subsequent TFE3 immunohistochemistry and fluorescence in situ hybridization confirmed TFE3 gene rearrangement, revising the diagnosis to TFE3-rearranged PEComa-like neoplasm.

Conclusions This case enhances our understanding of TFE3-rearranged PEComa-like neoplasm, especially its morphological spectrum and aggressive behavior, which are valuable for diagnosis and prognostic prediction.

Keywords TFE3-rearranged PEComa-like neoplasm, Melanotic Xp11 neoplasm, Epithelioid angiomyolipoma, Diagnosis, Prognosis

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Introduction

TFE3-rearranged perivascular epithelioid cell tumor (PEComa)-like neoplasm, alternatively designated as melanotic Xp11 neoplasm, is a newly recognized mesenchymal tumor, characterized by melanocytic immunophenotype and TFE3 gene rearrangement [1, 2]. However, unlike conventional PEComa, which shows co-expression of melanocytic and muscle markers, it often lacks smooth muscle differentiation [1, 2]. Due to its rarity, it is easily misdiagnosed when encountered in clinical practice. More studies are needed to elucidate the clinicopathological characteristics and the biological behavior of this rare tumor. In this study, we present a case of TFE3-rearranged PEComa-like neoplasm of the kidney, exhibiting carcinoma-like morphological pattern and rapid progression.

Case presentation

A 22-year-old female presented to our hospital with left lumbago for more than 20 days. She had no history of gross hematuria, increased urinary frequency, urgency, dysuria, or urinary pain. Abdominal computed tomography (CT) scan revealed a 120 mm × 100 mm mass in the upper pole of the left kidney, exhibiting heterogeneous density, calcification, cystic changes, necrosis, and ill-defined margins with adjacent parenchyma (Fig. 1A-B). Nephron-sparing surgery for renal neoplasia was performed.

Grossly, the mass was measured 120 mm × 90 mm × 60 mm, with a gray-tan to white cut surface and focal areas of necrosis and hemorrhage. Histologically, most areas of the mass were well demarcated from the adjacent renal parenchyma, and only focal areas showed ill-defined borders. The mass exhibited carcinoma-like morphology (Fig. 1C-D). Tumor cells were mainly arranged in nests and acinar pattern, interspersed with a rich capillary network (Fig. 1C). These cells were round or polygonal epithelioid cells with abundant eosinophilic or clear cytoplasm, and contained round nuclei with prominent nucleoli, resembling ganglion cells (Fig. 1D). The mitotic figures were rare, and necrosis and hemorrhage were observed in focal areas. Sclerotic fibrous tissue occurred in some regions of the tumor, with tumor cells in these areas arranged in cord-like or trabecular pattern (Fig. 1E). Immunohistochemically, HMB45 (Fig. 1F), melan-A, and cathepsin K (Fig. 1G) were positive in most tumor cells. SMA was focally positive (Fig. 1H). Pan-CK, PAX8 (Fig. 1I), SF1, Synaptophysin,

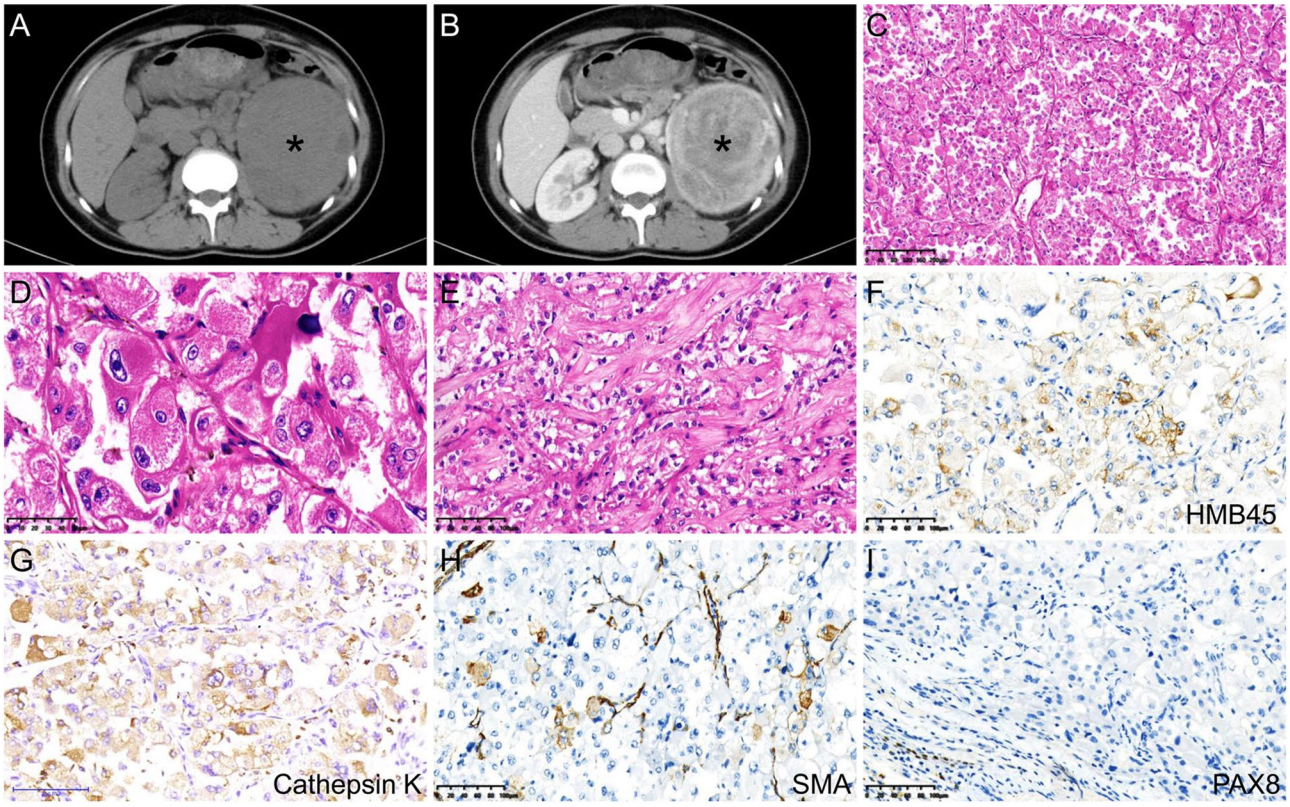

Fig. 1 CT images and pathological characteristics of the tumor at initial diagnosis. (**A, B**) Plain CT images (**A**) and contrast-enhanced CT images (**B**) of the tumor mass (asterisk). (**C**) Tumor cells arranged in nests and acinar pattern with rich capillary network. (**D**) Some tumor cells exhibiting ganglion cell-like appearances with abundant cytoplasm and prominent nucleoli. (**E**) Sclerotic fibrous tissue in some areas. (**F-I**) Representative immunohistochemical staining of HMB45 (**F**), cathepsin K (**G**), SMA (**H**), and PAX8 (**I**)

and CgA were negative. The Ki-67 proliferative index was less than 1%. The tumor was thus diagnosed as epithelioid angiomyolipoma/PEComa.

Two weeks post-surgery, thoracic and abdominal CT scan revealed renal subcapsular effusion and pneumatosis, with no signs of tumor recurrence (Fig. 2A). Nine months post-surgery, thoracic and abdominal CT scan showed no abnormalities (Fig. 2B). Thirteen months post-surgery, the patient experienced a recurrence of left lumbago, and identified a mass approximately 30 mm in diameter on the left side of her lower back. Since the pain could resolve spontaneously, she did not seek clinical examination or treatment at the hospital. Seventeen months post-surgery, she was admitted to our hospital due to worsening left lumbago. Thoracic and abdominal CT scan showed a 38 mm × 41 mm mass with soft tissue density and heterogeneous enhancement in the left kidney (Fig. 2C). It also revealed multiple nodules with soft tissue density surrounding the left kidney, and bone destruction involving the 8th thoracic vertebrae, 4th lumbar vertebrae and left 12th rib (Fig. 2C). These imaging findings of primary and metastatic lesions were further confirmed by SPECT/CT (Fig. 3A-C).

Given the rapid progression of the tumor, a multidisciplinary team consultation was convened. Consensus indicated excessive aggressiveness deviating from typical angiomyolipoma features, prompting CT-guided needle biopsy. The histological and immunohistochemical characteristics were similar to those in the first pathological examination (Fig. 4A-D). However, compared to the first examination, necrosis (Fig. 4A) and mitotic figures (Fig. 4B) were prominently evident in the current pathological examination. TFE3 staining was applied to the specimen and subsequently detected in the tumor

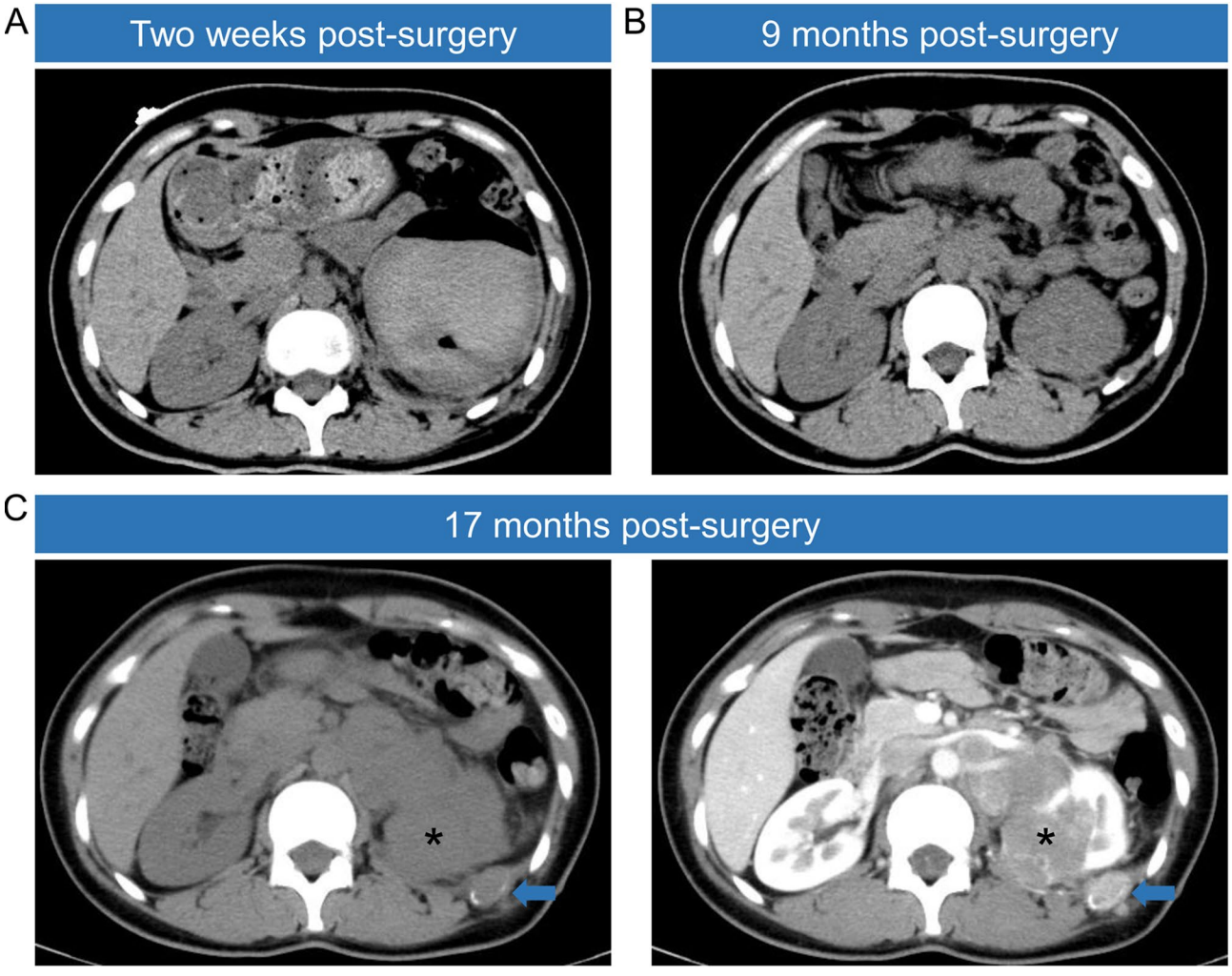

Fig. 2 CT images of the patient after surgery. (**A**) Plain CT image obtained two weeks post-surgery, showing renal subcapsular effusion and pneumatosis, with no signs of tumor recurrence. (**B**) Plain CT image obtained 9 months post-surgery, showing no signs of tumor recurrence. (**C**) Plain CT image (left) and contrast-enhanced CT image (right) obtained 17 months post-surgery, exhibiting the recurrent foci in the kidney (asterisk) and the metastatic foci in the left 12th rib (arrow)

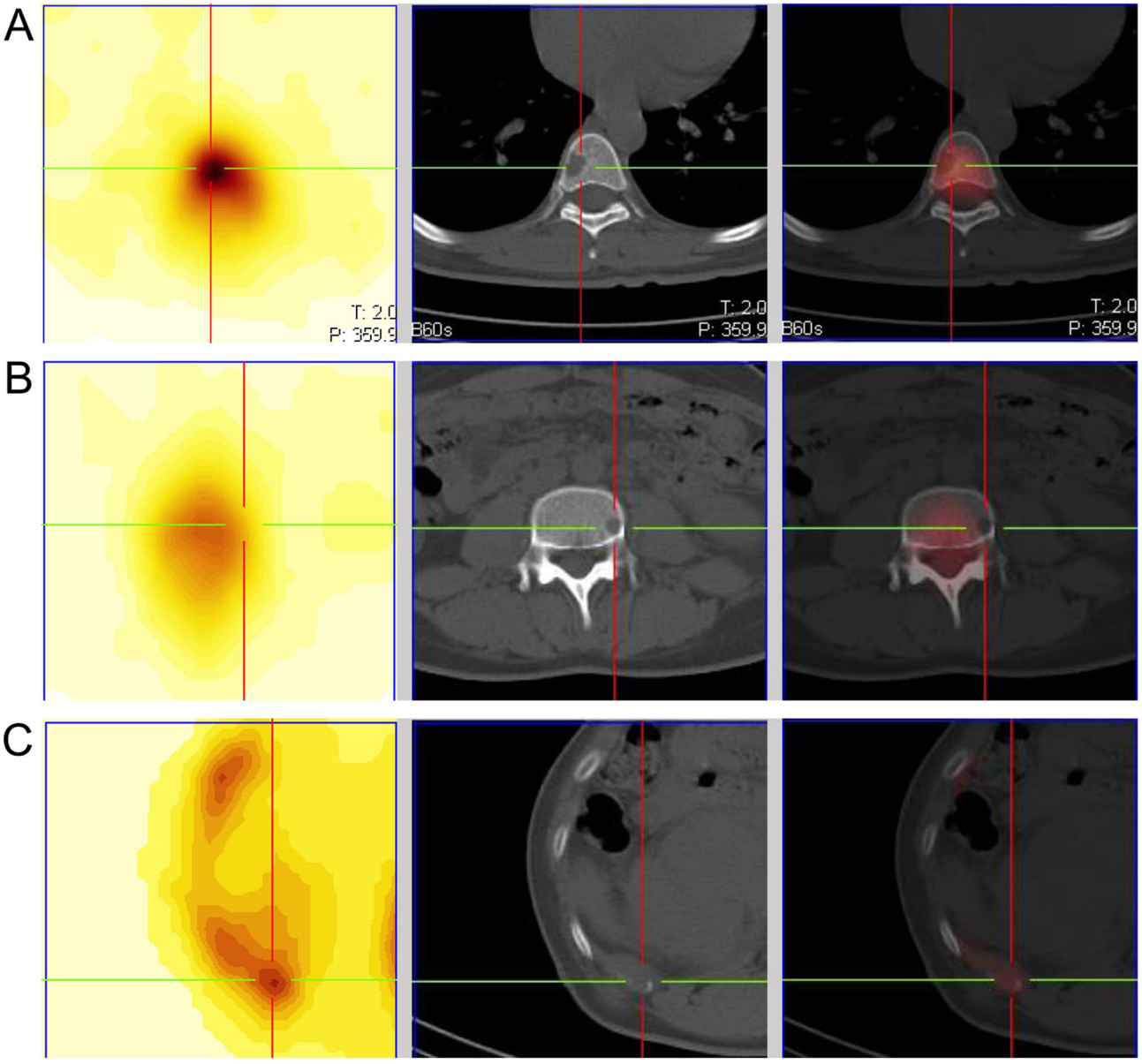

Fig. 3 SPECT/CT images showing the metastatic focis. (**A-C**) the metastatic focis in the 8th thoracic vertebrae (**A**), the 4th lumbar vertebrae (**B**), and the left 12th rib (**C**)

cells (Fig. 4E). Fluorescence in situ hybridization (FISH) confirmed the presence of TFE3 gene rearrangement (Fig. 4F). Consequently, the diagnosis was revised to TFE3-rearranged PEComa-like neoplasm. After definite diagnosis, the patient sought further medical evaluation at another hospital. She received everolimus 10 mg daily for 3 months, during which the disease remained relatively stable (imaging data from this period was unavailable). However, due to financial limitations, the patient discontinued everolimus therapy. Disease progression was observed after treatment cessation, and the patient died 7 months after discontinuation of everolimus therapy (27 months post-surgery).

Discussion

PEComa is a mesenchymal tumor characterized by the expression of melanocytic and smooth muscle markers, often associated with inactivation of TSC1 or TSC2 genes [2, 3]. Recently, a small subset of PEComa has been identified to possess TFE3 gene rearrangement [1, 2, 4–10]. There are various terms to designate this subset, including "Xp11 translocation PEComa", "melanotic Xp11 translocation renal cancer", "Xp11 neoplasm with melanocytic differentiation" and "melanotic Xp11 neoplasm" [1, 11–14]. In contrast to conventional PEComa, this subset often lacks smooth muscle differentiation and TSC1/TSC2 inactivation [1, 2]. Furthermore, its gene

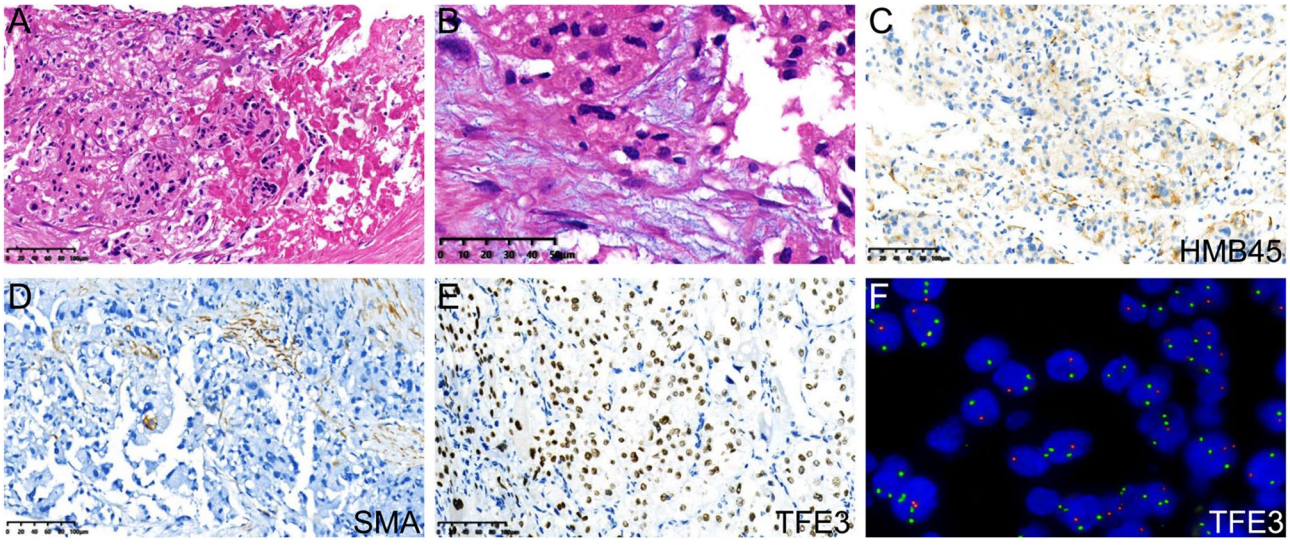

Fig. 4 Pathological and molecular characteristics of the tumor at recurrence. (**A, B**) Necrosis (**A**) and prominent mitotic figures (**B**) in focal areas. (**C-E**) Representative immunohistochemical staining of HMB45 (**C**), SMA (**D**), and TFE3 (**E**). (**F**) FISH showing the TFE3 break-apart signal

expression signature differs from that of conventional PEComa but resembles that of alveolar soft part sarcoma [1]. These findings indicate that it represents a distinct entity. Wang et al.. proposed the term "melanotic Xp11 neoplasm" to designate this entity [1], while Argani et al.. suggested the term "TFE3-rearranged PEComa-like neoplasm" [2].

The TFE3-rearranged PEComa-like neoplasm is a rare tumor, with fewer than 100 cases reported in the literature. It can occur at any age, with a median age of 28 to 38 years [1, 2, 9], and is more prevalent in women [1, 4, 9, 15, 16]. This tumor can affect the kidney as well as various extrarenal organs, including the bladder, ureter, prostate, uterus, lung, stomach, colon, pancreas, skin, and bone [1, 2, 10, 16]. Histologically, tumor cells typically exhibit epithelioid morphology characterized by abundant eosinophilic or clear cytoplasm and round nuclei with prominent nucleoli [1, 2]. The cells are mainly arranged in nests and acinar pattern, interspersed with a rich capillary network [1, 2]. Our case showed that a small number of tumor cells exhibited cord-like or trabecular pattern in the sclerotic area, expanding the morphological spectrum of TFE3-rearranged PEComa-like neoplasm. Melanin pigment may be absent or present in certain tumor cells [1]. However, it remains possible that some of the clinicopathological characteristics of melanotic TFE3-rearranged PEComa-like neoplasms may differ from those of their nonpigmented counterparts [2]. Immunohistochemically, tumor cells express melanocytic markers (HMB45, MelanA, etc.), TFE3 and Cathepsin K [1, 2, 7, 11, 12]. Smooth muscle markers, such as SMA, are often negative or sometimes focally positive [1, 2, 7, 11, 12]. Both epithelial markers such as pan-CK and nephrogenic markers such as PAX8 are consistently negative. Due to the rarity of TFE3-rearranged PEComa-like neoplasm, it is easily misdiagnosed when encountered. In our case, TFE3-rearranged PEComa-like neoplasm was not considered during the initial pathological examination. It was only after the rapid progression that TFE3 staining was performed on the specimen in the subsequent pathological evaluation, leading to the diagnosis of TFE3-rearranged PEComa-like neoplasm.

TFE3-rearranged PEComa-like neoplasm is also referred to as "melanotic Xp11 neoplasm". Notably, "melanotic Xp11 neoplasm" and "Xp11 translocation renal cell carcinoma" share similar nomenclature, potentially causing confusion. Both entities exhibit TFE3 gene rearrangement; however, the former is a mesenchymal tumor that does not express epithelial markers, while the latter is a nephrogenic tumor characterized by the expression of both epithelial markers (e.g., pan-CK) and nephrogenic markers (e.g., PAX8).

The TFE3-rearranged PEComa-like neoplasm shares many pathological characteristics with alveolar soft part sarcoma [1, 2, 9]. Both tumors exhibit comparable morphologies, presenting as solid nests or alveolar structures, and display a similar immunophenotype, being positive for TFE3 and Cathepsin K while negative for PAX8. Moreover, both harbor TFE3 gene rearrangement and portend poor prognosis. A distinguishing feature is that TFE3-rearranged PEComa-like neoplasm often expresses melanocytic markers, unlike alveolar soft part sarcoma, which typically lacks such expression [1, 2].

Compared to conventional PEComa, TFE3-rearranged PEComa-like neoplasm is more aggressive, with a 5-year overall survival rate of 47.6% for patients diagnosed with this entity [1, 17]. However, the inconsistency in the reporting potential prognostic factors may diminish

their utility for accurate prognostic prediction. Argani et al.. reported that tumors exceeding 50 mm, the presence of necrosis, and mitotic figures ≥ 2/10 HPF are associated with unfavorable outcomes [2]. Wang et al. reported that extrarenal involvement, infiltrative growth pattern, nuclear pleomorphism, mitotic figures ≥ 2/50 HPF, necrosis, and lymphovascular invasion are associated with poor prognoses [1]. Some cases may still progress even in the absence of aggressive features. Consequently, irrespective of their morphological characteristics, long-term follow-up is essential to ensure surveillance of disease evolution.

Currently, there is no established standard treatment for TFE3-rearranged PEComa-like neoplasm. Given its aggressive nature, radical surgery is recommended for affected patients. Since TFE3 can upregulate RagD expression, thereby activating the mTOR pathway [18], inhibiting this pathway may potentially provide therapeutic benefits for these patients. Purwar et al.. reported a case in which the patient received combination therapy with chemotherapy and the mTOR inhibitor everolimus, achieving a complete response within 6 months [19]. Zhang et al.. reported a case in which the patient was initially treated with the anti-VEGFR TKI apatinib but experienced disease progression after 15 months. Following this progression, the treatment was switched to the mTOR inhibitor everolimus, which alleviated her symptoms; however, the tumor progressed again after an additional 15 months [20]. In our case, the patient's condition remained stable during the treatment with everolimus. Notably, there have been reports of TFE3-rearranged PEComa-like neoplasms that demonstrate no response to mTOR inhibitors [21–23]. Whether adjusting the type or dosage of mTOR inhibitors can influence the outcome in TFE3-rearranged PEComa-like neoplasm requires further exploration.

Conclusion

TFE3-rearranged PEComa-like neoplasm is a more aggressive tumor compared to conventional PEComa. Therefore, routine TFE3 staining is recommended when evaluating potential cases of PEComa or PEComa-like neoplasm. In instances of positive TFE3 expression, FISH detection or gene sequencing may be utilized to analyze TFE3 gene rearrangement. The current case enhances our understanding of TFE3-rearranged PEComa-like neoplasm, especially its morphological spectrum and aggressive behavior, which are valuable for diagnosis and prognostic prediction. In the future, there is a need to establish a multicenter database for improving the classification and management of this rare tumor.

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Author contributions
ZJC and JC collected the data and wrote the original manuscript. LL, JJ, XCY and XWB reviewed the manuscript. MFC and GJD supervised and reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Southwest Hospital.

Competing interests
The authors declare no competing interests.

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