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Case report

Eosinophilic vacuolated tumor of the kidney can have distant metastasis: a histo-molecular case study

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Summary
Eosinophilic vacuolated tumor (EVT) is an emerging renal entity and further studies are required to characterize this neoplasm. EVT is considered generally indolent because metastasis or death from the disease has never been reported. Herein, we report the first case of EVT with mediastinal lymph node metastasis to validate its at least borderline behavior. Based on the morphological features, we additionally used a large panel of immunohistochemical antibodies and next-generation sequencing (NGS) to confirm the diagnosis of EVT and exclude other renal entities. This case report highlights the notion that EVT can exhibit mediastinal lymph node metastasis and patients with EVT need to be closely followed.

Key words: eosinophilic vacuolated tumor

Introduction

Eosinophilic vacuolated tumor (EVT) is an emerging renal entity recorded in the 5th edition of the WHO Classification. EVT is characterized by solid or nest growth of tumor cells with eosinophilic cytoplasm, prominent nucleoli, and variable cytoplasmic vacuoles. CK7 is often negative or very focal positive in tumor cells. Tumor cells are usually diffusely positive for CD117 expression. *TSC/mTOR* mutations are reported in this emerging entity and further studies are required to characterize this neoplasm. Accumulated evidence supports it as a novel entity because of its distinct morphology, consistent immunohistochemical profile, and frequent *TSC/mTOR* pathway mutations[1,2]. Metastasis or death from the disease has never been reported in patients with EVT. Therefore, EVT is considered generally indolent. Herein, we report the first case of EVT with mediastinal lymph node metastasis and validate its at least borderline behavior.

Case presentation

A 14-year-old male was admitted to the hospital with elevated blood pressure. Abdominal computed tomography (CT) revealed a mass in the right kidney. The patient underwent a radical nephrectomy. Grossly, the mass was brown solid with the largest size of 11.2 cm. Tumor cells exhibited mostly solid or nested and focally microcystic architecture embedded in hyalinized or myxoid stroma with large vessels (Figs. 1A

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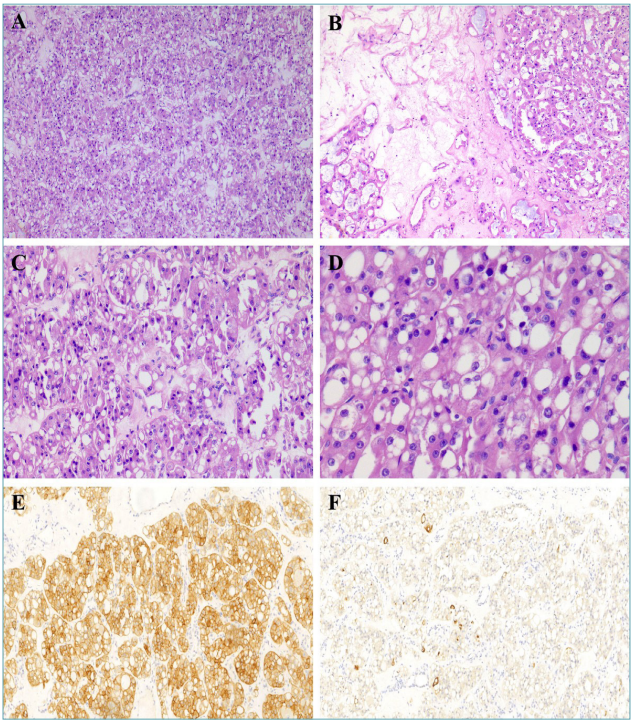

Figure 1. Tumor cells exhibited solid or nested architecture and were embedded in hyalinized or myxoid stroma (A and B). The tumor cells had eosinophilic cytoplasm, prominent nucleoli, and variable cytoplasmic vacuoles (C and D). Tumor cells diffusely expressed CD117 (E). CK7 expression was limited in the tumor cells (F).

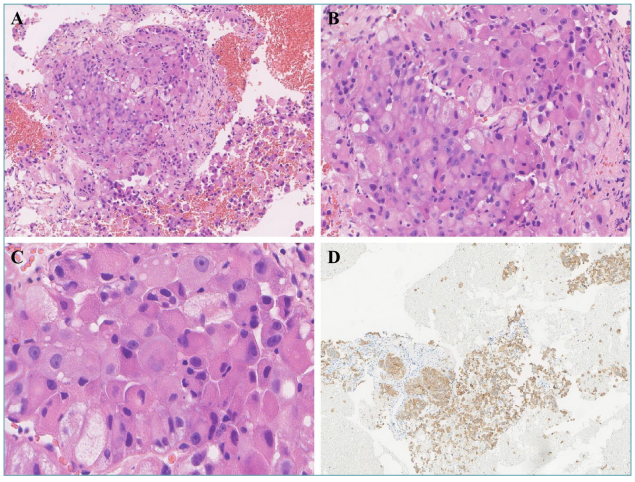

Figure 2. A mediastinal lymph node biopsy revealed eosinophilic tumor cells in the blood clots (A). The tumor cells had eosinophilic cytoplasm and prominent nucleoli. Vacuoles were observed in the tumor cells (B and C). The tumor cells were positive for CD117 (D).

and 1B). Papillary architecture were absent. The tumor cells showed eosinophilic cytoplasm, prominent nucleoli, and variable cytoplasmic vacuoles (Figs. 1C and 1D). Immunohistochemistry was performed on 4 µm-thick sections of formalin-fixed paraffin-embedded tissues. The tumor cells were diffusely immunopositive for PAX8, CD117 (Fig. 1E), SDHB, SMARCB1, and FH. Scattered CD10 membranous expression was observed in 10% of tumor cells. Scattered CK7 membranous expression (Fig. 1F) was observed in a few tumor cells. The tumor cells did not express vimentin, CA9, 2SC, CK20, TFE3, TFEB, ALK, melan A, or HMB45. The Ki-67 index was 5%.

Fifty-four months later, the patient came to hospital with chest symptoms. CT revealed enlarged mediastinal lymph nodes. Biopsy revealed eosinophilic cells in the blood clots (Fig. 2A). The tumor cells had eosinophilic cytoplasm and prominent nucleoli. Vacuoles were observed in cell nests (Figs. 2B and 2C). TTF-1, napsin A, CD68, and calretinin were all negative. Scattered CK7 and CK20 expression were positive in a few tumor cells. Diffuse expression of CD117 (Fig. 2D), PAX8, FH, and SDHB were observed. Qualified DNA extracted from two samples was sent to an NGS panel, including all exons and selected non-coding regions of 689 cancer-related genes. This panel includes common mutations in kidney and other cancers, such as *VHL*, *FH*, *SDHB*, and *ELOC*. NGS results revealed an insertion variant of uncertain significance in *mTOR* (exon30 c.4359_4379del p.H1454_L1460del) and a relatively low tumor mutation burden (TMB) (1.13 Muts/Mb) in the renal mass. Molecular results of mediastinal lymph node biopsy revealed the same variant in *mTOR* (exon30 c.4359_4379del p.H1454_L1460del) together with a likely pathogenic splice site variant in *NCOR* (exon43 c.6605+2T > A) and a low TMB (1.13 Muts/Mb). The patient was finally diagnosed with EVT and mediastinal lymph node metastasis.

Discussion

EVT was once named “high-grade oncocytic renal tumor” in a paper published in 2018 [3]. Subsequent studies demonstrated that somatic mutations in *TSC*/*mTOR* characterize a morphologically distinct renal entity with eosinophilic and vacuolated cytoplasm [4]. The name “eosinophilic vacuolated tumor” was proposed by The Genitourinary Pathology Society [5]. EVT usually exhibits solid and nest architecture with or without focal tubulocystic growth. Papillary architecture is not documented. The tumor cells have eosin-

ophilic and vacuolated cytoplasm and prominent nucleoli which correspond to WHO/ISUP grade 3. The tumor cells express renal markers and CD117. CK7 is usually negative or very focally expressed. Frequent *TSC/mTOR* pathway mutations are reported in this entity [1,2].So far, no aggressive behaviors have been documented and EVT is considered generally indolent. Herein, we report the first case of EVT with mediastinal lymph node metastasis and validate its at least borderline behavior.

EVT is an eosinophilic renal neoplasm characterized by *TSC/mTOR* mutations. Therefore, EVT needs to be differentiated from other eosinophilic renal entities or those with *TSC/mTOR* mutations. Actually, in the present case, EVT can be easily diagnosed based on this morphology. However, metastasis or death has never been reported in previous studies [1,2]. Therefore, it is challenging to diagnose a patient with EVT mediastinal lymph node metastasis. A large panel of immunohistochemical antibodies and NGS were used to exclude other renal entities. The tumor cells were diffusely immunopositive for PAX8. Therefore, a renal cell neoplasm was initially considered. Clear cell renal cell carcinoma (RCC) with eosinophilic cytoplasm is usually associated with higher grade and clinically more aggressive behavior. However, because of negative CA9 expression, absence of *VHL* mutation and the different morphology, clear cell renal cell carcinoma was not considered. Retained FH, SDHB, and SMARCB1 expression, negative 2SC expression, and the absence of these gene mutations could exclude FH-deficient RCC, SDH-deficient RCC, and SMARCB1-deficient renal medullary carcinoma. Negative TFE3, TFEB, ALK, and melanocytic markers helped exclude renal entities with gene rearrangements. Although tumor cells focally expressed CK20, microcystic architecture was observed in focal areas, and *mTOR* mutations were identified, eosinophilic solid and cystic RCC was not considered because granular basophilic cytoplasmic stippling were absent. The tumor cells exhibited prominent nucleoli. Therefore, low-grade oncocytic tumor and oncocytoma were excluded. Large pale and small eosinophilic tumor cells with wrinkled nuclei and perinuclear haloes were absent. Together with variable cytoplasmic vacuoles and *mTOR* mutation, classic or eosinophilic chromophobe RCC could be excluded. In conclusions, EVT can exhibit mediastinal lymph node metastasis. We propose that EVT should be considered as a borderline neoplasm and patients with EVT should be closely followed-up.

Data Sharing Statement

Data are available for bona fide researchers who request it from the authors.

Conflict of interest statement

The authors declare no conflict of interest

Ethical consideration

This study was approved by the Department of Pathology, Ruijin Hospital (Shanghai, China).

Patient consent statement: we have obtained written informed consent to publication of the patient's case details.

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