

## Case Report

# Premelanosome-negative inflammatory angiomyolipoma of liver with expression of cathepsin K and TFE3

Ke Sun<sup>1</sup>, Ming Zhao<sup>2</sup>, Hongtian Yao<sup>1</sup>, Lijun Wang<sup>1</sup>, Jianfeng Wei<sup>3</sup>

<sup>1</sup>Department of Pathology, <sup>3</sup>Department of Hepatobiliary Surgery, The First Affiliated Hospital, Zhengjiang University Medicine School, Hangzhou 310003, Zhejiang, P. R. China; <sup>2</sup>Department of Pathology, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang, P. R. China

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**Abstract:** We report the first case of inflammatory variant of hepatic angiomyolipoma (AML) with expression of transcription factor E3 (TFE3) protein but negativity for HMB45 and melan A in a 62-year-old female. Imaging studies revealed a tumor in the left lobe of liver, sized 5.8 cm in maximum diameter. Microscopically, the lesion was composed of large polygonal or epithelioid cells with copious eosinophilic granular cytoplasm. There was a very prominent stromal lymphoplasmacytic infiltrate. Immunohistochemically, the tumor cells showed very strong and diffuse positivity for smooth muscle actin, and cathepsin K, while S-100 protein, keratin, desmin, HMB45 and Melan-A are negative. However, there was multifocal and very convincing nuclear positivity for TFE3, thus confirms the diagnosis.

**Keywords:** Liver, angiomyolipoma, inflammatory, epithelioid tumor, TFE3, cathepsin K, differential diagnosis

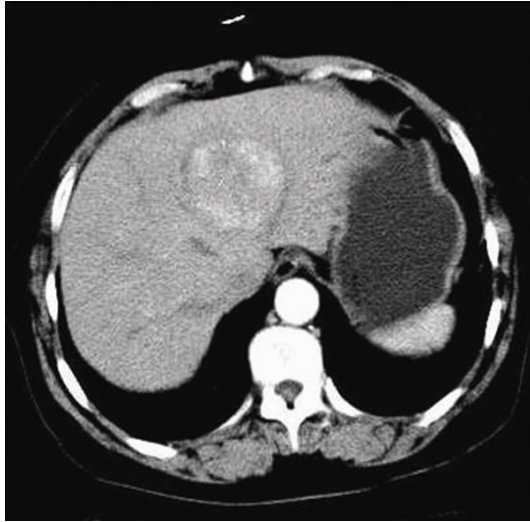
## Introduction

Originally believed to be a hamartomatous lesion, angiomyolipoma (AML) is currently defined as a benign mesenchymal tumor composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels. It is considered as a tumor of perivascular epithelioid cells (PEComa), and related lesions include clear cell "sugar" tumor, lymphangi-oleiomyomatosis, and clear cell myomelanotic tumor [1, 2]. Although most AMLs arise in the kidney, extrarenal AMLs are also described in various sites and among which the liver represents the second most frequent site of involvement, with approximate 200 cases had been reported in the English literature so far [2]. Depending on the variable proportion of the triphasic components, hepatic AML has a wide spectrum of morphologic and histologic appearances including lipomatous, myomatous, angiomatous, trabecular, epithelioid, inflammatory, and mixed pattern. Of these, inflammatory variant is the least common one with only 8 cases reported in the literature so far [3-6].

Transcription factor E3 (TFE3) is a member of the microphthalmia (MiT) transcription factor family, which includes MiTF, TFEB, TFEC and TFE3. Tumors of the MiT transcription factor family include conventional melanoma, alveolar soft part sarcoma, translocation-associated renal cell carcinomas, and clear cell sarcoma of the soft tissue [7]. Recently, several authors have described aberrant nuclear expression of TFE3 in a subset of PEComas [8]. In this report, we describe a case of hepatic inflammatory AML without HMB45 expression, but with TFE3 expression, to our knowledge, this kind of hepatic inflammatory AML has not been reported so far.

## Case presentation

The patient was a 62-year-old Chinese woman who was referred to our hospital for further evaluation of an incidentally found hepatic mass on abdominal ultrasonography during a health examination in a local clinic. Her past medical history was unremarkable with no known liver disease and she had no relevant clinical or family history of tuberous sclerosis. General physical exam was unremarkable.



**Figure 1.** Abdominal computed tomography showed a 5.8 × 5.2 cm circumscribed and hypervascular mass within the left liver lobe.



**Figure 2.** Macroscopic examination of resection specimen revealed a well-circumscribed 5.5 × 5 cm solid mass.

Chest radiographs and electrocardiogram were within normal limits. Her routine hemogram and blood biochemical analyses were within normal ranges. Hepatitis virus markers were negative. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) showed a 5.8 × 5.2 cm circumscribed and hypervascular mass within the left liver lobe (**Figure 1**). Both CT and MRI examinations showed no evidence of fat component in the tumor. A clinical diagnosis of hepatocellular adenoma (HCA) or focal nodular hyperplasia

(FNH) was made based on these image findings.

## Methods

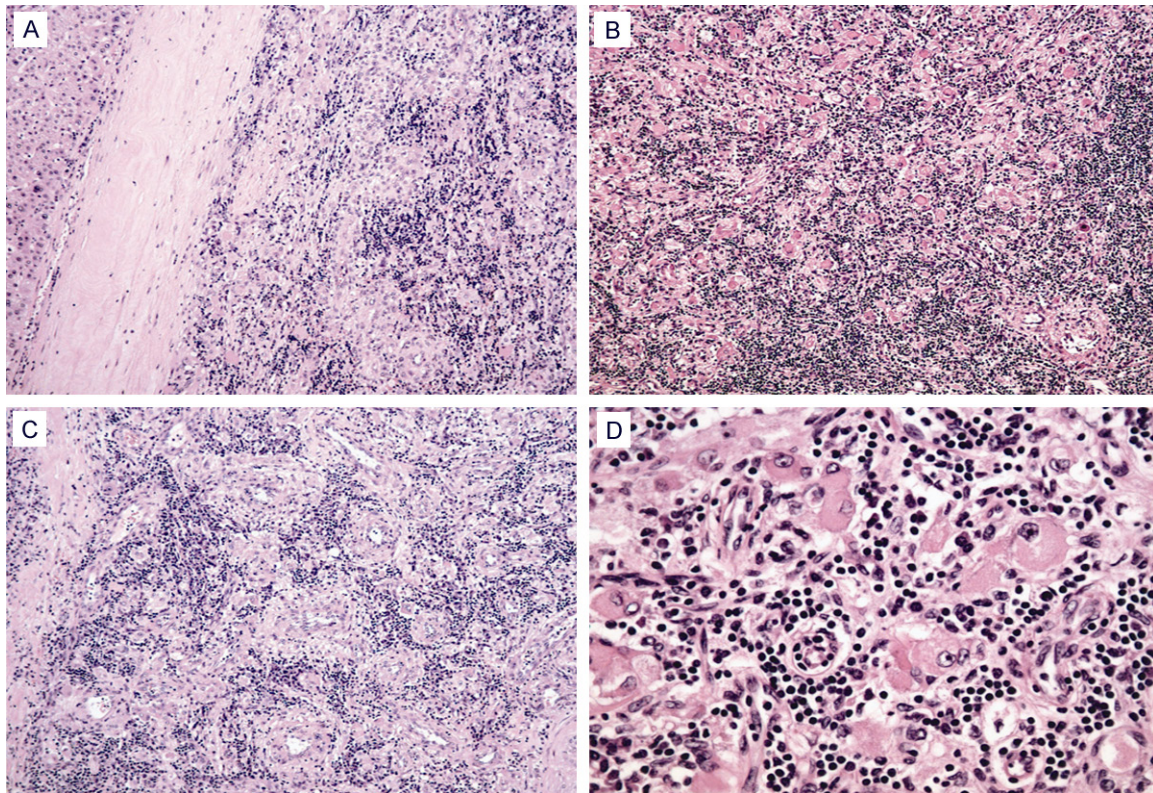
Tissues were fixed in 10% buffered formalin and embedded in paraffin blocks. Three-micrometer-thick sections were obtained and stained with hematoxylin and eosin for microscopic examination. Immunohistochemistry was performed on the 5-um-thick sections using the avidin-biotin complex method. The antibodies used in this study included the following (source, clone, dilution): HMB45 (Dako, HMB45, 1:60), melan A (Dako, A103, 1:80), smooth muscle actin (SMA) (Dako, 1A4, 1:400), Desmin (Dako, D33, 1:60), S-100 protein (Zhongshan, S1/61/69, 1:5000), CD68 (Zhongshan, KP1, 1:10000), CD34 (Dako, QBEND10, 1:200), hepatocyte paraffin-1 (HepPar-1) (Dako, OCH1E5, 1:200), CKpan (Changdao, AE1/AE3, 1:200), CD23 (Changdao, MHM6, 1:50), CD117 (Dako, C-KIT, 1:200), ALK (Dako, ALK1, 1:50), TFE3 (Zhongshan, MRQ37, 1:100), cathepsin K (Abcam, 3F9, 1:300), Ki-67 (Changdao, Ki-S5, 1:200). For detection of Epstein Barr Virus (EBV) in situ hybridization.

Bacterial artificial chromosome (BAC) clones were selected using the "CloneCentral human BAC Clone Locator" from EmpireGenomics (<http://www.empiregenomics.com/helixhq/clonecentral/search/human>). The BAC clones RP11-416B14 (182 kb) and RP11-107C19 (160 kb) located centromeric to the TFE3 gene were labeled with green 5-fluorescein dUTP. The BAC clones RP11-58H17 (200 kb) and RP11-352D11 (175 kb) located telomeric to TFE3 were labeled with red 5-ROX dUTP. The normal result is a combination (green and red) signal, Whereas TFE3 fusion results in a split signal.

## Pathologic findings

Biopsies of the hepatic mass showed epithelioid cells arranged concentrically around vascular channels, the tumor cells had abundant, clear, or partly granular cytoplasm, but the diagnosis remained difficult. A segmental resection of the left liver lobe was performed. Macroscopic examination of resection specimen revealed a well-circumscribed 5.5 × 5 cm solid mass with brown soft cut-surface, a clear fibrous capsule was found in the tumor (**Figure 2**). The background hepatic tissue was unre-





**Figure 3.** The lesion appeared to be well-circumscribed (A) and consisted of large polygonal or epithelioid cells with copious eosinophilic or somewhat paler granular cytoplasm (B), while the tumor cells had vesicular nuclei, in areas arranged concentrically around vascular channels (C). There was a very prominent stromal lymphoplasmacytic infiltrate (D).

markable. Microscopically, the lesion appeared to be well-circumscribed (**Figure 3A**) and consisted of large polygonal or epithelioid cells with copious eosinophilic or somewhat paler granular cytoplasm (**Figure 3B**), while the tumor cells had vesicular nuclei, in areas arranged concentrically around vascular channels (**Figure 3C**). The lesion exhibited a relatively abundant vascular component. There was a very prominent stromal lymphoplasmacytic infiltrate (**Figure 3D**). There was no evident adipocytic component and there no significant atypia or mitosis was evident. The patient recovered well and with no evidence of recurrence or metastasis 22 months after surgery.

Immunostains show very strong and diffuse positivity for SMA (**Figure 4A, 4B**), and moderately immunoreactive for Cathepsin K (**Figure 4C**), while S-100 protein, Ckpan, Desmin, HMB45 (**Figure 4D**), melan A, CD68, CD117, CD23, CD34, ALK and HepPar-1 are negative. However, importantly, there is multifocal and very convincing and moderately nuclear positiv-

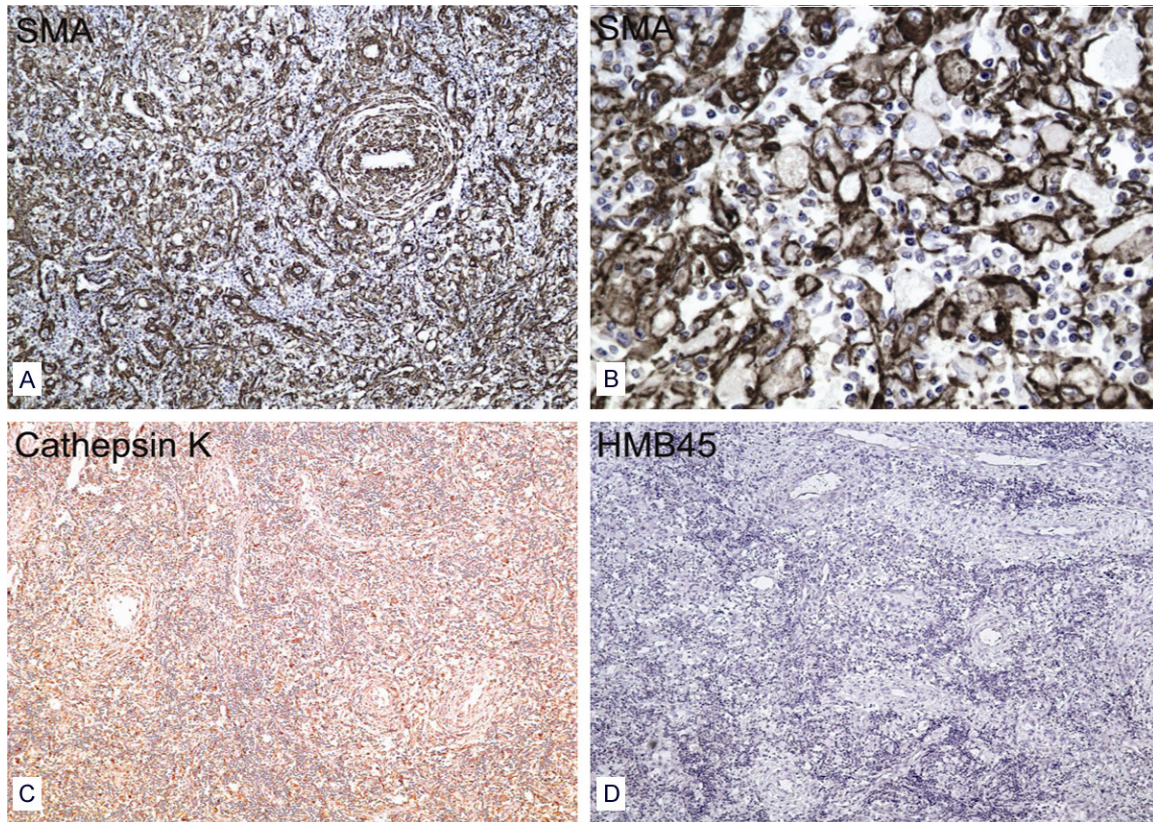
ity for TFE3. Ki-67 proliferative index of the tumor cells was approximately 5%.

The current case exhibited no evidence of TFE3 gene fusion (**Figure 5**).

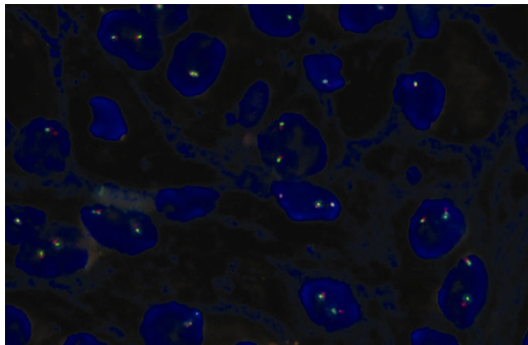
## Discussion

The inflammatory variant of hepatic AML is exceedingly rare, to date, only 8 cases have been reported in English literature [3-6]. Patients' ages ranged from 21 to 63 years, with a female predominance. No patients had evidence of tuberous sclerosis. Five of the lesions originated in the left live lobe. All tumors were well circumscribed but not encapsulated. Histological examination showed a predominance of inflammatory pattern comprising more than 50% of the lesion and the mature adipocytes were scatteredly distributed no more than 5% of lesion cells in all cases. However, we found that our case had several morphologic features different from reported cases. This current case was presence of the





**Figure 4.** Immunostains show very strong and diffuse positivity for SMA (A, B), and moderately immunoreactive for Cathepsin K (C), and immunonegative for HMB45 (D).



**Figure 5.** FISH examination demonstrated no evidence of TFE3 gene fusion.

capsule but there was no evident adipocytic component on HE sections in all sections in the lesion and there were no areas of classical AML. These unusual histological features led us to difficulty in making a final histological diagnosis. In our case, diffuse positivity with smooth muscle actin and multifocal nuclear positivity with TFE3 were demonstrated; however, HMB45 and Melan-A were negative. Similar findings were reported by Prieto-Granada

et al [9], they described a small-bowel PEComa expressing muscle markers and TFE3 protein, however, HMB-45 and Melan-A were negative. Kawauchi S et al [10] also analyzed three genuine PEComas absence of staining for HMB45 and Melan-A by comparative genomic hybridization and detected similar chromosomal imbalances in two of the three PEComas, that were very similar to those of the PEComas family reported by Pan et al. Pusiol T et al [11] reported a case of HMB-45 negative clear cell perivascular epithelioid cell tumor of the skin. On the other hand, Argani et al [12] reported TFE3 gene fusion-positive PEComas were probably negative for muscle makers. In general, PEComa family tumors have been characterized by positive immunoreactivity of the melanocytic markers HMB45, Melan-A and MiTF and muscle markers, however, it is still unclear whether all the PEComa family tumors have constant immunoreactivity of the antibody. The important thing is to consider PEComas in the differential diagnosis of epithelioid tumors even if there is no expression of melanocytic markers or muscle markers. Our case also

expression cathepsin K protein by IHC. Recently, Cathepsin K had been considered a powerful marker for the diagnosis of PEComas [13]. However, all reported 8 cases were positive for HMB45, and none of these cases examined TFE3 protein and cathepsin K by IHC. Based on the morphologic features, the smooth muscle immunophenotype, and the positivity with TFE3 and cathepsin K, this tumor was characterized as inflammatory AML.

Recently, aberrant immunoreactivity for TFE3 has been reported in PEComas. Some studies in the literature reported TFE3 immunoreactivity in a majority of PEComas [14]. But Argani et al [12] found the majority of PEComas to be negative for TFE3 by IHC, they also showed that strong (3+) TFE3 immunoreactivity did correlate with TFE3 gene alterations, in contrast, if there is no TFE3 gene fusion, the staining pattern has been described as moderate or weak or completely absent. Although, there are distinctive features and immunohistochemical findings present in these cases harboring TFE3 gene fusions, include a tendency to young age, the absence of association with tuberous sclerosis, predominant alveolar architecture and epithelioid cytology, and negative expression for smooth muscle markers. Recently, Rao et al [13] also suggested that the majority of common PEComas were negative for TFE3 protein by IHC. Our case exhibited multifocal and moderate positive TFE3 immunoreactivity and had no evidence TFE3 gene alteration. The mechanism of TFE3 nuclear expression in PEComas do not harboring TFE3 gene fusions remains unexplained. Rao et al [13] suggested it may be because of other events such as mutational activation, transcriptional deregulation and translational control deregulation.

Inflammatory AML should be distinguished from other hepatic tumors especially those with a prominent inflammatory cell infiltration in the background, include inflammatory pseudotumor (IPT), inflammatory myofibroblastic tumor (IMT) and follicular dendritic cell (FDC) tumor. Interestingly, in a recently published article, Agaimy A et al [6] described a inflammatory AML of the liver showing hybrid features of IgG4-related pseudotumor. Especially, without the scattered fatty vacuoles and immunohistochemistry for HMB45 and melan-A as the present case, the lesion would have been classified as IPT or IMT or FDC tumor. A panel of antibodies would be helpful for the correct diagnosis.

In summary, we reported an unusual case of hepatic inflammatory AML showing negative for HMB45 and Melan-A, and it was multifocal positive for TFE3 by IHC but had no TFE3 gene alteration by FISH.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Jianfeng Wei, Department of Hepatobiliary Surgery, The First Affiliated Hospital, Zhengjiang University Medicine School, 79 Qingchun Road, Hangzhou 310003, Zhejiang, P. R. China. E-mail: weij@zju.edu.cn

## References

- [1] Armah HB and Parwani AV. Perivascular epithelioid cell tumor. Arch Pathol Lab Med 2009; 133: 648-654.
- [2] Folpe AL and Kwiatkowski DJ. Perivascular epithelioid cell neoplasms: pathology and pathogenesis. Hum Pathol 2010; 41: 1-15.
- [3] Kojima M, Nakamura S, Ohno Y, Sugihara S, Sakata N and Masawa N. Hepatic angiomyolipoma resembling an inflammatory pseudotumor of the liver. A case report. Pathol Res Pract 2004; 200: 713-716.
- [4] Shi H, Cao D, Wei L, Sun L and Guo A. Inflammatory angiomyolipomas of the liver: a clinicopathologic and immunohistochemical analysis of 5 cases. Ann Diagn Pathol 2010; 14: 240-246.
- [5] Liu Y, Wang J, Lin XY, Xu HT, Qiu XS and Wang EH. Inflammatory angiomyolipoma of the liver: a rare hepatic tumor. Diagn Pathol 2012; 7: 122.
- [6] Agaimy A and Markl B. Inflammatory angiomyolipoma of the liver: an unusual case suggesting relationship to IgG4-related pseudotumor. Int J Clin Exp Pathol 2013; 6: 771-779.
- [7] Argani P, Lal P, Hutchinson B, Lui MY, Reuter VE and Ladanyi M. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am J Surg Pathol 2003; 27: 750-761.
- [8] Kuroda N, Goda M, Kazakov DV, Hes O, Michal M and Lee GH. Perivascular epithelioid cell tumor of the nasal cavity with TFE3 expression. Pathol Int 2009; 59: 769-770.

## Inflammatory angiomyolipoma of liver

- [9] Prieto-Granada C, Rosenblum F and Mueller JD. A case of HMB-45 negative, malignant perivascular epithelioid neoplasm of the small bowel [abstract]. *Arch Pathol Lab Med* 2011; 135: 1182.
- [10] Kawauchi S, Nawata H, Yamagata Y, Yaegashi H, Fukunaga M, Moriya T, Furuya T, Sugino N and Sasaki K. Chromosomal imbalances detected by comparative genomic hybridization provide evidence that HMB-45-negative uterine angiomyolipomas belong to the PEComa family. *Histopathology* 2010; 56: 974-977.
- [11] Pusiol T, Morichetti D, Zorzi MG and Dario S. HMB-45 negative clear cell perivascular epithelioid cell tumor of the skin. *Acta Dermatovenerol Croat* 2012; 20: 27-29.
- [12] Argani P, Aulmann S, Illei PB, Netto GJ, Ro J, Cho HY, Dogan S, Ladanyi M, Martignoni G, Goldblum JR and Weiss SW. A distinctive subset of PEComas harbors TFE3 gene fusions. *Am J Surg Pathol* 2010; 34: 1395-1406.
- [13] Rao Q, Cheng L, Xia QY, Liu B, Li L, Shi QL, Shi SS, Yu B, Zhang RS, Ma HH, Lu ZF, Tu P and Zhou XJ. Cathepsin K expression in a wide spectrum of perivascular epithelioid cell neoplasms (PEComas): a clinicopathological study emphasizing extrarenal PEComas. *Histopathology* 2013; 62: 642-650.
- [14] Francis F and Nonaka D. A study of MiTF/TFE transcription factors and melanocytic differentiation markers in angiomyolipoma [Abstract]. *Mod Pathol* 2009; 22: 13A-14A.