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Original Article

Fluorescence *in situ* hybridization for *WWTR1-CAMTA1* has higher sensitivity and specificity for epithelioid hemangioendothelioma diagnosis

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Abstract: Epithelioid hemangioendothelioma (EHE) is a rare medium-to-low-grade malignant vascular tumor characterized by vascular differentiation along with specific morphological and genetic alterations. Approximately 90% and 5% of EHE cases are associated with the *WWTR1-CAMTA1* and *YAP1/TFE3* fusion gene, respectively. Therefore, nuclear CAMTA1 protein expression is considered to be an effective marker for EHE diagnosis. However, the specificity and reliability of this approach have recently been put into question. The purpose of this study was to compare the detection of CAMTA1 expression in cases of EHE and histologic mimics using fluorescence *in situ* hybridization (FISH) and conventional protein immunohistochemistry via hematoxylin and eosin staining. Fifteen EHE and 37 histologic mimic samples were immunohistochemically stained with polyclonal anti-CAMTA1 antibody to evaluate the nuclear protein expression level of CAMTA1. In addition, 15 EHE samples and 10 vascular tumor samples were subjected to FISH to detect the *WWTR1-CAMTA1* fusion gene. Histologically, EHE typically showed a mucous hyaline or cartilaginous stroma, often forming a primitive vascular lumen, and expressed vascular endothelial markers. Twelve of the 15 EHE samples showed positive nuclear CAMTA1 expression with immunohistochemistry, whereas six of the 37 histologic mimics showed positive nuclear expression. FISH detected a red-green signal fusion in 14 of the 15 cases of EHE, but in none of the 10 vascular tumors. These results indicate that CAMTA1 is an effective and useful EHE marker, but that FISH fusion gene detection has better diagnostic value and clinical significance.

Keywords: CAMTA1, epithelioid hemangioendothelioma, FISH, immunohistochemistry

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare angiogenic tumor that forms between the hemangioma and angiosarcoma, originating from vascular endothelial or pre-endothelial cells. EHE was first discovered in the lung by Dail et al. in 1975, which was named intravascular bronchiolar alveolar tumor (IVBAT) [1]. Given that EHE is a malignant vascular tumor originating from endothelial cells that express endothelial-related factors [2-4], EHE became widely recognized as an independent pathological type in 1986. However, in the 2013 World Health Organization classification of bone and soft tissue tumors, EHE was classified as a medium and low-grade malignant vascular tumor with metastatic potential [5]. The prevalence of EHE is estimated at less than one per million individuals [6] and can occur at any age, although it is mostly seen in adults, especially in young and middle-aged women, and is rare in infants and young children. EHE can also occur at any location, but commonly develops in the superficial and deep soft tissues of the extremities, the liver, and the lung, and it is characterized by solitary or multiple masses. EHE can also occur in the anterior mediastinum, brain, oral cavity, spine, pleura, and meninges, and multiple organs can be involved simultaneously [6, 7]. Approximately half to two-thirds of all tumors are closely related to smaller veins, although very few originate directly from the small veins or arteries. Since the typical manifestation includes intracavitary masses, EHE is also referred to as a central vascular tumor. The

Table 1. Clinicopathologic features of the 15 cases of epithelioid hemangioendothelioma

Case	Age/Sex	Site	Size (cm)	IHC					FISH	Follow-up (mo)
				CAMTA1	CD31	CD34	ERG	FLI-1		
1	49/M	Humerus	-	-	+	+	+	+	+	AWD (17)
2	49/F	Liver	-	-	+	+	+	+	+	NED (10)
3	56/F	Liver	2.0	+	+	+	+	+	+	NED (9)
4	34/M	Groin	0.4	+	+	+	+	+	+	AWD (9)
5	61/F	Neck	-	+	+	+	+	+	+	NA
6	57/F	Lung	-	+	+	+	+	+	+	DOD (72)
7	56/F	Axilla	2.0	+	+	+	+	+	+	NED (71)
8	47/F	Intestine	0.5	+	+	+	+	+	+	AWD (74)
9	70/M	Foot	2.2	-	+	+	+	+	-	NA
10	64/M	Ilium	2.0	+	+	+	+	+	+	NA
11	38/F	Liver	-	+	+	+	+	+	+	NA
12	47/F	Lung	2.0	+	+	+	+	+	+	NED (33)
13	60/M	Lung	6.5	+	+	+	+	+	+	NA
14	53/M	Arm	2.5	+	+	+	+	+	+	NED (9)
15	63/M	Liver	3.0	+	+	+	+	+	+	AWD (12)

NA, not available; NED, no evidence of disease; DOD, death of disease; AWD, alive with disease; IHC, immunohistochemistry; FISH, fluorescence *in suit* hybridization.

diagnosis of EHE mainly relies on typical histological features and immunohistochemical markers such as CD31, CD34, FLI-1, and ERG. In general, most cases of EHE can be diagnosed, with these conventional methods; however, when only small biopsy specimens are available, or there is a distinct lack of endothelial differentiation, differential diagnosis is difficult, and EHE can be misdiagnosed with other types of vascular tumors.

Approximately 90% of EHE cases harbor a unique chromosomal translocation, t(1;3)(p36.23;q25.1), which results in the fusion of the transcription regulator 1 (*WWTR1*) gene and calmodulin-binding transcription activator 1 (*CAMTA1*) gene, within the 1p36 in the WW domain of 3q25 [8-10]. CAMTA1 expression is usually limited to the brain; however, with the fusion, *CAMTA1* is placed under the control of the *WWTR1* promoter, resulting in its overexpression at the tumor site. By contrast, WWTR1 protein is expressed in many different cell types [11]. Therefore, CAMTA1 is a more useful marker for diagnostic immunohistochemistry (IHC) outside of the brain. To date, it is generally widely accepted that CAMTA1 is a specific marker of EHE, and CAMTA1 IHC is typically used for clinical diagnosis; however, some reports suggest that CAMTA1 can also be expressed in histological mimics of EHE, thereby putting into question its specificity [12].

To clarify this controversy and determine the most appropriate method of EHE differential diagnosis, we used both IHC and fluorescence *in situ* hybridization (FISH) to investigate the expression of CAMTA1 at the protein and molecular levels in samples confirmed as EHE or its histological mimics.

Materials and methods

Patients and samples

Fifteen formalin-fixed paraffin-embedded (FFPE) EHE tissue samples were retrieved from the archives of the Department of Pathology, the First Affiliated Hospital of Bengbu Medical College and the Department of Pathology of Yijishan Hospital of Wannan Medical College that had been collected from 2012 to 2018. The male to female ratio of the 15 EHE patients in this group was 7:8. The patients' age ranged from 34 to 70 years, with a median age of 56 years. Of the 15 cases, four occurred in the liver, three in the lung, two in the bone (one each in the humerus and ilium), and one case each in the small intestine, right neck, left axilla, right upper limb, left groin, and left foot. Ten of the specimens were obtained from surgical resection, and the other five were puncture specimens (**Table 1**). For comparison, we included 37 samples of histologic mimics, including 15 cases of melanoma, eight cases

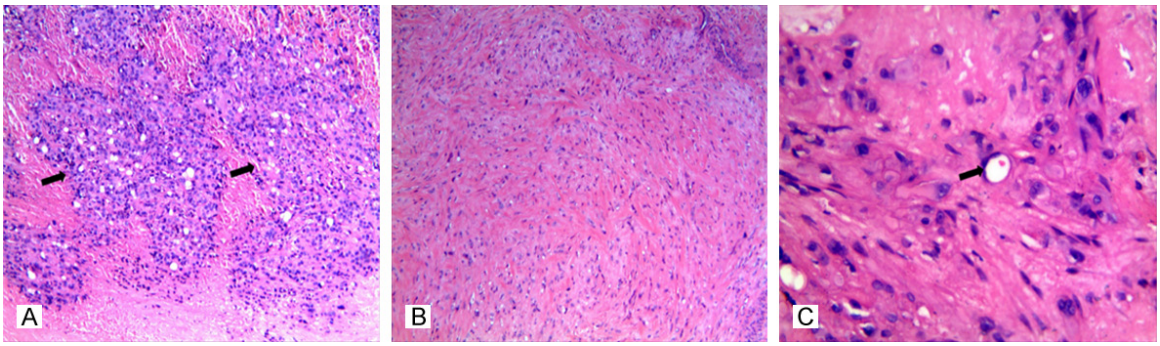

Figure 1. Histological characteristics of epithelioid hemangioendothelioma. A. The tumor cells are arranged in a cord-like structure with many intracellular vacuoles (arrow indicates the lesion area; magnification 100×). B. The background of the tumor tissue is a myxoid matrix, and some of the tumor cells are arranged in strips (magnification 100×). C. Intracellular lumen, representing the formation of the primitive vascular lumen (arrow indicates the intracellular lumen; magnification 400×).

of malignant mesothelioma, six cases of epithelioid sarcoma, five cases of epithelioid angiosarcoma, two cases of pseudomyogenic angioendothelioma and one case of epithelioid hemangioma (**Table 1**). All cases were reviewed, and the diagnosis was confirmed by two experienced doctors with advanced professional titles.

Five of the 15 patients with EHE were lost to follow-up. Among the 10 patients followed up, four patients survived with the tumor, five survived without the tumor, and one died from EHE progression. The follow-up time was 9-74 months, and the median follow-up time was 14.5 months (**Table 1**).

IHC

IHC was performed on 4 μm thick FFPE tissue sections that were incubated with polyclonal anti-CAMTA1 antibody (1:50, ThermoFisher) overnight at 4°C after pressure-boiling antigen retrieval in citrate buffer (pH 6). The labeled polymer secondary antibody was used to elicit an immune reaction. DAB was used for color development, followed by hematoxylin for nuclear staining. CAMTA1 expression was judged as positive if more than 5% of the cells showed noticeable nuclear staining, regardless of the cytoplasm expression pattern [13].

FISH

The *WWTR1-CAMTA1* fusion probe was used for interphase FISH, including rhodamine-conjugated in the distal region of WWTR1 that emits red fluorescence and fluorescein isothiocyanate conjugated at the proximal region of the CAMTA1 gene that emits green fluorescence. The slices (4 μM) were dewaxed with xylene, incubated at 56°C for 16 h and dehydrated with ethanol. All tissue slices were boiled in the pretreated solution for 30 min and then digested with protease K for 10 min according to the manufacturer's instructions. After a second dehydration step, the probe was applied to the slice, and the covered slide was sealed with a rubber adhesive, thermally denatured and left to hybridize at 37°C for 16 h. All tissue slices were then restained with DAPI in the installation medium and observed under a fluorescence microscope. Negative controls were used in each case. When at least 10 (20%) of the 50 counted tumor cells showed (yellow) fusion signals, the case was interpreted as positive for the fusion gene [14].

Statistical analysis

Data were compared based on cross-tables and the χ^2 test using SPSS 21.0 software.

Results

Histological characteristics

The surgically removed specimens were solid hoary and gray red nodules with a maximum diameter of 0.5-6.5 cm (**Table 1**). All EHE tumors were mainly composed of epithelioid cells, with some containing spindle cells arranged in cords (**Figure 1A**), clusters, or sheets, and distributed in a mucilaginous hyaline or mucilaginous chondroid matrix (**Figure 1B**). The tumor cells showed abundant light eosinophilic

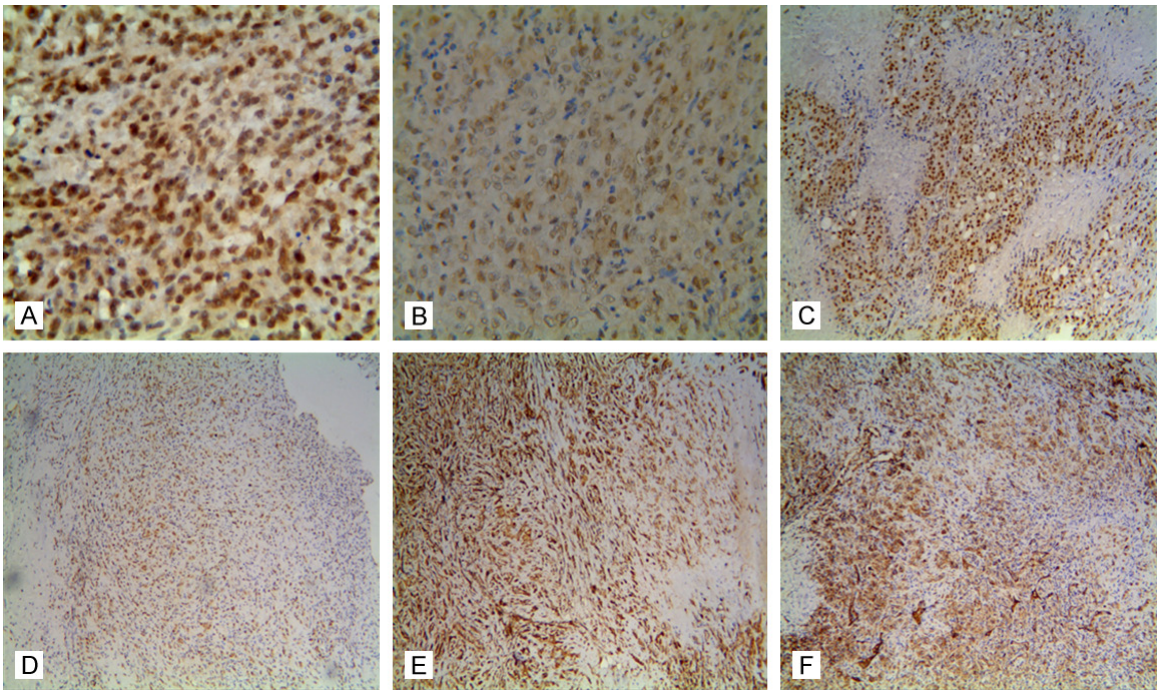

Figure 2. Expression of CAMTA1 in epithelioid hemangioendothelioma (EHE) and its histologic mimics, and expression of other immune markers in EHE. A. Positive nuclear expression of CAMTA1 in EHE (magnification 400×). B. Positive nuclear expression of CAMTA1 in an angiogenic tumor, epithelioid angiosarcoma (magnification 400×). C. Positive expression of ERG in EHE (magnification 100×). D. Positive expression of FLI-1 in EHE (magnification, 100×). E. Positive expression of CD31 in EHE (magnification 100×). F. Positive expression of CD34 in EHE (magnification 100×).

cytoplasm and oval vesicular nuclei, with evident small nucleoli, accompanied by calcification, ossification, and necrosis. Clear vascular channel formation was absent, and many cells presented as cytoplasmic vacuoles forming intracytoplasmic cavities, usually containing single red blood cells that are considered to represent a state of primitive angiogenesis and differentiation (**Figure 1C**), which is a typical characteristic of EHE. In addition, approximately half of the EHE samples were associated with vessels of medium or large size. According to the proposed risk stratification [15], three of the 15 EHE cases were classified as high risk (mitotic activity > 3/50 high-power fields or tumor size > 3 cm, not related to anatomical site, cytological atypia and spindle or necrotic tumor cells). However, the utility of this risk stratification for liver, lung, bone, and multifocal lesions remains unclear [9].

IHC findings

Positive nuclear expression of CAMTA1 was observed in 12 of the 15 EHE specimens (**Figure 2A**) and only six of the 37 histologic mimics (including three epithelial angiosarcomas, two epithelial sarcomas, and one epithelial hemangioma) (**Figure 2B**). The expression patterns of other markers (CD31, CD34, ERG, FLI-1) in the EHE (**Figure 2C-F**) and the histologic mimics are summarized in **Table 2**. CD34 was positively expressed in most of the vascular tumors, whereas CD31, ERG, and FLI-1 were more specific for vascular tumors. All cases of EHE expressed the vascular endothelial markers, but some reports have also indicated a positive expression of epithelial markers [4, 16, 17].

FISH findings

Fourteen of the 15 EHE cases subjected to FISH showed the red-green signal indicating presence the *WWTR1-CAMTA1* fusion gene (**Figure 3A-N**), whereas none of the 10 control vascular tumors showed signal fusion (**Figure 3O**).

Comparison of FISH and IHC

The results of IHC and FISH were in general agreement (kappa = 0.444). Although the positive rate of FISH was higher than that of IHC

Table 2. Summary of immunohistochemistry staining results in epithelioid hemangioendothelioma and its histologic mimics

Tumor Type	Total Cases	CAMTA1 Positive	CD31 Positive	CD34 Positive	FLI-1 Positive	ERG Positive
Epithelioid hemangioendothelioma	15	12	15	15	15	15
Epithelioid hemangioma	1	1	1	1	1	1
Epithelioid angiosarcoma	5	3	4	2	4	5
Epithelioid sarcoma	6	2	2	1	2	1
Pseudomyogenic hemangioendothelioma	2	0	1	0	2	2
Malignant melanoma	15	0	3	7	4	2
Malignant mesothelioma	8	0	2	2	0	0

(93.3% vs 80%), the difference was not statistically significant. The sensitivity and specificity of IHC was 85.7% and 100%, respectively, whereas the sensitivity and specificity of FISH were both 100% (**Table 3**).

Discussion

Approximately 90% of EHE tumors harbor the *WWTR1-CAMTA1* fusion gene, caused by the t(1;3) translocation, which is considered to be a pathogenic event in EHE tumors, resulting in chimeric transcription factors that initiate a new transcription program in cells with endothelial properties [10]. *WWTR1* encodes a transcriptional coactivator that is involved in the differentiation of mesenchymal stem cells, which is usually highly expressed in endothelial cells, whereas *CAMTA1* encodes a factor expressed in the brain and spinal cord [10, 18]. The region of *CAMTA1* located on chromosome 1p36 is often deleted in various malignant tumors, including neuroblastoma, glioma, colorectal cancer, and pheochromocytoma. Notably, *CAMTA1* has been proposed to function as a tumor suppressor gene [19, 20]. Driven by the promoter region of *WWTR1*, the *WWTR1-CAMTA1* fusion leads to overexpression of the C-terminus of *CAMTA1*. To date, this fusion gene has not been identified in other tumors and appears to be unique to EHE [9, 10]. Furthermore, the *YAP1-TFE3* fusion gene was found in about 5% of EHE cases, and the tumor cells rearranged with *YAP1/TFE3* show abundant eosinophilic cytoplasm, can form proper vascular channels, and diffuse expression of TFE3 can be detected by IHC staining [21].

Since the *WWTR1-CAMTA1* fusion gene was first identified in EHE, it has been widely accepted that overexpression of CAMTA1 caused by the fusion gene can be a useful marker in the pathological diagnosis of EHE by IHC [13, 22]. However, the nuclear expression of CAMTA1 protein reportedly unreliably discriminates EHE from its histologic mimics [12]. To resolve this issue, we used IHC to detect CAMTA1 expression 15 EHE and 37 mimic histologic tissues and further used FISH to detect the *WWTR1-CAMTA1* fusion in 15 EHE and 10 vascular tumors. We detected the positive nuclear expression of CAMTA1 in 80% (12/15) of the EHE samples with IHC, which is consistent with previous studies; however, positive CAMTA1 staining was also found in some other tumors with similar histologic characteristics. Although the expression range and staining intensity differed, the positive nuclear expression was nevertheless clear, which may indicate potential cross reactivity between the CAMTA1 polyclonal antibody and other antigens, or inconsistency between CAMTA1 antibodies of different reagent companies. Moreover, the lack of specificity suggests that the conventional IHC methods for CAMTA1 detection are not appropriately standardized, such as different repair conditions, or that the current commercial polyclonal anti-CAMTA1 antibodies may only be suitable for scientific research and are not adequate for clinical diagnosis. Among the 15 cases of EHE detected by FISH, 14 cases showed the red-green signal indicating the presence of the fusion gene, whereas none of the 10 vascular tumors showed the fusion signal.

Thus, our study demonstrates that CAMTA1 IHC detection can be used to diagnose EHE, but that FISH is a more sensitive and specific approach.

The current diagnosis of EHE is based on unique histological, immunohistochemical and molecular features, especially in small biopsy

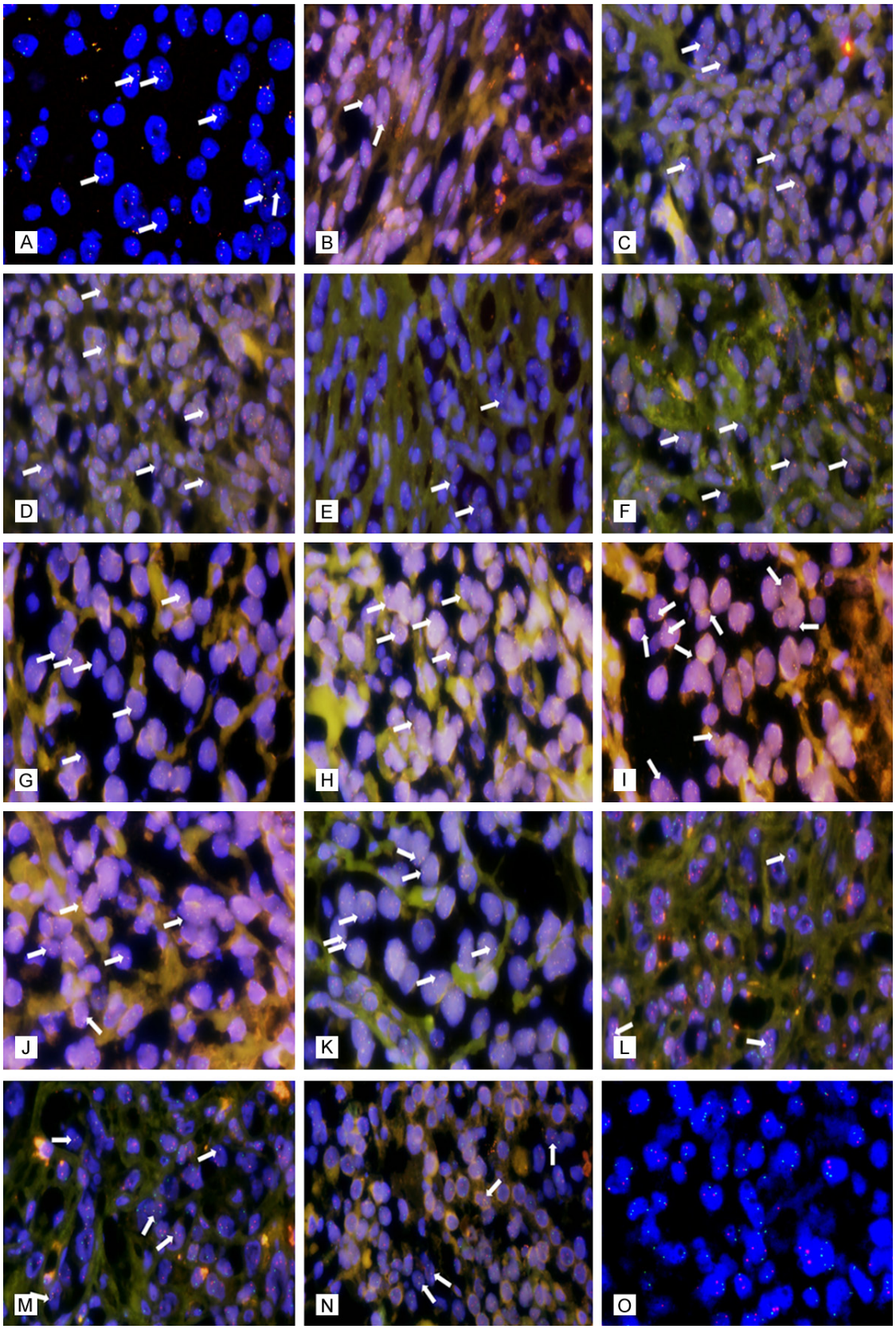

Figure 3. Expression of the *WWTR1/CAMTA1* fusion gene by fluorescence *in situ* hybridization. (A-N) Red-green fusion signal detected in an epithelioid hemangioendothelioma sample (from A-N are the FISH results of each case, and the arrows indicate the red-green fusion signal region); (O) No red-green fusion signal detected in an epithelioid angiosarcoma sample.

Table 3. Comparative analysis of Immunohistochemistry results and FISH results

Test method	Sensitivity	Specificity	P	Kappa
IHC	85.7%	100%	> 0.05	0.444
FISH	100%	100%		

specimens, where IHC or FISH is usually required to detect endothelial differentiation or gene rearrangements to exclude tissue mimicry. EHE includes a wide range of differential diagnoses, including epithelioid angiosarcoma, epithelioid hemangioma, epithelioid sarcoma, pseudomyogenic angioendothelioma, malignant mesothelioma, melanoma, and soft tissue metastatic carcinoma. For mesenchymal tumors, such as epithelioid sarcoma, malignant mesothelioma, and malignant melanoma, traditional endothelial markers are effective for a differential diagnosis of EHE, such as CD31, CD34, ERG, FLI-1, and CAMTA1. However, for angiogenic tumors with histology and morphology similar to EHE but different degrees of malignancy, such as epithelioid hemangioma, epithelioid angiosarcoma, and pseudomyogenic hemangioendothelioma, these traditional endothelial markers typically show different levels of positive expression, hampering the discrimination of EHE and vascular-derived soft tissue tumors. Our study demonstrates that CAMTA1 can serve as an effective immune marker for diagnosis of EHE, which is consistent with the results of most studies [13, 22]. However, due to the cross-reactivity of CAMTA1 polyclonal antibody with other antigens, as well as the heterogeneity of antibodies from different reagent companies, false positives can be detected, while FISH, which is more sensitive and specific, allows distinguishing EHE and vascular-derived soft tissue tumors effectively.

In summary, EHE is a low-grade malignant vascular tumor differentiated from the vascular endothelium with primitive vascular lumen differentiation and metastatic potential. The *WWTR1/CAMTA1* fusion gene can be detected in 90% of EHE cases, and 5% of EHE tumors harbor the *YAP1/TFE3* fusion gene. Our results show that the detection of CAMTA1 nuclear protein expression is an effective EHE marker for diagnosis with IHC. However, the antibodies and clone numbers differ among different reagent companies, making this method unreliable and unstandardized. Therefore, FISH detection of the *WWTR1/CAMTA1* fusion gene is a more sensitive and specific detection method.

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Disclosure of conflict of interest

None.

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