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COMMUNICATION

Occasional Staining for p63 in Malignant Vascular Tumors: A Potential Diagnostic Pitfall

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Abstract Expression of p63, a putative marker for epithelial or myoepithelial differentiation, has been used to distinguish spindle cell carcinoma from sarcoma. The specificity of p63 for epithelial differentiation has not been thoroughly evaluated however, since p63 expression has been explored in only a handful of mesenchymal tumors. After observing unexpected immunohistochemical staining for p63 in an angiosarcoma of the breast, we evaluated a series of benign and malignant vascular tumors to determine the frequency of such a finding. Nuclear immunoreactivity to p63 was detected, at least focally, in 24% of malignant vascular tumors other than Kaposi sarcoma, which was uniformly negative. Benign vascular tumors were also negative for p63. Although p63 expression in tumors of vascular differentiation is unusual, it may be seen occasionally in some malignant vascular tumors. Thus, p63 is not entirely specific for epithelial differentiation. Since soft tissue angiosarcomas and hemangioendotheliomas sometimes express cytokeratins, the finding of nuclear p63 represents another potential pitfall in the differential diagnosis between poorly-differentiated carcinomas and vascular neoplasms.

Keywords Angiosarcoma · Hemangioendothelioma · Hemangioma · Kaposi sarcoma · p63

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Abbreviations

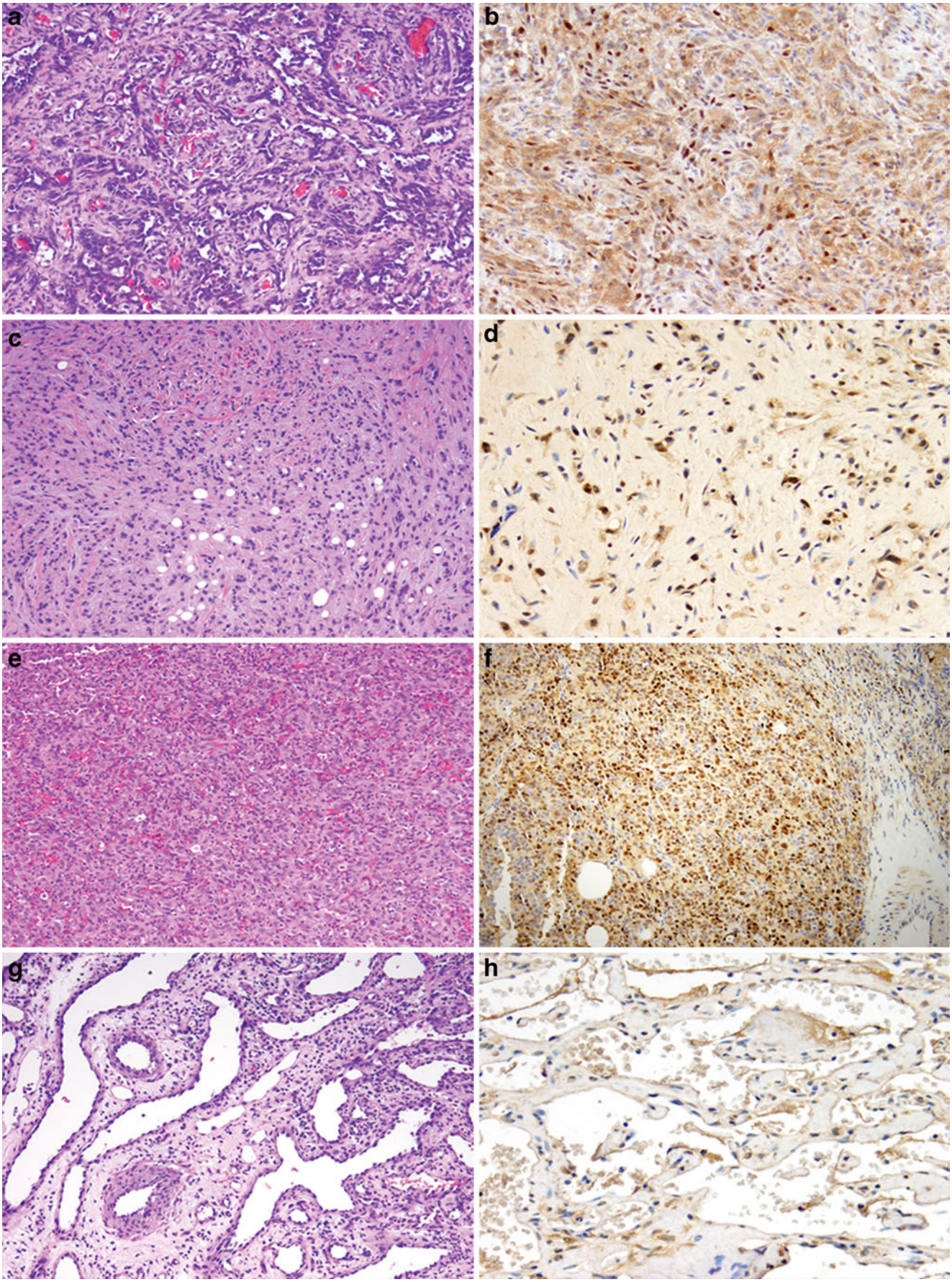
EHE	epithelioid hemangioendothelioma
KS	Kaposi sarcoma

Introduction

The protein isoforms derived from the *TP63* gene are involved in a complicated network of molecular interactions controlling proliferation and differentiation of stratified epithelia [1–6]. Although immunohistochemical staining for the p63 protein appears to be a useful marker for distinguishing spindle cell carcinoma from sarcoma [7–14], a limited number of mesenchymal tumors have been studied thus far [15–18]. Recently, we observed serendipitous staining for p63 in an angiosarcoma of the breast. Since p63 immunoreactivity has not been reported previously in angiosarcoma [17–20], we reasoned that further investigation of p63 expression in vascular tumors was warranted.

Materials and Methods

Representative cases of conventional angiosarcoma, epithelioid angiosarcoma, epithelioid hemangioendothelioma (EHE), Kaposi sarcoma (KS) and capillary hemangioma were identified retrospectively and one block from each case was selected for immunohistochemical study. Vascular differentiation was confirmed in each malignant vascular tumor by documentation of expression of at least one of the following endothelial markers: CD31, D2-40 or FLI1. After antigen retrieval in Target Retrieval Solution, Citrate pH 6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◀ **Fig. 1** Angiosarcoma of soft tissue (**a**, H&E, 100×) demonstrating focal nuclear staining for p63 (**b**, 100×). Epithelioid hemangioendothelioma (**c**, H&E, 100×) with scattered p63-positive nuclei (**d**, 200×). An epithelioid angiosarcoma of the breast (**e**, H&E, 100×) also showed extensive nuclear p63 expression (**f**, 200×). All 9 capillary hemangiomas (**g**, H&E, 100×) were negative for nuclear p63 (**h**, 200×)

(Dako, Carpinteria, CA, USA), endogenous peroxidase was inhibited with 3% H_2O_2 and sections were incubated in Protein Block Serum Free solution (Dako, Carpinteria, CA, USA). Sections were then incubated with anti-p63 (Sigma-Aldrich, St. Louis, MO) diluted 1:800 for 60 min at room temperature. Primary antibody was detected using the Dako EnVision™+ HRP/DAB System (Dako Carpinteria, CA, USA). A representative tissue section for which incubation with primary antibody was omitted served as a negative control. The percentage of lesional cells with nuclear staining for p63 cells was recorded.

Results

p63 expression was detected in 5 of 21 malignant vascular tumors (23.8%; 95% confidence interval 10.6%–45.1%), excluding KS (Fig. 1). In the two p63-positive angiosarcomas and one EHE, nuclear staining for p63 was observed in less than 10% of neoplastic cells. Approximately 60% of tumor cells in one other EHE were positive for p63. The one p63-positive epithelioid angiosarcoma showed nuclear staining in approximately 75% of cells. Thus, in most p63-positive vascular tumors, only a minority (mean, 33%; range, <10% to 75%) of tumor cell nuclei are immunoreactive. None of the benign vascular tumors or KS was positive for p63 (Table 1).

Discussion

The pathophysiology of p63 expression in endothelial cells has not been investigated, but evidence suggests that p63 can affect expression of vascular endothelial growth factor via interactions with hypoxia inducible factor-1α [21]. Nuclear p63 expression in tumors of vascular differentiation is unusual, but may be seen in 20%–30% of malignant vascular tumors other than KS, and may not be as specific for epithelial differentiation as previously suggested [8, 9, 11–16, 22]. Since soft tissue angiosarcomas and EHE may also co-express cytokeratins [22–24], the finding of nuclear p63 represents another potential pitfall in the differential diagnosis between poorly-differentiated carcinomas and vascular neoplasms. Consequently, a panel of immunohistochemical markers, including endothelial markers such as CD34, CD31 or FLI1 should be considered in the work-up of sarcomatoid carcinomas.

Table 1 p63 immunoreactivity in vascular tumors

	n	Nuclear p63+
Angiosarcoma	9	2 (22%)
Epithelioid angiosarcoma	5	1 (20%)
Epithelioid hemangioendothelioma	7	2 (29%)
Kaposi sarcoma	20	0 (0%)
Capillary hemangioma	9	0 (0%)

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