

Immunohistochemical Expression of Wt-1 Helps to Differentiate Cutaneous Vascular Tumors from Vascular Malformations

Sir,

Cutaneous vascular anomalies are commonly encountered in routine dermatology practice and often pose a diagnostic challenge due to their clinical and histopathologic similarities. In 2014, the 20th International society for the study of vascular anomalies (ISSVA) workshop classified vascular lesions into three categories, namely, vascular tumors, vascular malformations, and a new category of provisionally unclassified vascular anomalies.^[1] Despite their similar clinical presentation and histomorphology, vascular tumors and vascular malformations need to be differentiated due to their specific clinical behavior and approach to their management.

Wilms' tumor-1 (WT-1) was originally described as a tumor suppressor gene based on its mutational inactivation in a subset of Wilms' tumor. It plays an essential role in haematopoiesis and angiogenesis by regulating vascular endothelial growth factor, angioproteins, nestin, and proliferation of vascular smooth muscle cells.^[2] Human skin vasculature shows cytoplasmic WT1 protein expression, detected by an antibody recognizing the C-terminal of the protein (6F-H2). Reports have demonstrated that WT-1 protein is expressed in a variety of vascular anomalies. Defects in WT1 signalling might underlie the inability of endothelial cells in vascular malformations to undergo physiologic apoptosis and remodelling.^[3-5]

The objective of the present study is to seek diagnostic utility of WT-1 immunoexpression in differentiating cutaneous vascular proliferations and tumors from vascular malformations.

A total of 50 cases of cutaneous vascular anomalies including 25 vascular tumors and 25 malformations received during 2012–2015 were included in this study. The paraffin blocks of these skin biopsies were retrieved for WT-1 immunohistochemical staining with anti-WT1 mouse monoclonal antibody (clone 6F-H2, DAKO). Stained slides were examined to see the presence or absence of endothelial WT-1 staining in the vascular lesions.

The study was approved by the institutional ethics committee of the National Institute of Pathology, ICMR, Delhi. The informed patient consent from each patient was exempted as this study was performed on archival paraffin blocks.

For immunohistochemistry, sections were obtained on poly-l-lysine coated slides and sections were deparaffinized with xylene followed by dehydration in ethyl alcohol. Sections were then kept in 3% hydrogen peroxide for 30–45 min to quench the endogenous peroxidase activity and were washed with phosphate buffer saline at pH 7.2. Antigen retrieval was done by heating sections in microwave oven at 360 W for 10 min. This was followed

by incubation with primary antibody in 1:100 dilution at 37°C. Diaminobenzidine was used as chromogen for secondary labelling. The sections were counterstained with Harris hematoxylin, and antigen-antibody reaction was visualized as a brown color.

All vascular neoplastic lesions and vascular malformations underwent WT-1 staining with detailed immunoexpression, as shown in Table 1. All the 25 (100%) vascular tumors showed cytoplasmic expression of WT-1 in the endothelial cells. Figure 1 shows positive WT1 immunoexpression in (a) cherry angioma showing proliferation of capillary-sized blood vessels in papillary dermis, (b) lobular capillary hemangioma showing lobular capillary proliferation in dermis, (c) cavernous hemangioma composed of large dilated blood vessels, and (d) glomus tumor composed of round glomus cells around central blood vessels.

In contrast, 23/25 cases (92%) of vascular malformations showed negative WT-1 immunoexpression. Two out of 5 cases of verrucous hemangiomas showed positive WT-1 immunoexpression. All the other vascular malformations were negative for WT1. Figure 2 shows absence of WT1 immunoexpression in (a) portwine stain with capillary-sized blood vessels in upper dermis, (b) keratoacanthoma showing epidermal hyperkeratosis and dilated blood filled vessels in papillary dermis, (c) lymphangioma showing ectatic vessels filled with lymph, and (d) arteriovenous malformation showing irregular, dilated, and branching arteriovenules.

Timar *et al.*^[5] studied the expression of WT-1 in a mixture of 42 skin tumors and concluded that WT-1 protein is maintained during angiogenesis but may reappear during reparative neoangiogenesis or in the endothelial cells of vascular tumors. Lawley *et al.*^[6] studied WT-1 by immunohistochemistry, and reported that 21/23 vascular tumors expressed strong WT-1 expression in the endothelial cells whereas all 20 vascular malformations were negative or expressed very weak WT-1 protein in the endothelial cells.

Our study showed strong cytoplasmic expression of WT-1 in the endothelial cells of vascular tumors and no expression in the vascular malformations. Two out of 5 verrucous hemangiomas showed endothelial WT-1 expression. Al Dhaybi *et al.*^[7] evaluated 126 cases of vascular anomalies for WT-1 immunoexpression and found its strong cytoplasmic expression in all 64 tumors but no expression in 58/61 (95%) vascular malformations. In addition, similar to our observation, other authors have reported positive immunoexpression of WT1 in the cases of verrucous hemangioma. This suggests that, although verrucous hemangioma presents as a vascular malformation clinically, the expression of this primitive marker indicates that it might actually be a vascular tumor rather than a malformation.

Table 1: WT-1 expression in cutaneous vascular lesions

Vascular tumors	N=25	WT-1 Positive	WT-1 Negative
Infantile hemangioma	4	4	0
Pyogenic granuloma	10	10	0
Glomus tumor	5	5	0
Cherry angioma	1	1	0
Cavernous hemangioma	1	1	0
Tufted angioma	1	1	0
Angiosarcoma	1	1	0
Eccangioma Hamartoma	1	1	0
Glomeruloid hemangioma	1	1	0
Vascular malformations			
Portwine stain	2	0	2
Arteriovenous malformation	4	0	4
Lymphangioma	5	0	5
Glomovenous malformation	3	0	3
Angiokeratoma	5	0	5
Verrucous hemangioma	5	2	3
Lymphangiectasia	1	0	1

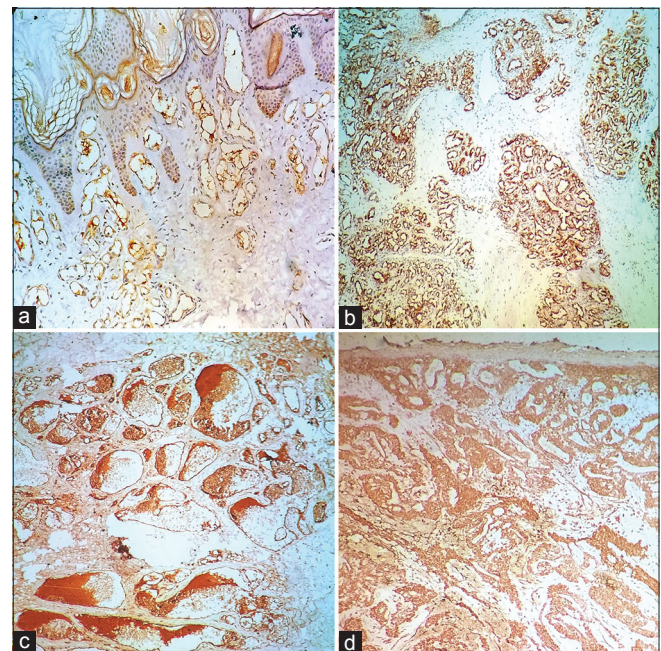


Figure 1: WT-1 immuno expression in (a) cherry angioma, (b) pyogenic granuloma, (c) cavernous hemangioma, and (d) Glomus tumor (×200)

In conclusion, WT-1 may be a useful immunohistochemical marker to differentiate a cutaneous vascular tumor from vascular malformation. In future, WT-1 gene may be explored as a molecular target for treating vascular skin tumors.

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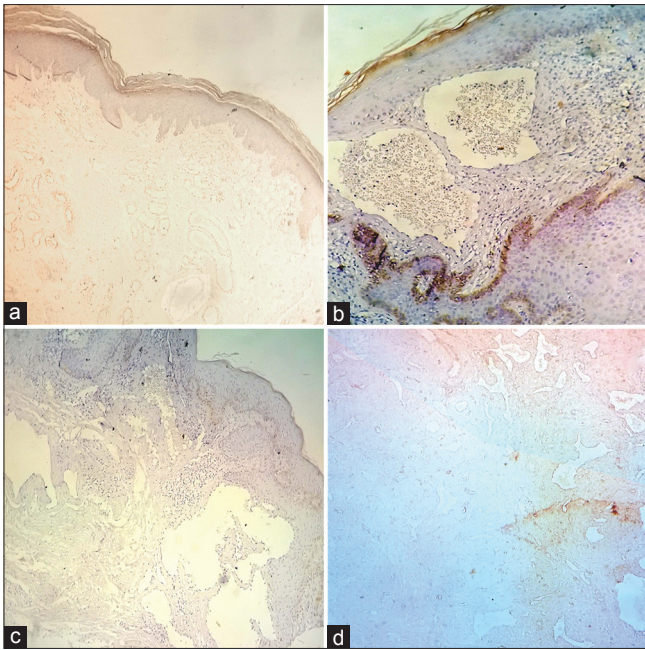


Figure 2: WT-1 expression in (a) portwine stain, (b) angiokeratoma, (c) lymphangioma, (d) and arteriovenous malformation (×200)

Conflicts of interest

There are no conflicts of interest.

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