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Review

The utility of GLUT1 as a diagnostic marker in cutaneous vascular anomalies: A review of literature and recommendations for daily practice

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ABSTRACT

Objective: To assess the utility of GLUT1 as an immunohistochemical marker in the diagnostics of cutaneous vascular anomalies.
Methods: A systematic literature search was conducted for studies on GLUT1 staining patterns in cutaneous vascular lesions. Data was grouped according to the latest ISSVA classification for vascular anomalies.
Results: Vascular tumors: GLUT1 staining was positive in 368/386 (95%) of infantile hemangiomas. Congenital hemangiomas (16 cases) and kaposiform hemangioendotheliomas (62 cases) were all negative for GLUT1. Angiosarcomas were GLUT1 positive in 12/39 (31%) and epithelioid hemangioendotheliomas in 2/27 (7%) of cases. Vascular malformations: All vascular malformations (33 arteriovenous malformations, 16 capillary malformations, 64 lymphatic malformations, 54 venous malformations, 3 venous-lymphatic malformations and 3 capillary venous-lymphatic malformations) were negative for GLUT1 staining. Unclassified vascular anomalies: Angiokeratomas were GLUT1 positive in 1/15 (7%) and verrucous hemangiomas in 71/100 (71%) of cases. Microvenular hemangiomas were negative for GLUT1 in all 9 cases.
Conclusions: GLUT1 can be used as an additional diagnostic tool in cutaneous vascular lesions. A negative GLUT1 stain renders a diagnosis of infantile hemangioma unlikely. A positive GLUT1 stain excludes vascular malformations and is suggestive of infantile hemangioma. One must be cautious, however, that the final diagnosis is made through interpretation of all clinical and diagnostic features, and not based on GLUT1 staining alone.

Contents

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1. Introduction

'Vascular anomalies' is an umbrella term used for lesions that stem from abnormalities in either blood vessels, lymphatic vessels, or both. Historically, the nomenclature for these vascular lesions has been vague and contradicting [1]. The first organized classification was published by Mulliken and Glowacki in 1982, distinguishing vascular tumors (lesions growing by endothelial hyperplasia, likehemangiomas) from vascular malformations (lesions with quiescent endothelium, considered localized defects of vascular morphogenesis) [2]. This basic classification system was adopted by the International Society for the Study of Vascular Anomalies (ISSVA) in 1993 [3]. Over the years, imaging techniques, immunohistochemistry and genetic studies have allowed for new diagnostic and classification opportunities in vascular anomalies, leading to various ISSVA classification updates [4–6]. Nonetheless, unambiguous classification of vascular anomalies remains a challenge. Wassef et al. published an introduction into the latest ISSVA classification update in 2015, striving for uniform classification of vascular anomalies by pathologists, clinicians, and researchers [6]. In 2000, North et al. found that the endothelial cells of infantile hemangiomas (IH) are immunoreactive for the Glucose Transporter Type 1 (GLUT1), contrary to the vascular endothelium in normal skin. They did not find comparable immunostaining in vascular malformations, rendering GLUT1 a potential marker for IH [7]. This led to new hypotheses regarding the origin of infantile hemangiomas, translating into the placental embolization theory of IH that still has supporters this day [8]. Although of undisputed scientific value, the clinical applicability of GLUT1 staining in infantile hemangiomas has not been addressed. Therefore, we aimed to define the utility of GLUT1 in the diagnostics of cutaneous vascular anomalies.

2. Materials and methods

The objective of this study was to assess the utility of GLUT1 staining in the diagnostics of cutaneous vascular anomalies. We searched PubMed for studies reporting on GLUT1 immunostaining patterns for different types of vascular anomalies (primary outcome). The search strategy was designed to entail all entities recognized by the latest ISSVA classification [Table 1] in combination with "GLUT1". Exclusion criteria were: studies of non-cutaneous vascular anomalies; studies where GLUT1 was not regarded an outcome measure but used as a standard for diagnosis; papers in languages other than English, Dutch or German; articles not attainable in full-text. Data on GLUT1 staining patterns in various vascular malformations was extracted from the relevant papers. Data was assembled and grouped according to the latest ISSVA classification.

3. Results

Our search rendered 197 results. Title and abstract screening led to the exclusion 156 citations. Out of the 41 remaining citations, 21 relevant papers were included [Table 2]. The results of data extraction are discussed below. Findings are summarized in Table 3.

3.1. Benign vascular tumors

IHs are typically not or hardly visible at birth. Disproportionate growth starts in de first weeks of life and may proceed until the age of 6–9 months, followed by a plateau phase and subsequent regression between the age of 2–4 years. Depending on size, level of skin infiltration and ulceration, residual lesions may retain.
GLUT1 immunostaining for IH was investigated in nine studies, adding up to 386 IHs [7,9–16]. Additionally, three cases of neonatal hemangiomatosis (NH) were investigated [17]. GLUT1 staining was positive in 368/386 (95%) of IH cases and in all NH cases. The intensity of GLUT1 staining in IH was described to be intense when compared to the positive controls [7,9,10]. Moreover, North et al. reported that GLUT1 staining was extensive, involving >90% of lesional vessels in 93% of GLUT1 positive IH.
Congenital hemangiomas (CH) are vascular tumors that are fully developed at birth and may regress in the first 8–14 months of life. CHs were studied in three papers, with a total of 16 cases (7 NICH, 3 RICH, 6 not specified) [9,12,14]. GLUT1 staining was negative in all reported CHs. Other benign vascular tumors investigated were consistently negative for GLUT1 immunostaining and included: epithelioid hemangioma (two studies, 10 cases [13,15]), spindle-cell hemangioma (one study, one case [14]), tufted angioma (five studies, 31 cases [9,10,13,14,18]) and pyogenic granuloma (seven studies, 78 cases [7,9,10,13–16]).

3.2. Locally aggressive or borderline vascular tumors

GLUT1 immunoreactivity of kaposiform hemangioendothelioma (KHE) was investigated in six papers, with a total number of 62 KHEs. [7,9,10,13,19,20] All cases were negative for GLUT1 immunostaining.

3.3. Malignant vascular tumors

Angiosarcomas (AS) were studied in four the papers with a total of 39 cases [7,10,16,21]. GLUT1 immunostaining was positive in 12/39 (31%) of cases. Among the GLUT1 positive angiosarcomas, intensity was reported to be "weak" (3 cases), "weak to moderate" (5 cases) or "strong" (4 cases). The extent of staining was reported to be "<10% of tumor cells" in three and "focal" in five of the cases [7,10]. It must be noted that the AS cases were of varying origin: skin (7 cases), extremities (6 cases), bone (≥4 cases), head and neck (≥3 case), nasal sinuses (3 cases), liver (≥2 cases), pericardium (≥2 case), pelvis (≥1 case), salivary gland (1 case), colon (1 case), inguinal (1 case). For the remaining AS cases, the location of the tumor was not reported.
Epithelioid hemangioendotheliomas (EHE) were investigated in four studies, rendering a cumulative 27 cases [7,10,16,21]. GLUT1 immunoreactivity was positive in 2/27 (7%) of cases, with staining described "strong" in one and "focally present" in the other case. Same as for AS, the EHE were of varying origin: bone (12 cases), extremities (4 cases), liver (3 cases), head and neck (3 cases), liver (2 cases), breast (1 case), spleen (1 case), abdominal wall (1 case), unknown (1 case).