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Original contribution

GLUT-1 expression in mesenchymal tumors: an immunohistochemical study of 247 soft tissue and bone neoplasms

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Summary GLUT-1, an erythrocyte-type glucose transporter protein expressed in juvenile hemangiomas, has recently been shown to be a sensitive marker of perineurial cells and their tumors in a small number of cases. However, GLUT-1 expression has not been systematically examined in other mesenchymal neoplasms. Prompted by a recent report of GLUT-1 expression in epithelioid sarcoma, a tumor not generally felt to show perineurial differentiation, we examined GLUT-1 expression in a wide variety of mesenchymal tumors. Sections from 247 mesenchymal tumors of a variety of histologic subtypes were retrieved from our archives and immunostained for GLUT-1 using heat-induced epitope retrieval and the DAKO ADVANCE detection system (DAKO, Carpinteria, CA). Scoring was as follows: negative (<5% of cells), 1+ (5%-25% of cells), 2+ (25%-50% of cells), and 3+ (>50% of cells). All benign nerve sheath tumors showed a peripheral rim of positive normal perineurial cells, with 2 neurofibromas and 3 schwannomas showing more extensive staining. Three of 4 perineuriomas showed strong GLUT-1 expression. All juvenile hemangiomas were GLUT-1 positive. GLUT-1 expression was also seen in a wide variety of benign and malignant mesenchymal tumors. However, GLUT-1 expression was absent in nonjuvenile hemangioma endothelial tumors and in almost all low-grade lesions that enter the histologic differential diagnosis of perineurial tumors, including low-grade fibromyxoid sarcoma, dermatofibrosarcoma protuberans, and myxofibrosarcoma. We conclude that GLUT-1 expression in mesenchymal tumors is by no means specific for perineurial differentiation, but may instead represent upregulation of this protein within hypoxic zones, secondary to upstream activation of proteins such as hypoxia-inducible factor 1-α.

1. Introduction

GLUT-1 is an erythrocyte-type glucose transporter protein and a member of the facilitative cell-surface glucose transporter family which includes 5 other isoforms [1]. It was originally purified from human erythrocyte membranes [2] and has been subsequently identified in the brain capillary endothelium, where it plays a critical role in the transport of glucose across the blood-brain barrier [3]. In addition to its role as a glucose transporter, GLUT-1 is also known to play an important role in the cellular response to hypoxia, as a downstream target of hypoxia-inducible factor 1-α (HIF1-α) [4]. Constitutive GLUT-1 expression has been documented

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in a variety of normal cell types, including placental trophoblast and perineurial cells [5,6]. Upregulation of GLUT-1 expression, presumably due to enhanced glycolytic metabolism, has recently been shown to be a relatively common feature in various carcinomas [7].

In mesenchymal neoplasms, expression of GLUT-1 has been shown to be a constant feature of juvenile capillary hemangiomas, where its expression is useful in the discrimination of such tumors from various mimics, such as vascular malformations and kaposiform hemangioendothelioma [8-11]. GLUT-1 expression has also been noted in a subset of soft tissue perineuriomas, consistent with its expression in normal perineurium [12-14]. Most recently, Smith et al [15] have documented GLUT-1 expression in a small number of epithelioid sarcomas and have suggested that this observation supports the concept of perineurial differentiation in this otherwise enigmatic sarcoma.

We undertook a large, retrospective study of GLUT-1 expression in a broad variety of mesenchymal tumors with the goal of better establishing the range of GLUT-1 expression in mesenchymal tumors.

2. Materials and methods

Formalin-fixed, paraffin embedded blocks from 247 well-characterized mesenchymal tumors were retrieved from the archives of Mayo Clinic. These cases included alveolar soft part sarcoma (2 cases), angiomatoid (malignant) fibrous histiocytoma (1 case), angiosarcoma (2 cases), atypical fibroxanthoma (1 case), angiomyolipoma/perivascular epithelioid cell tumor (3 cases), atypical lipoma/well-differentiated liposarcoma (1 cases), benign fibrous histiocytoma (4 cases), chondroblastoma (1 cases), chondrosarcoma (5 cases), chordoma (13 cases), clear cell sarcoma (2 cases), dermatofibrosarcoma protuberans (1 case), desmoplastic small round cell tumor (2 cases), dermatofibrosarcoma protuberans (9 cases), desmoid-type fibromatosis (7 cases), endometrial stromal sarcoma (3 cases), epithelioid hemangioendothelioma (1 case), epithelioid sarcoma (8 cases), extraskeletal myxoid chondrosarcoma (1 case), Ewing sarcoma (11 cases), fibroma (2 cases), fibrosarcoma (4 cases), gastrointestinal stromal tumor (14 cases), adult capillary hemangioma (1 case), juvenile capillary hemangioma (9 cases), inflammatory myofibroblastic tumor (1 case), leiomyosarcoma (10 cases), lipoma (9 cases), leiomyoma (1 case), liposarcoma (10 cases), low-grade fibromyxoid sarcoma (2 cases), malignant tenosynovial giant cell tumor (1 case), granular cell tumor (1 case), melanoma (6 cases), malignant peripheral nerve sheath tumor (3 cases), myoepithelioma (2 cases), myofibrosarcoma (1 case), myxofibrosarcoma (5 cases), neurofibroma (11 cases), nodular fasciitis (2 cases), perineurioma (4 cases), plexiform fibrohistiocytic tumor(1 case), rhabdomyosarcoma (4 cases), solitary fibrous tumor (11 cases), schwannoma (18 cases), synovial sarcoma (10 cases), osteosarcoma (2 cases), undifferentiated pleomorphic sarcoma (22 cases), and xanthoma/xanthogranuloma (2 cases). The diagnoses for all cases were confirmed on rereview of available histologic sections and immunostains by an experienced soft tissue and bone pathologist (ALF).

For immunohistochemistry, GLUT-1 expression was evaluated using a rabbit polyclonal antihuman GLUT-1 antibody at a dilution of 1:200 (DAKO, Carpinteria, CA). Paraffin slides were deparaffinized and placed in a preheated solution (95°C-97°C) of 1 mmol/L EDTA, pH 8.0, for 30 minutes. This pretreatment was accomplished using a vegetable steamer. The slides were placed on a DAKO Autostainer. Slides were incubated with GLUT-1 antibody for 30 minutes. Detection was accomplished using a highly sensitive 2-step polymer system from DAKO, ADVANCE. The chromogen used was DAKO DAB+. All slides were counterstained with hematoxylin and coverslipped for microscopic examination. The antibody conditions had been optimized using normal perineurium and surrounding nonneural tissue as positive and negative controls, respectively. The tumors were scored as negative (<5% of cell positive), 1+ (5%-25% of cells positive), 2+ (25%-50% of cells positive), and 3+ (>50% of cells positive). Only a membranous pattern of positivity was considered to represent true GLUT-1 expression.

3. Results

The immunohistochemical results are summarized in Table 1. When available, normal perineurial cells invariably served as a positive internal control. All benign nerve sheath tumors showed at least some GLUT-1–positive cells, presumably representing perineurial cells, with 4 neurofibromas and 4 schwannomas showing more extensive expression in the form of a peripheral rim of positive cells (Fig. 1). Three of 4 perineuriomas showed GLUT-1 expression (the negative case was an epithelial membrane antigen (EMA)–positive low-grade perineurial sarcoma). GLUT-1 expression was seen in 5 of 8 epithelioid sarcomas (Fig. 2) and in all chordomas (Fig. 3). All juvenile capillary hemangiomas were uniformly GLUT-1 positive; all other endothelial neoplasms were negative. Among lesions which typically enter the histologic differential diagnosis of perineurioma, such as low-grade fibromyxoid sarcoma, dermatofibrosarcoma protuberans, and myxofibrosarcoma, GLUT-1 expression was confined to only focal positivity in a single myxofibrosarcoma.

As detailed in Table 1, GLUT-1 expression was also seen in a wide variety of benign and malignant bone and soft tissue tumors (Fig. 4). GLUT-1 expression was frequently seen in association with foci of spontaneous or therapy-induced tumor cell necrosis, often chiefly in the neoplastic cells in closest proximity to the necrotic zones (Fig. 5). Overall, 87 (35%) of 247 cases showed at least 1+ GLUT-1 expression.