Glut-1, Best Immunohistochemical Marker for Perineurial Cells

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Sir, historically, transmission electron microscopy (TEM) was used to characterize perineurial cells and to confirm the diagnosis of perineuriomas. Perineurial cells typically present thin and long cytoplasmic processes containing numerous pinocytotic vesicles, with the external surface coated by a discontinuous basal lamina, and well-developed tight junctions at points of cells contact. With the advent of immunohistochemistry, epithelial membrane antigen (EMA) became a useful marker for perineurial cells, substituting the laborious and time consuming preparations for TEM. EMA is a non-specific antibody positive in many cells and tissues including perineurial cells, and although its expression in perineuriomas is faint and/or focal, it is the most widely used marker for this neural lesion. Afterwards it was noted that Claudin-1, a tight junction protein, was also positive in perineurial cells and that it could also be useful for the diagnosis of perineuriomas [1, 2]. Glut-1, an erythrocyte glucose transporter, was then reported to be also expressed in perineurial cells [3, 4] and in perineurioma, for the first time in five cases of sclerosing perineurioma [5]. This was not a surprise, since Glut-1 is positive not only for erythrocytes, but also for epithelial intercellular junctions. Perineurial cells are found in the perineurial sheath of normal nerves. Neurofibromas besides axons, Schwann cells and endoneurial fibroblasts can show perineurial cells, mainly at the periphery, probably representing remains of the perineurial sheath [1]. Perineuriomas either intra or extraneural are characterized

by the proliferation of perineurial cells, and express the three above cited immunohistochemical markers [2, 6].

We revised 10 cases of oral perineuriomas and 15 cases of oral neurofibromas. Normal nerves present at the periphery of these lesions were also evaluated. Eight cases of perineurioma were classified as intraneural and two as extraneural, while 11 neurofibromas were diffuse and four were plexiform. All of them were immunostained with EMA (clone E29, 1:100; DAKO), Claudin-1 (polyclonal, 1:100; BioSystems) and Glut-1 (polyclonal, 1:100; BioSystems). Retrieval antigen was made in a microwave oven using a 10 mM citrate buffer (pH 6.0), followed by overnight incubation with primary antibodies. For visualization the streptavidin biotin system was used (LSAB + HRP, Dako). The reaction was developed with diaminobenzidine hydrochloride (Sigma, St Louis, MO) and was lightly counterstained with Carazzi hematoxylin. The intensity of the staining was determined subjectively by three oral pathologists, as weak, medium and strong, considering comparatively the three markers used. Neurofibromas showed positive areas mainly at the periphery of the tumors and/or surrounding isolated nerve fascicles. Normal nerves were uniformly positive on the perineurial sheath. Intraneural perineuriomas showed the typical concentric pattern around axons, while in the extraneural type the cells were more diffusely marked. In all cases of normal nerves, neurofibromas and perineuriomas, the expression of EMA and Claudin-1 was weak and diffuse, and sometimes difficult to identify. On the other hand Glut-1 showed always strong and evident expression (Figs. 1, 2). Higher and lower concentrations of primary antibodies were tested in known positive controls, but it did not improve the results of the three markers used. However, independent of the dilution when comparing the markers, always EMA and Claudin-1 showed weaker expression than Glut-1.

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Fig. 1 Perineurial cells of normal nerve fiber, positive for Glut-1, Claudin-1 and EMA. **a** Strong and evident expression of Glut-1 highlighting the perineurial sheath. Erythrocytes inside various vessels are strongly positive serving as internal control. **b** Similar area showing weak expression of Claudin-1 and **c** EMA ($\times 100$ original magnification)

Considering the antibodies used and pattern of expression, Glut-1 appears to be a more sensitive immunomarker than EMA and Claudin-1 for perineurial cells, and therefore the preferable marker to distinguish perineuriomas from morphologic mimics. Also, as erythrocytes are ubiquitous practically in all histologic preparations, they serve as a useful internal control for Glut-1.

Fig. 2 Perineurial cells in intraneural perineurioma, positive for Glut-1, Claudin-1 and EMA. **a** Strong Glut-1 positivity in concentric pattern surrounding axons. **b** Similar area showing lesser and more focal expression of Claudin-1 than the seen with Glut-1. **c** Weak expression of EMA ($\times 400$ original magnification)

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