Extracutaneous infantile haemangioma is also Glut1 positive

R M Drut, R Drut


Aim: To investigate whether extracutaneous infantile haemangioma-like tumours are immunohistochemically similar to cutaneous infantile haemangiomas.

Methods: Mammary, salivary gland, liver (one each), and placental (two cases) capillary haemangiomas and typical examples of cutaneous (eight cases) infantile haemangioma were investigated immunohistochemically for α smooth muscle actin and Glut1, a proposed marker for the skin localised lesion. Positive internal controls included red blood cells, perineurium, trophoblast, and endothelial cells of the placental capillaries. Extralosomal vessel endothelium acted as a negative control (except in the placenta). The liver haemangioma and both chorioangiomas presented in patients with Beckwith-Wiedemann syndrome.

Results: The endothelial cells of all the vascular lesions were Glut1 positive. These were consistently surrounded by α smooth muscle actin positive pericytic cells. Controls reacted appropriately.

Conclusions: All infantile haemangiomas were immunohistochemically positive for Glut1: expression of this molecule was not limited to infantile haemangiomas of the skin. These tumours comprise proliferations of both endothelial and pericytic cells. The association with Beckwith-Wiedemann syndrome may provide a clue to the molecular genetics of infantile haemangioma.

RESULTS

Skin IH showed numerous vessels with some variations in its structure according to the site of the lesion. In general, central areas appeared more cellular and contained small vessels with plump endothelium surrounded by plump multilayered pericytic cells. At the periphery of the lesions, the small vessels presented larger lumina, less prominent endothelial cells, and thinner walls. Although the vessels retained a back to back pattern in most of the lesion, the tumours were unencapsulated and at the periphery the vessels intermixed with the subcutaneous adipose tissue. Cutaneous adnexa, mainly sweat glands, appeared unaffected amidst the tumour vessels.

Abbreviations: IH, infantile haemangioma
Chorioangiomas presented the typical images of numerous capillaries with plump endothelial cells surrounded by one or more layers of pericytic cells in a myxoid stroma. The back to back arrangement of the capillaries varied from site to site.

Breast and submaxillary gland lesions showed similar features to skin IH, including and surrounding mammary ducts and salivary ducts, respectively. Particularly remarkable was the back to back pattern of the vessels (fig 1A, B).

The hepatic lesion contained several nodules that showed similar histological features to IH. The vessels were associated with portal areas and surrounded the biliary ducts. These portal areas were the only parts that displayed a few larger irregularly shaped vessels, probably dilated veins (fig 2).

The endothelial cells of all the IH and IH-like lesions were consistently positive for Glut1 (fig 3A–D), whereas the pericytic cells were positive for α smooth muscle actin (fig 4A–C). Keratin immunostaining highlighted the ducts in all the lesions which were densely surrounded by the tumour vessels (fig 5A–C).

The smooth muscle component of normal vessels was positive for α smooth muscle actin.

**DISCUSSION**

Confirming extensive studies already published, Glut1 was present in the endothelial cells of all cases of cutaneous IH. These also consistently contained smooth muscle actin positive pericytic cells.

Glut1 positivity in the endothelial cells of chorioangiomas seems to be an expected and straightforward finding because capillaries of the placental villi normally express this marker (P North, H Kozakewich H. Society for Pediatric Pathology. Washington, DC: Annual Meeting Workshop Handout, March 2003:22–3).

As expected, Glut1 showed positive immunoreactivity in red blood cells, basal keratinocytes, perineurium (fig 3A), apical brush border, basal membrane of the trophoblast (fig 3B), and microvascular endothelial cells of the fetal brain. Glut1 immunoreactivity was not detected in the endothelial cells of adjacent normal tissues or in the vessels of the liver haemangiendothelioma.

Hepatic vascular lesions encompass the so called infantile haemangiendothelioma types I and II, cavernous haemangioma, epithelioid haemangiendothelioma, and angiosarcoma. In a recent review of a large series of vascular lesions of the liver, North and Kozakewich (P North, H Kozakewich H. Society for Pediatric Pathology. Washington, DC: Annual Meeting Workshop Handout, March 2003:22–3) noticed that when liver haemangiomas were grouped as solitary or multiple lesions an unusual pattern emerged. Solitary lesions showed the histological features of classic infantile liver haemangiendothelioma, reproducing that of the so called rapidly involuting capillary haemangioma of the skin, whereas in multiple lesions the microscopic images of cutaneous IH were seen. This second pattern is the one recognised in our case, which presented several nodules.

IH in the region of the mammary gland is a rarely recognised lesion. Vascular tumours involving this gland include the so called perilobular haemangioma, atypical

<table>
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**Figure 1** (A) Salivary gland and (B) mammary tissue involvement by infantile haemangioma. Extensive proliferation of capillaries with plump endothelial cells associated with ductal structures. Haematoxylin and eosin stain.

**Figure 2** Liver tissue involvement by infantile haemangioma. Haematoxylin and eosin stain.
perilobular haemangioma, cavernous haemangioma, capillary haemangioma, and haemangioma with atypical features. Rosen investigated a series of nine non-parenchymal haemangiomas of mammary subcutaneous tissue, including one probably similar to ours, which he named juvenil haemangioma. Our case probably represents secondary involvement of ducts of the mammary gland (a modified sweat gland) by IH which developed in the subcutaneous adipose tissue of the breast.

With regard to the salivary gland occurrence of IH, Childers and colleagues recently published their experience with 10 haemangiomas of the salivary gland, seven of which were found in the parotid gland of infants and were diagnosed as juvenile haemangioma. The authors stressed that the lobular arrangement was preserved, with acinar effacement and retention of nerves and ductal structures. One of their cases and another referred from the literature were associated with cytomegalovirus infection of the ductal epithelium. These cases fit with the features of our cases in the submaxillary gland.

One of the components of the vessels in IH, whatever its site—skin, placenta, liver, breast, or salivary gland—is the pericytic cells. This is a consistent finding, which seems to be related to the progressive maturation of the endothelial cells and formation of small vessels. Hence, IH appears to contain two types of vasoformative cells undergoing divergent differentiation in an organoid vascular pattern, which probably reproduce large villous vessels rather than placental capillaries. An unusual condition associating both cells is present in the placenta, namely chorioangiomatosis. This should be distinguished from chorioangiosis and chorioangioma, which are related but different lesions. Chorioangiomatosis is characterised by increased numbers of vessels in the villi, which are made up of endothelial and...
smooth muscle pericytic cells, presenting as focal, segmental, and/or diffuse multifocal subgroups. Chorioangioma is associated with an increased risk of extreme prematurity, congenital malformations, intraterine growth retardation, delayed villous maturation, avascular villi, and placentomegaly. Placental chorioangiosis is not associated with smooth muscle pericytic cells.

Figure 5 Keratin immunostaining was positive in the ductal epithelium in (A) mammary gland, (B) salivary gland, and (C) liver tissue involved by infantile haemangioma. Immunoperoxidase for keratin (AE1/AE3).

Multiple chorioangiomas and multiple Glut1 positive liver IH, as found in our cases of Beckwith-Wiedemann syndrome, coupled with data from the literature, points to the IGF2 gene and its product as the possible underlying molecular alteration in the genesis of this tumour.

References

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