

CASE REPORT

Multiple disseminated glomuvenous malformations: do we know enough?

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Abstract

Multiple glomuvenous malformations (GVMs), also known as glomangiomas, are uncommon entities with histological features of both glomus cells proliferation and venous malformation. A 14-year-old boy was admitted to our clinic with multiple dermal blue nodules, disseminated in different segments of the body. The patient's family history was positive for similar lesions; his mother and maternal grandmother had some asymptomatic blue nodules on their body. Histological examination showed a tumor composed of multiple cavernous vessels surrounded by glomus cells, positive for alpha smooth muscle actin, HHF35 (pan-actin), and h-caldesmon. This is a case of multiple GVMs, a rare disease caused by mutations in glomulin gene, with an autosomal dominant pattern of inheritance. The clinical and histopathological features are briefly discussed.

Keywords: glomangioma, glomuvenous malformation, glomulin.

Introduction

Glomuvenous malformations (GVMs), also known as glomangiomas or multiple glomus tumors are tumor-like malformations or hamartomas of the glomus body [1]. They have features of both glomus cells proliferations and venous malformations, but their clinico-pathological features are sufficiently distinctive to permit the differential diagnosis [2].

GVMs can appear sporadically or are inherited as an autosomal dominant disease with reduced penetrance and variable expressivity. Familial cases are caused by mutations in the glomulin gene on chromosome 1p21–22 [3, 4].

These cutaneous lesions are typically found in infancy or childhood and can be solitary or multiple. Multiple lesions are uncommon, representing less than 10% of all reported cases. Multiple GVMs are classified into three forms: localized, disseminated, and congenital plaque-type [5].

Patient, Methods and Results

A 14-year-old boy was admitted to our clinic with multiple blue nodules, disseminated in different segments of the body. The first nodule appeared three years earlier on the right wrist. It was followed by other three similar lesions in different regions of the body. Two lesions were occasionally associated with spontaneous paroxysms of pain.

The patient's family history was positive for similar lesions. His mother and maternal grandmother had some

asymptomatic nodules on their body, but the lesions had never been subject to a workup.

Past medical history included allergic rhinitis triggered by multiple allergens (pollens, acariens, cat-hair), treated with oral antihistamines. The patient had no history of gastrointestinal bleeding.

Physical examination revealed four blue dermal nodules. The lesions ranged in size from 5 to 10 mm and were localized on the right wrist, left arm, left leg, and right thigh (Figure 1). The nodules were incompressible and tender upon palpation.



Figure 1 – Glomuvenous malformation: a blue dermal nodule localized on the dorsal aspect of the right wrist.

The laboratory and imagistic findings were normal. Two painful nodules were excised.

Histological examination of the biopsy specimens revealed a proliferation composed of multiple cavernous

vessels with a layer of flat endothelial cells, surrounded by several rows of glomus cells with eosinophilic cytoplasm and monomorphic nuclei (Figure 2).

Immunohistochemical analysis showed a diffuse positive staining for alpha smooth muscle actin (Figure 3), h-caldesmon (Figure 4), HHF35 (pan-actin), and a focally staining for calponin (Figure 5). CD34 was

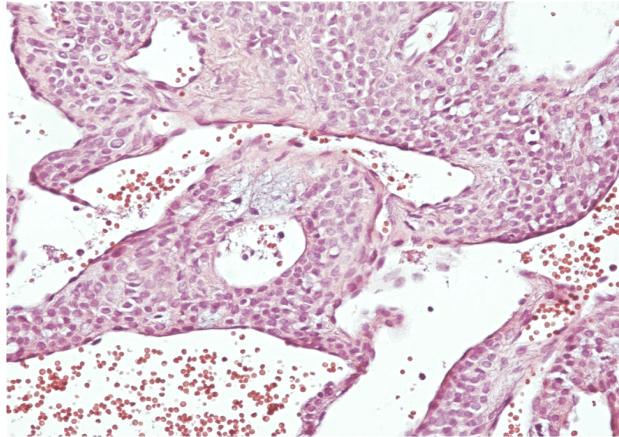


Figure 2 – Multiple cavernous vessels surrounded by glomus cells, HE stain, ob. 10×.

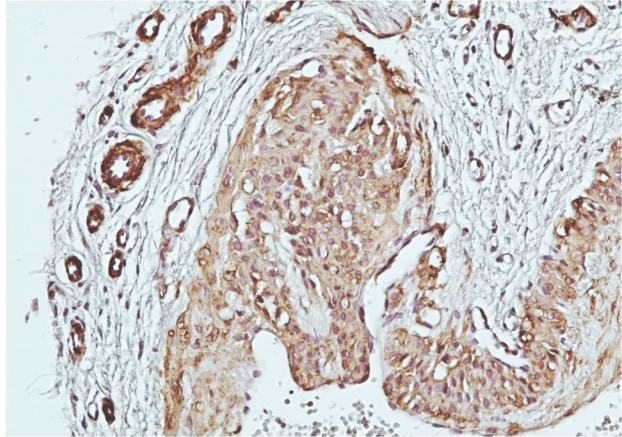


Figure 3 – Immunohistochemistry: diffuse staining for smooth muscle actin, ob. 10×.

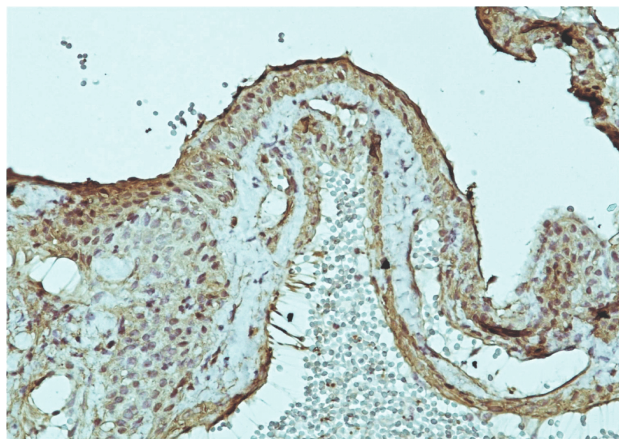


Figure 4 – Immunohistochemistry: diffuse staining for caldesmon, ob. 10×.

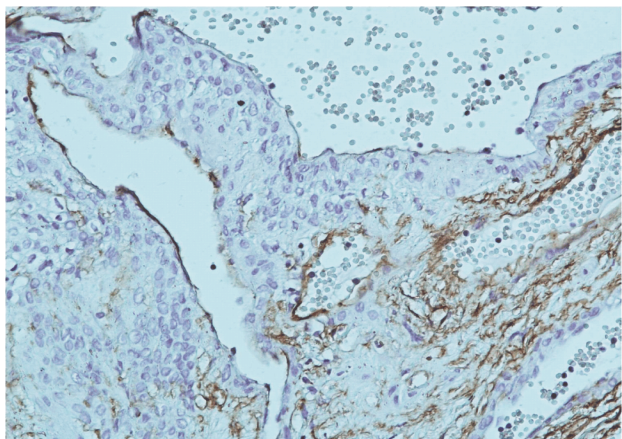


Figure 5 – Immunohistochemistry: focally staining for calponin, ob. 10×.

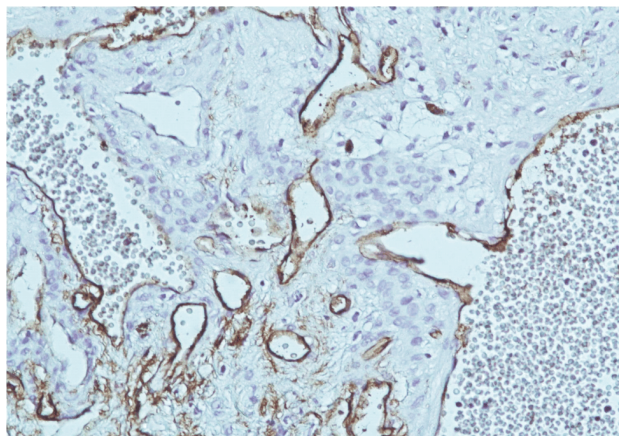


Figure 6 – Immunohistochemistry: staining of endothelial cells for CD34, ob. 10×.

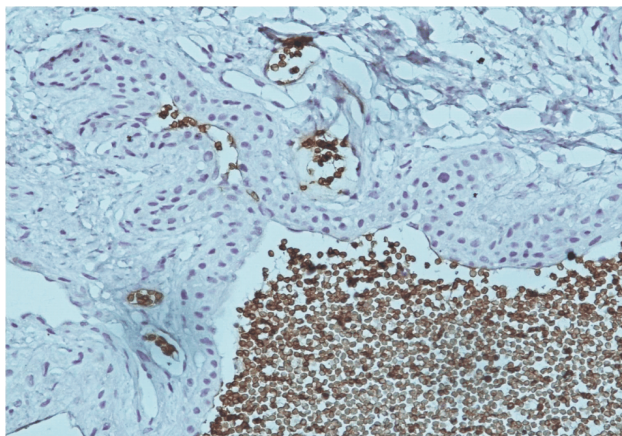


Figure 7 – Immunohistochemistry: staining of erythrocytes for Glut1, ob. 10×.

Discussion

In 1936, Touraine A *et al.* reported a patient with multiple disseminated glomus tumors. The patient had a

positive in endothelial cells and negative in tumor cells (Figure 6). The tumor was also negative for S100, AE1-AE3, and Glut1 (Figure 7). Less than 1% of tumor cells were positive for Ki-67.

The diagnosis of hereditary multiple glomuvenous malformations was established. The patient was advised to return for periodical observation.

positive family history and an autosomal dominant inheritance was suggested. This probably represents the first publication describing this rare disease [6].

Our patient presented with many of these same features. In our report, three close relatives from three consecutive generations had similar lesions.

In the past, GVMs were improperly called "glomangiomas" or "multiple glomus tumors", terms that are still widely used for describing this condition.

A word search in *PubMed* literature database about glomangioma reveals publications describing distinct disorders, which could create confusions. Glomangioma often appears to be synonymous with: glomus tumor, glomuvenous malformation, glomangiomyoma, or paraganglioma. Especially paragangliomas have to be distinguished from the others, because they have a different etiology, originating from the APUD cell system, whereas glomangiomas derive from smooth muscle cells or pericytes [7].

In the past, glomangioma, glomangiomyoma, and solid glomus tumors were classified as histological types of glomus tumor (GT). Some authors still use this classification and denominate as glomangiomas those tumors with wide vascular lumina, diffuse angiomatous growth and a striking glomus component. On the contrary, glomangiomyoma describe those tumors with smooth muscle differentiation [8, 9].

Other authors suggest that the two terms (glomangioma vs. glomangiomyoma) designate the same lesion (both forms of GVMs), with differences regarding the existence of transitional areas from typical glomus cells to conventional smooth muscle cells [10].

Nowadays, glomangiomas or GVMs are treated as separate entities and are considered vascular malformations caused by mutations in glomulin gene that generate a truncated glomulin protein. To date, little is known about the roles of glomulin. It seems to play a role in vascular smooth-muscle cells differentiation and late maturation. Data also suggest that glomulin could regulate signaling through TGF- β receptors [4, 11].

Histologically, GVMs are non-encapsulated tumors with large, irregular cavernous vessels similar to venous malformations, but the vascular spaces are lined by glomus cells. The glomus cells are monomorphic, round or polygonal, with plump nuclei and eosinophilic cytoplasm. Immunohistochemistry is an important diagnostic tool. GVMs clearly exhibit smooth muscle characteristics. As modified smooth muscle cells, glomus cells are positive for alpha smooth muscle actin, while vascular endothelium is positive for CD34 [7]. Our case was also positive for HHF35 (pan-actin) and h-caldesmon, useful additional markers.

The differential diagnosis includes blue rubber bleb-nervus syndrome, Maffucci syndrome, glomus tumor, hemangiomas, spiradenoma, angioliipoma, leiomyoma, or hemangiopericytoma [12–15].

GVMs differ clinically from glomus tumors: occur frequently in childhood (rarely congenital) and become more apparent with maturity, are usually asymptomatic but may become painful after compression, and do not have predilection for subungual sites [12]. By contrast, glomus tumors occur in young adults and are painful solitary lesions, localized especially in the nail bed. The histology of solitary glomus tumor is more cellular, with a dense glomus cell infiltration. GVMs are less likely to encapsulate than glomus tumors [13].

Venous malformations (VM) are isolated bluish lesions, compressible under external pressure, and painful in association with stasis and expansion; phleboliths are suggestive. Unlike VM, GVMs are less compressible and may become painful under compression. The history and physical findings help to distinguish GVM from VM; these clinical criteria also help in the differentiating other cutaneous venous anomalies, such as blue rubber bleb nevus syndrome, and Maffucci syndrome [1].

Blue rubber bleb-nervus syndrome is a rare disorder characterized by multifocal cutaneous and visceral venous malformations; the lesions are blue easily compressible nodules, involving the skin or soft tissues. It occurs in a mostly sporadic pattern and bleeding hemangiomas of the gastrointestinal tract are cause of morbidity and mortality [14].

Maffucci syndrome associates multiple enchondromas and subcutaneous hemangio-endotheliomas, which are vascular nodules localized on the fingers and toes [15].

The other benign tumors are usually acquired later in life. Clinical characteristics (blue and poorly compressible nodules) and pathological features are helpful in distinguish GVMs [12–15].

GVMs are often treated similar to typical venous malformations (surgical excision, laser treatment or sclerotherapy), but surgical excision seems to be the treatment of choice for painful lesions. Treatment is not always indicated, particularly in asymptomatic cases [16, 17].

Conclusions

To date, there have not been reported associations between GVMs and allergic reactions and it is difficult to conclude that these conditions are linked. GVMs are still misdiagnosed and can prove to be a diagnostic challenge; therefore, we have to be aware of this condition, especially in young patients with multiple lesions and a positive family history.

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Received: August 20th, 2012

Accepted: December 14th, 2012