

CASE REPORT

Glomangiomas: Multiple nodular and plaque-like lesions

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ABSTRACT

Glomangiomas are rare benign neoplasm arising from the glomus body, first described by Hoyer in 1877. They are usually solitary, small bluish, painful lesions usually located under the fingernails. They are more common in females than in males. Multiple lesions are slightly more common in males and they develop 10–15 years earlier than single lesions; about one third of the cases of multiple tumors occur in those younger than 20 years. In rare cases, the tumors may present in other body areas. Multiple tumors are less likely to be painful. Congenital glomus tumors are rare; they are plaque like in appearance and are considered a variant of multiple glomus tumors. Familial glomangiomas have been associated with a variety of deletions in the glomulin gene, and are inherited in an autosomal dominant manner, with incomplete penetrance.

KEY WORDS: glomangiomas, glomus tumor, multiple, nodular, plaque

INTRODUCTION

Tumors arise from glomus cells, a thermoregulatory shunt concentrated in the fingers and toes, are uncommon, benign perivascular tumours.¹ They have been categorized into subtypes, which include solitary, multiple, solid, diffuse, adult, and pediatric.² More recently, these tumors have been classified into two major subtypes: solitary glomus tumors and multiple glomus tumors, which are also known as glomangiomas or glomuvenous malformations.³ Each variant has distinct clinical and histopathologic characteristics.

Glomangiomas usually asymptomatic multiple pink-to-blue nodules or plaque like lesions. They occur in childhood and adolescence, and do not have a predilection for the subungual region.⁴⁻⁵

Multiple glomangiomas are rare and comprise about 10 percent of all glomus tumors.⁶

In this issue, we describe two cases with different variants of glomangiomas.

CASE 1

A 28 year-old Indian male patient presented 6 months before-to Dermatology OPD/ Jahra Hospital with asymptomatic multiple lesions of about 15 years duration. The patient experienced that the condition started with few lesions and progressively increased in number. Clinical examination demonstrated numerous painless, blue nodules of different size 0.5-1.5 cm scattered all over the body including; face, chest, back, upper and lower extremities (Fig. 1-5). Some of the nodules are grouped together (Fig. 6-8). Most of the nod-

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ules are firm in consistency, but some are partially compressible and non-tender to palpation or pressure. Mucous membranes, hair and nail were free. Medical history and examination were also free. Family history was negative for similar cases.

A biopsy was taken from one of the nodules on the left forearm. Histological examination revealed non-capsulated inflammatory infiltrate with multiple irregular vascular channels lined with endothelial cells. The infiltrate composed mainly from monomorphic round or polygonal glomus cells with round or ovoid nucleus and scant eosinophilic cytoplasm. Several layers of these cells are present in the walls of vascular channels and in the adjacent stroma. Multiple RBCs are also, present within the vascular channels (Fig. 9-11). So, this patient was fitting, both clinically and pathologically, with multiple nodular glomangiomas.



Fig. 1 A small, keratotic blue glomus nodule on the neck.



Fig. 2 A small slightly bluish glomus nodule on the right side of the right ring finger.



Fig. 3 A small blue glomus nodule on the left leg.



Fig. 4 A large slightly bluish glomus nodule on the ulnar side of the right forearm.



Fig. 5 A large slightly bluish glomus nodule on the left thigh.



Fig. 6 Multiple glomus nodules on the left arm.



Fig. 7 Multiple grouped glomus nodules on the left forearm.



Fig. 8 Multiple closely set glomus nodules on the back.

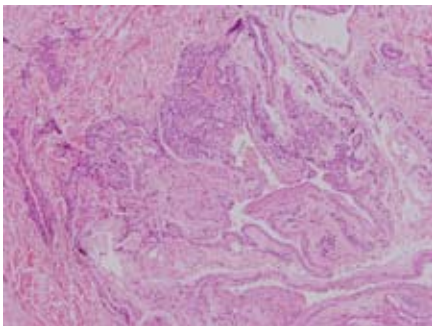


Fig. 9, 10x Multiple, irregular vascular channels surrounded with inflammatory infiltrate.

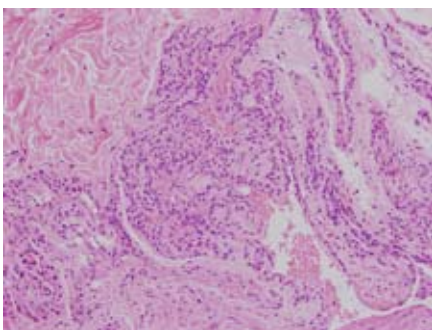


Fig. 10, 20x Vascular channels are lined with endothelial cells that coated with glomus cells.

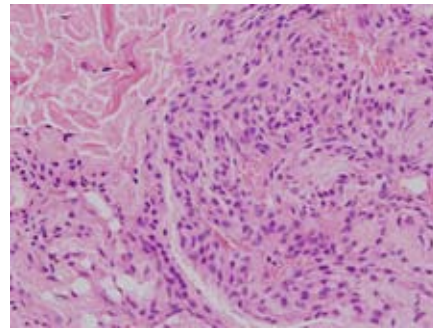


Fig. 11, 40x Higher magnification shows prominent monomorphic, eosinophilic glomus cells. Vascular channels contain RBCs.

CASE 2

A 36 year-old Kuwaiti male patient presented 5 months before-to Dermatology OPD/ Jahra Hospital with asymptomatic large lesion on left leg of about 25 years duration. Clinical examination demonstrated a large 5×15cm sized, raised hyperkeratotic dark blue nodular plaque with a cobblestone-like appearance, located on the medial side of the lower portion of the left leg. Multiple similar closely set, satellites, nodules were also present in the adjacent area. Some of these nodules were angiomatous and bluish pink in appearance (Fig. 12 A,B). The nodules were slightly compressible but not emptied by external pressure or elevation of the leg. They were associated with minor pain on pressure. Mucous membranes, hair and nail were free. Medical history and examination were also free. Family history was negative for similar cases. Unfortunately, the patient refused to take a biopsy from the lesion and mentioned that he adapted on this condition and he is looking only for some creams to relief the sensation of dryness, he feels. However, this case was compatible clinically with plaque type glomangiomas.



Fig 12 (A) Large keratotic nodular plaque on the medial side of the lower portion of the left leg.



Fig 12 (B) Closeup.

COMMENT

Glomus tumours are uncommon benign neoplasia, first described by Hoyer in 1877, while the first complete clinical description was given by Masson in 1924.⁷ Glomus tumors are thought to represent neoplastic proliferations of modified smooth muscle cells, called glomus cells, located in the walls of the Sucquet-Hoyer canal, a specialized arteriovenous anastomosis found most often in the fingers and play an important role in thermoregulation.¹

Glomus tumors are classified into solid glomus tumors, glomangiomas, or glomangiomyomas according to the predominant histologic component present, that is, glomus cells, vascular spaces or blood vessels (angiomatoid), or smooth muscle fibers, respectively.⁸

Solid Glomus tumors are usually present in young adults (ages 20-40) as a small, solitary, blue-red papule or nodule of the distal extremities, with a predilection for subungual sites. They are typically painful, often causing paroxysmal pain in response to temperature changes or pressure.¹

Glomangiomas, also known as glomuvenous malformations, are a rare multiple variant accounting for 10% of cases, most often seen in children or adolescence, and in general show no gender predilection.⁹ Glomangiomas are thought to be inherited in an autosomal dominant pattern with incomplete penetrance and variable expression. Familial glomangiomas have been associated with a variety of deletions in the glomulin gene mapped to chromosome 1p21-p22. Glomangiomas are thought to be a result of loss of function mutations in the cytoplasmic protein glomulin.¹⁰⁻¹¹

Glomangiomas are subdivided clinically into nodular and plaque-like lesions. They can vary in color from pink-to-blue and often become darker, and sometimes hyperkeratotic with age. Interestingly, while glomus tumors predominate on the hands and fingers especially, glomangiomas can occur in a wide anatomic distribution, to include sites not known to contain glomus cells. Extracutaneous sites have been reported, including involvement of the gastrointestinal tract, trachea, nerve, bone, mediastinum, liver, pancreas, and ovary. One ex-

planation for this finding is that these tumors may arise from pluripotent mesenchymal perivascular cells that can differentiate into glomus cells or even arise from ordinary smooth muscle cells.¹

Some authors¹ subdivide glomangiomas into regional or localized, disseminated, and congenital plaque-like forms, as follows:

- **Regional variant** - Consists of blue-to-purple partially compressible papules or nodules that are grouped and limited to a specific area, most commonly to an extremity.
- **Disseminated type** - Consists of multiple lesions distributed over the body with no specific grouping; less common than the regional variant.
- **Congenital plaque like glomus tumors** - Consist of either grouped papules that coalesce to form indurated plaques or clusters of discrete nodules; rarest variant of multiple glomus tumors.

Congenital glomangioma is extremely rare, with less than 20 well documented cases in world literature.¹²⁻¹³ Lesions of the plaque type were predominant over nodules. Often, present at birth, increases proportionally to child's growth in weight and stature and can be extremely painful. One case of congenital multiple glomangioma showed partial spontaneous regression.¹⁴

The prognosis for patients with glomangiomas is excellent, and most patients never experience any related medical problems. However, in one report, a patient with more than 400 glomangiomas had thrombocytopenia as a result of platelet sequestration (ie, Kasabach-Merritt syndrome).¹⁴ Malignant

transformation (glomangiosarcomas) within glomus tumors is extremely rare and typically represents a locally infiltrative malignancy; however, metastases have been described and are associated with a very poor prognosis.¹⁵⁻¹⁶ Features of glomangiosarcomas may include the following:¹⁵

- Size larger than 2 cm
- Rapid growth
- Deep soft tissue involvement

Glomangiomas differ clinically from glomus tumors in that they occur in childhood and adolescence, usually asymptomatic, do not have a predilection for the subungual region, and often are multifocal.⁴⁻⁵ Histologically, Glomangiomas are less well circumscribed (not capsulated) and less solid appearing than their solitary counterparts. They contain multiple irregular, dilated, endothelium-lined vascular channels that contain red blood cells. The vascular spaces are larger than those in a solitary glomus tumor. Small aggregates of cuboidal, glomus cells are present in the walls of these channels and in small clusters in the adjacent stroma. Each cell has a round or ovoid nucleus and scant eosinophilic cytoplasm. The overall appearance of multiple glomus tumors accounts for their alternate name, glomangiomas.¹⁻⁸ Glomangiosarcomas resemble benign glomus tumors. However, glomangiosarcomas have more atypia, pleomorphism, and mitotic figures, and an invasive growth pattern.¹⁵⁻¹⁶

Tumor cells of glomangiomas are positive for α -smooth muscle actin and vimentin but negative for CD31, CD34, von Willibrand factor, and S-100.^{3-4,10} Most cases are also negative for desmin, but rare desmin expression has been reported.¹⁷

Routine laboratory studies are not helpful in patients with glomangiomas. CBC count is required only in rare cases with widely disseminated lesions in which platelet sequestration is a concern.¹ High-resolution is probably the criterion standard for the imaging of glomus tumors, followed by contrast-enhanced CT. Glomustumors are strongly enhancing masses by both CT and MRI.¹⁸

The main differential diagnosis of inherited glomangiomas or glomuvenous malformation (GVM) is inherited venous malformations (VMs) (Table 1). In a retrospective study of patients with superficial venous anomalies, Laurence et al., in 2004, found that GVM are accounted for 5.1% of venous anomalies and are frequently inher-

ited (63.8%), whereas VMs are rarely familial (1.2%).¹⁹

The diagnosis is more likely GVM if the lesion is pink to bluish purple or dark blue and has a cobblestone-like appearance with minor hyperkeratosis, especially if the lesion is located on an extremity. For segmental GVM, the lesion is pink in infancy and rapidly worsens, thickens, and turns to purple or dark blue.

However, the diagnosis is more likely to be VMs if there is an isolated bluish mucosal or subcutaneous lesion, involving skin and underlying muscles, or an isolated intramuscular or periarticular vascular mass. Phleboliths are suggestive of VMs, and the diagnosis is further suggested if

Table 1 DD between Glomangiomas (Glomuvenous malformations, GVM) & Venous malformations (VMs)¹⁹

	GVM	VMs
Inheritance	Usually familial , AD	Sporadic, rarely familial
Gene mutations	glomulin gene	TIE2/TEK gene
Appearance	Raised, with a cobblestone-like appearance	Typically hemispherical
Color	Pink in infants / deep blue to deep purple in children and adults	Various hues of blue
Depth	Skin and subcutis , rarely mucosa	Skin and oral mucosa, but also occur in skeletal muscles
Site	Extremities; common	Cervicofacial area (50%) and extremities (37%)
Surface	Slightly hyperkeratotic	-
Trauma	Development of new lesions (17%)	-
Compression	Usually not compressible	Soft and easily emptied by external pressure or when in a dependent position
Pain	Slightly painful with external pressure (54.9%)	Painful after activity or with changes in temperature (44%), or with hormonal changes but not by compression
Elastic compressive garments	Aggravate the pain	Improve the pain
Coagulopathy	-ve	Localized coagulopathy causes thromboses, pain and phleboliths,
Pathology	Venous-like channels surrounded by poorly differentiated smooth muscle-like glomus cells that stain positively for smooth muscle α -actin.	large, ectatic channels with thin walls and sparse smooth muscle
Therapy	Resection of small lesions	Compression, Sclerotherapy,

GVM; Glomuvenous malformations, Glomangiomas

VM; venous malformations

the lesion shrinks by external pressure or when in a dependent position. VMs are typically painful in the morning, probably due to stasis and expansion, whereas GVM are typically painful when compressed. More than 50% of patients with VMs noted increased pain with onset of puberty, menstrual cycles, antiovalant drugs, or pregnancy. This type of hormonal modulation was reported, only by few patients with GVM.

Distinguishing between GVM and VMs is important in planning therapy. Elastic compressive garments often aggravate the pain in a patient with GVM. In contrast, a patient with large VMs in an extremity is symptomatically improved by external compression. Resection of a small GVM is usually easily accomplished, as these lesions are located superficially in the cutaneous and subcutaneous tissue. In contrast, VMs are often difficult to excise completely, because they permeate surrounding tissues and often involve deep structures. Sclerotherapy is more effective in shrinking VMs²⁰ compared with GVM.²¹ Extensive VMs, mainly if located in the trunk or a limb, was associated with a lifelong, low-grade localized intravascular coagulopathy, characterized by low fibrinogen and high D-dimer levels. This could evolve to disseminated intravascular coagulopathy following trauma, operation, or sclerotherapy. Localized intravascular coagulopathy causes thromboses, pain and phleboliths, and intraoperative and postoperative bleeding and should be treated with low-molecular-weight heparin. Interestingly, this coagulopathy was not observed in patients with extensive GVM.²²

These clinical criteria also help in the differential diagnosis of other cutaneous venous anomalies,

such as Blue nevus, Bluerubber bleb nevus syndrome (BRBNS), also known as Bean syndrome, Maffucci syndrome and Kaposi sarcoma. It has been suggested that many glomangiomas have been incorrectly diagnosed in the literature as BRBNS.⁴⁻²³ Unlike BRBNS, glomangiomas are less compressible and there have not been reports of gastrointestinal involvement with multiple glomangiomas. Dilated venous spaces can be observed on histopathologic examination with both diseases; however, BRBNS lacks the characteristic glomus cells.²³⁻²⁴

Hyperkeratotic glomangiomas must also be differentiated from cutaneous hyperkeratotic capillary-venous malformation (HCCVMs), known to be associated with familial cerebral cavernous malformations (CCMs)²⁵⁻²⁶ which cause headaches, seizures and sometimes intracranial hemorrhage. HCCVMs are congenital crimson-coloured or red-to-purple, irregularly shaped, hyperkeratotic macules, plaques or patches, the size of which can extend to several centimetres.²⁵ Tiny hyperkeratotic papules (3-10 mm) have also been reported.²⁷⁻²⁸ By light microscopy, the lesions extend into both dermis and hypodermis and are composed of dilated capillaries and blood-filled venous-like channels. These abnormal vascular spaces lined by a single layer of endothelium and thin fibrous adventitia without smooth muscle cells.

Excision for multiple glomangiomas, may be difficult because of their poor circumscription, multifocal nature and the large number of lesions. So, excision should be limited to symptomatic lesions only. In a recent series of large facial glomangiomas,²¹ MRI was the best modality for definition of the extent of the lesions and

their relationship to other anatomic structures. In this same series, surgical resection reduced the area of discoloration and improved facial contour. Other reported treatment modalities, more useful in treating multiple lesions, include argon and carbon dioxide laser therapy, electron-beam radiation, and sclerotherapy with hypertonic saline or sodium tetradecyl sulfate. However, sclerotherapy was found to be less effective than for venous malformations.²⁰⁻²¹ Periodic observation of asymptomatic lesions is usually required.²

The treatment recommendations for glomangiomas are based on a few case reports. Wide local excision is adequate treatment and probably is the treatment of choice. However, geometric excision is probably a reasonable alternative in cosmetically sensitive areas.¹⁵

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