Glomuvenous Malformations: A Case Report and Review

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ABSTRACT:

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Glomuvenous malformations (GVMs), previously known as glomangiomas, are benign localized tumors of the skin arising from glomus cells. GVMs often appear during infancy and childhood as a small solitary, or multiple papulonodular lesions commonly located on extremities. The disease diagnosis is based on clinical and microscopic finding with a definite diagnosis confirmed by genetic test. The treatment of choice is surgical resection for isolated GVMs. Sclerotherapy and vascular laser therapy may also be helpful for multiple variant. In this report, we describe a rare case of sporadic GVMs in a 22-year-old male presented with a history of multiple dark violaceous to bluish papules and nodules on the left wrist, left ankle and left side of lower back since he was 10 years old. His clinical and histopathological features were compatible with disseminated pattern of multiple GVMs. In addition, literature review on the clinical features, diagnosis, differential diagnosis, clinical course and treatment of the disease was done.

Key words: Glomuvenous malformations, glomangioma, vascular malformation

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Case report

A 22-year-old Thai male presented with multiple dark violaceous to bluish papules and nodules since he was 10 years old. Initially, the lesion appeared on the left wrist as a bluish papule. There was a gradual increase in the number and size of the lesions. New lesions continued to appear on the left ankle and the left side of lower back. Some of the lesions were painful, precipitated by trauma or pressure. He had no evidence of anemia or bleeding from visceral site. Neither similar skin lesion nor tumor was present in his family members.

Physical examination revealed multiple dark violaceous to bluish papules and nodules scattered on the left wrist, left ankle and the left side of lower back (Figure 1). These lesions were non-compressible and tender upon deep palpation. There was no associated thrill or bruit.

A punch biopsy from a lesion on the left wrist revealed irregular branching dilated vascular channels with benign endothelium, surrounded by cuboidal cells with uniform round nuclei and eosinophilic cytoplasm (glomus cells), presented throughout the reticular dermis (Figure 2). The endothelial cells were positive for CD31 and CD34 and surrounding glomus cells positive for α-smooth muscle actin (Figure 3). Genetic testing was planned but the test was not performed due to financial problem. A diagnosis of glomangioma was made from the clinicopathological finding.

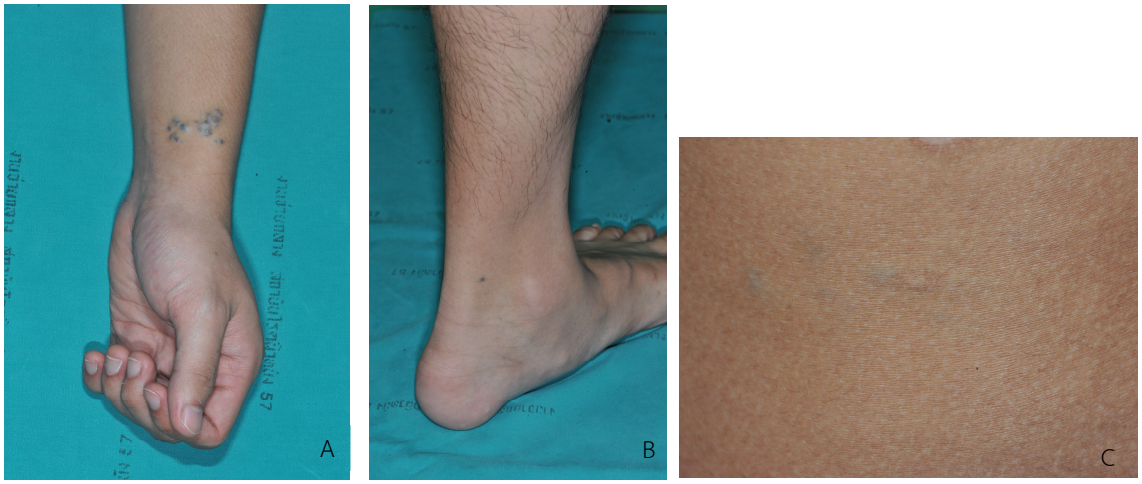

Figure 1 Multiple dark violaceous to bluish papules and nodules scattered on A) the left wrist, B) left ankle and C) left lower back.

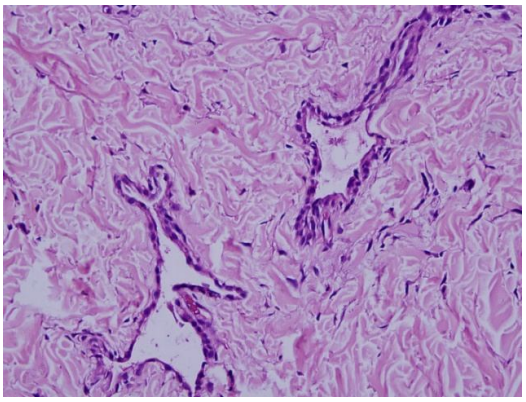

Figure 2 Histopathologic examination of a punch biopsy specimen from the left wrist reveals dilated vascular channels surrounded by cuboidal cells with uniform round nuclei and eosinophilic cytoplasm in reticular dermis (hematoxylin and eosin staining, original magnification X40).

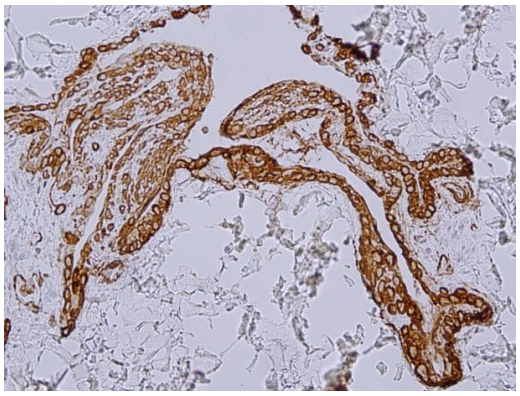

Figure 3 Positive reaction of glomus cells on immunohistochemistry (**α**-smooth muscle actin staining, original magnification X40).

Discussion

Glomuvenous malformations (GVMs), previously known as glomangiomas, are benign localized tumors of the skin arising from glomus cells[1]. They are composed of thin-walled vascular channels surrounded by proliferating glomus cells and nerve fibers. Glomus cells are modified smooth muscle cells involved in arteriovenous anastomoses and play a role in thermoregulation. They are comprised of glomus bodies, which are normally present in acral skin. However, these tumors can be found in other locations on the body[2,3]. GVMs can be either sporadic or inherited. Approximately two-thirds of patients with GVMs have a family history of similar lesions. Inherited GVMs result from a heterozygous germline mutation in the *glomulin* gene (*GLMN*), which is localized to chromosome 1p21- 22. This generates a truncated glomulin protein that interferes with vascular smooth muscle differentiation and late maturation of vascular smooth muscle cells, resulting in the formation of glomus cells. They are often inherited in an autosomal dominant pattern with incomplete penetrance and variable expressivity[4,5].

GVMs often appear during infancy, childhood and adolescence as a small solitary lesion, or widely scattered red to blue papulonodules, or large segmental plaques. GVMs may be present at birth and slowly expand during childhood. GVMs have a predilection for the extremities but can occur on the head and back as well[4-7]. GVMs could be a solitary or multiple type. The most common type is a solitary nodule that may be

painful. The episodes of pain can be elicited by change in temperature and tactile stimuli. Multiple GVMs are uncommon and represent less than 10% of all reported cases. In relative to solitary lesions, multiple GVMs usually present with earlier onset; one third presenting before 20 years of age[8]. Multiple type can be subdivided into regional, disseminated, and congenital plaque-like forms[9]. Congenital plaque-like form is the rarest form, consisting of either grouped pink or light blue papules that coalesce to form indurated dark blue plaques or clusters of discrete nodules[8,10].

Microscopic finding can confirm the final diagnosis and also determine subtype of GVM. Solitary lesion appears as a well-circumscribed nodule with vascular spaces surrounded by clusters of round or polygonal cells with plump nuclei and scant eosinophilic cytoplasm (glomus cells). Multiple lesions are not well circumscribed, with an overall appearance more representative of a hemangioma. They contain numerous, irregular, dilated, vascular channels that are larger than those observed in a solitary lesion. Focal, narrow, aggregates of glomus cells are present in the walls of these channels[2,3]. Glomus cells stain positively for α-smooth muscle actin and vimentin, but negative for desmin, S-100, and von Willebrand factor. Genetic testing can differentiate small multifocal GVMs from other venous malformations (VMS) (Table 1)[11].

The clinical differential diagnosis of GVMs includes venous malformation (VM), inherited mucocutaneous venous malformation (VMCMs) and blue rubber bleb nevus syndrome (BRBN) (Table 1). GVMs differ in clinical presentation from VM in a number of aspects. They tend to be more nodular or cobblestone-like in appearance (especially on the extremities), more bluish in color, less compressible by palpation, and do not swell with exercise or dependency. Differentiating GVMs from other vascular malformation is important due to different effective treatment options[11-12].

Congenital glomuvenous malformations are usually gradually increased in size with age, and can present as grouped papules coalescing to form indurated plaques. Most patients develop new small satellite lesions later in life, often during puberty.[2] Congenital plaque-type form of GVM is severe and extensive. However, like other forms of GVM, congenital plaque-type GVM is limited to the skin and subcutaneous tissue. Visceral organs, joints and oral mucosa are typically spared[8,10].

Table 1 Differential diagnosis of GVM[8,11,16,17]

	GVM	VM	VMCM	BRBN
Lesions	- Pink to bluish purple, dark blue papules or nodules - Cobblestone appearance - Painful when compressed	- Dark blue-purple plaques - Painful in the morning (50% associated with hormonal change)	-Multifocal bluish lesions -less compressible	Multifocal hyperkeratotic bluish blebs
Location	Acral areas and extremities (rare mucosal involvement and no visceral involvement)	Cervicofacial areas and lower extremities (may have mucous membrane and visceral involvement)	Extremities and mucosa	-Palms and soles -Visceral involvement
Organ involvement	Limited to skin and subcutaneous tissue	Often involve muscle and joints	Limited to skin and subcutaneous tissue	Often involve muscle and joints
Progression	Rapidly progressive and enlarging	Slow growth	Enlarged with time	Increased in size and number over time
Histological findings	Irregular cavities lined by glomus cells; positive for vimentin and α-smooth muscle actin and negative for desmin	Enlarged venous channels, flat layer of endothelial cells, sparse smooth muscle cells		
Mutated gene	*Glomulin* gene; (Chromosome 1p21-22) loss of function mutation	*TIE-2/TEK* gene; somatic activation	*TIE-2/TEK* gene; (Chromosome 9p) germinal activation	*TIE-2/TEK* gene; somatic activation
Inheritance	Autosomal dominant	Sporadic	Autosomal dominant	Sporadic

Abbreviations: GVM, glomuvenous malformation; *TIE-2*, protein receptor tyrosine kinase, epithelial specific; VM, venous malformation; VMCM, inherited mucocutaneous venous malformation; BRBN, blue rubber bleb nevus syndrome

Regarding to benign nature of the disease with no previous report of malignant change, the goal of treatment is symptomatic treatment. However, management of multiple GVMs is quite difficult. While the treatment of choice for isolated cutaneous GVMs is surgical resection, it is often impractical in cases of multiple lesions and gradual recurrence is common[13]. Mounayer C. et al[12]. has demonstrated that surgical resection can reduce the area of discoloration in facial "glomangioma", while sclerotherapy has been proven to be less effective for venous malformations. Residual lesions following subtotal surgical resections may slowly re-expand. Laser surgery employing carbon dioxide, Nd:YAG, and pulsed dye lasers may also be helpful for small lesions[13-14]. Genetic counseling is indicated for inherited GVMs. Genetic counseling should include the review for undiagnosed lesions among the relatives and discussion of the autosomal dominant inheritance with incomplete penetrance and variable expressivity nature of the disorder[8].

Genetic screening for *glomulin* mutations on genomic DNA can aid the diagnosis. Seventy percent of families with inherited GVM share one of the four common mutations (108C → A, 157delAAGAA, 554delA+556delCCT and 1179delCAA), whereas the other 30% have unique mutations. Thus, screening of these four common mutations should be the first step in molecular diagnosis of GVMs.[4]

Our patient was a sporadic case who presented in childhood with multiple dark violaceous to bluish papules and nodules, fitting in with the multiple variants of GVMs. The patient has been counseled about the natural course of the disease. Laser treatment has been suggested yet the patient has denied due to personal matter.

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