Glomuvenous Malformation (Glomangioma) and Venous Malformation

Distinct Clinicopathologic and Genetic Entities

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Objectives: To develop clinical criteria that permit clinical distinction between inherited glomuvenous malformation (GVM), known as glomangioma, and inherited cutaneomucosal venous malformation and to test these criteria on sporadic lesions.

Design: Clinical data were compiled for 1685 patients with inherited or sporadic cutaneous venous anomalies. Based on a cohort of patients with a mutation in the TIE2 or glo- mulin gene or a histologic diagnosis, we defined clinical criteria for inherited GVM and cutaneomucosal venous malformation. We then applied these criteria to sporadic cases in a blinded manner and genetically or histologically confirmed this clinical diagnosis whenever possible.

Results: Glomuvenous malformations accounted for 5.1% of venous anomalies and were frequently inherited (63.8%), whereas venous malformations were rarely familial (1.2%). Glomuvenous malformations were nodular and scattered, or plaque-like and segmental, with color varying from pink to purplish dark blue, whereas most venous malformations (VMs) were soft, blue, and often localized vascular lesions. Glomuvenous malformations were mainly located on the extremities and involved skin and subcutis, whereas VMs commonly affected muscles and joints (P<.001). Glomuvenous malformations had a distinct raised, often hyperkeratotic cobblestone-like appearance and could not be completely emptied by compression, unlike VMs. Glomu- venous malformations were painful by compression, whereas VMs were painful on awakening, after activity, or with hormonal changes. Elastic compressive garments aggravated pain in GVMs, in contrast to VMs.

Conclusions: This large series of patients with superficial venous anomalies established clinical features that distinguish VMs and GVMs. This differential diagnosis is essential, as the outcome and the treatment for GVMs differ.

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Patients with venous malformation (VM) are the second most common referrals to centers for vascular anomalies. Venous lesions typically involve skin, subcutis, and mucosa, but they also arise in muscle, bones, and internal organs. Depending on size and location, these slow-flow malformations can cause pain, create anatomic distortion, and occasionally threaten life because of bleeding, expansion, or obstruction of a vital structure.

Diagnosis and management of VMs have been hampered by imprecise and improper terminology. The erroneous label “cavernous hemangioma” continues to cause confusion with hemangioma, the most common tumor of infancy. A clinical and biologic classification of vascular anomalies that separates tumors from malformations, first proposed in 1982, was accepted at the 1996 biennial meeting of the International Society for the Study of Vascular Anomalies. This simple binary nosologic system has been confirmed by radiological and immunohistochemical studies.

Venous malformations are composed of ectatic, thin-walled channels lined by flat endothelial cells and surrounded by a media that is irregularly deficient in smooth muscle cells. These abnormal channels permeate the epithelium; this explains the typical blue hue of cutaneomucosal venous lesions. However, some VMs have variable numbers of “glomus cells,” and, in the past, these have been called multiple glomus tumors or glomangiomas. Because they are not neoplastic, the more accurate term glomuvenous malformation (GVM) has been proposed.

Most VMs are sporadic; however, there are a few families that exhibit autosomal dominant transmission of VM or GVM. Linkage analysis revealed 2 different entities: one localizing to 9p21 and the other to 1p21. By histologic criteria, the 9p21-
linked families had cutaneomucosal venous malformation (CMVM) (Online Mendelian Inheritance in Man [OMIM] 600195), whereas families linked to 1p21 had GVM (glomangioma) (OMIM 138000). Cutaneomucosal venous malformation is caused by a single amino acid change in the angiotropin receptor TIE2/TEK, leading to a gain of function \(^{20,23}\) (OMIM 600221), whereas inherited GVM is caused by several loss-of-function mutations in glomulin \(^{17}\) (GLMN) (OMIM 601749).

Inheritable CMVM and GVM are specific vascular anomalies by histologic and molecular analyses; however, the clinical differences between these 2 lesions have not been formally examined. The aim of this study was to establish these different phenotypes. On the basis of genetic determinants, we defined statistically significant criteria for presentation, signs, and symptoms that permit clinical differentiation between inherited CMVM and inherited GVM. Furthermore, we applied these criteria to differentiate sporadic GVM from sporadic VM.

**METHODS**

This study was based on 1685 patients with venous anomalies (138 familial and 1547 sporadic) who were evaluated at Cliniques Universitaires Saint-Luc, Children’s Hospital, and Hôpital Lariboisière. All patients had venous anomalies located in the skin, subcutis, muscle, or joint. We omitted patients with cerebral, gastrointestinal, or hepatic VM.

First, we assessed clinical criteria that might permit differentiation between the 2 known inheritable venous lesions, ie, CMVM caused by mutations in the TIE2/TEK gene\(^{20,23}\) and GVM caused by mutations in the glomulin gene.\(^{17,23,24}\) For each patient (n = 138), we completed a clinical questionnaire (available from the author) that included inquiries regarding age at appearance of the venous anomaly, location, color, size, and number of lesions, as well as an assessment of pain and other symptoms. Histologic diagnosis on the basis of the histology report from the 3 institutions or genetic diagnosis was available for at least 1 affected member in each of the 30 families (4 from Brussels, 9 from Boston, and 17 from Paris).

Once the clinical criteria for the inherited disorders were established, they were used to study sporadic VM and GVM in 1547 patients seen at the 3 vascular anomalies centers (135 from Brussels, 394 from Boston, and 1018 from Paris). Patients from Brussels were reexamined without knowing the initial diagnosis and classified into 2 groups using the clinical criteria that had been defined for inherited venous anomalies. Patients from Boston were also blinded examined on the basis of colored photographs and medical records. Data for patients from Paris were obtained from clinical and anatomicopathological files. Histological diagnosis was available for 547 patients (35.4%). The data were statistically analyzed using Fisher exact test (2-tailed) with SYSTAT software (version 10; SPSS UK Ltd, London, England). Finally, we determined the ratio of GVM to VM, combining the patients from all 3 vascular anomalies centers.

**RESULTS**

**CLINICAL CRITERIA FOR INHERITED GVM AND INHERITED CMVM**

We evaluated 138 patients (30 families) with inherited venous anomalies. Thirty-three patients (2 families) with inherited CMVM had the gain-of-function mutation in TIE2\(^{20,23}\) (A. Irrthum, PhD, and Drs Enjolras, Boon, Mulliken, and Vikkula, unpublished data; April 2002), and 105 patients (28 families) with inherited GVM had loss-of-function mutations in the glomulin gene\(^{17,23,24}\) (P. Brouillard, PhD, M. Ghasseb, MS, and Drs Enjolras, Boon, Mulliken, and Vikkula, unpublished data, 2001). The diagnosis was histologically confirmed in 27 of these 30 families in which a biopsy or surgical resection had been done (Figure 1). The clinical findings and statistical analyses are summarized in the Table.

No sexual preponderance was noted for inherited GVM or CMVM. Sixty-four percent of families with inherited GVM had only 1 severely affected member with a lesion, often an extensive segmental GVM, whereas other members with the same mutation typically had minor scattered papulonodular lesions. This wide phenotypic variation was not seen in the 2 families with CMVM.

We identified 8 features that distinguish between patients with the 2 inherited venous anomalies:

1. Cutaneomucosal venous malformations were of various hues of blue, while GVMs varied from pink in infants to deep blue to deep purple in children and adults (Figure 2C and D and Figure 3A and C).
2. All GVMs involved skin and subcutis (P < .001), rarely mucosa (P < .001), and never extended deeply...
CLINICAL CRITERIA FOR SPORADIC GVM AND SPORADIC VM

In our cohort of 1685 patients with venous anomalies, 1547 had nonfamilial lesions, and of these, 30 had GVM and 1517 had VM. Histological findings confirmed that there were no pathologic differences between inherited and sporadic GVM or between inherited and sporadic VM. The pertinent clinical results and statistical analysis are summarized in the Table.

No sexual preponderance was found for sporadic GVM or VM. Sporadic GVM and inheritable GVM were clinically similar, and both could be differentiated from VM by several features. Sporadic GVM, like inherited GVM, (1) always involved skin and subcutis ($P < .001$), rarely involved mucosa ($P = .04$), and did not permeate muscle ($P < .001$) or a nearby joint space ($P = .16$) (Figure 2); (2) was bluish purple, raised, and cobblestone-like in appearance, except for the rare plaque-like GVM ($n = 1$); (3) could not be completely emptied by compression (Figure 3); (4) did not exhibit phleboliths on plain-film radiography, computed tomography, or magnetic resonance imaging (a finding typical of slow-flow lesions with stasis and thrombosis); and (5) was painful by compression in 52.1% of patients. Pain in GVM correlated with lesion size: 71.8% of painful cervicofacial lesions and 79.7% of painful extremity lesions were large (>$5\, cm$) ($P = .04$ and $P < .001$, respectively). However, pain was unrelated to changes in weather, time of day, activ-
ity, lesional location, or hormonal changes (puberty or menstrual cycle). In contrast, 61.9% of VMs were painful in the morning on awakening, but pain was not elicited by compression. In contrast, hormonal changes (puberty, menstruation, and pregnancy) increased pain in 73.9% of patients with VM. One infant with GVM had a von Willebrand factor deficiency.

In contrast to the clear clinical differences between VMs and GVMs, there were only a few features that significantly distinguished the inherited forms of these lesions from their sporadic counterparts: (1) unlike inherited lesions, all sporadic GVMs and CMVMs were diagnosed at birth ($P < .001$); (2) sporadic lesions were often single and extensive ($P < .001$); and (3) sporadic GVM was more common in the head and neck compared with inherited GVM (27.3% vs 7.7%) ($P < .001$).

**Figure 2.** Venous malformation (VM) compared with glomuvenous malformation (GVM) in the same location. A, Ten-year-old girl with uncommon hemifacial plaque-like inherited GVM. B, Nine-year-old boy with right facial cutaneous mucosal venous malformation that distorts the mouth. C, Twenty-six-year-old woman with extensive cutaneous and subcutaneous inherited GVM. Note the cobblestone-like appearance. D, Fourteen-year-old girl with extensive VM of the right lower extremity involving skin, subcutaneous tissue, muscle, and joint space, causing orthostatic hypotension and localized intravascular coagulopathy. E, Sixteen-year-old boy with thoracic plaque-like sporadic GVM. F, Ten-year-old boy with thoracic VM involving muscle.

**Figure 3.** A, Inherited glomuvenous malformation of the foot, unchanged by elevation (B). C, Collapse of venous malformation of the hand with elevation (D).

**COMMENT**

Patients with GVM in our 3 centers represented 5.1% of all venous anomalies. The frequency of inheritance for GVM was 63.8%, after omission of patients who were family members of index cases in the genetic studies. In contrast, only 1.2% of VMs were inherited.

Analysis of this large group of patients with superficial venous anomalies, supported by correlation with genetic and histological diagnostic information, permitted definition of clinical differences between VM and GVM. Either can be familial; however, the frequency differed. Glomuvenous malformations accounted for 5.1% of the total cohort of patients with venous anomalies and was familial in 63.8% of patients. The higher frequency of inheritable GVM in our series, compared with 38% reported in the literature, probably reflects the careful examination of family members. Often, there was only 1 severely affected member (the index case), whereas the
other family members had inconspicuous and asymptomatic lesions. No sexual predilection in patients with sporadic or inherited GVM was found in our series, although other authors have reported a male predominance. In contrast to GVM, inherited CMVM was uncommon (1.2% in our series), as expected by the small number of these families (n=4) described in the literature.

No major differences were found between sporadic and inherited lesions. However, we were able to define criteria that allow clinical differentiation between GVM and VM. 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 VM if there is an isolated bluish mucosal or subcutaneous lesion, involving skin and underlying muscles, or an isolated intramuscular or perivascular mass. Phleboliths are suggestive of VM, and the diagnosis is further suggested if the lesion shrinks by external pressure or when in a dependent position. Venous malformations are typically painful in the morning, probably due to stasis and expansion, whereas GVMs are typically painful when compressed. More than 50% of our patients with VM noted increased pain with onset of puberty, menstrual cycles, antiovulant drugs, or pregnancy. This type of hormonal modulation was not reported by patients with GVM.

Therefore, history and physical findings help to distinguish GVM from CMVM and VM, without need for genetic or histologic studies. These clinical criteria also help in the differential diagnosis of other cutaneous venous anomalies, such as blue rubber bleb nevus syndrome, also known as Bean syndrome and Maffucci syndrome. Hyperkeratotic GVM must also be differentiated from cutaneous hyperkeratotic capillary-venous malformation, known to be associated with familial cerebral cavernous malformations.

Distinguishing between GVM and VM is important in planning therapy. Elastic compressive garments often aggravate the pain in a patient with GVM. In contrast, a patient with a large VM 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 VM compared with GVM. Extensive VM, 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 any of our patients with extensive GVM or CMVM.

In conclusion, analysis of this large retrospective study of patients with superficial venous anomalies, supported by correlation with genetic and histological diagnostic information, permitted definition of clinical criteria for distinction between VM and GVM. Accurate diagnosis is important for the management of these patients.

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REFERENCES


