

# Congenital Plaque-Type Glomuvenous Malformations Presenting in Childhood

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**Background:** Glomuvenous malformations (GVMs) are now considered a separate entity from venous malformations. The rarest type of GVM is the generalized congenital plaque-type GVM.

**Observations:** We present 10 new cases of congenital plaque-type GVM and describe their clinical progression and treatment. Mutations in the glomulin gene were found in those patients who participated in the genetic study.

**Conclusions:** Congenital plaque-type GVMs are unique in their congenital nature, extensive distribution, difficult to diagnose and treat, and progressive involvement after birth. Most cases are familial, yet affected relatives usually have only minor lesions. The lesions of congenital plaque-type GVM are severe, visible at birth, and usu-

ally mistaken for extensive venous malformations. Vascular malformations are divided by hemodynamic type into slow-flow and fast-flow lesions. Slow-flow lesions are subcategorized as capillary, lymphatic, and venous.<sup>1</sup> Capillary malformations are flat, sharply demarcated, red-pink vascular stains of the skin commonly referred to as port-wine stains. These persist throughout life and are characterized histologically by dilated capillaries within the dermis. They slowly increase in size with age. Lymphatic malformations are spongelike collections of abnormal channels and spaces that contain clear lymphatic fluid, causing an excess of fluid to accumulate and dilate the lymphatic channels. This results in swelling of the affected area and, if extensive, can cause enlargement of soft tissues and bones.

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**V**ENOUS ANOMALIES ARE composed of malformed channels lined by media that are focally deficient in smooth muscle cells. Some venous malformations (VMs) have an increased number of rounded cells in their walls known as glomus cells. In the past, these have been known as glomus tumors or glomangiomas. However, these lesions have now been renamed *glomuve-nous malformations* (GVMs) to stress the fact that they are not true tumors as suggested by the suffix *-oma*<sup>2</sup> but are indeed malformations presenting in the fetus. These lesions have been associated with a mutation in the glomulin gene.

We herein describe 10 patients with the rare generalized congenital plaque-type GVM. These lesions are unique in their congenital nature, extensive distribution, difficult to diagnose in a young patient, and progressive involvement after birth.<sup>1</sup>

## REPORT OF CASES

Patients were accrued in the following way: 6 from France (examined by O.E.), including patients originally from Central Africa,

Portugal, Iran, Algeria, and France; 2 from the United States (examined by S.B.M. and F.B.); 1 from Sweden (examined by A.-M.R.); and 1 from Spain (examined by E.B.).

## CASE 1

An adopted white male infant from the United States with a normal prenatal history presented at 1 month of age with a vascular anomaly over his right leg (**Figure 1**) and a patchy macular vascular stain on his left arm. Both lesions were present from birth. By 6 months of age, he demonstrated a purple-pink vascular patch on his left leg, scrotum, and bilateral plantar feet. By 21 months of age, small vascular plaques were noted on his lower lip and face. At 17 months of age, magnetic resonance imaging of the brain, abdomen, and lower limbs was performed to evaluate the extent of the VM. Findings in the brain and abdomen were normal, with no evidence of abnormally dilated vascular structures. Findings in his lower extremity demonstrated numerous varicosities in the subcutaneous tissue of the right anteromedial thigh and leg. The venous system of both lower extremities was

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**Figure 1.** A male infant at 1 month of age (case 1) with a red-purple plaque on the inner thigh and atrophy of the overlying cutis.

patient. Results of biopsies of shoulder and thigh lesions performed at 19 months of age showed GVM. Molecular studies were not performed. With time, it has become apparent that he has a mild form of autism but is otherwise healthy. At 2½ years of age, the lesions had become more apparent and nodular (**Figure 2**).

#### CASE 5

A girl from Portugal was first examined in France at 9 years of age. She had a medical history of a ventricular septal defect. A large bluish purple plaque on her right trunk included her posterior shoulder and midline abdomen. She had a large, poorly compressible plaque on the posterior and anterior aspects of her right thigh that was composed of purple and blue nodules (**Figure 3**). She also had scattered blue nodules on the left thigh. Her lesions had been present at birth as flat, bluish or pink patches. With age, all the lesions slowly extended and thickened, particularly those on the thigh. A magnetic resonance image of the thigh showed only cutaneous and subcutaneous involvement. Results of a biopsy revealed GVM. She had no family history of similar lesions. No molecular studies were performed. She had no surgical treatment because she developed a keloid after her first biopsy.

#### CASE 10

A newborn boy from Spain was seen shortly after birth with erythematous plaques that had been present since birth (**Figure 4**). He was born by spontaneous vaginal delivery at 34 weeks' gestation from a twin pregnancy after in vitro fertilization. His twin sister did not have any skin lesions.

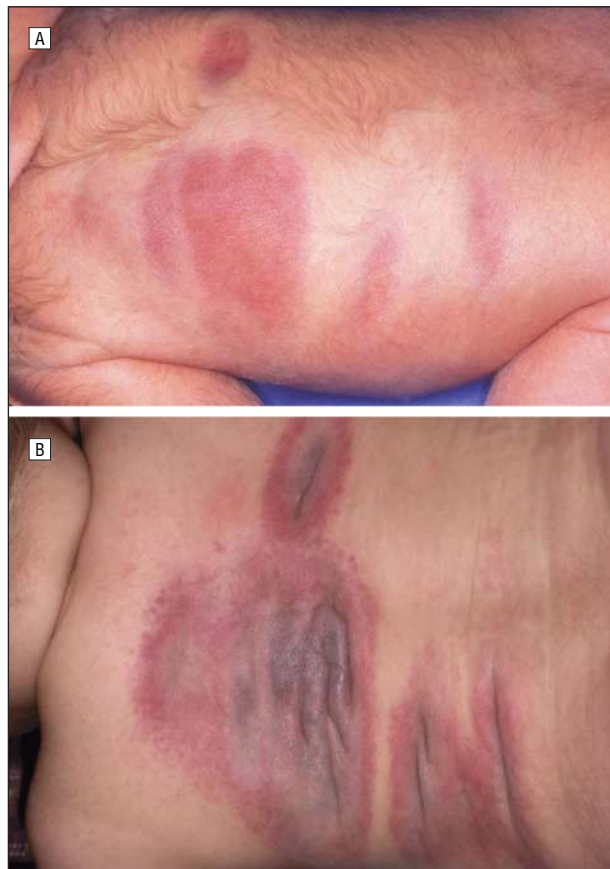
On physical examination, there were 4 erythematous, bluish, poorly demarcated patches on his back (Figure 4A). The patches were slightly depressed and warm to palpation, and the overlying skin was thickened. There was no thrill or bruit. No family history of similar lesions was obtained.



**Figure 2.** The patient in Figure 1 (case 1) at 2½ years of age. Lesions on the inner thigh have become more pronounced and nodular and do not change with compression of the area.



**Figure 3.** A girl at 9 years of age (case 5) with thickened purple nodules on the thigh.



**Figure 4.** A male infant (case 10). A, As a neonate, he had pink patches with a surrounding dusky halo on his back. B, At 6 months of age, follow-up showed progression of the lesions with purple prominent vessels.

Results of a complete blood cell count, measurement of liver enzyme levels, renal function tests, and coagulation studies were normal. Ultrasonographic findings of the spine and abdomen were normal. A biopsy specimen revealed an increased number of ectatic vessels in the dermis, which were lined by 2 layers of cells and were interpreted as a capillary malformation.

On follow-up at 6 months of age, no new lesions had appeared, but lesions had become more prominent and annular (Figure 4B). The centers of the plaques were bluish and depressed, with prominent ectatic vessels. The periphery of each plaque was erythematous and petechial. The lesions were more prominent during crying and the Valsalva maneuver.

A second biopsy was performed, and results revealed numerous dilated vascular lumina in the dermis, which were lined by a single layer of flat endothelial cells and several rows of cuboidal cells with a pale nucleus and eosinophilic cytoplasm. Immunohistochemical staining demonstrated a positive reaction for  $\alpha$ -smooth muscle actin, characteristic of glomus cells. Genetic testing was not performed.

#### COMMENT

At one time, GVMs were considered to be a subtype of VM, but are now known to be a separate entity because of their separate origin (**Table 1**). Molecular studies have

**Table 1. Comparison of GVM and VM**

	GVM	VM
Appearance at birth	Blue-purple papules or nodules, poorly compressible plaques	Flat, sharply demarcated, red-pink vascular stain
Appearance in later life	Thickened, blue-purple extensive plaques; compression causes pain	Darker blue-purple plaques, easily compressed
Location	Most common on acral areas and extremities, with rare mucosal involvement and no visceral involvement	Most common on lower extremities and cervicofacial areas; may have mucous membrane and visceral involvement
Tissue involvement	Limited to skin and subcutaneous tissue	Often involve muscle and joints
Progression	Rapidly progressive and enlarging	Slow growth proportionate with body size
Histological findings	Nonencapsulated tumors with large, irregular cavities lined by glomus cells; positive for vimentin and $\alpha$ -smooth muscle actin and negative for desmin	Malformed channels lined by media deficient in smooth muscle cells
Genetic findings	Glomulin gene; loss of function mutation	<i>TIE-2</i> gene; gain of function mutation
Chromosomes	1p21	9p21-22

Abbreviations: GVM, glomuvenous malformation; *TIE-2*, protein receptor tyrosine kinase, epithelial specific; VM, venous malformation.

permitted us to differentiate between inheritable cutaneomucosal VM (the inherited form of VM) and GVM, as they map to 2 different chromosomes with different genes.<sup>3-5</sup> Familial VM (cutaneomucosal VM, 1%-2%<sup>3</sup>) is linked to a mutation of the protein receptor tyrosine kinase, epithelial-specific (*TIE-2*) gene, mapped to 9p21-22,<sup>6</sup> whereas familial GVM (>64%<sup>3</sup>) is linked to a mutation of the glomulin gene, mapped to chromosome 1p21.<sup>2,4,7</sup> Glomuvenous malformations occur as sporadic and inherited lesions. A large series of 135 patients with GVM showed no sex prevalence. A minimum of 64% of these cases were familial.<sup>3</sup> The pattern of inheritance for multiple GVMs is autosomal dominant with incomplete penetrance and variable expressivity<sup>2,8,9</sup> and involves mutations in the glomulin gene. The identification of a double-hit mutation in 1 patient with GVM suggests paradominant inheritance due to a complete loss of function of the glomulin gene.<sup>2</sup> According to Happle and Konig,<sup>10</sup> the large plaque-type GVM, superimposed on the ordinary phenotype of this autosomal dominant disorder, could be classified as a type 2 segmental manifestation caused by loss of heterozygosity in the embryo. Brouillard et al<sup>11</sup> found that 70% of GVM families demonstrate 1 of the 4 common glomulin gene mutations.

Histologically, GVMs are nonencapsulated tumors with large, irregular cavities similar to VMs (cavernous hemangiomas), but the vascular spaces are lined by 1 or 2 layers of glomus cells. Glomus cells are rounded or polygonal cells with centrally placed round or ovoid nuclei and have scant eosinophilic cytoplasm.<sup>12</sup> Multiple GVMs are less well circumscribed and less solid-



**Table 2. Characteristics of 10 Cases of Congenital Plaque-Type GVM**

Case No./Sex/ Age at Presentation	Place of Origin	Areas Involved	Family History	Treatment	Biopsy Finding	Genetic Finding	Associated Conditions
1/M/1 mo	United States	Right leg, left arm, scrotum, feet, lower lip, face	None	None	GVM	NA	Autism
2/F/1 y	France	Sternum, left lateral abdomen and arm, right thigh	Yes	None	GVM	Glomulin	None
3/F/3 mo	France	V3 area of face*	Yes	Failed arterial embolization, surgical debulking	GVM	Glomulin	None
4/M/birth	Central Africa	Thighs, feet, perineum	Yes	Surgical resection	GVM	NA	von Willebrand Factor deficiency, hexadactyly on both feet
5/F/9 y	Portugal	Right trunk, shoulder, abdomen, bilateral thighs	None	None	GVM	NA	Ventricular septal defect, keloid formation
6/F/30 y	Iran	Right arm, shoulder, foot, and leg; breast; abdomen	Yes	Sclerotherapy	GVM	NA	None
7/M/16 y	Algeria	Right face, trunk, buttocks	None	Surgical resection	GVM	NA	None
8/F/birth	Sweden	Right groin and thigh, back	None	None	GVM	NA	None
9/F/birth	United States	Shoulders, chest, abdomen, nape, left leg	None	Pulsed-dye laser, sclerotherapy	GVM	Glomulin	None
10/M/birth	Spain	Back	None	None	GVM	NA	None

Abbreviations: GVM, glomuvenous malformation; NA, not applicable; V3, corresponding to cranial nerve V, mandibular branch.

\*Shown in Figure 5.

appearing than solitary GVMs. They have more narrow and focal aggregates of glomus cells and larger vascular spaces than solitary GVMs.<sup>13</sup> Immunohistochemical analysis demonstrates that GVM are positive for vimentin and  $\alpha$ -smooth muscle actin but negative for desmin.<sup>14-16</sup> By in situ hybridization, glomulin has been shown to be expressed in murine embryonic and adult vascular smooth muscle cells.<sup>17</sup> These findings support the proposed mesenchymal origin of GVM and provide evidence for abnormal vascular smooth muscle differentiation.<sup>17,18</sup>

We can divide GVMs into solitary and multiple types. The most common type is a solitary nodule that may be painful. Multiple GVMs are rare and account for less than 10% of all reported cases.<sup>12,19</sup> They have an earlier age of onset than solitary lesions, with one third presenting before 20 years of age. Multiple lesions can be subdivided into localized, disseminated, and congenital plaque-type forms.

The rare congenital plaque-type GVM was first described by Landthaler et al<sup>18</sup> in 1990. They reported 2 cases of congenital multiple plaque-type GVM and proposed that the classification of multiple GVMs include this variant in addition to the disseminated and localized variants. In both cases reported by Landthaler et al,<sup>18</sup> the lesions were noted within the first month of life and presented as plaques on the back. Histological features were identical to those reported in localized and disseminated types. In 1995, Glick et al<sup>20</sup> reviewed the published reports of congenital plaque-type GVM in the world literature. Finally, Carvalho et al<sup>21</sup> presented the first Brazilian case in 2001 and further reviewed the world literature.

We have been able to draw several conclusions from our case reports (**Table 2**). First, this specific congenital plaque-type form of GVM is severe, extensive, and visible at birth. However, like other forms of GVM, congenital plaque-type GVM is limited to the skin and sub-



**Figure 5.** Case 3 at 2 years of age with a blue, thickened plaque on the face.

cutaneous tissue. Some cases are familial, whereas others appear to be sporadic.

Second, in the familial cases, family members usually have minor lesions, often consisting of only 1 small nodule. Genetic counseling should include review of relatives for undiagnosed lesions and discussion of the nature of the disorder's autosomal dominant inheritance with incomplete penetrance and variable expressivity.

Third, congenital plaque-type GVM is often subtle, flat, and pink, bluish, or both at birth. These lesions are often misdiagnosed as capillary malformations, early VM, early hemangiomas, or even blue nevi. Some are particularly difficult to diagnose because they look partly atrophic at birth (eg, cases 1, 4, and 8). Any location (face, trunk, and extremities) may be affected.

Fourth, the typical clinical course of these lesions is progressive thickening (**Figure 5**), with new development of papules and nodules. The lesions tend to extend to adjacent areas not obviously involved at birth. If

lesions are unilateral at birth, scattered nodules often develop on the contralateral side (plaque-type lesions are usually predominant on 1 side of the body) or in distant areas. Large lesions are poorly compressible.

Fifth, lesions progress from pink or light blue plaques in infancy to deep, dark blue plaques in late childhood and adolescence. They also become painful when exacerbated by pressure during childhood. This symptom is well documented in the follow-up of our patients.

Sixth, histologically and genetically, there is no difference between this type of GVM and the more common type of GVM; however, some of our patients seem to have more rows of glomus cells in their vessel walls.

Seventh, treatment is difficult. Surgical excision should probably begin in infancy when lesions are not infiltrated, but this needs to be verified with future cases. Sclerotherapy and embolization in older patients, when GVM lesions are already thickened, did not help in some of our experiences. One patient (case 9) responded to flash-lamp pulsed-dye laser treatment.

In conclusion, we present 10 cases of congenital plaque-type GVM and verify that they are caused by a mutation in the glomulin gene in the 3 cases in which genetic studies were performed.

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## REFERENCES

1. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). *Adv Dermatol.* 1997;13:375-423.
2. Brouillard P, Boon LM, Mulliken JB, et al. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). *Am J Hum Genet.* 2002;70:866-874.
3. Boon LM, Mulliken JB, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. *Arch Dermatol.* 2004;140:971-976.
4. Boon LM, Brouillard P, Irrthum A, et al. A gene for inherited cutaneous venous anomalies ("glomangiomas") localizes to chromosome 1p21-22. *Am J Hum Genet.* 1999;65:125-133.
5. Boon LM, Mulliken JB, Vikkula M, et al. Assignment of a locus for dominantly inherited venous malformations to chromosome 9p. *Hum Mol Genet.* 1994;3:1583-1587.
6. Vikkula M, Boon LM, Carraway KL III, et al. Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. *Cell.* 1996;87:1181-1190.
7. Irrthum A, Brouillard P, Enjolras O, et al. Linkage disequilibrium narrows locus for venous malformation with glomus cells (*VMGLOM*) to a single 1.48 Mbp YAC. *Eur J Hum Genet.* 2001;9:34-38.
8. Rudolph R. Familial multiple glomangiomas. *Ann Plast Surg.* 1993;30:183-185.
9. Tran LP, Velanovich V, Kaufmann CR. Familial multiple glomus tumors: report of a pedigree and literature review. *Ann Plast Surg.* 1994;32:89-91.
10. Happle R, König A. Type 2 segmental manifestation of multiple glomus tumors: a review and reclassification of 5 case reports. *Dermatology.* 1999;198:270-272.
11. Brouillard P, Ghassibe M, Penington A, et al. Four common glomulin mutations cause two thirds of glomuvenous malformations ("familial glomangiomas"): evidence for a founder effect. *J Med Genet.* 2005;42:e13.
12. Taafe A, Barker D, Wyatt EH, Bury HP. Glomus tumours: a clinico-pathological survey. *Clin Exp Dermatol.* 1980;5:219-225.
13. Farmer ER, Hood AF, eds. *Pathology of the Skin.* East Norwalk, Conn: Appleton & Lange; 1994:827-834.
14. Tarnowski WM, Hashimoto K. Multiple glomus tumors: an ultrastructural study. *J Invest Dermatol.* 1969;52:474-478.
15. Dervan PA, Tobbia IN, Casey M, O'Loughlin J, O'Brien M. Glomus tumours: an immunohistochemical profile of 11 cases. *Histopathology.* 1989;14:483-491.
16. Kaye VM, Dehner LP. Cutaneous glomus tumor: a comparative immunohistochemical study with pseudoangiomatous intradermal melanocytic nevi. *Am J Dermatopathol.* 1991;13:2-6.
17. McIntyre BA, Brouillard P, Aerts V, Gutierrez-Roelens I, Vikkula M. Glomulin is predominantly expressed in vascular smooth muscle cells in the embryonic and adult mouse. *Gene Expr Patterns.* 2004;4:351-358.
18. Landthaler M, Braun-Falco O, Eckert F, Stolz W, Dorn M, Wolff HH. Congenital multiple plaque-like glomus tumors. *Arch Dermatol.* 1990;126:1203-1207.
19. Goodman TF, Abele DC. Multiple glomus tumors: a clinical and electron microscopic study. *Arch Dermatol.* 1971;103:11-23.
20. Glick SA, Markstein EA, Herreid P. Congenital glomangioma: case report and review of the world literature. *Pediatr Dermatol.* 1995;12:242-244.
21. Carvalho VO, Taniguchi K, Giraldo S, et al. Congenital plaque-like glomus tumor in a child. *Pediatr Dermatol.* 2001;18:223-226.