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Case Presentation

Multiple bluish papules and nodules in a 12-year-old child with lower gastrointestinal bleeding: a diagnostic challenge

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Keywords: BRBNS, gastrointestinal hemorrhage, glomus tumor, GVM, vascular malformations

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Abstract

Blue rubber bleb nevus syndrome (BRBNS) and familial multiple glomuvenous malformations (GVM) are genetic disorders characterized by multiple cutaneous vascular malformations. Unlike multiple GVM, BRBNS comprises a risk of systemic involvement with vascular malformations in other organs, potentially causing life-threatening bleeding. The correct distinction between these two conditions is challenging due to their clinical similarity, but it is crucial in light of the pivotal differences in prognosis and follow-up. We report a case of multiple glomuvenous malformations in a child with lower gastrointestinal bleeding that posed a thought-provoking diagnosis.

Introduction

Familial multiple glomuvenous malformations (GVM) and blue rubber bleb nevus syndrome (BRBNS) are genetic disorders with an autosomal dominant pattern of inheritance, characterized by multiple cutaneous vascular malformations.^{1,2} Unlike multiple GVM, BRBNS comprises a risk of systemic involvement with vascular malformations in other organs, namely the gastrointestinal tract, potentially causing intestinal bleeding.^{1,3,4} The distinction between these two conditions is challenging owing to their clinical similarity.²

Case Synopsis

We report a 12-year-old boy, Fitzpatrick phototype III, with a one-day history of lower gastrointestinal bleeding presenting as three episodes of hematochezia, who was admitted for treatment and etiologic investigation. This was his first episode of gastrointestinal bleeding, with no previous history of abdominal pain, nocturnal diarrhea, weight loss, anorexia, nausea, or vomiting. Additionally, there was no history of other organ system bleeding. The patient had not taken any previous medications, including nonsteroidal anti-inflammatory drugs, and he denied any other complaints.

During his hospital stay, a dermatologic evaluation was requested because of the presence of numerous bluish cutaneous lesions. After detailed history, the patient's mother mentioned that he had multiple cutaneous asymptomatic bluish papules and nodules that appeared shortly after birth and increased in number and size over time. The child's intrauterine and neonatal periods were unremarkable. He was fully immunized according to the national vaccination program and had no relevant comorbidities, chronic medication, or drug allergies. The patient was the firstborn of non-consanguineous parents. However, his father had a single similar lesion on his right arm. His mother and only sister were healthy, and no other family member had a history of cutaneous lesions or bleeding.

On the patient's physical examination, there were clusters of bluish-to-violaceous papules and nodules, located on the right scapular, left axillary (**Figure 1A**), and right gluteal regions, as well as on the legs (**Figure 1B**).

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Figure 1. Clusters of bluish-to-violaceous, firm, non-compressible, non-tender papules and nodules, located on **A)** the patient's left axilla and **B)** anterolateral aspect of the left leg.

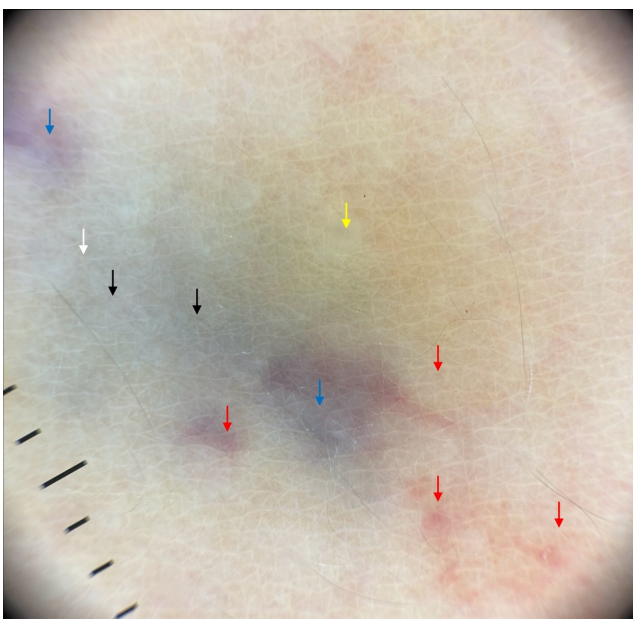


Figure 2. Dermoscopy of the patient's cutaneous lesions showing blue lacunae (blue arrow), bluish-to-purple (black arrow) and yellowish (yellow arrow) ill-defined structureless areas, blue-white veil (white arrow), red dots, and arborizing and linear vessels (red arrow).

On palpation, the lesions were firm, non-compressible, and non-tender. There was no pulsation or tactile fremitus. Dermoscopy of the nodules (**Figure 2**) showed blue lacunae, bluish-to-purple and yellowish ill-defined structureless areas, blue-white veil, red dots, and arborizing and linear vessels. The patient's father's physical examination (**Figure 3**) revealed a single bluish-to-violaceous, firm, non-compressible, non-tender papule, located on the anterior aspect of the right arm. The clinical hypothesis of BRBNS was considered given the combination of cutaneous vascular malformations and lower gastrointestinal bleeding. Laboratory examination revealed a normal complete blood count, normal coagulation studies and platelet function tests, normal iron and ferritin levels.



Figure 3. A single bluish-to-violaceous, firm, non-compressible, non-tender papule located on the anterior aspect of the patient's father's right arm.

Skin ultrasound (**Figure 4**) revealed dermal and hypodermal pseudonodular structures of mixed echogenicity, with hypoechoic and heterogeneous areas and anechoic, pseudocystic tubular and lacunar zones, alongside arterial and venous vessels with a low flow; there were no arteriovenous shunts.

The histopathologic examination of a 4mm punch skin biopsy (**Figure 5A-B**) demonstrated large, dilated, blood-filled vascular channels in the dermis and hypodermis, surrounded by layers of glomus cells, compatible with GVM.

The laboratory examination was unremarkable. Total colonoscopy showed a juvenile polyp in the sigmoid colon, which was subsequently removed. The histopathologic examination confirmed the clinical diagnosis of benign polyp. Additional investigations, including upper gastrointestinal endoscopy, capsule endoscopy and full-body computed tomography angiography, excluded the presence of vascular malformations in other organs than the skin.

With the collaboration of the genetics department, a multigene next-generation sequencing (NGS) panel for vascular malformations was performed on genomic DNA extracted from the peripheral blood of the proband, upon written informed consent. The heterozygous variant c.1319G>A p.(Trp440*) of the glomulin (*GLMN*) gene (1p21-p22) was identified and no mutations in the *TEK* gene were found. This genetic variant of the *GLMN* gene causes a premature termination codon in a gene with haplo-insufficiency and has been recognized as a rare and likely pathogenic variant associated with familial multiple GVM. Therefore, it was considered clinically rele-

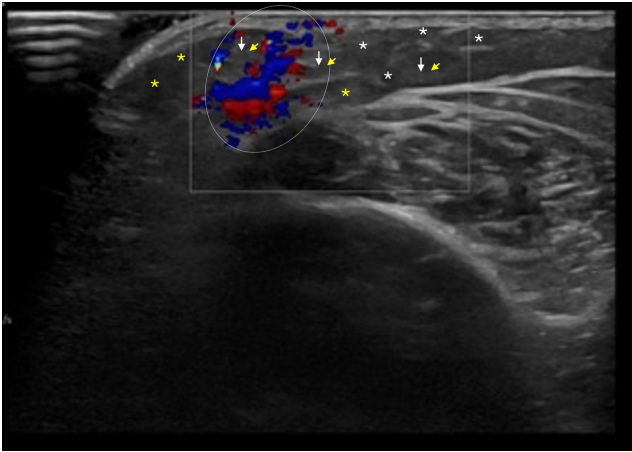


Figure 4. Skin ultrasound of the patient's left leg glomuvenous malformation revealing moderately delimited dermal and hypodermal pseudonodular structures (yellow arrows) of mixed echogenicity, with hypoechoic and heterogeneous areas (white arrows), alongside anechoic, pseudocystic tubular zones (white asterisks), and anechoic lacunar zones (yellow asterisks). Color Doppler ultrasound shows clear red and blue blood vessels, with slow movement and low flow (white oval), but no turbulent flow suggestive of arteriovenous shunts.

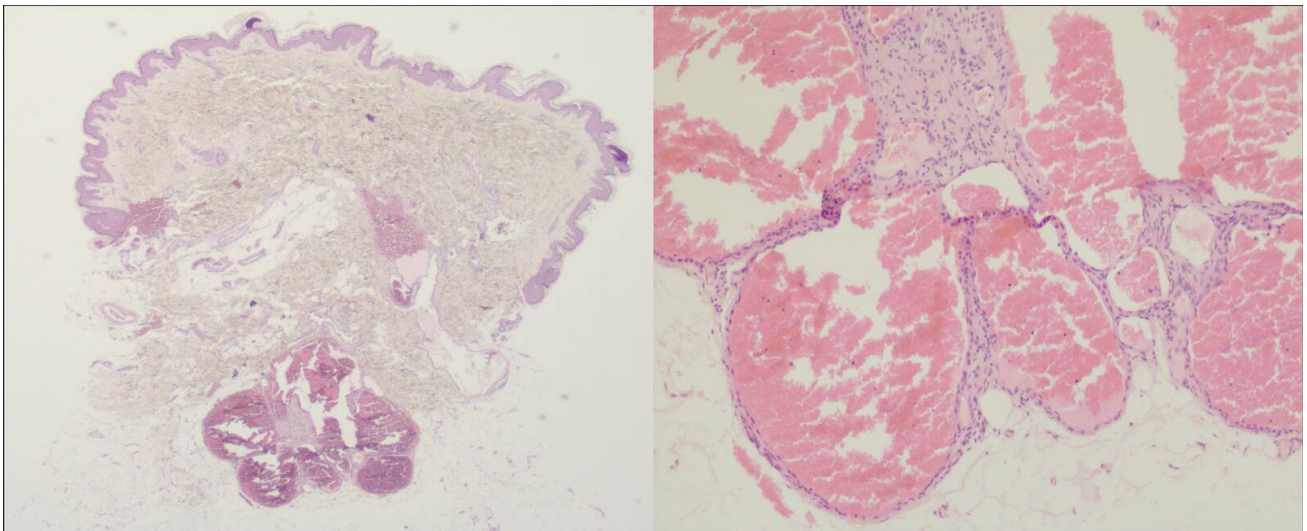


Figure 5. Histopathological examination of the patient's cutaneous lesions demonstrates **A)** large, dilated, blood-filled vascular channels in the dermis and hypodermis. H&E, 16×. **B)** Higher magnification reveals that these vascular spaces are lined by endothelial cells and layers of cuboidal cells with uniform round to ovoid nuclei (glomus cells) in a hyalinized stroma. H&E, 100×.

vant. Segregation studies confirmed that this variant was inherited from the father and no mutations were found in the patient's mother and sister. The diagnosis of familial multiple GVM was established, alongside a solitary sigmoid colon juvenile polyp as the cause of lower gastrointestinal bleeding.

Information regarding the diagnosis and its prognosis was provided to the patient and his family, alongside genetic counseling. Upon discussion of the different thera-

peutic options, we decided to maintain surveillance and performed Nd:YAG laser treatment on the cutaneous vascular malformations, with improvement. After two years of follow-up, no recurrence of gastrointestinal bleeding was observed, and the patient remains otherwise asymptomatic.

Table 1. Clinical and genetic features of multiple familial GVM and BRBNS.

	Multiple familial GVM	BRBNS
Genetic profile		
Inheritance	Autosomal dominant	Autosomal dominant
Gene	GLMN	TEK
Type of mutation	Loss of function	Gain of function
Age of onset	Early childhood	At birth
Gender	Male > Female	Male = Female
Cutaneous vascular malformations	Blue, blue-purple vascular-appearing papules, nodules or plaques	
Location	Any location, widespread; more frequently on the extremities	Any location, widespread
Mucous membrane involvement	Rare	More frequent
Surface	Hyperkeratotic (cobblestone appearance)	Soft
Pain	Usually painless, but more likely to be painful	Painless
Firmness	Firm	Soft
Compressibility	Partially compressible	Fully compressible
Dermoscopy	Blue lacunae, bluish-to-purple and yellowish ill-defined structureless areas, blue-white veil, red dots, and arborizing and linear vessels	Bluish, bluish-red lacunae and red-brown structureless areas, red dots and globules
Systemic disease	Very rare	Frequent (gastrointestinal bleeding)
Prognosis	Very good	Depends on systemic involvement (risk for life-threatening hemorrhage)
Surveillance	Not mandatory	Active surveillance of systemic disease mandatory
Treatment	Not mandatory	Possible need for systemic treatment

Abbreviations:

BRBNS, Blue rubber bleb nevus syndrome

DNA, Deoxyribonucleic acid

GLMN, Glomulin gene

GVM, Glomuvenous malformations

Nd:YAG, Neodymium-doped yttrium aluminum garnet

NGS, Next Generation Sequencing

TEK, Tyrosine kinase receptor gene

Case Discussion

Familial multiple GVM and BRBNS are genetic disorders that lead to multiple similar cutaneous vascular malformations.^{1,2} The distinction between these two diseases is challenging owing to their clinical similarity. In fact, it has been suggested that several cases reported in the literature of BRBNS might actually be cases of GVM.^{2,5} Clinical and genetic features of both diseases are compared (Table 1).

The primary lesions of both clinical entities have been described as blue, blue-purple, or blue-black vascular-appearing papules, nodules, or plaques, which tend to be painless. However, painful lesions are not uncommon.

These lesions have a broad cutaneous distribution and can appear on the face, trunk, or extremities and slowly grow in size and number with age. Dermoscopy and skin ultrasound of these entities are also similar.^{2-4,6}

Some differentiating clinical findings have been pointed out in the literature, although they are controversial. BRBNS is often congenital and multiple GVM typically first occurs during early childhood. Multiple GVM shows male predominance and nodules are more common on the extremities, more likely painful, firmer, less compressible, and hyperkeratotic (with a cobblestone appearance).^{1-5,7} However, none of these differentiating features have been validated, making histopathology crucial for accurately diagnosing the cutaneous vascular

malformations. Both diseases are characterized by dilated vascular spaces lined by inactive endothelial cells, but the presence of glomus cells lining the endothelium is unique to GVM, a feature lacking in BRBNS. Therefore, several authors recommend that a biopsy should be performed on all such lesions.^{1-3,5,7}

Regarding the genetic profile of these diseases, both sporadic cases and autosomal dominant inheritance have been demonstrated,²⁻⁸ although familial cases of multiple GVM occur more frequently than in BRBNS.^{2,7} BRBNS is associated with gain-of-function mutations in the *TEK* gene. On the other hand, multiple GVM are caused by loss-of-function mutations in the *GLMN* gene.^{3,4,6,9} The latter has incomplete penetrance and variable expression, even among members of the same family with the same genetic variant.^{1,6,8} In our case, the patient had multiple multifocal lesions, whereas his father only had a single small nodule. Additionally, a second-hit mutation in the *GLMN* gene may affect the size, shape, and depth of the lesions.¹

Unlike multiple GVM, BRBNS comprises a risk of systemic involvement with vascular malformations in other organs, namely the gastrointestinal tract, potentially causing intestinal bleeding and iron deficiency anemia. The central nervous system and other internal organs may also be involved.¹⁻⁴ Consequently, patients with BRBNS are advised to have strict follow-up and surveillance and may need systemic treatment. In contrast, given the absence of risk for systemic involvement, the overall prognosis of familial multiple GVM is good and

specific treatment of the cutaneous vascular malformations is not mandatory as these cutaneous malformations do not pose a health risk. Nonetheless, different therapeutic modalities have been reported, including surgery, sclerotherapy, and laser treatment, with variable efficacy.¹⁰

Conclusion

This uncommon clinical case highlights that the differential diagnosis between multiple GVM and BRBNS is frequently difficult, and our patient was particularly challenging given the coincident gastrointestinal bleeding. The clinical mimicry between multiple GVM and BRBNS, combined with a reluctance to perform biopsies on cutaneous lesions because of concerns of excessive bleeding, may lead to misdiagnosis and inappropriate management of these patients.^{2,3} Therefore, a multidisciplinary approach with adequate etiologic investigation (including cutaneous biopsy, imaging, endoscopic exams, and genetic testing) allows for the correct distinction between these two clinical entities.

Potential conflicts of interest

The authors declare no conflicts of interest.

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