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McMahon, M.H., Tahir, N. and Balasubramanian, M. orcid.org/0000-0003-1488-3695 (2022) GLMN causing vascular malformations: the clinical and genetic differentiation of cutaneous venous malformations. BMJ Case Reports, 15 (6). e246114. ISSN 1757-790X

https://doi.org/10.1136/bcr-2021-246114

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BMJ Case Reports

TITLE OF CASE

GLMN causing vascular malformations - The clinical and genetic differentiation of cutaneous venous malformations

SUMMARY

Cutaneous venous malformations frequently present with blue-pink lesions on the skin or mucosal surfaces. They can be problematic for patients who experience pain or unsightly lesions, and can also be associated with significant bleeding. A proportion of venous malformations have been noted to occur in families, in particular glomulovenous malformations (GVMs). A “two-hit” occurrence of genetic pathogenic variants appears to explain the appearance of GVMs, with the initial change in the germline copy of *GLMN* followed by a second somatic hit.
Here we discuss a report of siblings experiencing such lesions which were diagnosed as glomulovenous malformations by genetic testing. We include a review of the literature regarding the clinical and genetic differences between these groups of venous malformations.

BACKGROUND

Vascular anomalies often present in a variety of ways to paediatricians and adult physicians, from mild innocuous lesions to sources of profound bleeding or local intravascular coagulopathy. Differentiating between the types can be a diagnostic challenge. Recent advances in identifying the causative genes and genetic processes involved have helped to establish inheritance patterns allowing afflicted families a degree of understanding of the prognosis of their condition.
Vascular anomalies include vascular malformations and vascular tumours. Vascular tumours develop due to endothelial cell proliferation. They typically regress with the patient’s age, in contrast to vascular malformations which progress with age and never regress on their own[1].
Vascular malformations represent structural defects in vascular development[2,3]. All are present from birth although they may not become clinically apparent until adulthood, and are life-long. They appear as blue to purple, sometimes tender lesions. Vascular malformations can be high or low flow, with high flow being from arterial or arterio-venous fistulas and low flow being from capillary, venous or lymphatic systems. Venous malformations are the most common group overall.
Venous malformations can be subdivided into various types with differences in clinical features and inheritance pattern. The International Society for the Study of Vascular Anomalies (ISSVA) devised a classification system which has been widely adopted (most recently updated in 2018)[4]. The venous malformations are subdivided into sporadic (or common) venous malformation, cutaneomucosal venous malformation, cerebral cavernous malformations, glomulovenous malformations, verrucous malformation and intraosseous malformation. The blue rubber bleb naevus syndrome, (sometimes known as “bean” syndrome) is another group.
In a patient with multiple cutaneous venous malformations the possible diagnoses include sporadic venous malformation, cutaneomucosal venous malformation, glomulovenous malformation and blue rubber bleb naevus syndrome. We will be

focussing on these groups in this report.

Glomulovenous malformations (GVMs) have historically been known as “glomangiomas” [5]. GVMs classically have a blue-purple or pink cobblestone raised appearance and are hard and tender on palpation, they do not compress easily. They are usually present peripherally and rarely on mucosa. The lesions usually develop in childhood and are life-long, although more lesions may develop later, usually by the third decade[6].
Histologically GVMs have defects in the smooth muscle cell layer with characteristic round “glomus cells” which are adjacent to the distended vascular channels[2,4]. These glomus cells have a thermoregulatory role, their exact cellular aetiology is not known but immunohistochemistry and electron microscopy suggest they are modified smooth muscle or pericyte cells [7]. GVMs can be treated by surgical excision, partial excision or by sclerotherapy[5]. Unlike other venous malformations compressive stockings are not recommended as they worsen the pain.

Blue rubber bleb naevus syndrome can involve both cutaneous and visceral lesions, therefore unlike GVMs it is associated with gastrointestinal lesions leading to severe iron deficiency anaemia[8]. The cutaneous lesions are small, rubbery and easily compressible, often affecting the palms and soles.

Cutaneomucosal venous malformations usually appear in the cervicofacial region and are always blue[9]. Although usually on the skin, cutaneomucosal malformations can involve the skeletal muscle, GI tract and other organs[9]. Histologically the defect in cutaneomucosal venous malformations and blue rubber bleb naevus syndrome is related to vascular smooth muscle cell recruitment[8]. In both conditions there is an associated risk of associated consumptive coagulopathy and profound iron deficiency anaemia and patients require investigations looking for anaemia and coagulopathies. Sporadic venous malformations can be isolated or multiple, occur in the same regions and are clinically similar to cutaneomucosal venous malformations.

Although clinical differentiation of the types of venous malformations is possible it can be challenging. Imaging such as ultrasound and MRI are used but do not differentiate between types of venous malformations [8]. D-dimers can point towards GVMs if not elevated [10]. Histology may give a diagnosis of GVM, especially if cuboid glomus cells are seen, however they are not present in all lesions [5].
Genetics have been able to provide support in identifying those lesions where other diagnostic testing cannot help.

Here we describe a report of siblings with cutaneous vascular abnormalities in which genetic testing was required to reach a diagnosis.

CASE PRESENTATION

Two siblings were referred to the Clinical Genetics service due to blue lesions noted on their extremities. The older brother was in his early teens and had blue-purple naevi on his left foot. He had no associated pain or discomfort from the lesions and they did not bleed. His younger brother, had more significant lesions on the right foot affecting the lateral side and base which were painful (see Figures 1&2). He also had a similar lesion on his lower back which did not cause discomfort. Both boys were otherwise fit and well and had been born at full term via vaginal deliveries.
Their parents were fit and well and did not have any lesions.

The younger boy had initially been seen by a specialist radiologist and at age 6 years had received sclerotherapy to the painful foot lesions (see Figures 3&4). At this time the presumptive diagnosis was glomulovenous tumour. However, the Clinical Genetics team raised the possibility of blue rubber bleb naevus syndrome as a likely diagnosis. Due to the potential complications of consumptive coagulopathy, iron deficiency anaemia and gastrointestinal tract malformations, the boys were referred to Haematology for further investigations. They were both found to have normal clotting profiles and blood films.

OUTCOME AND FOLLOW-UP

The brothers were diagnosed with glomulovenous malformations following genetic testing. Genomic DNA from blood samples of both brothers were sent for targeted vascular skin disorders gene panel testing and revealed that they were heterozygous for a pathogenic NM_053274.2 *GLMN* c.108C>A,p.Cys36* nonsense variant [glomulin gene] [MIM 601749][11].This variant was first reported to lead to glomulovenous malformations [MIM 138000] by the Brouilliard group in 2002[13]. It is predicted to introduce a stop codon leading to premature truncation of the protein. ACMG evidence used for classification of variant included PVS1_very strong (predicted to introduce a stop codon leading to premature truncation of protein); PS4_moderate (reported in the literature multiple times as being associated with GVMs); PM2_moderate (present at low frequency n gnomAD population database (Richards et al., 2015)
The family have been informed and reassured that there are no malignant consequences of GVM, or risks of severe bleeding. Both brothers have a 50% chance of passing on the condition to their offspring.
Mother did not carry this variant and unfortunately, father was not available for testing.

DISCUSSION

To understand the inheritance pattern of this condition and how the children had been affected, it is necessary to take a closer look at the genetics of GVMs.
The glomulin gene [*GLMN*] on the short arm of chromosome 1 at 1p21p22 has been shown to be responsible for GVMs by the Broulliard group[12,13]. It is likely that glomulin has a role in vasculature development, as seen by its high expression in mouse vasculature [14]. This role is significant as in mouse embryos where both *GLMN* copies have a pathogenic variant the embryo is not viable [15]. Glomulin has been shown to have a role in regulating proliferative proteins by binding to Ringbox protein-1, reducing ubiquination, and also interacting with an F box protein (Fbw7) [16]. It is also involved in transforming growth factor beta (TGF- β) signaling which regulates endothelial cell migration and proliferation. [17].

In families where *GLMN* contains loss of function variants there is tendency for the development of GVMs[13] presumably through unregulated proliferation[15]. At least 162 such families have been identified, with at least 40 different variants [18]. 87 of these cases are explained by one of 16 changes.

Interestingly, the single pathogenic variant in *GLMN* alone does not automatically give rise to GVMs. It shows variable expressivity, with some carriers of the variants having

very mild symptoms to those more severely affected, even within the same family. In a study of 381 patients with *GLMN* variants a high but incomplete penetrance of 90% was demonstrated with 37 patients being completely unaffected despite carrying the gene with a known pathogenic variant[18]. Studies have now been able to find a series of somatic variants affecting the second *GLMN* allele. This concept that a second, tissue level change is needed for phenotypic expression of GVM is known as the “two-hit” hypothesis[13,18]. The stage in development of occurrence of the second change, as well as angiogenic activity locally could contribute to the variable expressivity [18].

The development of cutaneomucosal venous malformations, sporadic venous malformations and blue rubber bleb naevus syndrome are all due to variants in the *TEK* gene located on 9p21-22(see Table 1.). This gene produces the tyrosine kinase receptor TIE2 which is involved in normal angiogenesis through binding with angiopoeitins.

Cutaneomucosal vascular malformations are inherited in an autosomal dominant pattern with a high degree of penetrance[18]. Alterations in germline *TEK* have been shown to be responsible for cutaneomucosal vascular malformations [24]; at times this is associated with a second somatic alteration [21]. The presence of the second variant doesn’t appear to have any effect on phenotype [22].
Sporadic venous malformations have now been shown to occur as a result of somatic changes in *TEK*, without germline pathogenic variants[21]. In unifocal sporadic lesions one pathogenic variant occurs, where there are multiple lesions there has often been an earlier somatic change in a progenitor cell followed by a second somatic change in the same allele. The Soblet group classed this as an initial somatic mosaicism followed by a second mosaic hit, with 1-5% of the initial mutation being detected in blood samples as opposed to just tissue samples for the other variants [22]. They also discovered that in 20% of unifocal lesions a different gene pathway was involved, PIK3A, these lesions were clinically identical to those occurring due to variants in the TEK/TIE2 pathway.
The process in blue rubber bleb naevus syndrome is that there is a double hit in one somatic *TEK* allele (T1105N-T1106P) thought to both occur at the same time in an earlier endothelial progenitor cell[22].
The relevance of understanding the gene involved as well as its place in the molecular signalling is that this could open new doors for targeted therapy. The use of sirolimus in TIE-2 mediated venous malformations has had some success to date [23]. The use of such molecular targeted treatments for GVMs is an exciting possibility.

Table 1: Summary of venous malformations

	Symptoms	*Gene pathway*	*Inheritance*
GVM	Painful on compression, not associated with significant bleeding complications	*GLMN*	Germline variant plus second somatic variant in the other allele
Cutaneomucosal	Associated with bleeding complications and IDA, coagulopathy	*TEK/TIE2*	Germline variant with or without second somatic variant in same or other allele
Sporadic	Associated with bleeding complications and IDA, coagulopathy	*TEK/TIE2* *PIK3CA* in 20% of unifocal	No germline mutation Unifocal 1 somatic mutation Multifocal 2 somatic mutations (mosaic somatic + later somatic in single allele)
BRBN	Associated with bleeding complications and IDA, coagulopathy	*TEK/TIE2*	Double variant in single *TEK* allele

LEARNING POINTS/TAKE HOME MESSAGES

- In assessing patients with multiple venous malformations, GVMs need to be considered as the condition is relatively benign compared to blue rubber bleb or cutaneomucosal malformations and lacks the complications of severe bleeding or coagulopathy
- Diagnosis via a genetic blood test can avoid long term surveillance testing and anxiety around the risk of GI bleeding
- GVMs are caused by a pathogenic variant in both the germline and somatic copies of the same gene, this is an example of the “two-hit” hypothesis in action

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FIGURE/VIDEO CAPTIONS

Figure 1: Photograph of lesion on the dorsum of the younger brother's foot

Figure 2: Photograph of lesions on the lateral aspect of the younger brother's foot

Figure 3: Direct venogram of the abnormal veins (red circles) using needles punctured into them. These needles are then used to inject sclerosant for treatment.

Figure 4: Axial, coronal and sagittal post-contrast MRI images of the foot showing abnormal veins at the lateral aspect of the foot (blue circles).

Table 1: Summary of venous malformations

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Date: 01.08.21

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Consent

Consent was given by the mother of the children discussed in this case report for publication of clinical details and photographs in medical literature.