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Cancer Prone Disease Section

Mini Review

Glomuvenous malformation (GVM)

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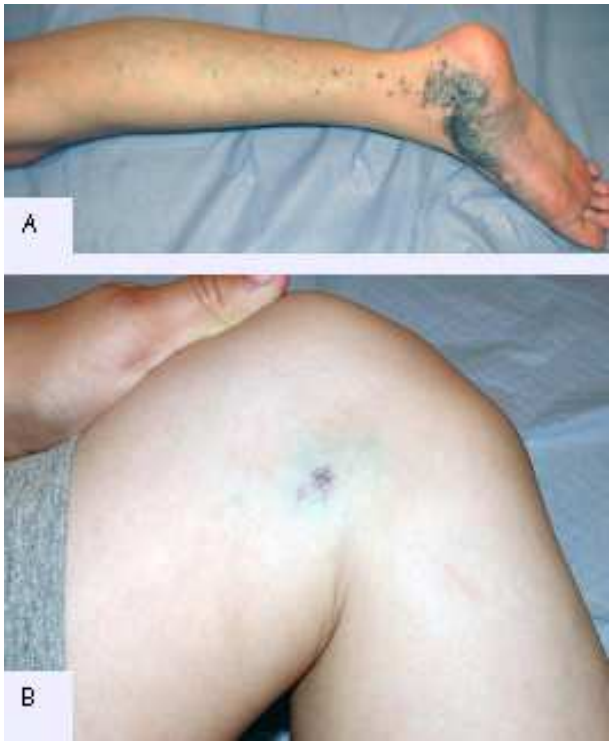
Identity

Other names: Venous malformation with glomus cells (VMGLOM); Glomangioma; Multiple glomus tumor.
Note: Glomuvenous malformation (GVM) is a localized bluish-purple cutaneous vascular lesion, histologically consisting of distended venous channels with flattened endothelium surrounded by variable number of maldifferentiated smooth muscle-like "glomus cells" in the wall. GVM account for 5% of venous anomalies referred to centers for vascular anomalies. Previously, these lesions have been called "multiple glomus tumors" or "glomangioma".
Inheritance: GVM is often, if not always, hereditary (64%), and transmitted as an autosomal dominant disorder. Expressivity varies, as does penetrance, which is age dependent and maximal (93%) by 20 years of age.

Clinics

Phenotype and clinics

There is a wide phenotypic variation between GVM patients, even within the same family (with the same germline mutation). An individual can have an extensive lesion, affecting for example a whole extremity or most of the trunk, while others have minor, scattered papulonodular lesions of a few millimetres in diameter. The lesions are often multiple, and they can affect any body part.
Seven features characterize GVM lesions :
(1) Colour: GVMs can be pink in infants, the most are bluish-purple;
(2) Affected tissues: the lesions are localized to the skin and subcutis, and they are rarely mucosal and never extend deeply into muscles;
(3) Localization: lesions are more often located on the extremities, although they can be found all over the body;
(4) Appearance: lesions are usually nodular and multifocal, raised with a cobblestone-like appearance, except for the rare plaque-like variant. They are often hyperkeratotic;
(5) The lesions are not compressible;
(6) The lesions are painful on palpation;
(7) New lesions can appear with time, likely after trauma.



Examples of GVMs: (A) Extended GVM on leg. (B) Small GVM on knee.

At the histological level, the mural glomus cells are positive for smooth muscle alpha-actin and vimentin, but negative for desmin, Von Willebrand factor and S-100. Under electron microscopy, glomus cells show smooth muscle myofibrils and “dense bodies”, characteristics of vascular smooth muscle cells (vSMCs). Thus, these cells are most likely incompletely or improperly differentiated vSMCs.

Neoplastic risk

GVM has no neoplastic histological characteristics and never becomes malignant.

Treatment

The gold-standard treatment for GVM consists of surgical resection, as lesions are superficial and rarely affect deeply the underlying muscle, and sometimes sclerotherapy. In contrast to venous malformations, the use of elastic compressive garments often aggravate pain and should thus be avoided.

Evolution

GVM is a developmental lesion that grows proportionally with the child. After partial resection, recurrence is frequent. New small lesions can appear with time. The red plaque-like lesions of the young darken with age.

Cytogenetics

No cytogenetic abnormally has been reported for GVM.

Genes involved and Proteins

Glomulin

Location: 1p22.1

DNA/RNA

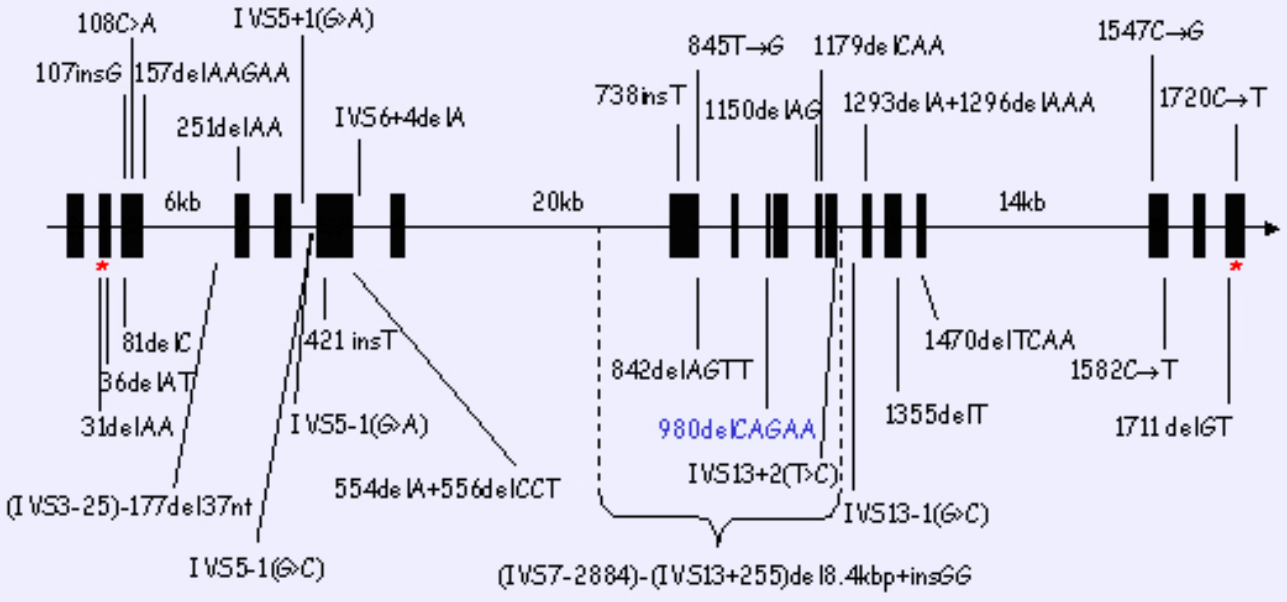
Description: The glomulin gene spans about 55 kbp and contains 19 exons coding for 1785 bp.
Transcription: 2 kb transcript.

Protein

Glomulin was identified by reverse genetics, and its function is currently unknown.
Description: Glomulin gene encodes a protein of 594 amino acids (68 kDa).
Expression: The high level of glomulin expression in the murine vasculature indicates that glomulin may have an important role in blood vessel development and/or maintenance.
Localisation: Glomulin is likely an intracellular protein.
Function: The exact function of glomulin is unknown.
Glomulin has been described to interact with FKBP12, an immunophilin that binds the immunosuppressive drugs FK506 and rapamycin. FKBP12 interacts with the TGFbeta type I receptor, and prevents its phosphorylation. Thus, FKBP12 safeguards against the ligand-independent activation of this pathway. Glomulin, through its interaction with FKBP12, could act as a repressor of this inhibition.
Glomulin has also been described to interact with c-MET. Glomulin interacts with the inactive, non phosphorylated form of c-MET. When c-MET is activated by HGF, glomulin is released in a phosphorylated form. This leads to p70 S6 protein kinase (p70S6K) phosphorylation. It is not known whether glomulin activates p70S6K directly or indirectly. The p70S6K is a key regulator of protein synthesis. Glomulin could thereby control cellular events such as migration and cell division.
The third reported glomulin partner is Cul7. This places glomulin in an SCF-like complex, which is implicated in protein ubiquitination and degradation.

Mutations

There is no phenotype-genotype correlation in GVM.
Germinal: To date, 29 different inherited mutations (deletions, insertions and nonsense substitutions) have been identified. The most 5' mutation are located in the first coding exon. The majority of them cause premature truncation of the protein and likely result in loss-of-function. One mutation deletes 3 nucleotides resulting in the deletion of an asparagine at position 394 of the protein.
More than 70% of GVMs are caused by eight different mutations in glomulin: 157delAAGAA (40,7%), 108C to A (9,3%), 1179delCAA (8,1%), 421insT and 738insT (4,65% each), 554delA+556delCCT (3,5%), 107insG and IVS5-1(G to A) (2,3% each).
Somatic: The phenotypic variability observed in GVM could be explained by the need of a somatic second-hit mutation. Such a mechanism was discovered in one GVM (somatic mutation 980delCAGAA), suggesting that the lesion is due to a complete localized loss-of-function of glomulin. This concept can explain why some patients have bigger lesions than others, why new lesions appear, and why they are multifocal. This could also explain, why some mutation carriers are unaffected.



Schematic representation of glomulin : The two stars indicate the start and the stop codons, in exon 2 and 19 respectively. All known mutations are shown. Somatic second hit is in blue.

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