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Hand/Peripheral Nerve

# A Review of Multiple Venous Malformations of the Upper Limb: Classification, Genetics, and Pathogenesis

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**Summary:** Venous (cavernous) malformations are commonly seen in the upper limb. There is no consensus in the literature regarding the classification of venous malformations. Patients may be viewed as 2 clinical entities: patients with single or multiple lesions. Single venous malformations are sporadic and nonsyndromic, whereas the presence of multiple malformations indicates the presence of either an inherited or an overgrowth (noninherited) disorder. In this article, the author reviews multiple venous malformations of the upper limb, offers a novel classification, and describes their clinical entities along with their genetics and pathogenesis. These clinical entities will also be described by categorizing the cases as per the clinical presentation. Furthermore, the number of cases seen by the author (during an experience of 28 years of practice in Saudi Arabia) in each category will be reviewed to give the reader an overall view of the frequency of presentation of each category to the hand/plastic surgery clinic. Clinically, patients may present in 4 different presentations depending on the distribution of the lesions: the late-onset malformations confined to the upper limb; malformations involving the limbs/face/trunk with no mucosal lesions; widespread malformations of the skin, oral mucosa, and the intestine; and venous malformations presenting as a well-known syndrome. The author has seen a total of 84 patients, and the most 2 common presentations were late-onset type (n = 26) and malformations involving the limbs/face/trunk with no mucosal lesions (n = 36). This is the most comprehensive review of multiple venous malformations of the upper limb.
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## INTRODUCTION

Venous (cavernous) malformations are commonly seen in the upper limb. There is no consensus in the literature regarding the classification of venous malformations. Patients may be viewed as 2 clinical entities: patients with single or multiple lesions. Single venous malformations are sporadic and nonsyndromic, whereas the presence of multiple malformations indicates the presence of either an inherited or an overgrowth (noninherited) disorder. Inherited disorders are caused by germline mutations (the term "germline" mutation means that the mutation is present in all body cells) and there is usually a positive family history. Overgrowth noninherited disorders are caused by somatic mutations that only affect the involved tissues (the abnormal gene is present only in the pathological lesions), and family history is always negative.

## METHODS

In this study, the author reviews multiple venous malformations of the upper limb, offers a novel classification, and describes their clinical entities along with their genetics and pathogenesis. These clinical entities will also be described by categorizing the cases as per the clinical presentation. Furthermore, the number of cases seen by the author (during an experience of 28 years of practice in Saudi Arabia) in each category will be reviewed to give the reader an overall view of the frequency of presentation of each category to the hand/plastic surgery clinic.

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## RESULTS

### Classification

Our proposed classification of multiple venous malformation of the upper limb is shown in Table 1, and it divides this entity into 2 main groups: lesions associated with inherited disorders and those associated with overgrowth noninherited disorders.

The onset of presentation may be congenital or late-onset. Almost all venous malformations are congenital, being present at birth. They grow with the growth of the child; in some cases, the lesions are first noted early in childhood.[1–3] Rarely, multiple venous malformations of the upper limb present late in childhood or in adolescence, and it is likely that the lesions were "subclinical" since birth. These lesions have been described as "acquired" malformations, but we believe that the term "late-onset" is more appropriate.[4,5]

Decision for intervention to treat venous malformations is largely dependent on the severity of symptoms. Mild symptoms include the presence of the masses and the cosmetic concerns. Moderate symptoms include recurrent pain, which is usually related to thrombosis within the lesion (Fig. 1). Severe symptoms include those associated with nerve compression, muscle contracture, bone resorption, and consumption coagulopathy. Most of the reported cases of venous malformations in the literature were seen in relation to peripheral nerves, causing nerve compression. In these cases, the malformations arose from the vasa nervorum of the nerve, the venae comitantes of an adjacent artery, or an intramuscular vein.[6–12] Congenital intramuscular venous malformations may initially present as asymptomatic masses, but may result in muscle contracture in adolescence. Untreated congenital venous malformations that are circumferential around the fingers may result in bone resorption and finger deformity (Fig. 2). Giant venous malformations of the proximal part of the upper limb may extend to the thoracic cavity and may be associated with consumption coagulopathy because of platelet trapping within the lesions.[13]

Finally, venous malformations may either be superficial (within the skin and subcutaneous tissue) or deep (subfascial). Magnetic Resonance Imaging (MRI) also identifies the extent of the lesion and determines if the malformation is localized or diffuse. Localized lesions are usually treated surgically, whereas diffuse lesions are best treated by sclerotherapy (Fig. 1). However, sclerotherapy may also be used for localized venous malformations of the hand if the malformation is surrounding the neurovascular bundles and the intrinsic muscles. Sclerosants used to treat venous malformations include ethanol, sodium tetradecyl sulphate, polidocanol, and bleomycin.[13]

### The Pathogenesis of Multiple Venous Malformations

Our review will demonstrate that all multiple venous malformations of the upper limb are related to the 2 main pathways controlling cellular proliferation: The Ras (RAS is a small GTPase) and the PI3K (Phosphatidyl Inositol 3-Kinase) pathways (Fig. 3). It is interesting to note that both pathways interact with each other because RAS is a direct stimulator of PI3K activity.[14]

**Table 1. Classification of Multiple Venous Malformations of the Upper Limb**

| The 2 Main Groups of Patients | Other Features |
|---|---|
| 1. Patients with inherited disorders (germline mutations) | Time of presentation: Congenital or late-onset<br>Symptoms: Mild, moderate, or severe<br>Size of the lesion: Small (<3 cm), large (3–20 cm), or giant (>20 cm)<br>Depth of the lesion: Superficial or deep |
| 2. Patients with noninherited overgrowth disorders (somatic mutations) | Localization of the lesion: Localized or diffuse |

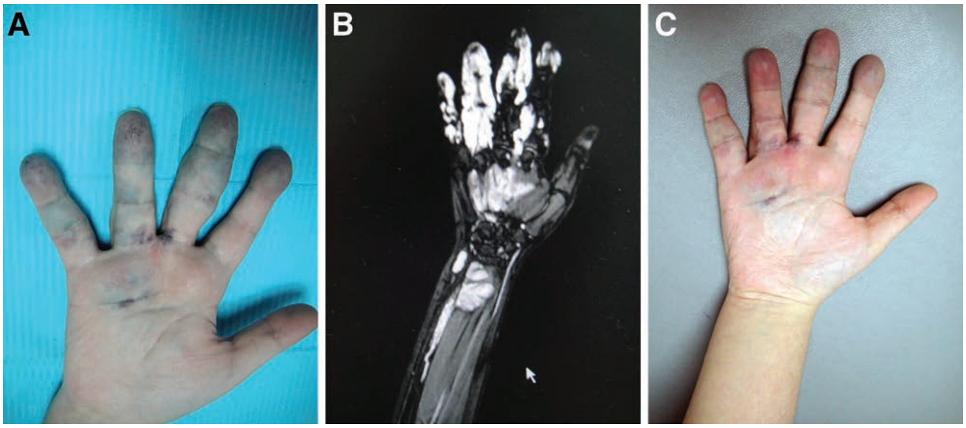


**Fig. 1.** Multiple congenital venous malformations of the hand with recurrent pain related to thrombosis within the lesions. A, Appearance prior to sclerotherapy. B, MRI showing the diffuse lesions. C, Improvement after sclerotherapy. The patient has also been maintained on daily aspirin. This was effective to reduce the severity of pain episodes related to intralesional thrombosis.

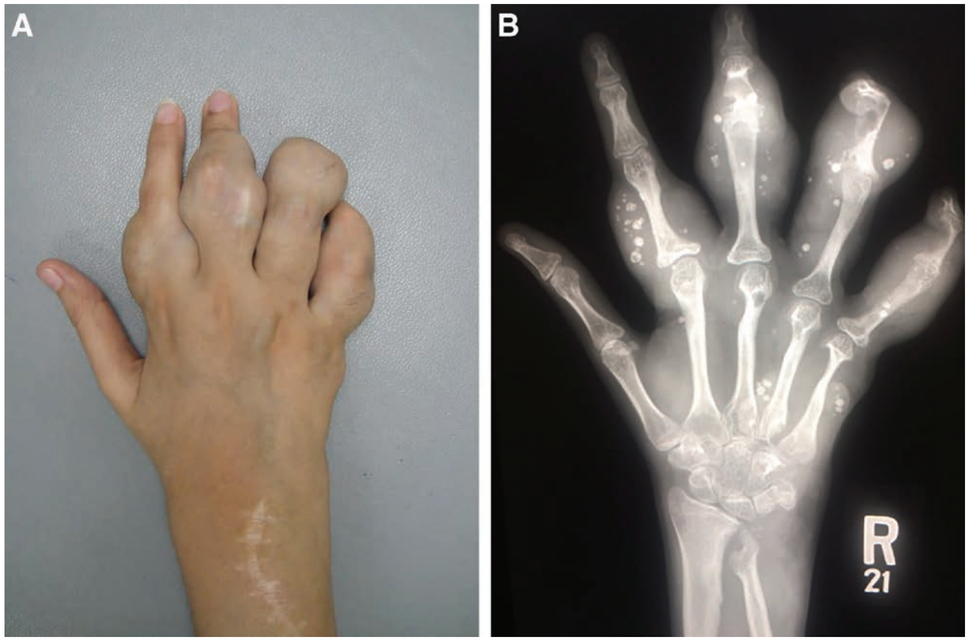


**Fig. 2.** Untreated congenital venous malformations of the hand. The circumferential lesions around the fingers resulted in bone resorption. A, Clinical appearance of the hand. B, X-ray showing the bone resorption around the untreated venous lesions.

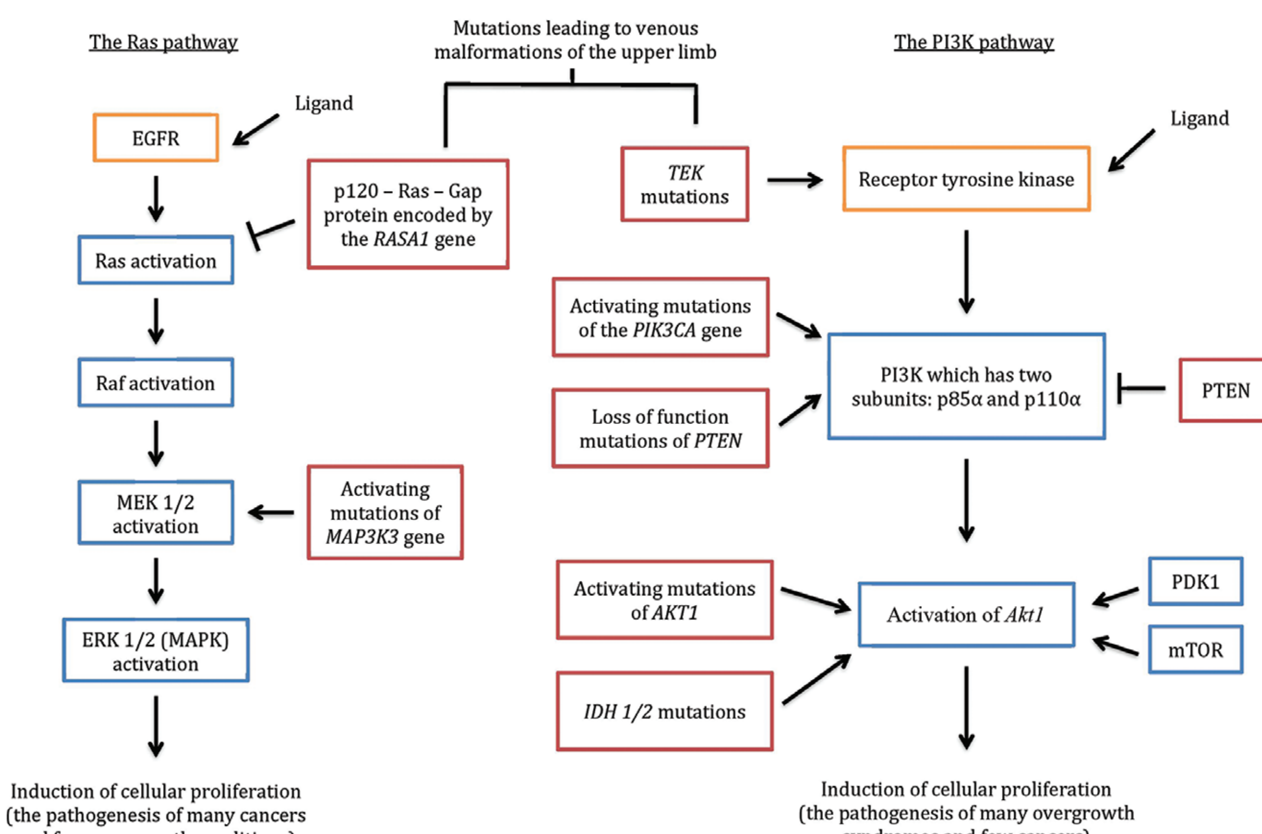


**Fig. 3.** The Ras and PI3K pathways for cellular proliferation (see text for details).

**The Ras Pathway (Fig. 3)**

Stimulation of EGFR (Epidermal Growth Factor Receptor) results in the activation of Ras, Raf (Rapidly accelerated fibrosarcoma), MEK1/2 (MAPK/ERK Kinase 1/2), and finally, the activation of ERK1/2 (Extracellular Receptor Kinase), which is also known as MAPK (Mitogen Activated Protein Kinase). As shown in Figure 3, mutations of the *RASA1* and the *MAP3K3* genes are known to accelerate this pathway, leading to the development of multiple venous malformations of the upper limb.[15–17]

**The PI3K Pathway (Fig. 3)**

Stimulation of the Receptor Tyrosine Kinase will activate PI3K. PI3K is a heterodimer composed of a regulatory p85 α subunit and a catalytic p110 α subunit. The *PIK3CA* gene encodes the catalytic subunit. The activated PI3K will then participate in the activation of Akt1 (protein kinase B). Other proteins that participate in the activation of Akt1 include PDK1 (phosphoinositide-dependent Kinase 1) and m-TOR (mechanistic-target of rapamycin). The PI3K pathway is negatively regulated by PTEN (phosphatase and tensin homolog). Activating (gain-of-function) mutations of the *TEK* (which encodes the Tie-2 Receptor),[18–21] *AKT1*[22], and *PIK3CA*[23,24] genes, as well as loss-of-function mutations of the *PTEN* gene[22] will accelerate this pathway, leading to the development of multiple venous malformations of the upper limb. Finally, somatic mutations of *IDH1* and *IDH2* genes (the genes encoding ISOCITRATE DEHYDROGENASE 1 and 2) will also lead to excessive activation of Akt1 (Fig. 3), resulting in multiple venous malformations seen in the Maffucci syndrome.[25]

**Clinical Entities with Multiple Venous Malformations of the Upper Limb**

**Entities Caused by Germline Mutations (Table 2)**

These entities are inherited and syndromic. Hence, the vascular lesions are seen not only in the limbs, but also in other sites such as the face, trunk, brain, and the gastrointestinal tract. Furthermore, a positive family history and characteristic features of the syndrome are encountered.

Familial multiple venous malformation syndrome (OMIM 600195) presents with multiple cutaneous and mucosal venous malformations. Cutaneous lesions usually involve the trunk and limbs. The syndrome is caused by germline mutations in the *TEK* gene (*TYROSINE KINASE-ENDOTHELIAL*). The gene encodes the Tie-2 Receptor (Tyrosine-Protein Kinase Receptor Tie-2). The receptor is highly expressed in endothelial cells and is crucial for angiogenesis and vascular maintenance. The ligands for the Tie-2 receptor are the angiopoietins. When angiopoietins bind to the mutated receptor, there will be excessive activation of Akt1 protein and excessive cellular proliferation.[18] The blue-rubber-bleb syndrome (OMIM 112200) has a phenotype similar to that of the familial multiple venous malformation syndrome and is also known to be caused by germline *TEK* mutations.[19] However, the venous lesions of the blue-rubber-bleb syndrome are very characteristic: being deep blue in color and feels like rubbery blebs on palpation (Fig. 4).

Another syndrome that presents with multiple venous and intramuscular arteriovenous malformations of the upper limb is the Cowden syndrome (OMIM 158350). Other characteristic features of the syndrome include macrocephaly, facial skin lesions (multiple trichilemmomas are characteristic), gastrointestinal hamartomas, lipomas, and increased risk of developing cancer. The syndrome is caused by germline loss-of-function mutations of the *PTEN* gene. Loss-of-function of the encoded PTEN protein results in acceleration of cellular proliferation in the PI3K pathway.[22] A Cowden-like syndrome (OMIM 615109) is caused by an activating mutation of the *AKT1* of gene, also leading to acceleration of the PI3K pathway.[22]

Another entity of multiple vascular lesions of the limb is the “capillary malformation – arteriovenous malformation 1” (OMIM 608354). The syndrome is an autosomal dominant disorder characterized by capillary, venous, and arteriovenous malformations of the limbs and face. The syndrome is caused by germline mutations of the *RASA1* gene, which encodes a protein known as the p120-RasGAP protein (p120 Ras GTPase activating protein). Loss-of-function of the protein leads to acceleration of the Ras pathway of cellular proliferation.[16]

**Entities Caused by Somatic Mutations (Table 3)**

In these entities, there is overgrowth of the affected tissues only. Somatic mutations of the *TEK* gene are known to cause either a phenotype similar to that of the blue-rubber-bleb syndrome,[20] or multiple congenital venous malformations of the skin of the limbs and trunk.[21]

Limaye et al[23] described a nonhereditary, nonsyndromic entity with multiple cutaneous and mucosal venous malformations involving the limbs, trunk, and oral mucosa and linked the entity to somatic *PIK3CA* mutations. Another nonhereditary but syndromic entity known as the CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi,

**Table 2. Clinical Entities with Germline Mutations and Multiple Venous Malformations of the Upper Limb**

| The Germline Gene Mutations | Name of Entity/Syndrome (OMIM number, if available) | Pathogenesis |
|---|---|---|
| *TEK* gene | A) Familial multiple cutaneous and mucosal venous malformations syndrome (OMIM 600195)<br>B) Blue-Rubber -Bleb syndrome (OMIM 112200) | The encoded Tie-2 receptor binds to angiopoietin and is involved in the activation of the PI3K pathway |
| *PTEN* gene | Cowden syndrome (also known as Bannayan-Riley syndrome) (OMIM 158350) | Loss-of-function of the PTEN protein accelerates the PI3K pathway |
| *AKT1* gene | Cowden-like syndrome (OMIM 615109) | An activating mutation reading acceleration of the PI3K pathway |
| *RASA1* gene | Capillary malformation: arteriovenous malformation 1 (OMIM 608354) | The encoded protein (p120-Ras-Gap) affects the Ras pathway |

**Fig. 4.** A close-up of the characteristic cutaneous venous malformation of the blue-rubber-bleb syndrome.

Spine abnormalities) is also caused by somatic *PIK3CA* mutations[24] (Fig. 5). Al-Qattan[26] described a syndrome of muscle overgrowth with the following characteristic features: the muscle overgrowth only affected the upper limbs and presented in a proximo-distal gradient (the hand being the most severely affected), mild hypoplasia of the index finger, hyperextension deformity of the metacarpophalangeal joint of the thumb, and ulnar deviation of the fingers. This syndrome has also been linked to somatic *PIK3CA* mutations.[27] Rarely, this syndrome is associated with multiple venous malformations of the proximal part of the upper limb and adjacent trunk (Fig. 6). Another entity of multiple vascular lesions of the limb is the Klippel-Trenaunay-Parkes-Weber syndrome (KTPWS, OMIM 149000). The limb is enlarged with hypertrophy of soft tissues. Vascular lesions in the limb include capillary, venous, and arteriovenous malformations. These abnormalities are usually seen in 1 lower limb, but may also involve 1 upper limb (Fig. 7). About 25% of patients with KTPWS have somatic *PIK3C* mutations.[28] This indicates locus heterogeneity (other gene mutations may cause the syndrome). One of these other genes linked to KTPWS is the *AGGF1* gene encoding the AGGF1 (Angiogenic Factor with G-patch and FHA Domains 1) protein. Tissue biopsies from KTPWS patients show increased expression of the AGGF1 protein. This leads to an accelerated angiogenesis through the activation of the PI3K pathway because the AGGF1 protein is known to activate both the regulatory p85 α and the catalytic p110 α subunits of the PI3K protein[29] (see Fig. 3).

A specific somatic mutation of the *MAP3K3* gene (C.1323 C>G, p. Iso441Met) is known to be associated with another type of venous malformation known as the "verrucous venous malformation or VVM."[15] VVM is nonhereditary, and the multiple venous malformations are seen in the skin of the limbs and trunk. There is no involvement of the deeper structures within the limbs or the internal organs. Lesions are seen at birth as small reddish-blue birth marks, which gradually enlarge and become raised, verrucous, and darker in color.

Another specific mutation of the *MAP3K3* gene (c.1723T>C, p.Tyr 575 His) within the veins of the upper limb is known to cause an entity known as the late-onset multiple venous malformation of the upper limbs.[4,17] This entity has 3 unique features: the multiple venous malformations are usually first noted around adolescence, the lesions are always well localized (not diffuse), and they are confined to the upper limbs. The reason for confinement of these malformations to the upper limbs remains a mystery. The lesions may be subcutaneous or subfascial leading to mild nerve compression, and they vary in size from 1 to 20 cm[17] (Fig. 8).

Somatic mutations of *IDH1* and *IDH2* genes are associated with the Ollier-Maffucci syndrome spectrum,[30] which may

**Table 3. Clinical Entities with Somatic Mutations and Multiple Venous Malformations of the Upper Limb**

| The Somatic Gene Mutations | Name of Entity/Syndrome (OMIM number, if available) | Pathogenesis |
|---|---|---|
| *TEK* gene | a) A phenotype similar to the blue-rubber-bleb syndrome<br>b) Nonhereditary, nonsyndromic, multiple cutaneous venous malformations of the skin of the limbs and trunk | The encoded Tie-2 receptor binds to angiopoietin and is involved in pathway |
| *PIK3CA* gene | a) Nonhereditary, nonsyndromic, multiple cutaneous and mucosal venous malformations (limbs/trunk/mouth/intestine)<br>b) Nonhereditary syndrome: CLOVES syndrome (OMIM 612918)<br>c) Nonhereditary syndrome: Upper limb muscle overgrowth-index finger hypoplasia syndrome. This syndrome may present with muscle overgrowth in 1 upper limb and venous malformations in the contralateral upper limb<br>d) Nonhereditary syndrome: Klippel-Trenaunay-Parkes-Weber syndrome (OMIM 149000) | Activating the activation of the PI3K mutations leading to acceleration of the PI3K pathway in the affected tissues |
| *MAP3K3* gene | a) Nonhereditary, nonsyndromic, multiple verrucous venous malformations of the limbs and trunk<br>b) Nonhereditary, nonsyndromic, late-onset multiple venous malformations confined to the upper limbs | An activating mutation leading to acceleration of the Ras pathway in the veins |
| *IDH1* and *IDH2* genes | Maffucci syndrome (OMIM 614569) | Mutations of the *IDH1* and *IDH2* genes activate the PI3K pathway |


**Fig. 5.** A child with CLOVES syndrome and a *PIK3CA* somatic mutation. A, Multiple venous malformations of the upper limb. The deep lesions were relatively asymptomatic. The superficial lesion at the wrist was rapidly growing, ulcerating, with a history of bleeding. B, The trunk showing a large lipomatous overgrowth with an overlying capillary malformation. C, A characteristic feature of the CLOVES syndrome is the "splayed" foot appearance. D, The superficial ulcerating lesion was excised.

be subclassified into 3 subtypes—Type I (Ollier syndrome): multiple enchondromas of the hands; Type II (Maffucci syndrome): multiple enchondromas and venous malformations of the hands/forearms; and Type III: A Maffucci phenotype with other vascular malformations seen outside the upper limb including the trunk and oral mucosa.[31,32] Severe cases may end with amputation of the hand because of malignant transformation of the enchondromas (into chondrosarcoma) or disease progression, leading to a complete loss of function. The main function the IDH 1 and 2 protein enzymes is the conversion of isocitrate to 2-ketoglutarate. This reaction also produces NADPH (the reduced form of Nicotinamide Adenine Dinucleotide Phosphate), which is necessary for many cellular processes. The normal enzymatic activity within the cells also appears to be important in the homeostasis of the PI3K pathway.[25] Hence, somatic mutations of *IDH1* and *IDH2* genes activate Akt1, explaining the multiple venous malformations in Types II and III of the Ollier-Maffucci spectrum.[25] Some patients do not develop vascular lesions (Type I of the spectrum), and the reason for this remains to be unknown and requires further studies.

### An Approach to the Diagnosis of the Various Clinical Entities Presenting with Multiple Venous Malformations of the Upper Limb

Clinically, patients presenting with multiple venous malformations of the upper limb should be examined for the presence of cutaneous or mucosal lesions outside the upper limbs, and should also be screened for any other congenital abnormalities.

As shown in Table 4, the clinical presentation may be categorized into 4 groups. If the venous malformations are confined to the upper limbs (ie, with no other cutaneous or mucosal lesions outside the upper limbs) with no other congenital defects, the most likely diagnosis is the nonhereditary late-onset type (*MAP3K3* mutations). In the second category, the malformations are cutaneous/subcutaneous in the limbs/face/torso and there are no mucosal lesions. This entity may be related to *RASA1* germline mutations, the classic venous malformations (classic lesions are compressible and develop phleboliths) caused by *TEK* somatic mutations, or the verrucous malformations caused by somatic *MAP3K3* mutations. The third clinical category presents with widespread cutaneous and mucosal lesions and indicates a blue-rubber-bleb syndrome phenotype. Finally, the fourth category represents a well-known syndrome with characteristic features, including multiple venous malformations of the upper limbs. The author has seen a total of 84 patients; the most 2 common presentations were late-onset category with lesions confined to the upper limb (n = 26) and the widespread cutaneous lesions without involvement of the mucosa (n = 36) (Table 4).

## DISCUSSION

This study specifically reviews the entity of multiple venous malformations of the upper limb. We could not find a similar review in the literature. As mentioned in the "Introduction" section, there has been no consensus regarding the classification of this entity; and our review offers such a classification (Table 1). The review


**Fig. 6.** A case of Al-Qattan muscle overgrowth syndrome of the right upper limb, multiple venous malformations of the left upper limb, and a somatic *PIK3CA* mutation. A, Appearance of the hands. Note the mild hypoplasia of the index finger and the ulnar deviation of the fingers of the right hand. B, X-ray showing the widened inter-metacarpal spaces in the right hand because of the enlarged intrinsic muscles. C, The multiple venous malformations of the left upper limb. D, MRI showing the muscle overgrowth of the right upper limb (without any vascular lesions) and the multiple venous malformations of the left upper limb.

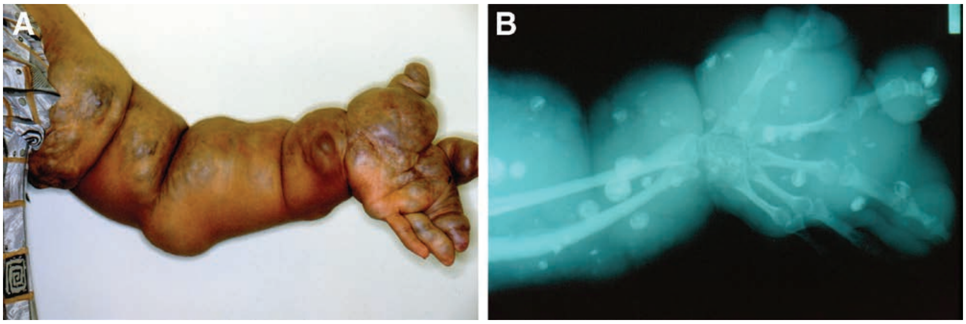


**Fig. 7.** A case of Klippel-Trenaunay syndrome (associated with somatic *PIK3C* mutations) involving the upper limb. A, Clinical appearance. B, X-ray showing the multiple phleboliths within the venous malformations.

also identifies all clinical entities with multiple venous malformations of the upper limb (Tables 2 and 3). One interesting finding is the fact that all these clinical entities are linked to either germline or somatic mutations. Furthermore, all mutations are known to result in the acceleration of cellular proliferation within the affected veins through the activation of either the Ras or the PI3K pathways (Fig. 3). The review also offers an approach for the diagnosis of the various clinical entities presenting with multiple malformations of the upper limb (Table 4).

The current review is derived from Saudi Arabia. It is based on a review of the literature and the experience of the author over the last 28 years of practice in Saudi Arabia. It is important to realize that all clinical entities (Tables 2–4) are related to gene mutations. Therefore, there should be no differences in presentation for Saudi patients when compared with other ethnic groups.

Table 4 also shows the number of patients seen by the author in each clinical entity. Although this gives the reader an overall idea on the frequency of cases

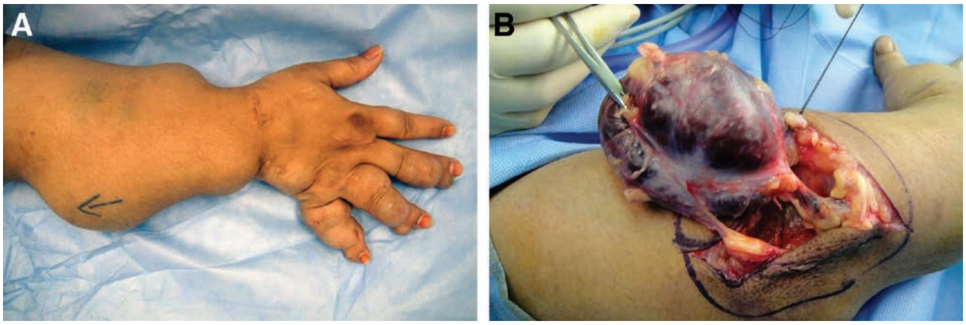

**Fig. 8.** A patient with late-onset multiple venous malformations confined to the upper limb who presented to the author and was found to have the *MAP3K3* somatic mutation: (c.1723T>C). This mutation is specific for this entity. A, Clinical appearance of the multiple hand and forearm lesions. B, Intraoperative view showing the excision of a giant subcutaneous forearm lesion arising from a dorsal vein.

**Table 4. An Approach for the Diagnosis of the Various Clinical Entities with Multiple Venous Malformations of the Upper Limb**

| Clinical Presentation (Number of Patients in Each Category Seen by the Author in His Practice) | Clinical Diagnosis | Gene Mutation |
|---|---|---|
| The malformations are confined to the upper limbs only and are late-onset in presentation (n = 26 patients) | Late-onset type (n = 26) | *MAP3K3* (somatic) |
| The malformations are cutaneous in the limbs/face/trunk; with no mucosal lesions (n = 36 patients) | Capillary malformation: arteriovenous malformation type 1 (0M1M 608354) (n = 3) | *RASA1* (germline) |
| | Nonhereditary classic venous lesions (n = 23) | *TEK* (somatic) |
| | Nonhereditary verrucous venous lesions (n = 10) | *MAP3K3* (somatic) |
| Widespread malformations in the skin/oral mucosa, and may include the gastrointestinal tract (n = 6) | Blue-Rubber-Bleb syndrome (n = 1) | *TEK* (germline) |
| | Blue-Rubber-Bleb-like syndrome (n = 5) | *TEK* (somatic), *PIK3CA* (somatic) |
| The venous malformations of the upper limb are part of a well-known syndrome (n = 16) | Cowden syndrome (n = 2) | *PTEN* (germline) |
| | Cowden-like syndrome (n = 1) | *AKT1* (germline) |
| | CLOVES syndrome (n = 8) | *PIK3CA* (somatic) |
| | Al-Qattan upper limb overgrowth-index hypoplasia syndrome (n = 1) | *PIK3CA* (somatic) |
| | Klipple-Trenaunay-Parks-Weber syndrome (n = 2) | *PIK3CA* (somatic) |
| | Maffucci syndrome (n = 2) | *IDH1/IDH2* (somatic) |

presenting to the hand/plastic surgery clinic, the numbers do not represent the prevalence of the entities in the general population. For example, Klipple-trenaunay syndrome is a well-known syndrome that almost always affects the lower limb. Involvement of the upper limb is very rare, and the author has only encountered 2 cases over 28 years. Another example is Al-Qattan upper limb muscle overgrowth-index hypoplasia syndrome. The syndrome was described by the current author based on several cases.[26,27] The syndrome is characterized by pure muscle overgrowth: usually without vascular lesions. Cases with concurrent vascular malformations are rare, and the author has only seen 1 case (Fig. 6). As seen in Table 4, the 2 most common clinical entities are the late-onset type (previously described by the author[4,17]) and patients presenting with widespread cutaneous lesions. The third category is uncommon and includes all patients with cutaneous and mucosal lesions. The gastrointestinal lesions may remain quiescent for a long time, presenting late with severe bleeding. Hence, one of the responsibilities of the plastic surgeon is to refer these patients to the gastroenterology service to rule out intestinal lesions. The last entity (Table 4) is relatively easy to diagnose from the clinical features of the syndrome, and most patients present with features of CLOVES syndrome.

As mentioned earlier, the 2 main modalities of management of venous malformations are surgery and sclerotherapy. Recurrence and the development of new lesions remain to be major problems with both modalities. Knowledge of the genetic basis of these lesions may have implications for investigating new therapeutic options. The use of small molecule inhibitors of the pathways of cellular proliferation is now under trial in the management of cancer.[33] The same concept has been applied for the medical management of overgrowth syndromes and vascular malformations of the upper limb. Proteus syndrome (OMIM 176920) is a progressive overgrowth syndrome characterized by asymmetric and disproportionate overgrowth of body parts, which is associated with connective tissue nevi and dysregulated adipose tissue. Marsh et al[34] reported on a child with Proteus syndrome and enlarging mediastinal and abdominal hamartomas resulting in tachypnea at rest, feeding problems, and the need for regular analgesics because of recurrent abdominal pain. The child was found to have a germline *PTEN* mutation with acceleration of the PI3K pathway. Medical treatment was done using oral rapamycin, which is an inhibitor of m-TOR in the PI3K pathway (see Fig. 3). All serious symptoms resolved, and there was reduction of mediastinal and abdominal hamartomas radiologically.

Another example is the case reported by Iacobas et al.[35] A 6-year-old boy with Cowden syndrome and germline *PTEN* mutation (see Table 2) presented to the authors with symptomatic multiple venous and arteriovenous malformations of the hand and forearm. There was progressive loss-of-function of the hand, flexion contractures of the fingers, and significant pain. Sclerotherapy and embolization failed. Surgery resulted in recurrence and there was development of new lesions. The child was treated with oral rapamycin and this was effective to decrease the size of all vascular lesions, and a full range of motion of the hand was regained. The reduction in the size of the mutated venous malformations with the use of rapamycin has also been demonstrated experimentally in animal models.[36] This suppressive effect on venous malformations will not only improve function and cosmesis of the upper limbs, but will also reduce the bleeding episodes of concurrent gastrointestinal venous malformations.[19]

RAS inhibitors are also under trial in the management of tumors positive for somatic mutations along the Ras pathway.[37] These inhibitors may be tried in severely symptomatic cases of multiple venous malformations of the upper limb if the identified gene mutation is along the Ras pathway.

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