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## Vascular anomalies of the upper limb

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## **Vascular anomalies of the upper limb**

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## **ABSTRACT**

Vascular anomalies are common in the upper extremity, but there continues to be a relative paucity of information about them in the hand and upper limb surgical literature. The wide spectrum of pathology and an inconsistent use of terminology make vascular anomalies susceptible to incorrect diagnosis and as a result to misdirected management. This article aims to provide an update on vascular anomalies relevant to the upper limb, focusing on significant advances in pathogenesis and genetics, classification systems, diagnosis, and treatment.

Level of Evidence: V

1 **Vascular anomalies of the upper limb**

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## ABSTRACT

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7 relative paucity of information about them in publications dealing with surgery in the  
8 hand and upper limb. The wide spectrum of pathology and an inconsistent use of  
9 terminology make vascular anomalies susceptible to incorrect diagnosis and as a  
10 result, to misdirected management. This article aims to provide an update on vascular  
11 anomalies relevant to the upper limb, focusing on significant advances in  
12 pathogenesis and genetics, classification systems, diagnosis, and treatment.

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## **INTRODUCTION**

Vascular anomalies account for 2-6% of all tumours in the upper extremity (Jacobs et al., 2010; McClinton, 1993; Mendel and Louis, 1997). However, there is a relative paucity of information about them in publications concerning surgery of the hand and upper limb. The wide spectrum of pathology ranging from minor "birthmarks" to complex life-threatening conditions (Wassef et al., 2015), as well as an inconsistent use of terminology make vascular anomalies susceptible to incorrect diagnosis and as a result, to misdirected management. This article aims to provide an update on vascular anomalies relevant to the upper limb by reviewing recent significant advances in pathogenesis and genetics, and to assess their influence on the evolution of classification systems, diagnosis, and treatment.

## **VASCULAR DEVELOPMENT AND PATHOGENESIS OF VASCULAR ANOMALIES**

The upper limbs of the developing human embryo form from around day 26 post-fertilization and are fully formed by around day 56 (DeSesso, 2017; Vargesson and Hootnick, 2017). Vascular development is central to the normal formation and outgrowth of the limb, and occurs through the process of angiogenesis whereby existing vessels produce new vessels by the proliferation and migration of endothelial cells into new, previously avascular areas (usually induced through cellular hypoxia). Intersegmental arteries (that run in between the somites from the aorta) vascularize the limb bud by forming a capillary vascular plexus throughout the developing limb

40 bud and immediately after limb bud formation. (Vargesson, 2019 In Press ) Rapidly  
41 (within a day) one of the intersegmental vessels, the subclavian artery, becomes  
42 dominant and from then on solely supplies the outgrowing limb vascular plexus  
43 (Vargesson and Hootnick, 2017). As outgrowth of the limb bud continues, the  
44 vascular plexus starts to differentiate (with regression of some areas) in a proximal to  
45 distal manner, into distinctive arterial and venous patterns, which, owing to molecular  
46 differences, are prevented from fusing to maintain normal blood flow (Vargesson,  
47 2003). For example, the vascular plexus of the upper limb begins to differentiate so  
48 that the subclavian artery feeds into the axillary artery, which then feeds into the  
49 brachial artery (supplying parts of the humerus and upper arm). Subsequently, further  
50 differentiation of the vascular plexus occurs by splitting into the radial and ulnar  
51 arteries, which will ultimately lead into the arteries (e.g. the anterior interosseous)  
52 supplying the digital plate (DeSesso, 2017; Rodríguez-Niedenführ et al., 2001;  
53 Vargesson and Hootnick, 2017; Vargesson, 2019 In Press). This process, whereby the  
54 embryonic vascular plexuses develop into the adult vascular patterns, is also known as  
55 the vascular transition and occurs between week 5 and 7 (Levinsohn et al., 1991;  
56 Vargesson and Hootnick, 2017). The vascular transition accompanies and is  
57 intimately linked to the appearance of cartilage precursors of the bony elements, also  
58 in a proximal to distal fashion (Vargesson and Hootnick, 2017). For example, the  
59 humerus forms before the radius and ulna, which form before the digits – and as the  
60 elements form, they require vascularization to maintain outgrowth (Vargesson, 2003;  
61 Vargesson and Hootnick, 2017). Failure of the vascular transition or an inhibition into  
62 the correct vascular patterns causes vessels to be in the wrong position and can result  
63 in bony elements with reduced or no vascularization, which then results in malformed  
64 or missing bony elements (Levinsohn et al., 1991; Vargesson and Hootnick, 2017).



65 Consequently, this mechanism has been proposed as an explanation for some  
66 congenital limb reduction syndromes (such as radial dysplasia) as well as for  
67 teratogen-induced limb differences (Levinsohn et al., 1991; Vargesson, 2015;  
68 Vargesson and Hootnick, 2017; Vargesson, 2019 In Press).

69

70 In summary, the development of a functional and controlled vasculature is essential  
71 for normal limb development. Vascular failure, inhibition or disruption can result in  
72 congenital limb differences. Teratogens such as thalidomide can cause vessel failure  
73 and are linked with causation of limb differences through vascular loss (Therapontos  
74 et al., 2009; Vargesson, 2015). Other processes, such as thrombi from the maternal  
75 placenta as well as constriction bands have also been linked to the causation of limb  
76 differences (Holmes et al., 2018).

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79

## CLASSIFICATION

80

### 81 **Clinical classification**

82 The 1996 International Society for the Study of Vascular Anomalies (ISSVA) divided  
83 vascular lesions into proliferative vascular lesions or tumours (Enjolras, 1997) or  
84 vascular malformations. Vascular malformations were further subdivided on the basis  
85 of their predominant vessel type into capillary (CM), venous (VM), lymphatic (LM),  
86 arterial (AM), arterio-venous (AVM), or combined malformations (CVM). Additional  
87 disease entities have been identified and a more detailed understanding of the  
88 histopathology and genetics has led to the 2014 updated ISSVA classification (Table  
89 1). Vascular malformations can be further categorized based on their flow

90 characteristics, as determined by Doppler ultrasound, into low/no-flow (CM, LM,  
91 VM) and high-flow anomalies (AVM, arterio-venous Fistulas, AVF) (Mulliken et al.,  
92 2000; Mulliken and Glowacki, 1982).

93

#### 94 **Genetic classification**

95 More recently, modern genetic sequencing techniques have enabled the  
96 reclassification of vascular anomalies based on causative genetic mutations rather  
97 than on phenotypic subdivisions. Somatic mosaic mutations in the  
98 Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)  
99 gene, which encodes the catalytic subunit of the enzyme Phosphatidylinositol 3-  
100 kinase (PI3K), have been found in malformation/overgrowth syndromes (Figure 1).  
101 This led to the designation of the term “PIK3CA-Related Overgrowth Spectrum” of  
102 disorders (PROS), ranging from isolated anomalies to more complex segmental  
103 overgrowth disorders (Keppler-Noreuil et al., 2015). These recent genetic findings are  
104 likely to have significant impact on the understanding of vascular anomalies and their  
105 classification and medical treatments.

106

107

## 108 **CLINICAL PRESENTATIONS AND MANAGEMENT OF SPECIFIC** 109 **VASCULAR TUMOURS**

110

### 111 **Benign vascular tumours**

112

113 Infantile haemangioma (IH) is the most common tumour of infancy (Kilcline and  
114 Frieden, 2008) with an incidence within the limbs of around 15%. Most IHs appear

115 during the neonatal period within the first two weeks of life, but about one- third  
116 would already be present at birth, usually in the form of telangiectasia or a pink  
117 macular stain (Mulliken et al., 2000). Classically, IHs appear cherry red and lie in the  
118 papillary dermis (Figure 2). IHs are characterized by a typical pattern of initial rapid  
119 proliferative growth during the first 6 to 12 months, followed by a period of slow  
120 involution or regression over several years. In 50% of infants, involution is complete  
121 by five years , in 70% by seven years and the remainder by 10 years of age. After  
122 regression, 50% of affected children present with normal skin in the area of the  
123 former lesion, but larger lesions tend to leave an area of wrinkled skin overlying  
124 fibro-fatty tissue.

125

126 As opposed to IHs, congenital haemangiomas (CH) are characterized by a distinct  
127 clinical course and histopathology. They form in utero, can be detected as early as in  
128 the second trimester of pregnancy, and are fully formed at birth (Boon et al., 1996;  
129 Bronshtein et al., 1992). CHs can be further divided into rapidly involuting (RICH),  
130 partly involuting (PICH), and non-involuting (NICH) types. Regression in RICH  
131 begins early, with full involution by 9 to 14 months. NICHs persist as the child grows  
132 (Boon et al., 1996; Enjolras et al., 2001). Unlike IHs, their endothelial cells do not  
133 express Glut-1 (Wassef et al., 2015).

134

135 Most haemangiomas on the upper limbs are small and regress following a predictable  
136 pattern without the need for intervention. Hence, they should be allowed to proliferate  
137 and involute under careful observation (Fevurly and Fishman, 2012). In cases of  
138 larger, more functionally incapacitating lesions, systemic propranolol might be  
139 considered as a first-line treatment (Holland et al., 2010). Topical Beta-blockers are

140 occasionally used but have so far shown only modest results (Pope and  
141 Chakkittakandiyil, 2010).

142

143 Most commonly, decisions about surgery are delayed until complete involution has  
144 taken place. Early surgical intervention during the proliferative phase may be  
145 indicated in cases of recurrent infection, ulceration, or bleeding, especially when the  
146 haemangioma is well-localized. Early excision may also be considered in cases where  
147 removal is very likely to be required, even after involution, and the same optimal  
148 cosmetic result can be achieved (Fevurly and Fishman, 2012).

149

#### 150 **Locally aggressive or borderline vascular tumours**

151 More invasive, benign, or locally aggressive and borderline vascular tumours of  
152 clinical significance are tufted angiomas (TA) and kaposiform  
153 hemangioendotheliomas (KHE). TA and KHE can be present at birth and are  
154 probably more of a spectrum of lesions than distinct entities although both lesions  
155 show distinct histopathological features. Clinically, they present with erythematous or  
156 brown plaques with surrounding ecchymosis and occasionally generalized petechiae  
157 (Figure 3).

158

159 TA and KHE can be associated with profound thrombocytopenia (Kasabach-Merritt  
160 Phenomenon, KMP) (Enjolras et al., 1997), with a significant risk for intracranial,  
161 pleural-pulmonic, intraperitoneal, or gastro-intestinal haemorrhage with a mortality of  
162 up to 30% (Martinez-Perez et al., 1995). Sirolimus, an inhibitor of the PI3K/mTOR  
163 pathway, has now become a first-line treatment in KHE, and its use is rapidly

164 expanding in the treatment of other vascular malformations and overgrowth  
165 syndromes (Enjolras et al., 2000; Gruman et al., 2005).

166

### 167 **Malignant vascular tumours**

168 In atypical presentations, malignant vascular tumours, although rare, must be kept in  
169 mind within the differential diagnosis. In unclear cases, a biopsy and  
170 histopathological diagnostics should be obtained. Management depends on the  
171 aggressiveness of the subtype and includes surgery and chemotherapy (Board, 2002).

172

173

## 174 **CLINICAL PRESENTATION AND MANAGEMENT OF SPECIFIC**

## 175 **VASCULAR MALFORMATIONS**

176

### 177 **Low flow vascular malformations**

178 Capillary malformations (CMs), often referred to as “port wine stains” are composed  
179 of dilated capillaries and post-capillary venules that are located within the superficial  
180 dermis (Smoller and Rosen, 1986). Present at birth, they are the commonest vascular  
181 malformations, occurring in 0.3% of all new-borns (Jacobs et al., 2010). CMs  
182 generally persist lifelong and may demonstrate thickening and darkening due to vessel  
183 dilatation. They can be associated with overgrowth, or may be indicative of the  
184 presence of other vascular malformations (LM, VM) or syndromes (combined  
185 vascular malformations, vascular malformations associated with other anomalies)  
186 (Wassef et al., 2015).

187

188 CMs on the upper extremity rarely require treatment other than for cosmetic reasons.  
189 The pulse-dye laser demonstrates good clinical response rates with a minimal  
190 complication risk. The optimal timing for laser treatment remains controversial, but  
191 early treatment appears beneficial (van der Horst et al., 1998).

192

193 Lymphatic malformations (LMs) are composed of dilated channels or cysts and can  
194 be classified into microcystic (cysts <1cm), macrocystic (cysts >1cm), or mixed type  
195 lesions, depending on the diameter of the cysts (Figure 4). In the upper limb, LMs are  
196 generally of mixed type, but tend to be microcystic below the elbow. On inspection,  
197 the overlying skin of larger cysts can have a bluish appearance. Involved skin can also  
198 be thickened or puckered and may develop vesicles that have a propensity to weep,  
199 which increases the risk of infection. In the upper limbs, LMs are often associated  
200 with fibro-fatty tissues, and are most often confined to the skin and subcutis without  
201 penetration into the deep fascia or muscle. Occasionally, LMs are associated with  
202 skeletal overgrowth and distortion (Boyd et al., 1984), although they do not typically  
203 infiltrate bone or joints (Upton and Marler, 2005 ).

204

205 Compression garments can be effective as a first line measure for some symptomatic  
206 lesions (Jacobs et al., 2010); however, a lack of compressibility and the sheer size of  
207 some lesions can render compression ineffective. Additional problems associated with  
208 LMs include weeping, infections, and intralesional bleeding. Intralesional bleeding  
209 usually presents as rapid painful enlargement within the LM with associated  
210 ecchymosis. These episodes typically resolve with rest and analgesia. Pain and  
211 swelling may also occur as a result of bacterial or viral infection, which can be  
212 transmitted from a systemic infection into a LM. Early broadband spectrum antibiotic

213 treatment is indicated, and prolonged intravenous therapy may be required in order to  
214 adequately treat infection in recalcitrant cases.

215

216 Sclerotherapy is a well-established treatment modality for LMs, especially those with  
217 a significant macrocystic component. Sclerotherapy is also used as an adjunct pre-  
218 and post-surgical debulking (Morgan et al., 2016). There is a growing body of  
219 evidence supporting the efficacy of sirolimus (Morgan et al., 2016), which has been  
220 shown to be effective in trial cases of LMs and mixed lympho-venous malformations  
221 (Ricci, 2017; Trenor, 2016).

222

223

224 Surgery for LMs can be complex, and careful planning is essential. Complete  
225 resection is often not possible, and recurrence rates of up to 30% have been reported  
226 (Morgan et al., 2016). The resection is often best done in a staged manner (Upton and  
227 Marler, 2005) with the use of manoeuvres such as the administration of tranexamic  
228 acid, tourniquet control and diathermy assisted dissection to help minimize intra-  
229 operative blood loss (Ghadimi et al., 2016). Pre-operative D-Dimer and fibrinogen  
230 levels can be useful predictors of the degree of vascularity in cases of mixed  
231 lymphovenous lesions. Incisions across joints and extensions into the axilla should be  
232 zigzagged to prevent joint contractures and allow for future growth. For each side of a  
233 digit, hand, or forearm, separate procedures should be used, and combined dorsal and  
234 palmar dissections should be avoided (Upton and Marler, 2005 ). Mid-lateral or  
235 medial incisions are less visible and therefore preferred over dorsal scars. Extensive  
236 poorly delineated lesions in the hand and forearm may be better suited to treatment  
237 with cautious sclerotherapy.

238

239 Venous malformations (VM) are mostly sporadic, generally occurring as solitary  
240 lesions. Clinically, they present as soft compressible masses that often have a bluish  
241 appearance when superficial (Figure 5). VMs are present at birth and can sometimes  
242 go unnoticed initially but will grow commensurately with the child. Expansion of  
243 venous lesions typically occurs during the adolescent growth spurt. Painful episodes  
244 of thrombosis within VMs are common due to a low rate of blood flow, and can lead  
245 to the formation of characteristic phleboliths (Wassef et al., 2015). VMs can be  
246 extensive, even involving the axilla and chest wall and extend across the deep fascia  
247 into muscles. Despite significant involvement, affected musculature of the upper limb  
248 may still function well. Recurrent haemarthrosis can be a debilitating problem in VMs  
249 surrounding joints (Upton et al., 1999).

250

251 Glomuvenous malformations (GVMs) are distinct subsets of vascular malformation,  
252 characterised by the presence of a variable number of glomus cells (Boon et al.,  
253 2004). They are typically found on the extremities and account for approximately 5%  
254 of all VMs. GVMs are characterised by their superficial location, characteristic pink  
255 to purple-blue colour, and so-called cobblestone appearance. Unlike VMs, GVMs are  
256 typically firm, and pain is aggravated by compression garments (Boon et al., 2004).  
257 They are usually well- localized and respond well to surgical excision.

258

259 The basic surgical principles in VMs are very similar to those outlined for LMs. All  
260 possible measures to reduce bleeding must be considered. Pre-operative sclerotherapy  
261 is useful in some cases to reduce the risk of bleeding from surgery (James et al., 2011;  
262 Morgan et al., 2016) and pre-operative optimization of clotting factors and treatment



263 with low molecular weight heparin to raise low fibrinogen levels can be beneficial in  
264 some cases with localised intravascular coagulation (LIC) (Dompmartin et al., 2008;  
265 Mazoyer et al., 2002; Zhuo et al., 2017). Complete resection is often not possible, as  
266 VMs tend to extend beyond the deep fascia and involve muscles more commonly than  
267 LMs. Furthermore, it must be remembered that muscle function is often remarkably  
268 good despite extensive infiltration. Therefore, resection of involved muscles must be  
269 considered very carefully (Upton and Marler, 2005 ). Post-operative custom-made  
270 compression garments are very useful for tamponading surgical fields and dressing  
271 around difficult anatomical contours, for example the axilla and limbs.

272

273 Fibro-adipose vascular anomaly (FAVA) is a newly described fibro-fatty muscle-  
274 infiltrating complex vascular malformation with clinical, radiological and  
275 histopathological features distinct from intramuscular VMs (Alomari et al., 2014;  
276 Fernandez-Pineda et al., 2014). FAVA patients typically present with unusually high  
277 levels of pain and sometimes joint contractures, and usually show a poor response to  
278 treatments such as sclerotherapy. In the upper limb, FAVAs typically affect the  
279 forearm musculature-

280

281 FAVAs are characterized by a more solid, heterogeneous diffuse appearance on MRI  
282 and ultrasound imaging unlike classical VMs, which are more fluid (Johnson and  
283 Navarro, 2017). Surgery for FAVAs within the upper limb is difficult, as extensive  
284 muscle involvement and neurovascular entrapment are common (Figure 6). In these  
285 cases, compartment decompression, partial resection, neurolysis, and tendon  
286 lengthening can be very effective. In addition, image-guided percutaneous

287 cryoablation is emerging as a safe and effective treatment for symptomatic FAVA  
288 (Fernandez-Pineda et al., 2014; Shaikh et al., 2016).

289

### 290 **High flow vascular malformations**

291

292 Owing to their locally aggressive nature, AVMs are the most formidable vascular  
293 malformation with potential to threaten limb and life. They are high-flow lesions,  
294 consisting of disorganized arteries and veins that directly communicate by bypassing  
295 the high-resistance capillary bed (Fevurly and Fishman, 2012). With increased  
296 shunting, a phenomenon of blood flow ‘steal’ can occur, which leads to problems of  
297 distal ischaemia including pain, ulceration, and tissue necrosis (Upton and Marler,  
298 2005 ). The clinical progression of AVMs from quiescent to aggressive lesions with  
299 cardiac failure is reflected by the staging system described by Schobinger (Kohout et  
300 al., 1998; Lowe et al., 2012) (Table 2). However, AVMs, particularly those affecting  
301 the upper limb, do not necessarily progress consecutively through each stage (Upton  
302 and Marler, 2005).

303

304 Indications for operative treatment include uncontrollable progressive pain, digital  
305 ulceration, bleeding, compartment syndrome, cardiac failure or overall failure to  
306 thrive (Upton and Marler, 2005 ). Operative treatment is usually a combination of  
307 angiographic embolization and surgical resection. Pre-surgical embolization can  
308 improve outcomes and reduce morbidity (Morgan et al., 2016).

309

### 310 **Combined vascular malformations**

311 Combined vascular malformations (CVMs) contain at least two vascular  
312 malformations in one lesion; they can be simple malformations, malformations of  
313 major named vessels or a combination of both types. Multiple combinations exist;  
314 these lesions are often associated with skeletal and soft tissue overgrowth and  
315 abnormalities of the viscera and in rare cases undergrowth (Boyd et al., 1984). The  
316 principles of CVM management are similar to those outlined above for simple  
317 vascular malformations.

318

### 319 **Vascular malformations associated with other anomalies**

320 Klippel-Trenaunay-syndrome (KTS) represents a triad of capillary malformation,  
321 lympho-venous malformation and limb overgrowth. More recently, it has been shown  
322 that what was classically described as KTS is actually part of a spectrum of conditions  
323 that result from PIK3CA-related somatic mosaic mutations (Figure 1). KTS  
324 characteristically affects one lower extremity (88%) (Figure 7A), but bilateral cases  
325 and involvement of an upper extremity (29%) (Figure 7B), and extension into the  
326 trunk (23%) are not uncommon (Jacob et al., 1998; Lobo-Mueller et al., 2009).

327

328 CLOVES is an acronym (Congenital, Lipomatous, Overgrowth, Vascular  
329 malformations, Epidermal naevi and Spinal/Skeletal anomalies and/or Scoliosis,  
330 Seizures) for a syndrome with underlying somatic activating mutations in PIK3CA  
331 (Alomari, 2009; Kurek et al., 2012; Sapp et al., 2007). The clinical signs are usually  
332 present at birth and may be identified by prenatal imaging (Fevurly and Fishman,  
333 2012). CLOVES is characterized by limb asymmetry with involvement of the upper  
334 limb in 50% of cases. The typical lipomatous masses on the trunk and/or limbs are  
335 accompanied by overlying CM and other associated low flow lesions (VM, LM) and

336 high-flow (AVM) vascular malformations. Other manifestations include epidermal  
337 nevi, bony anomalies including scoliosis, acral anomalies such as wide or triangular  
338 feet, syndactyly or macrodactyly and a widened gap between the first and the second  
339 toes (sandal gap).

340

341 Proteus syndrome (PS) is a rare condition that typically presents with segmental  
342 overgrowth, vascular anomalies including CM, VM, and LM, epidermal nevi,  
343 hyperplasia of multiple tissues, and a propensity to develop tumours (Figure 8). A  
344 mosaic somatic mutation of the *AKT1* gene has been found in more than 90% of  
345 patients with PS (Johnson and Navarro, 2017). The striking phenotypic resemblance  
346 of Proteus to “PIK3CA-Related Overgrowth Spectrum” of disorders (PROS) might be  
347 because AKT1 is a downstream of PIK3CA and therefore activates similar  
348 downstream elements. In contrast to PROS disorders, the lesions in PS are not present  
349 at birth, but are characterized by progressive disproportionate overgrowth and may  
350 present with pathognomonic connective tissue naevi (Biesecker et al., 1999).

351

352 Parkes Weber syndrome (PWS) is distinguished from KTS by the presence of a high-  
353 flow arterio-venous malformation, in addition to a capillary one (CAVM) and limb  
354 hypertrophy (Weber, 1908; Weber, 1918; Young, 1988). PWS is caused by mutations  
355 in *RASA1*, an inhibitor of cellular growth, proliferation and differentiation. The  
356 lesions involve skin, muscle, and bone, and the overgrowth becomes increasingly  
357 prominent with growth, especially at puberty, after trauma to the limb, or during  
358 pregnancy. The lesions are present at birth and marked by a pink, warm, macular CM  
359 overlying the asymmetrically enlarged limb, often with an AVM heralded by an  
360 audible bruit and palpable thrill. Although PWS is more common in the lower

361 extremity, the upper limb is affected in about 23% of cases (Upton and Marler, 2005).  
362 The high-flow lesions can lead to symptoms as severe as heart failure.  
363  
364 Maffucci syndrome is a rare congenital condition that is characterized by  
365 simultaneous occurrence of multiple enchondromas and spindle cell haemangiomas  
366 that most commonly affect both hands resulting in deformities. Malignant  
367 transformation has been described, and over 30% of the enchondromas progress to  
368 chondrosarcomas. Patients with Maffucci syndrome also have an increased risk for  
369 other secondary malignancies, including gliomas. In 77% of these patients, somatic  
370 mutations in Isocitrate dehydrogenase (IDH) have been identified. Similar to Ollier's  
371 disease (which does not include haemangiomas and is typically unilateral),  
372 monitoring with periodic physical and radiographic examination is required because  
373 of the risk of malignant transformation (Fatti and Mosher, 1986).

374

375

376

## SUMMARY

377 The management of vascular anomalies remains demanding, but advances in  
378 interventional radiology, surgery and newer medical treatments have been promising.  
379 Systemic therapies, which could inhibit overgrowth and reduce vascular  
380 malformations by altering the PI3K-AKT-mTOR pathway in patients with PIK3CA  
381 mutations (Lackner et al., 2015) have the potential to revolutionize the management  
382 of vascular malformations (Keppler-Noreuil et al., 2015). Sirolimus, an inhibitor of  
383 the PI3K/mTOR pathway, is now being broadly applied in trials to a wide range of  
384 pathologies across the spectrum of vascular anomalies. Furthermore, newer  
385 generations of similar drugs are under development, including everolimus (Ricci,

386 2017; Trenor, 2016). Overall, these advances will aid the multi-disciplinary  
387 management of this wide ranging and often complex spectrum of conditions.

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614

615 **Figure legends**

616

617 **Figure 1: PI3K-AKT Pathway and associated clinical overgrowth disorders**

618 (reproduced with permission from Keppler-Noreuil et al., 2014 (John Wiley and  
619 Sons))

620

621 **Figure 2: Infantile haemangioma**

622 A patient with an infantile haemangioma on forearm and wrist. Note areas of  
623 involution with settling of discolouration.

624

625 **Figure 3: Kaposiform haemangioendothelioma (KHE)**

626 A patient with KHE affecting the right arm. This patient was successfully treated with  
627 sirolimus.

628

629 **Figure 4: Lymphatic malformation**

630 A patient with an extensive lymphatic malformation affecting the length of the arm.  
631 Note the lesion predominantly affects the tissues above the deep fascia.

632



633 **Figure 5: Venous malformation**

634 A patient with a venous malformation affecting the thumb pulp. Note the lesion  
635 engulfs the neurovascular structures within the thumb and involves the entire pulp  
636 tissue.

637

638 **Figure 6: Fibro-adipose vascular anomaly (FAVA) of the forearm.**

639 A patient who had extensive involvement of the flexor compartment of the forearm.  
640 Intra-operative pictures of a forearm compartment decompression and neurolysis of  
641 the median and ulna nerves. Note a central area of focal thrombosis has been excised  
642 from the flexor digitorum superficialis (FDS) musculature.

643

644 **Figure 7: Patient with PIK3CA overgrowth spectrum**

645 (A) Involvement of the leg with a low flow malformation, limb overgrowth, and a  
646 capillary malformation.

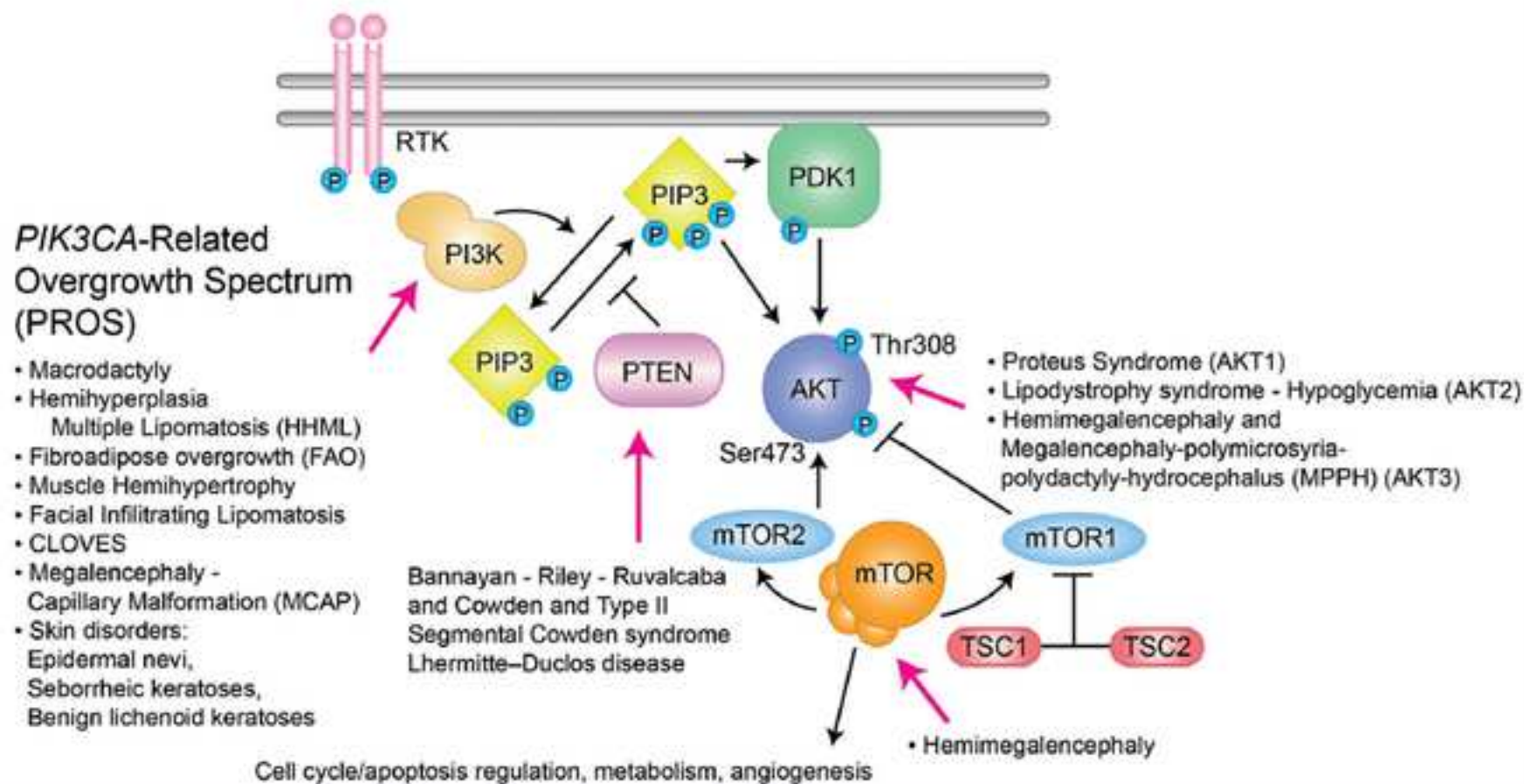
647 (B) Same patient with macrodactylous overgrowth of the ring finger.

648

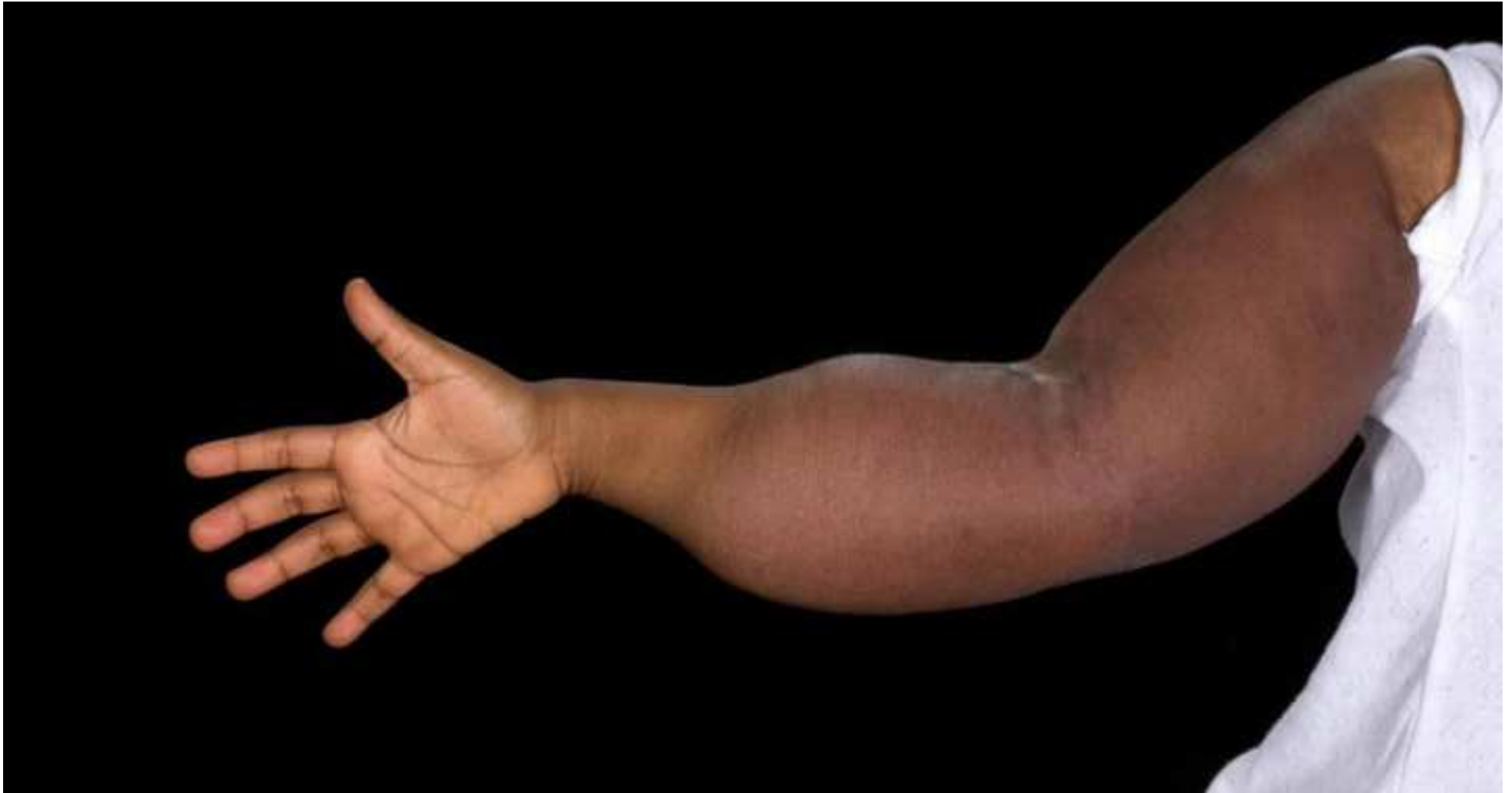
649 **Figure 8: Proteus syndrome**

650 Hand manifestations of a patient with Proteus syndrome.

## PI3K-AKT Signaling Pathway





















**Table 1.** Vascular anomalies based on the International Society for the Study of Vascular Anomalies (ISSVA) classification, 2014. Modified from (Morgan et al., 2016).

<b>Vascular tumours</b>	<b>Vascular malformations</b>	
	<b>Simple</b>	<b>Combined</b>
<b>Benign vascular tumours:</b>	Capillary malformations (CM)	Defined as two or more vascular malformations identified in one lesion. Can be composed of any combination CM, LM, VM, AVM.
Infantile haemangioma (IH)		
Congenital haemangioma	Lymphatic malformations (LM)	
Rapidly involuting (RICH)		
Non-involuting (NICH)	Venous malformations (VM)	
Partially involuting (PICH)		
Tufted Angioma (TA)	Arteriovenous malformations (AVM)	
Spindle-cell haemangioma		
Epitheloid haemangioma	Arteriovenous fistulas (AVF)	
Pyogenic granuloma (PG)		
Others	<b>Of named major vessels</b>	<b>Associated with other anomalies</b>

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<b>Locally aggressive vascular tumours:</b>	“Channel type” or “truncal” malformations	Klippel-Trenaunay-syndrome (KTS)
Kaposiform Haemangioendothelioma (KHE)		Parkes Weber syndrome (PWS)
Retiform haemangioendothelioma		Servelle-Martorell syndrome
Composite haemangioendothelioma		Sturge-Weber syndrome
Dabska tumour		Limb CM + limb hypertrophy
Kaposi sarcoma		Maffucci syndrome
others		Macrocephaly-CM
<b>Malignant vascular tumours</b>		Microcephaly-CM
Angiosarcoma of the soft tissue		CLOVES syndrome
Epitheloid haemangioendothelioma		Proteus syndrome (PS)
Others		Banayan-Riley-Ruvalcaba syndrome

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**Table 2.** Schobinger clinical staging system for AVM. From (Kohout et al., 1998).

<b>Stage</b>	<b>Description</b>
<b>I Quiescent</b>	Pink-bluish stain, increased warmth, arteriovenous shunting detectable with continuous Doppler scanning or 20 MHz colour Doppler scanning
<b>II Expansion</b>	Stage I + Enlargement, pulsations, thrill and bruits and tortuous/tense veins
<b>III Destruction</b>	Stage II + either dystrophic skin changes, ulceration, bleeding, persistent pain or tissue necrosis
<b>IV Decompensation</b>	Stage III + Cardiac failure