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Abstract:	Vascular anomalies are common in the upper extremity but there is 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.

Vascular anomalies of the upper limb

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ABSTRACT

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Level of Evidence: V

1   **Vascular anomalies of the upper limb**

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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

3

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).

77

78

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), <u>arterio-venous (AVM),</u> or combined malformations <u>(CVM)</u>. 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

during the neonatal period within the first two weeks of life, but about one- third

would already be present at birth, usually in the form of telangiectasia or a pink

macular stain (Mulliken et al., 2000). Classically, IHs appear cherry red and lie in the

papillary dermis (Figure 2). IHs are characterized by a typical pattern of initial rapid

proliferative growth during the first 6 to 12 months, followed by a period of slow

involution or regression over several years. In 50% of infants, involution is complete

by five years , in 70% by seven years and the remainder by 10 years of age. After

regression, 50% of affected children present with normal skin in the area of the

former lesion, but larger lesions tend to leave an area of wrinkled skin overlying

fibro-fatty tissue.

As opposed to IHs, congenital haemangiomas (CH) are characterized by a distinct

clinical course and histopathology. They form in utero, can be detected as early as in

the second trimester of pregnancy, and are fully formed at birth (Boon et al., 1996;

Bronshtein et al., 1992). CHs can be further divided into rapidly involuting (RICH),

partly involuting (PICH), and non-involuting (NICH) types. Regression in RICH

begins early, with full involution by 9 to 14 months. NICHs persist as the child grows

(Boon et al., 1996; Enjolras et al., 2001). Unlike IHs, their endothelial cells do not

express Glut-1 (Wassef et al., 2015).

Most haemangiomas on the upper limbs are small and regress following a predictable

pattern without the need for intervention. Hence, they should be allowed to proliferate

and involute under careful observation (Fevurly and Fishman, 2012). In cases of

larger, more functionally incapacitating lesions, systemic propranolol might be

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 sclerotherpy

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.

388

389

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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
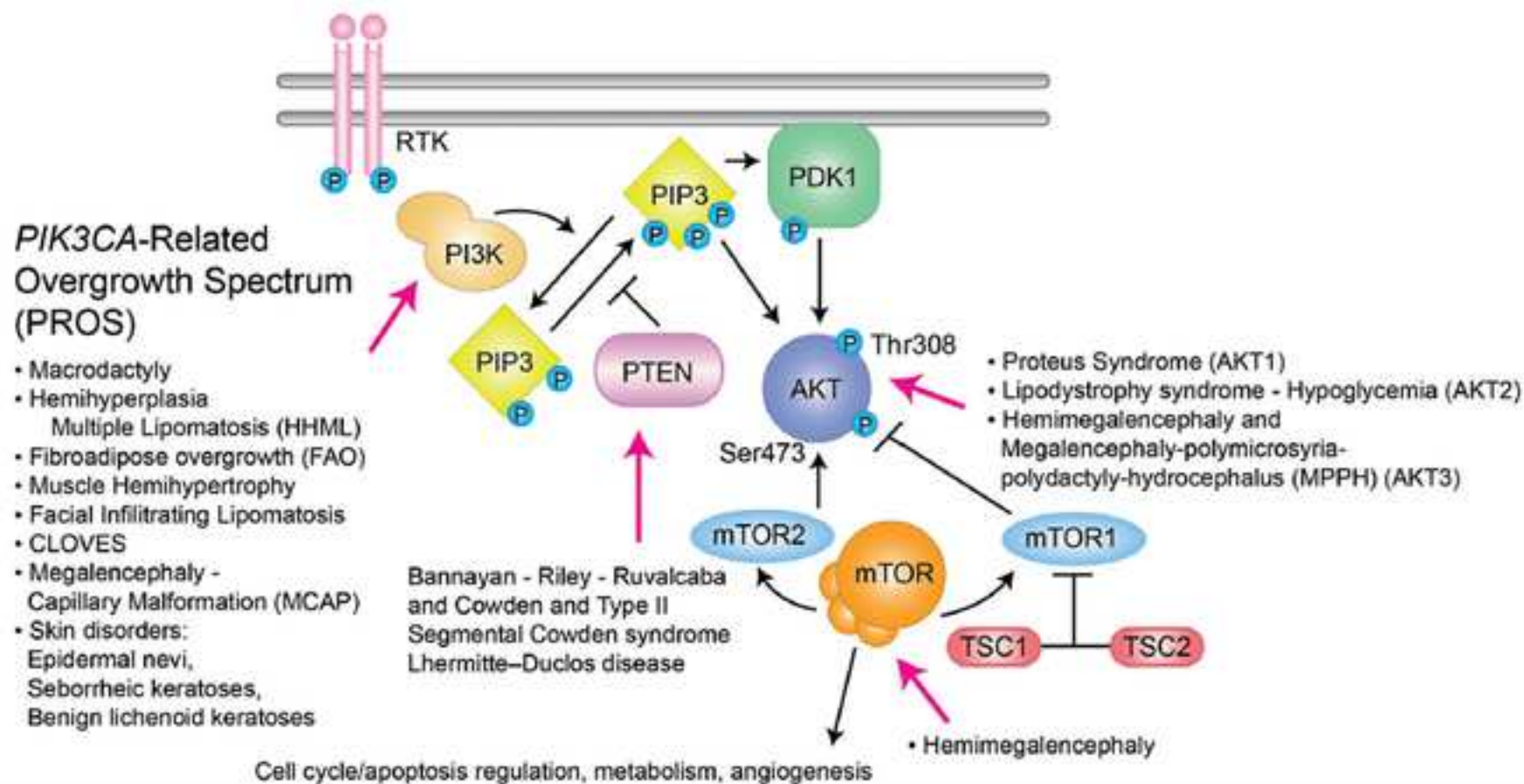
646 capillary malformation.

647 (B) Same patient with macrodactylous overgrowth of the ring finger.
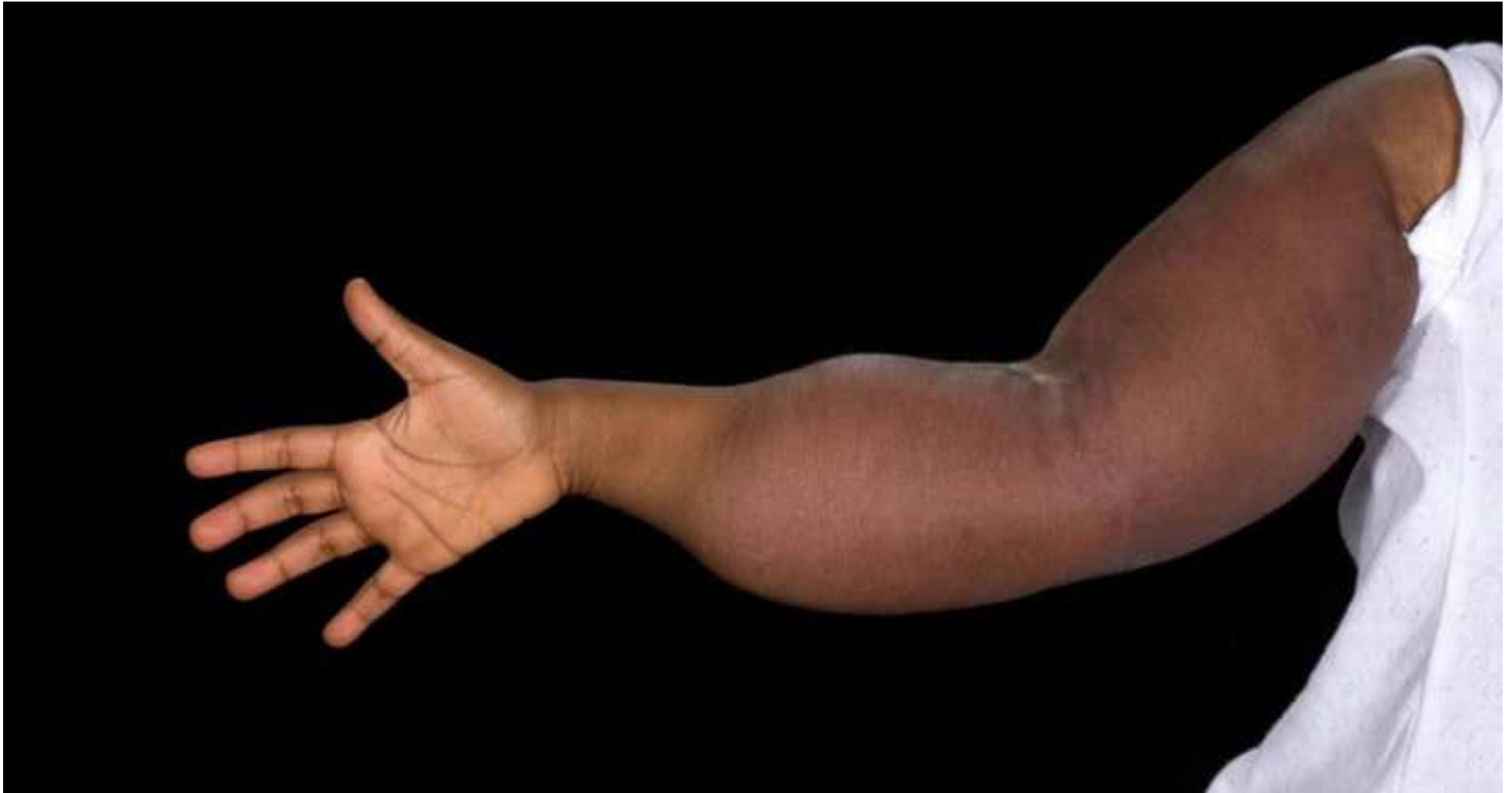
648

649 **Figure 8: Proteus syndrome**

650 Hand manifestations of a patient with Proteus syndrome.

Figure 1

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PI3K-AKT Signaling Pathway

Figure 2

Figure 3

Figure 4

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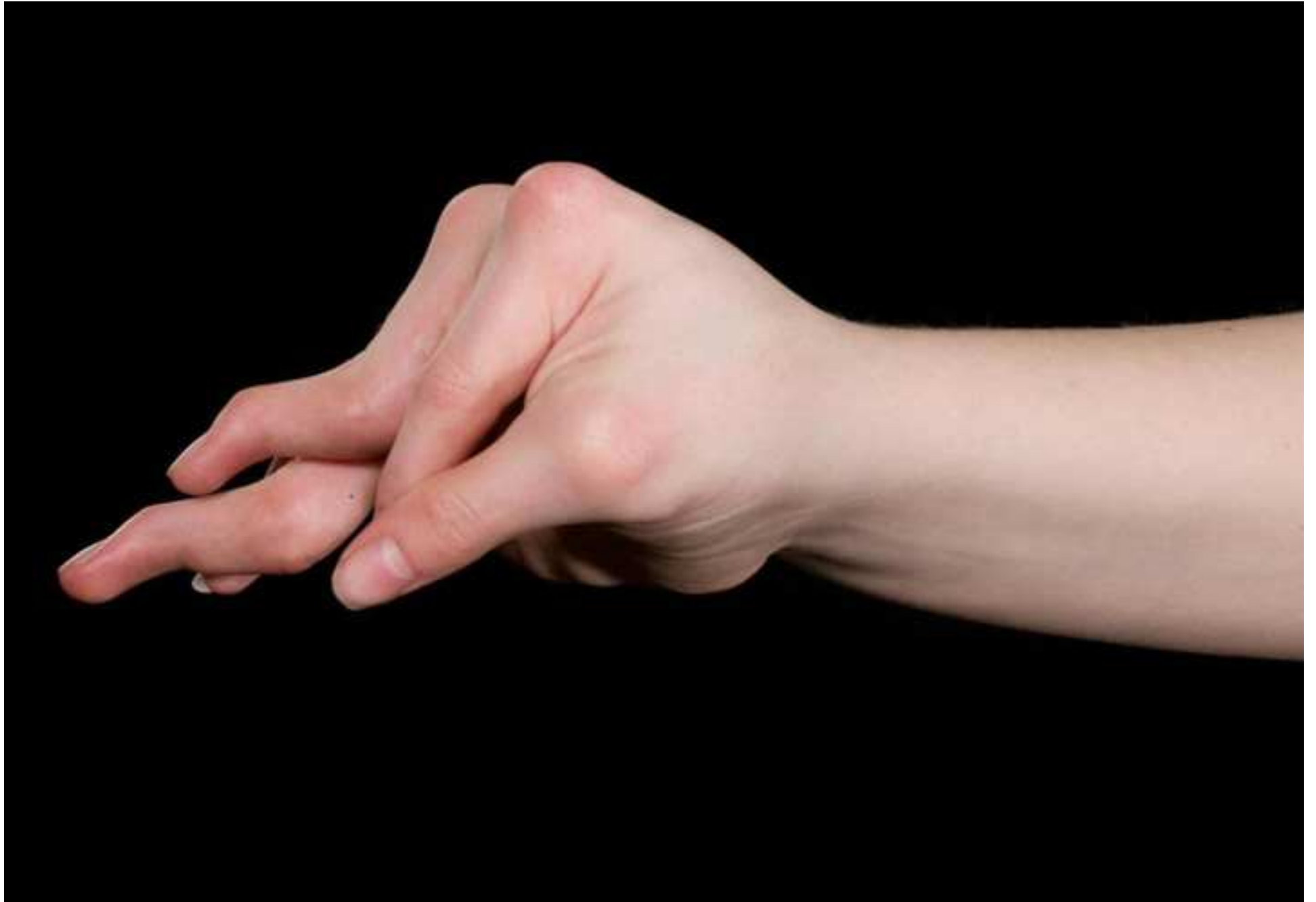
Figure 5

Figure 6

Figure 8

Table 1

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

Vascular tumours	Vascular malformations	
	Simple	**Combined**
Benign vascular tumours:	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	**Of named major vessels**	**Associated with other anomalies**

Locally aggressive vascular tumours:	"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 sacroma		Maffucci syndrome
others		Macrocephaly-CM
Malignant vascular tumours		Microcephaly-CM
Angiosarcoma of the soft tissue		CLOVES syndrome
Epitheloid haemangioendothelioma		Proteus syndrome (PS)
Others		Banayan-Riley-Ruvalcaba syndrome

Table 2

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

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