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Capillary Malformations

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Capillary Malformations

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KEYWORDS

• Capillary malformations • Dermatology • Pediatric • Port-wine stain • Skin • vascular anomalies

KEY POINTS

- Capillary malformations are the most common type of vascular malformation.
- Most capillary malformations are non-syndromic and benign.
- Recognizing the uncommon occurrence of syndromic or high risk capillary malformations is critical.

INTRODUCTION

Capillary malformations (CMs) are the most common type of vascular malformation (VM). They are slow flow, composed of enlarged capillaries and venules with thickened perivascular cell coverage in skin and mucous membranes.[1] They occur in approximately 0.3% to 0.5% of the population with an equal sex distribution.[1–3]

While most CMs occur as isolated skin findings, a wide range of disorders feature CMs. The clinical presentation, systemic associations, genetic mutations, and prognosis vary greatly within and between disorders; therefore, identifying a disorder clinically can be difficult. Genotype–phenotype correlation aids in diagnosis and is important in better classifying syndromic CMs.

This article provides an overview of the clinical features, genetics, and current classifications of CMs and associated syndromes. Additionally, it clarifies the ambiguous nomenclature present in the existing literature.

Clinical Characteristics

CMs are slow-flow VMs, which may appear anywhere on the body. They present at birth and grow proportionately with the individual. Coloring ranges from vibrant pinks to reds to purples (**Fig. 1**). CMs most commonly appear on the head and neck[1–3] and may extend to the lips, gingiva, or oral mucosa.[4] On the face, CMs often follow a dermatomal distribution respecting the midline; in some cases, however, they can involve neighboring dermatomes. In the early neonatal period, distinguishing CMs from an infantile hemangioma can be difficult; infantile hemangiomas, however, tend to darken and thicken over days to weeks, whereas CMs exhibit little change.

In most affected individuals, CMs are isolated and not associated with any underlying abnormalities or genetic syndromes. Nonetheless, local complications may occur including hyperkeratosis and soft tissue hypertrophy, especially in facial lesions. Other complications in lesions of any site include pyogenic granuloma-like proliferations, which may ooze and bleed (**Fig. 2**). Eczematous dermatitis overlying a CM, termed the Meyerson phenomena, can lead to pruritus (**Fig. 3**). Additionally, stigmatization and disfigurement may contribute to significant morbidity in some patients. In more rare cases, CMs occur in association with genetic disorders with additional features as discussed in this article.

Pathogenesis

An error in vascular development during embryogenesis causes CMs.[4] Histopathological examination is rarely performed in CMs, and only clinically difficult cases are biopsied. Most of the involved vessels are located in the papillary and reticular dermis with the number of anomalous vessels decreasing with increasing depth.[4] Lesions in a V3 dermatome, neck, and trunk regions are more superficial in comparison to the V2 dermatomal area and distal extremities that have more deeply placed vessels.[4,5] This becomes clinically relevant with regard to laser treatment.

Mutations causing CMs are usually sporadic. Several genes have been identified with both

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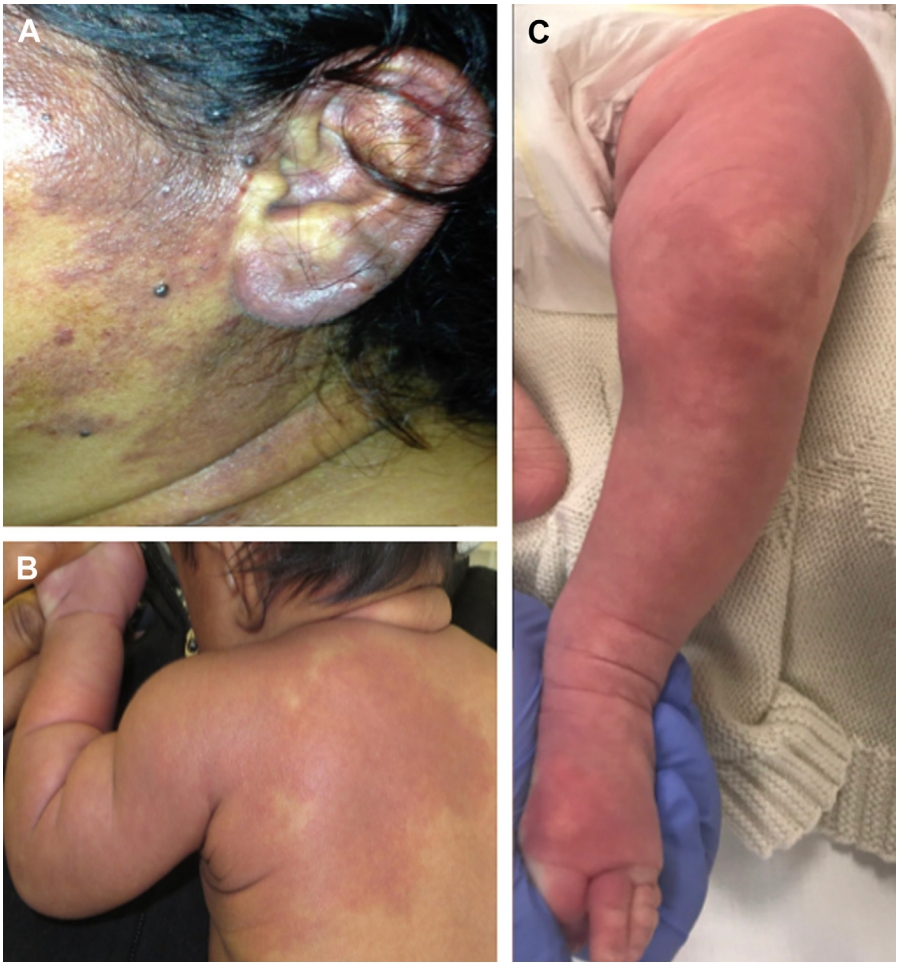

Fig. 1. Various port-wine birthmarks on different skin tones. Vascular blebs can be seen in image A in an adult patient.

isolated and syndromic lesions (see Genetics chapter for additional details).

Nevus Simplex/salmon Patch - "angel kiss," "stork bite"

Nevus simplex (NS), often called salmon patch, "angel kiss," or "stork bite," are common vascular lesions of childhood. They are seen in up to 82% of newborns at birth or soon after as a pale pink to red, ill-defined patch(es).[6–8] They are often seen on the mid-forehead, upper eyelids, philtrum, and nape of the neck. Less common sites include the occipital scalp, parietal scalp, and upper back.[6] The lumbosacral spine can also be affected (**Fig. 4**). When lesions are extensive, the term NS complex is used. NS complex is benign, however, a thorough physical examination to seek out additional signs of spinal dysraphism is required as NS with additional signs, such as an atypical pit, lipoma, aplasia cuti, sinus tract, localized hypertrichosis, or tag, may identify cases of dysraphism.[8]

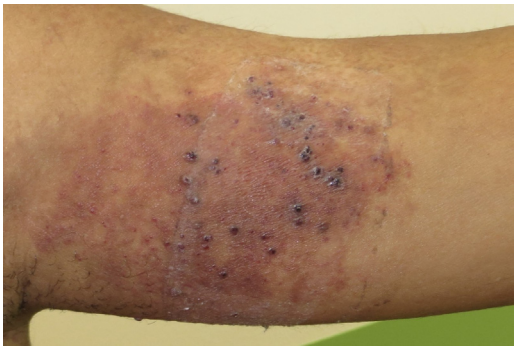

Fig. 2. CM with pyogenic granuloma-like proliferations.

Although NS are considered CMs by the International Society for the Study of Vascular Anomalies (ISSVA), NS are caused by dilated capillaries within the papillary dermis and are likely due to a lack of autonomic regulation of local vessels in the affected skin as opposed to being true CMs.[1] The vast majority of NS over the eyelids and

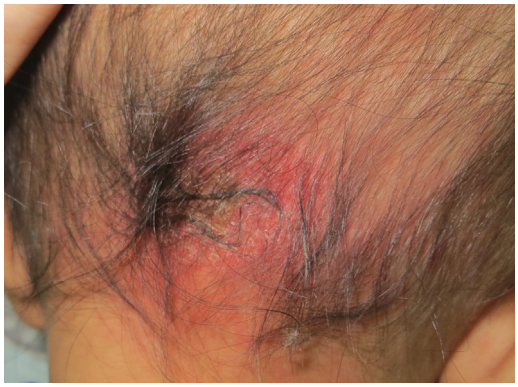

Fig. 3. CM with overlying eczematous dermatitis, also known as the Meyerson phenomena.

forehead fade over time, whereas those located at the nape of the neck tend to persist into adulthood albeit without significant darkening. Additionally, unlike true CMs, NS on the face does not follow a dermatomal distribution and are not associated with Sturge–Weber syndrome (SWS).

Large, persistent facial NS can be associated with underlying syndromes such as Beckwith–Wiedemann syndrome (BWS) and macrocephaly-CM syndrome (M-CM).[1,9] BWS is the most frequent genetic overgrowth syndrome, characterized by pre and postnatal overgrowth, macrosomia, macroglossia, a persistent NS, abdominal wall defects, neonatal hypoglycemia, and renal anomalies. Wilms tumors and other malignancies are also a feature, especially in early childhood. Persistent NS is also seen in megalencephaly–CM–polymicrogyria syndrome (MCAP), nova syndrome, odontodysplasia, M-CM, and Roberts syndrome.[1,6]

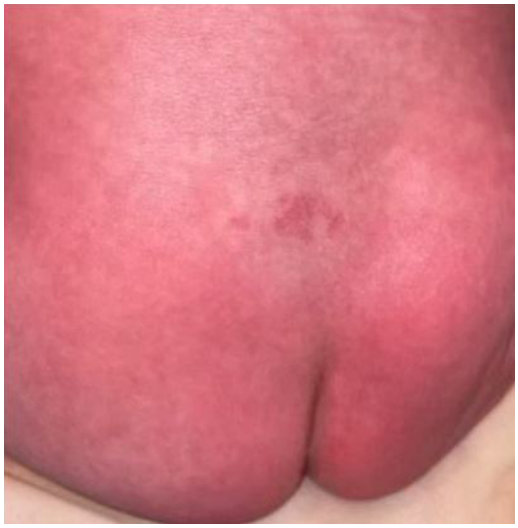

Fig. 4. Nevus simplex of lumbosacral spine.

CUTANEOUS AND/OR MUCOSAL CAPILLARY MALFORMATIONS - "PORT-WINE STAIN"

PWS or nevus flammeus, seen in 3 to 5 per 1000 live births, refers to a well-demarcated pink-red patch.[6,8] The classic presentation is a unilateral patch with a segmental distribution and midline demarcation, most frequently located on the face.[6,10] A bilateral distribution may also be seen. Although most CMs are stable over time, PWS can darken and form nodules. In 55% to 70% of cases, progressive hypertrophy of the soft tissue or underlying bones is observed, especially if the CMs are located on the lip or cheek (within the V2 distribution).[8,11,12] PWS are caused by a sporadic somatic mosaic activating mutation in GNAQ or GNA11 as well as a defective expression of smooth muscle actin (SMA) in the pericytes.[10]

Capillary Malformations with Central Nervous System and/or Ocular Anomalies – Sturge–Weber Syndrome

SWS is a sporadic neurocutaneous syndrome that occurs in 1/50,000 infants, characterized by a triad of facial CMs, ipsilateral leptomeningeal angiomatosis, and glaucoma with bone and/or soft tissue involvement (**Fig. 5**).[6,11,13] Most of the cases are caused by a somatic activating mutation in GNAQ or GNA11.[13,14] A relatively recent study clarified that facial CMs are defined by embryonic craniofacial vascular patterns of development rather than trigeminal innervation, a long-held notion.[6,11] Infants with facial CMs at higher risk of suffering from this syndrome are those for which

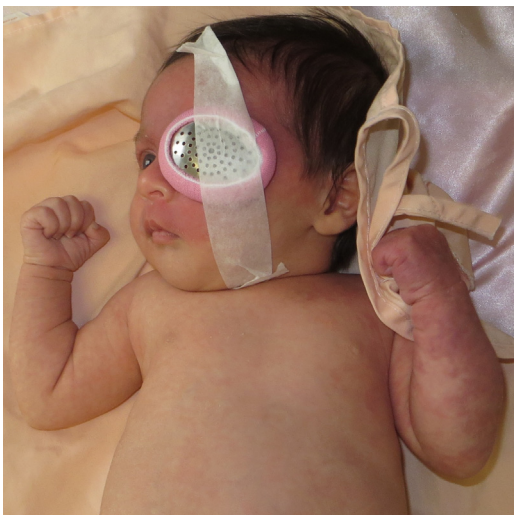

Fig. 5. A 1-month-old infant with Sturge–Weber syndrome with extensive facial, trunk, and extremity port wine birthmark with her eye patched due to glaucoma surgery.

the PWS affects the frontonasal placode (forehead, hemifacial or median phenotype).[13] This frontonasal distribution is common to nearly all patients with SWS and a multidermatomal lesion and/or bilateral distribution place a patient at higher risk.[15,16]

Children with SWS are at risk for seizures, stroke-like episodes, and cognitive delays due to the vascular stasis and poor perfusion in the cortex beneath the leptomeningeal CMs. Further, ipsilateral CMs can occur in the choroid plexus, leading to glaucoma, retinal detachment, and choroidal bleeding.[11] Leptomeningeal angioma are mostly situated over occipital and posterior parietal lobes. Laminar cortical necrosis and calcification develop due to stasis and ischemia of the neighboring leptomeningeal angiomatosis. Dental issues are also common such as gum hypertrophy and overgrowth of the maxilla.[2,3,17]

A multidisciplinary approach including dermatology, neurology, and ophthalmology with the inclusion of additional specialists is required to monitor and treat patients with SWS.

Diffuse Capillary Malformations with Overgrowth

Diffuse capillary malformation with overgrowth (DCMO) is characterized by multiple and/or extensive CMs associated with overgrowth.[18,19] Overgrowth typically involves the soft tissue or bone of an extremity and does not necessarily correlate with the location or severity of the CMs.[20] Overgrowth may affect only one extremity, ipsilateral or contralateral to the CM, or less often, an entire side of the body and is proportionate over time.[8] The CMs in DCMO are usually reticulate, pale, diffuse, involve multiple anatomic regions, and are stained contiguously (**Fig. 6**).[20] Patients with DCMO may have prominent subcutaneous veins and varicosities, but they do not have lymphatic anomalies.[8] DCMO may arise as a consequence of somatic activating mutations in PIK3CA, GNAQ and GNA11.[14,21] Many patients with DCMO are on the PIK3CA-related overgrowth spectrum (PROS) and share several features seen in other PROS conditions such as multiple CMs, facial asymmetry, limb overgrowth, and hand/foot anomalies such as macrodactyly and syndactyly.[19] Similar to other PROS phenotypes, the association with Wilms tumor continues to be under investigation. A recent retrospective review of 89 patients with DCMO did not identify any cases of Wilms tumor.[20] Thus, a diagnosis of DCMO generally portends a favorable prognosis with most complications arising from potential leg length discrepancy and those seen with extensive PWS.

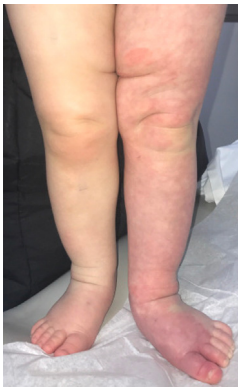

Fig. 6. Image of DCMO with GNAQ mutation.

RETICULATE CAPILLARY MALFORMATIONS

Capillary Malformations of Microcephaly-capillary Malformation

Microcephaly-capillary malformation syndrome (MIC-CAP) is a rare neurologic and vascular disorder characterized by congenital and progressive microcephaly, profound developmental delay, intractable epilepsy, optic atrophy causing blindness, small CMs on the skin, and poor somatic growth.[6,21,22] MIC-CAP is caused by homozygous or compound heterozygous mutations in the STAM-binding protein gene (STAMBP). Patients with MIC-CAP display reduced STAMBP expression, accumulation of ubiquitin-conjugated protein aggregates, elevated apoptosis, and insensitive activation of the RAS-MAPK and PI3K-AKT-mTOR pathways.[23]

Capillary Malformations of Megalencephaly-capillary Malformation-polymicrogyria

Patients with MCAP present with congenital or early postnatal megalencephaly, segmental overgrowth, reticulated or confluent CMs, and polymicrogyria.[2,21] Often there is a prominent midline facial CMs and segmental reticulated CMs on the body, with overgrowth and polydactyly or syndactyly.[6] Other neurologic manifestations include ventriculomegaly and cerebellar tonsillar ectopia, which may be complicated by hydrocephalus and Chiari malformation, respectively.[20] Neurologic involvement can manifest as developmental delay and seizures.[6] Patients should be followed for MCAP is caused by an activating somatic mutation in the PIK3CA gene.[2]

Capillary Malformations of CM-AVM

Capillary Malformations-Arteriovenous Malformation (CM-AVM) affects 1/100,000 individuals.[4]

CM-AVM is characterized by CMs associated with high-flow AVMs or arteriovenous fistulas (AVFs). Unique to CM-AVM is that new CMs may develop over time. CMs are usually multiple, multifocal, small (ranging from <1 cm to 3 cm in diameter), round to oval in shape, and pink to dull red annular macules or papules.[2,3,6,24] The pinkish macules can exhibit a brownish hue, a perilesional whitish halo of vasoconstriction, and hypotrichosis. The white halo suggests vascular steal and shows high flow or a bruit on Doppler ultrasound.[1,24] These pink macules are considered to be cutaneous micro-AVMs.[24] CMs can be present with or without AVMs and AVFs.[3] AVM/AVF occur in the skin, muscles, and bones of the face, ears, thorax, and extremities, as well as in the brain and spine.[2,3] It is essential to perform ultrasound Doppler if any warmth or palpable thrill is noted in a vascular lesion. Genetic counseling and magnetic resonance angiography (MRA) screening for high-flow brain or spinal AVMs may be helpful.[6] In approximately one-third of individuals with CM-AVM with AVMs, the AVM involves the bone and soft tissue of the leg; these patients have Parkes Weber Syndrome (PKWS) as part of CM-AVM.[3,25]

CM-AVM is an autosomal dominant disorder caused by germline heterozygous inactivating mutations in the RASA1 gene (p120-rasGAP) located on chromosome 5.[3,10] A second-hit somatic mutation in endothelial cells is responsible for the complete inactivation of RASA1, which is necessary for both skin lesions and high-flow lesions to develop.[10,25] Although the penetrance of this condition is greater than 95%, the number of CMs and the presence of AVMs is variable among affected family members.[3,25] Mutations in the EPHB4 gene cause a similar vascular disorder to that caused by RASA1 mutations, hence, the terms CM-AVM1 and CM-AVM2 syndrome are designated for patients with mutations in RASA1 and EPHB4, respectively.[9]

CUTIS MARMORATA TELANGIECTATICA CONGENITA

Cutis marmorata telangiectatica congenita (CMTC) is an uncommon, distinctive cutaneous VM noted at or very soon after birth with an unknown cause.[1,26] Violaceous, reticulated or mottled patches resemble physiologic cutis marmorata but are persistent despite local warming and may exhibit atrophy (**Fig. 7**).[1,10] Lesions tend to lighten gradually over the first few years of life. Patches may be limited to one or several extremities or may be much more extensive but typically demonstrate demarcation at the midline. Ulceration may occur. Affected limbs can display limb

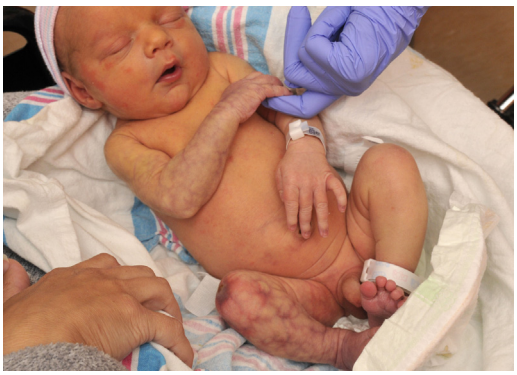

Fig. 7. CMTC in infant.

hypoplasia although hyperplasia is also seen. The most common associated finding is limb asymmetry (33%-68%), requiring orthopedic surgery involvement when limb length discrepancy becomes substantial.[26] Other organ systems may be involved (eyes, CNS, heart, and so forth) but systemic involvement is thought to be rare and seen only in those with very extensive skin lesions. Patients with CMTC should undergo a careful physical examination to assess for other congenital anomalies.[26] CMTC may be mistaken for reticulate PWS and, although no gene has been identified for CMTC, this is one reason genetic evaluation may be sought.

PHAKOMATOSIS PIGMENTOVASCULARIS

Phakomatosis pigmentovascularis (PPV) is a neurocutaneous syndrome consisting of CMs in addition to melanocytic lesions (**Fig. 8**). The melanocytic lesions may be dermal melanocytosis (Mongolian spots), nevus spilus, and/or nevus of Ota.[27] The classification system for PPV has changed throughout the years, but more recently a four-type scheme, created by Rudolf Happle, is utilized.[28] Type 1 PPV (phakomatosis cesio flammea) is characterized by the coexistence of dermal melanocytosis and a nevus flammeus. Type 2 PPV (phakomatosis spilorosea) is characterized by the association of a nevus spilus and a pale-pink nevus. Type 3 PPV or phakomatosis cesio marmorata is the coexistence of dermal melanocytosis with CMTC and the last group is unclassifiable PPVs.[27,29] The pathogenesis behind PPV is activating GNAQ/GNA11 mutations; these mutations were also detected in ocular melanoma.[30,31] This syndrome can also be associated with other complications such as SWS, ocular melanosis, Klippel–Trenaunay syndrome (KTS), overgrowth, leg-length discrepancy, iris mammillations, iris hamartomas, glaucoma, epilepsy, scoliosis, and others.[27]

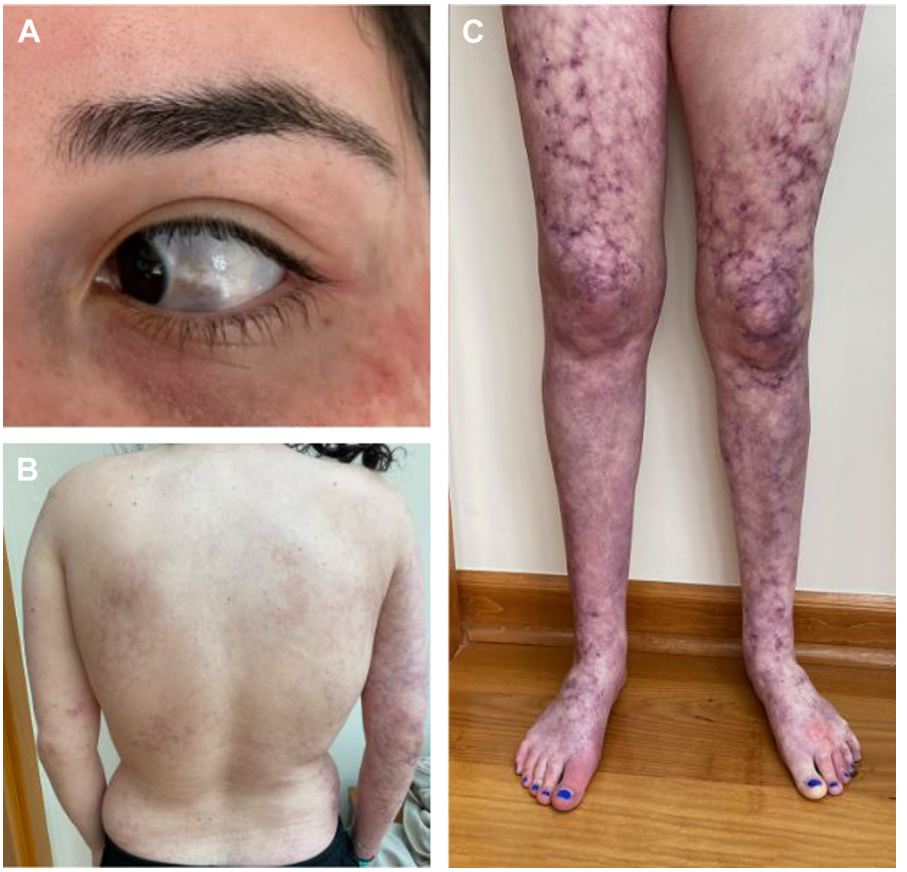

Fig. 8. 21-year-old woman with violaceous reticulated confluent patches and slight unilateral overgrowth of left limb compared to right.

Therefore, these patients require ophthalmology consultation and other specialists depending on additional features.[32]

TELANGIECTASIA

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Rendu–Weber syndrome, is a genetically heterogeneous, autosomal dominant disorder with high penetrance but considerable intrafamilial variability.[2,26] Incidence is estimated at 1/8000.[2,33] HHT is characterized by mucocutaneous and visceral telangiectasias and AVMs that also affect internal organs. Patients typically present in the first 2 decades of life.[26] Initial manifestations include recurrent epistaxis, which can be severe, and cutaneous or mucosal CMs that rupture and bleed after minor trauma.[2] Telangiectasias are frequently located on the lips, oral mucosa, upper extremities, nail beds, tongue, ears, and conjunctivae. In adulthood, telangiectasias develop in the gastrointestinal mucosa and result in significant bleeding in 16% of patients.[2,26] HHT can frequently be complicated by the presence of clinically significant AVMs in the lungs and brain, leading to respiratory and neurologic complications, including emboli, stroke, migraines and seizures.[13,26]

Commonly mutated genes in HHT are ENG, ACVRL1, GDF2, and SMAD4. All genes are members of the same signaling pathway (TFG-β) and various alterations in this pathway may lead to different variants of the disease. Mutations in ENG gene encoding for endoglin, a receptor for TGF-β signaling proteins, correlate with HHT type 1. Mutations in the ACVRL1 gene encoding for the anaplastic lymphoma receptor tyrosine kinase, correlate with HHT type 2. Mutations in SMAD4 may result in HHT as well as the autosomal dominant cancer predisposition syndrome, juvenile polyposis syndrome.[2]

CAPILLARY MALFORMATIONS ASSOCIATED WITH OTHER ANOMALIES

Klippel Trenaunay–Weber Syndrome

KTS is traditionally defined by the triad of CMs, venous malformation, bone and/or soft-tissue

hypertrophy of the affected limb. Additional features may include LM or VLM, and varicose veins with or without deep venous anomalies.[1,6,20,26] KTS has likely been vastly overdiagnosed as features greatly overlap with other CMs syndromes including DCMO. The ability to genotype patients with VMs has improved diagnostic certainty. KTS is caused by a somatic activating mutation in PIK3CA, which regulates cell survival and growth through the activation of the mTOR1-ATK pathway.[20] KTS is associated with limb overgrowth and significant arteriovenous shunting of the involved limb.[26] The findings in KTS are classically isolated to a lower extremity, with extension onto the lower trunk.[20] The CMs are often sharply circumscribed, geographic violaceous plaques, often with visible nodules (lymphatic blebs), which become thicker over time and bleed as the patient matures.[1,4,26] Geographic lesions are often located on the lateral aspect of the thigh, knee, and lower leg.[20,26] Nongeographic CMs are pink to red and scattered over the affected limb. In patients with nongeographic CMs, other KTS symptoms (varicose veins and overgrowth) manifest later in life than in patients affected with a geographic one, whose KTS is usually obvious at birth.[26] Reticulate or blotchy CMs on the extremities can also be associated with overgrowth and venous varicosities but are less likely to demonstrate extensive underlying LM. In KTS, progressive worsening of the venous stasis and/or lymphedema is inevitable, and ulceration, pain, coagulopathy, thrombosis, pulmonary emboli, and pulmonary artery hypertension are all potential comorbidities.[1]

Parkes Weber Syndrome

Parkes Weber syndrome (PKWS) is a congenital disorder caused by a mutation in RASA1, defined by the presence of cutaneous VMs including capillary, venous, lymphatic, and AVFs.[13] Patients present with cutaneous red or pink large patches with underlying quiescent AVMs and extremity overgrowth affecting bones and soft tissue.[2] It may affect either the upper or lower extremities, including pelvic vessels, but the lower extremities are more often affected than the upper extremities.[2,13] PKWS is often distinguished from KTS by the presence of multiple high-flow vascular lesions in the affected limb. A lymphatic component may be present in some patients and congenital VMs are common. Heart failure due to arteriovenous shunting, as well as ischemic pain, ulceration, and edema, may rarely occur.[34]

Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevis, Spinal/Skeletal Anomalies/Scoliosis Syndrome

Congenital lipomatous asymmetric overgrowth of the trunk with lymphatic, capillary, venous, and combined-type vascular malformations, epidermal nevi, scoliosis/skeletal and spinal anomalies (CLOVES) is a PIK3CA nonprogressive overgrowth syndrome.[6] CMs tend to show a deep purple hue and their arrangement is usually lateralized.[7] The CMs are often geographic, however, distinctive findings include primarily thoracic lipomatous masses mixed with LMs, venous malformations, AVMs of the spine, soft overgrowth of feet and/or hands, macrodactyly of the third finger, sandal gap deformity of the toes and/or cubital deviation of the fingers, and a high risk of coagulopathy. The lipomatous lesions may infiltrate the retroperitoneum, mediastinum, pleura, and paraspinal spaces.[6]

Proteus Syndrome

Proteus syndrome is characterized by asymmetric overgrowth, connective tissue nevi, epidermal nevi, cranial hyperostosis, visceral hamartomas, and vascular anomalies, including CMs. The most characteristic manifestations are plantar cerebriform connective tissue nevi.[13,26] Proteus syndrome is caused by a somatic activating mutation of AKT.[6] This syndrome is associated with a high risk of pulmonary abnormalities such as thrombosis, pulmonary embolism (the leading cause of death in affected patients), and pulmonary cysts which may be rapidly progressive, and lead to recurrent infections.[13,26]

Capillary Vascular Malformation of the Lower Lip, Lymphatic Malformations of the Head and Neck, Asymmetry, and Partial or Generalized Overgrowth Syndrome

Capillary malformations of the lower lip, LM of the face and neck, asymmetry, and partial/generalized overgrowth (CLAPO) is a rare syndrome. CLAPO is characterized by midline symmetric lower lip CMs associated with facial or cervical LMs that are sometimes accompanied by asymmetric overgrowth.[35] CMs of the lower lip are present in 100% of CLAPO cases. LMs may not be evident at birth. CLAPO may arise sporadically as a consequence of somatic activating mutations in PIK3CA.[36]

SUMMARY

CMs are complex congenital slow-flow VM of dermal capillaries and postcapillary venules. In

most cases, a diagnosis can be made on clinical appearance and patient history. While CMs are often isolated skin anomalies, they are rarely associated with complex malformation syndromes, some of which may be subtle. Identifying these syndromes is vitally important as the clinician can differentiate benign, innocuous CMs from those associated with life-threatening tumors, coagulopathies, AVMs, and more. Genotyping can be an extremely helpful tool when needed. Imaging studies are not routinely performed on routine CMs, but ultrasonography or magnetic resonance may be necessary for the evaluation of associated syndromes.[7,26]

Furthermore, even small, isolated CMs can be disfiguring and a source of significant psychological stress for patients.[37] The goals of treatment (discussed in the treatment section) are aimed at reducing skin discoloration and preventing complications such as thickening, nodularity, or ulceration.

CMs present both a diagnostic and therapeutic challenge to physicians. Overlapping clinical features can be observed in many cases of syndromic CMs. The classifications presented here can aid clinicians in better identifying CMs and provide consistent terminology to facilitate the interdisciplinary management of the diverse vascular anomalies.

CONFLICTS OF INTEREST

Dr. M. N. Jahnke has served as a consultant for Sanofi Genzyme. Dr. K. Pandher and Karla Escobar do not have any financial or commercial interests to disclose. There were no funding sources for this article.

CLINICS CARE POINTS

- PIK3CA, GNAQ and GNA11 mutations are the most common mutations in CMs.
- Most CMs of the face (PWS) are not associated with SWS, however, those involving the frontonasal placode and are bilateral convey the highest risk.
- Although CMs are generally stable over time, cutaneous complications may include darkening, thickening, vascular blebs, pyogenic granuloma-like lesions and soft tissue hypertrophy.
- Due to the autosomal dominant inheritence of the RASA1 gene mutation in CM-AVM, it is one of the more common yet worrisome syndromes associated with CMs and recognition is critical due to the risk of internal AVMs and AVFs.
- HHT presents with CMs and extensive telangiectasias of the skin and muscosa with risk for GI hemorrhage and AVMs.

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