Drug treatment of vascular anomalies

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INTRODUCTION

Congenital vascular anomalies include a heterogeneous group of pathologies. This represents a challenge when it comes to performing an adequate diagnosis and treatment owing to their phenotypical variability and their wide range of symptoms and severity. In addition, an erroneous and confusing nomenclature has been used for many years, which had led to incorrect diagnoses, unnecessary tests, inadequate monitoring, and ineffective treatments[1].

In 1996, the International Society for the Study of Vascular Anomalies (ISSVA) reviewed the classification initially described by Mulliken and Glowacki in 1982, which differentiated vascular tumors from vascular malformations based on their clinical, biological, radiological, and histological characteristics[2]. This classification was updated in 2014 and subsequently in 2018, adding the description of the genetic causes known[3]. The study of those genetic mutations enhances the knowledge about these anomalies' physiopathology and opens up new possibilities regarding the discovery of potential molecular targets for new specific medical treatments.

Historically, the treatment of vascular anomalies has been mainly surgical, with limited and ineffective medical treatments. However, recent findings about useful drug agents for the treatment of vascular anomalies has increased the number of therapeutic options available, reducing the need for procedures with high risk of complications and sequels, and improving patients' quality of life in the long term[4].

The objective of this update is to provide a detailed classification of vascular anomalies and a comprehensive review of medical treatments according to the publications currently available.

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VASCULAR TUMORS

Vascular tumors are characterized by an abnormal proliferation of endothelial cells and aberrant blood vessels. The ISSVA 2018 classification classifies vascular tumors into benign, locally aggressive, and malign. In the past, corticoids and traditional chemotherapy agents in monotherapy or adjuvant to surgical resections were the only tools available for the management of these tumors. However, these treatments had a variable effectiveness and caused numerous side effects and sequels. Some drugs such as propranolol, timolol, or sirolimus have been used for years in other pediatric pathologies, but they recently emerged as safe and effective drugs in the treatment of many vascular tumors.

Infantile hemangioma

Infantile hemangioma (IHs) are the most frequent benign tumors in childhood, with a 4-10% incidence in children under 1 year of age. They usually present in Caucasian female patients, with a higher incidence in premature children and low-weight newborns[5]. Diagnosis is clinical, and evolution typically confirms diagnosis without the need for biopsy in most cases. IHs do not present at birth or occur as a precursor lesion. They start with a rapid proliferative phase in the first months of life, go through a period of stability, and end with a slow involutional phase where the lesion loses color and size but may last for many years and often leaves esthetic and functional sequels[6].

Oral corticoids used to be the treatment of choice for complicated IHs, in spite of the lack of response in one third of cases and the high incidence of side effects at high doses. In 2008, various authors reported involution cases in hemangioma in patients treated with oral propranolol, a

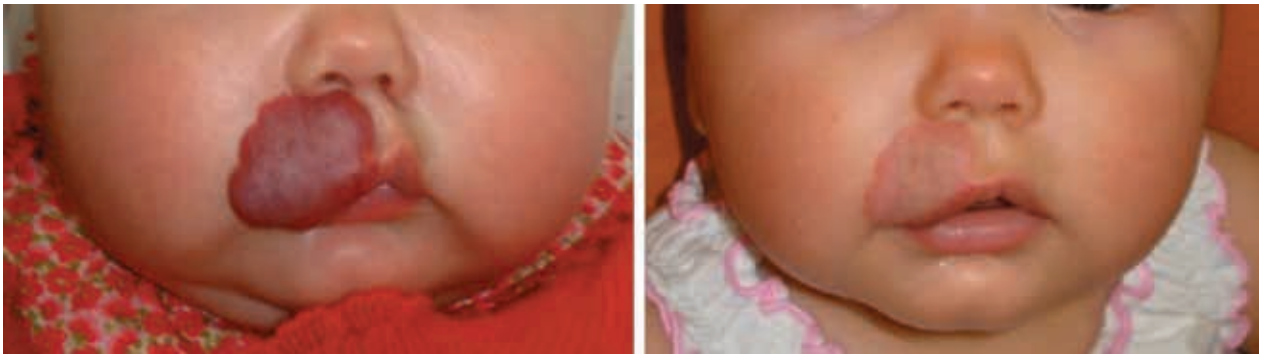

Figure 1. Proliferative infantile hemangioma with response to propranolol treatment.

non-selective beta-blocker[7] (Fig. 1). Propranolol became the first-line treatment for IHs, and its effectiveness and safety were confirmed in a double-blind, randomized, multicenter clinical study in patients with proliferative IH. The study concluded that propranolol was effective at a 3 mg/kg/day dose over 6 months for IH treatment, with very few side effects[8].

Subsequently, numerous studies were carried out to identify which patients should be treated, when, and for how long. In 2016, a Spanish consensus on infantile hemangioma management was published, stating the IHs that should be treated: potentially deadly IHs, IHs compromising functional capacity, ulcerated IHs with pain or lack of response to basic measures of injury care, and IHs with risk of permanent scar or disfigurement. Treatment should be initiated between week 5 and month 5 of age for 6 months, with a clinical follow-up and a weight-adjusted dose. However, in some patients, treatment should be carried out for more than 12 months[9].

Topic timolol has also proven to be effective in non-ulcerated superficial IHs as it reduces color, size, and volume[10]. Surgical resection is now only used for the treatment of sequels, with propranolol having significantly reduced the sequels requiring surgical correction.

Congenital hemangioma

Contrarily to IHs, congenital hemangiomas (CHs) are rare, are present at birth, and are most frequently located in the head, the neck, and the limbs. They are a prominent purple-like lesion with thick telangiectasias combined with paler areas and with a peripheral white halo. They are also different from IHs from a histological perspective, as they are typically GLUT-1 negative, which allows for a definitive diagnosis, apart from the clinical presentation as such[11]. Evolutional history allows CHs to be classified into three groups: rapidly involutional CHs (RICH), which begin to regress in the first weeks of life until they virtually disappear at 1-2 years of age, non-involutional CHs (NICH), which do not regress and grow proportionally to the patient, and recently described partially involutional CHs (PICH), which initially regress rapidly and subsequently stabilize without fully disappearing (Fig. 2). CHs tend to be solitary and can be associated with moderate thrombocytopenia, hypofibrinogenemia, and anemia. This process should not be mixed up with Kasabach-Merritt syndrome (KMS) and spontaneously resolves in 1-2 weeks. Even though they are mostly located at the cutaneous and subcutaneous level, they can also present at the visceral level in the liver, with a similar behavior as compared to their cutaneous equivalent[12].

CH management is initially conservative but subsequently it becomes surgical basically, indicated in sequels following involution or in lesions compromising functionality or presenting ulceration or persistent bleeding. Pulsed laser treatment can reduce the superficial color of residual telangiectasias, while embolization may prove useful in case of cardiac insufficiency as a complication. CHs do not respond to propranolol or other drug treatments known up until now, but GNAQ and GNA11 mutations can be the first step towards the treatment of those CHs not regressing with specific inhibitors[13].

Kaposiform hemangioendothelioma and tufted angioma

First described in 1993, kaposiform hemangioendothelioma (KHE) and tufted angioma (TA) are extremely rare vascular tumors presenting at childhood and associated with severe thrombocytopenia and coagulopathy within the Kasabach-Merritt syndrome (KMS). Today, KHE and TA are considered variants of the same spectrum, since both present as solitary lesions in soft tissues, with an indurated aspect and red-like or purple-like color. However, TA is regarded as benign, while KHE is considered as locally aggressive as it can infiltrate deep tissues[14]. They typically present in the limbs, the trunk, and the neck. Histologically speaking, they express lymphatic endothelial markers and are GLUT-1 negative. These lesions can cause pain and color changes when they grow, frequently activated by a

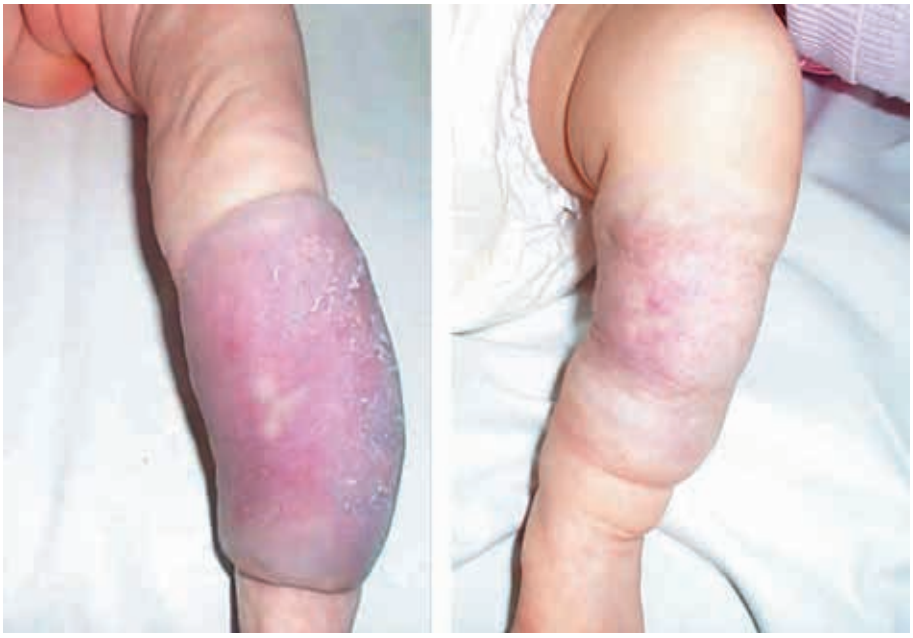

Figure 2. Rapidly involutional congenital hemangioma (RICH) in the left lower limb regressing in the first months of age.

systemic infection, local damage, or transfusions. KMS occurs in 70% of KHE patients, causing platelet capture in the tumor, coagulation cascade activation, and secondary consumption of coagulation factors, which entail a potentially deadly coagulopathy characterized by severe thrombocytopenia, hypofibrinogenemia, and D-dimer increase[15].

Historically, complete surgical resection used to be the gold standard technique in KHE/TA treatment. However, this was not possible in most cases owing to tumor infiltration and high morbidity and mortality risks, so drug treatment gained a fundamental role. Over the last decades, various treatments including corticoids, vincristine, alpha interferon, ticlopidine, clopidogrel, aspirin, cyclophosphamide, and bevacizumab have been used, with little consistent results. In 2013, a group of experts published a consensus based on the clinical experience available with recommendations for complicated KHE/TA management, indicating combined corticoid and vincristine therapy as the first option[14]. Even though management should be individualized according to patient symptoms, treatment will largely depend on the presence or absence of KMS.

Monotherapy corticoid treatment had an irregular response, so it was combined with vincristine, which improved global effectiveness in the retrospective series. Alpha interferon also proved successful in some cases published, but the fact it was associated with spastic diplegia in patients under 8 months of age advised against its use. Some anti-platelet agents such has ticlopidine and clopidogrel have been used in combination with other therapies such as aspirin and vincristine, with good results in terms of thrombocytopenia control, but not in terms of tumor size[16].

In 2010, Blatt et al. published the first primer case of compassionate treatment with sirolimus in a KHE child, with a good response[17]. In 2011, Hammill et al. published a series of retrospective cases where sirolimus had been used in complex vascular anomaly patients, among whom a KHE patient[18]. Since then, numerous publications have proved successful in KHE patient treatment, with a clinical improvement, platelet count recovery, coagulopathy correction, and very few side effects[19]. Owing to such promising results, many currently believe sirolimus should become the first-line treatment of complicated KHE/TA with KMS.

VASCULAR MALFORMATIONS

Vascular malformations are characterized by abnormal blood vessel networks formed during fetal development but not presenting with rapid endothelial cell proliferation. ISSVA 2018's vascular malformation classification divides them into simple malformations, combined malformations, great vessel malformations, and malformations associated with other anomalies. Simple malformations consist of one type of vessel (capillary, lymphatic, or venous), except for arteriovenous malformations (AVM). Combined malformations consist of two or more abnormal vessels combined, and are named after the vessels involved. Great vessel malformations tend to involve great caliber vessels and are characterized by anomalies in origin, route, length, number (absence, duplication), diameter (hypoplasia, dilatation), or valves. Last, malformations associated with other anomalies are classified separately and usually respond to specific syndromes[1,3].

Vascular malformations are always congenital and present at birth, but sometimes they are not diagnosed until the first months or years of age. The grow proportionally

with the child, but occasionally they may increase dramatically in size due to bleeding, infections, or abnormal vessel dilatation, which usually occurs with hormone changes or following traumas. Vascular malformations are highly variable – they can be localized or diffuse, and they may have different presentations and complications according to location, the structures involved, and other associated anomalies[4].

Historically, vascular malformations used to be treated through interventional procedures such as surgical resection or debulking, laser, or embolization. Medical management used to be limited to support therapies such as pressotherapy, non-steroidal anti-inflammatory drugs, and anticoagulants. This approach is particularly problematic in case of complex and diffuse vascular malformations not eligible for surgical treatment[1]. Many drug treatments have been used, with highly variable and often disappointing results.

Thanks to the discovery of the molecular pathways and the mutations that cause many vascular malformations, some drugs previously used in other pathologies have recently proved to be effective for the individualized management of these malformations.

Lymphatic malformations

Lymphatic malformations (LMs) are caused by lymph channel dilatation or endothelial cell covered cysts. They can be classified into simple lymphatic malformations – which can be macrocystic, microcystic, and mixed, according to size – and complex lymphatic malformations. Simple LMs tend to occur in the head and the neck, and most of them are diagnosed before 2 years of age. They present as soft, non-compressible masses, occasionally with clear (or red-like in case of intralesional bleeding) vesicles if they involve the skin surface or the mucosa. LMs can bring about symptoms due to intralesional bleeding, which causes pain, and to recurrent inflammation, which can give rise to cellulitis. In addition, depending on location, they can compromise the respiratory airway or the digestive tract, they can impair vision and speech, they can impact limb functionality, and in most cases, they entail considerable disfigurement, which causes a significant cosmetic problem. Complex LMs used to be called lymphangiomatosis and currently include generalized lymphatic anomaly (GLA), Gorham-Stout's syndrome (GSD), kaposiform lymphangiomatosis (KLA), and central conducting lymphatic anomaly (CCLA). This type of LMs are present in soft tissues, organs (usually the spleen), and bones. They are usually associated with pleural or pericardial effusion, ascites, and osteolysis, with high morbidity and mortality[20].

LMs are caused by somatic PIK3CA mutations, activating the PIK3/Akt/mTOR path which promotes cell proliferation, growth, angiogenesis, and protein synthesis[21].

Traditionally, LM treatment used to be based on sclerotherapy in the case of macrocystic lymphatic malformations, and surgical resection in the case of microcystic lymphatic malformations, according to size, functional deficit, deformity degree, and surrounding structure involvement. Other treatments include radiofrequency for LMs involving the mucosa, and various types of laser. However, these procedures are not free from complications and often cause unbearable sequels.

Certain drug treatments, such as sildenafil or propranolol, have been used in LMs with variable results – improvement in some clinical cases, and no effect in others. But sirolimus has been the great revelation in LM management in the last years. It is an mTOR inhibitor which was formerly used to prevent organ rejection in renal transplant patients before being applied to vascular anomalies. Apart from acting as an immunomodulator, sirolimus has an antiangiogenic and anti-lymphoproliferative effect which make it the perfect tool for vascular anomaly management[18]. At first, it was tested as a compassionate treatment drug in vascular anomalies refractory to other treatments, but good results, especially regarding LMs, have allowed it to be currently used in multiple pathologies, even as a first-line treatment[22]. In simple LMs, sirolimus reduces malformation size and vesicle count, removes lymphorrhea, and diminishes the number of infections and intralesional bleeding episodes (Fig. 3). In complex LMs, sirolimus stabilizes osteolysis, impairing its progression, and reduces pericardial or pleural effusion and ascites. In addition, as it has already been showed with KHE, sirolimus can correct consumption coagulopathy and severe bleeding in KLA[23]. Even though it is usually administered orally, at a 0.8 mg/m^2/12 h dose, superficial microcystic LMs have also been demonstrated to improve following topical sirolimus administration[24].

The whole sirolimus experience, which is based on renal transplant patients, has now been extrapolated to vascular anomaly patients. Sirolimus has been confirmed as an effective – especially in LMs – and safe treatment, with very few side effects, and it has also been demonstrated to be innocuous even in neonates[25]. But questions on recommended dose, blood levels to be achieved, and how long it should be administered for remain unanswered. Our experience when treating our patients reveals that sirolimus treatment should be individualized, and that dose and level goals should be adapted to each patient's phenotype and symptoms[26].

Venous malformations

Venous malformations (VMs) consist of dilated venous channels, like a sponge, and variable in size. They usually present as a soft, blue-like, non-pulsating, compressible mass increasing in size following the Valsalva manoeuver. Histologically, they have poorly developed walls with plain muscle layer defects and absence of valves, which makes them dilate progressively. They can involve any tissue, including bones and organs; and even though they tend

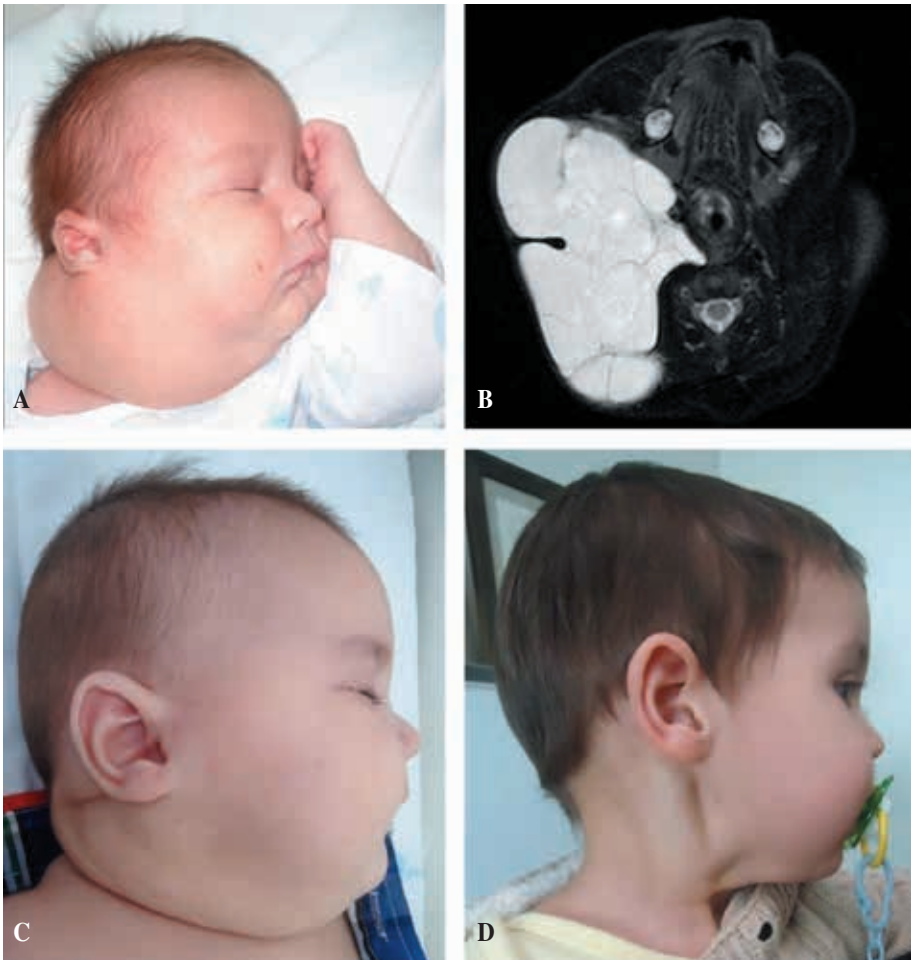

Figure 3. Macrocystic cervicofacial lymphatic malformation with complete response to sirolimus. A) 48 hours after treatment, the patient could be extubated. B) Baseline MRI with lymphatic malformation in the face, the neck, and the retropharyngeal region. C) Full regression at 12 months of age. D) No recurrence at 2 years of age.

to be localized and well defined, they can sometimes be diffuse and infiltrating[27]. Symptoms are due to blood stasis in the abnormal vessels, giving rise to localized thrombosis causing pain and inflammation. Thrombosis can end up causing localized intravascular coagulation (LIC), a consumption coagulopathy characterized by high D-dimer and low fibrinogen[28]. Calcified thrombi or phleboliths are found within the malformation and are pathognomonic.

Family VMs are due to mutations in TEK, which codifies the TIE2 tyrosine-kinase receptor, as it happens with half of **sporadic VMs**[29]. Of the remaining sporadic VMs, half of them have PIK3CA mutations. Venous malformations can also present as independent entities such as Blue Rubber Bleb Nevus Syndrome, BRBNS, or Bean's syndrome, which is associated with multiple venous malformations with cutaneous and gastrointestinal involvement, causing potentially deadly digestive bleeding[30]. This syndrome can also be caused by TEK mutations.

Standard VM treatment should be individualized and cross-disciplinary, and it consists of pressotherapy, sclerotherapy, laser diode, and/or surgical resection. But drug treatment recently emerged in the management of VMs refractory to other treatments and as a feasible option before more aggressive and disfiguring procedures are carried out. It can be focused on treating symptoms or directly malformation as such[29].

Non-steroidal anti-inflammatory drugs and other analgesics are the first option to be considered when it comes to reducing pain caused by thrombi or phleboliths. Another option is aspirin at low doses, but its efficacy has not been adequately described[31]. However, to prevent thrombus formation, especially in patients with high LIC risk, low molecular weight heparin can be administered for two weeks[29]. The use of other oral anti-Xa anticoagulants such as rivaroxaban or dabigatran has also been reported, but they have not received approval for pediatric patient use yet, so they are administered in a compassionate fashion.

MTOR inhibitor sirolimus recently showed promising results in VM treatment as it reduces pain and malformation size, and it prevents thrombus formation[32]. TEK mutations activate the PIK3CA cascade through TIE2, which explains sirolimus' effect on VMs with both TEK and PIK3CA mutations. Most publications refer to case series, so prospective randomized studies are required to confirm such response. Sirolimus has also demonstrated a good response in Bean's syndrome, reducing pain epi-

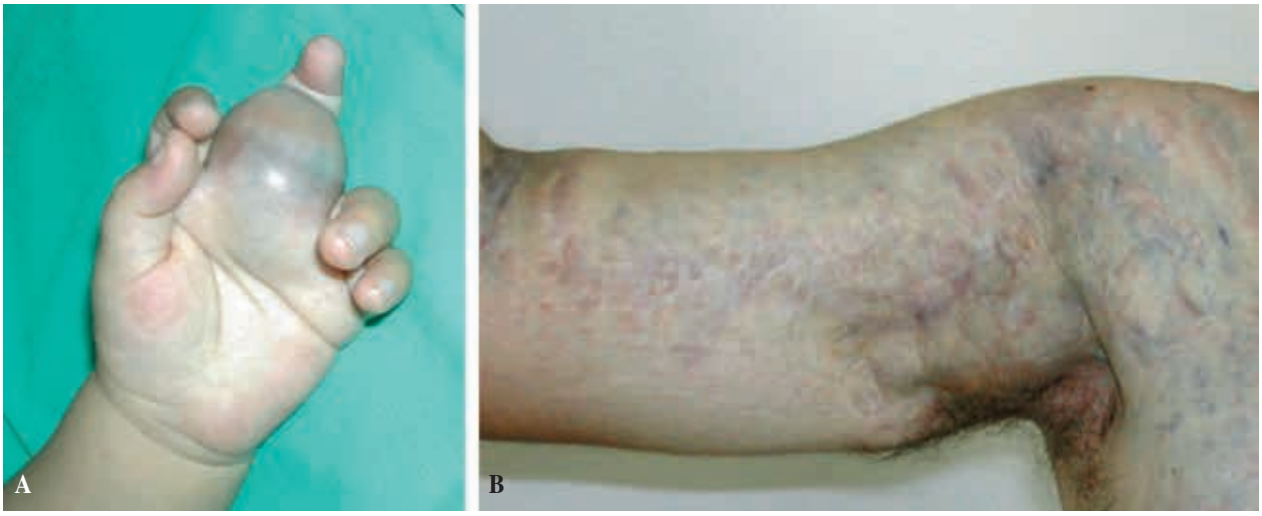

Figure 4. A) Venous malformation in the third finger of the left hand. B) Diffuse venous malformation in the right upper limb.

sodes and intestinal bleeding, improving quality of life, and minimizing the need for transfusions[33].

Capillary malformations

Capillary malformations (CMs) consist of dilated capillaries in the superficial dermis. They present as flat pink or red lesions with irregular borders at the skin and the mucosal level (Fig. 5). They can be focalized or diffuse, and in some cases they have a specific distribution, as it is the case with the face, where they follow the V1, V2, or V3 distribution. The most frequent type is nevus simple, commonly known as 'port-wine stain'. And even though they usually occur in an isolated fashion, CMs can be a symptom of other malformations or syndromes, such as Sturge-Weber syndrome, Klippel-Trenaunay syndrome, and Parkes-Weber syndrome. As the patient grows up, CMs can get darker, gain prominence, and even acquire a nodular shape[34].

CM standard management is an expectant one, but in cases of cosmetic concern, especially with facial involvement, pulsed dye laser is the gold standard technique[35]. However, the lesion fully disappears in 20% of patients only, and in another 20% of them, improvement is barely achieved. It can sometimes be associated with ND-YAG laser or topic sirolimus, which improve pulsed dye laser results[36]. Today, there is no medical treatment known which improves CM results alone, but some targeted treatments could be effective because CMs are associated with GNAQ, GNA11, and GNA14 mutations. For example, systemic sirolimus associated with aspirin has demonstrated to be effective in focal crisis prevention in a Sturge-Weber syndrome patient[37].

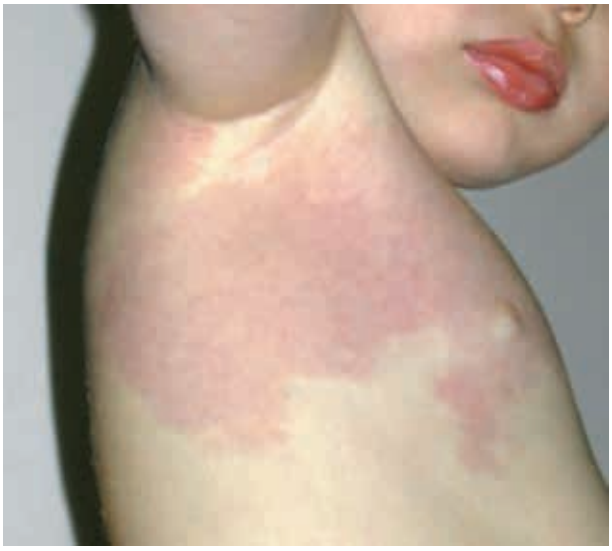

Figure 5. Capillary malformation in the right thoracic region.

Arteriovenous malformations

Arteriovenous malformations (AVM) are high flow malformations caused by nidus shunts between the arterial and venous systems, presenting as hot, pulsating lesions[38]. Classic evolution is detailed in Schobinger stages, causing progressive surrounding tissue destruction, pain, ulceration, bleeding, and cardiac overload[4] (Fig. 6). Classic AVM treatment consists of a combination of embolization and surgical resection, but complete resection cannot often be achieved without causing significant sequels owing to the lesion's infiltrating nature.

KRAS, NRAS, BRAF, and MAP2K1 (also known as MEK1) mutations have been found, which could lead to targeted treatments in the future[39]. MEK1 inhibitors, which are already used in cancer, can be a compassionate use option for these patients, who currently have few non-invasive alternatives.

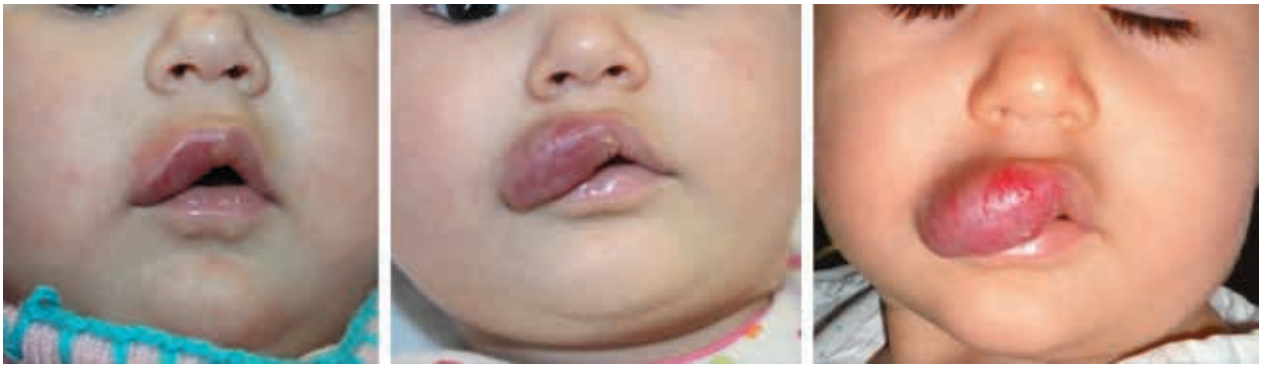

Figure 6. Arteriovenous malformation in the right upper lip with progressive evolution.

Combined malformations

Combined malformations, especially those within the overgrowth spectrum associated with PIK3CA (PIK-3CA-related overgrowth syndrome, or PROS), have always been treated using a cross-disciplinary approach focusing on the element causing symptoms or functional compromise. Standard treatment used to include conservative measures such as pressotherapy, drug treatment such as anticoagulants, interventional treatment with embolization, and surgical treatment, which used to be limited to debulking and reestablishing functionality. These treatments allowed symptoms to be partially controlled, but did not prevent progression and often did not improve patients' quality of life.

The discovery of PIK3CA mutations in this spectrum, including isolated pathologies such as macrodactyly, or true syndromes such as CLOVES syndrome, apart from other previously non-characterized overgrowths, has opened up new possibilities regarding the use of targeted treatments for these mutations. PIK3CA inhibitors for the treatment of multiple cancers are already being used in these patients with promising results. Alpelisib (BYL719) demonstrated a spectacular response in 19 PROS patients, and a new international clinical assay will soon be carried out. If successful, this will become a real option to improve these patients' symptoms and quality of life[40].

CONCLUSION

Over the last decade, clinical and experimental research, as well as technological progress, have enhanced our knowledge about vascular anomalies' physiopathology, histology, and genetics. The ISSVA-updated vascular anomaly classification has improved diagnosis and treatment. In addition, the new findings regarding the genetic mutations that cause vascular anomalies and the drugs that prove effective to treat them has increased the number of therapeutic options available and helped improve these patients' quality of life.

Propranolol and sirolimus have become the most disruptive advances for tumor and vascular malformation management in the 21st century, but there is still a long way to go. Understanding vascular anomalies' molecular biology can help us discover new uses for existing drugs and develop new targeted therapies.

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