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RESEARCH ARTICLE

# Vascular malformations in pediatric patients: 10-year experience of a vascular anomalies clinic

*Sofía Valdés-Loperena[1], Adolfo E. Lizardo-Rodríguez[2], Carlos G. Hinojosa-Gutiérrez[2,3], Max A. Bernal-Moreno[2,3], Gerardo A. Montejo-Ruiz[2,3], Manuel Guerrero-Hernández[2,3], Jaime Shalkow-Klincovstein[3†], Rodrigo Díaz-Machorro[3], Daniel Hernández-Arrazola[3], José M. Palacios-Acosta[3†], Oscar Colín-Martínez[4], Gerardo Fernández-Sobrino[5], Ana M. Borbolla-Pertierra[6], Carola Durán-Mc Kinster[1‡], and María Teresa García-Romero[1‡*]*

*[1]Servicio de Dermatología; [2]Departamento de Radiología; [3]Servicio de Cirugía Oncológica; [4]Servicio de Ortopedia; [5]Servicio de Cirugía Plástica; [6]Servicio de Oftalmología. Instituto Nacional de Pediatría, Mexico City, Mexico*

*[†]These authors are not currently working at the Instituto Nacional de Pediatría, ‡Both authors should be considered as the last authors*

## Abstract

**Background:** *Vascular malformations (VaMs) are caused by errors in vascular morphogenesis. Diagnosis and treatment can be complex. Few specialized centers care for these patients, and limited literature exists regarding their characteristics and clinical course. The vascular anomalies clinic (VAC) at the Instituto Nacional de Pediatría (National Institute for Pediatrics) is a multidisciplinary team and has been a reference center for patients with VaMs since 2012. We sought to describe the characteristics of patients cared for at the VAC, types of VaMs, treatments used, and clinical course.* **Methods:** *This was a descriptive, observational, retrospective, and cross-sectional study conducted from 2012 to 2022.* **Results:** *We included 435 patients with VaMs; the median age of presentation was 1 month. The most frequent signs and symptoms were increased volume (97.2%), superficial color change (65.5%), and pain (43.3%). The most common VaMs were lymphatic (36.7%) and venolymphatic (18.3%). Sclerotherapy was the most frequent treatment (73.4%), followed by medical treatment with sirolimus (18.5%); response to both was excellent/good in > 85% of cases.* **Conclusion:** *In this retrospective study of children with VaMs, we found that low-flow malformations were the most common, and sclerotherapy and sirolimus were the most frequently used treatments. The therapeutic response was excellent/good in most cases.*

***Keywords:*** *Vascular malformations. Pediatrics. Interdisciplinary health team.*

## *Malformaciones vasculares en pacientes pediátricos: experiencia de 10 años en una clínica de anomalías vasculares*

## Resumen

**Introducción:** *Las malformaciones vasculares (MaV) son secundarias a errores en la morfogénesis vascular. El diagnóstico y tratamiento puede ser complejo. Existen pocos centros especializados en su atención y escasa literatura respecto a características y evolución clínica. La Clínica de Anomalías Vasculares (CAV) del Instituto Nacional de Pediatría es un equipo*

***Correspondence:**
María Teresa García-Romero
E-mail: teregarro@gmail.com

Date of reception: 05-10-2023
Date of acceptance: 22-04-2024
DOI: 10.24875/BMHIM.23000144

Available online: 30-08-2024
Bol Med Hosp Infant Mex. 2024;81(4):232-244
www.bmhim.com

*multidisciplinario y centro de referencia para estos pacientes desde 2012. Buscamos describir las características de los pacientes atendidos en la CAV, tipo de MaV, tratamiento y evolución clínica.* **Métodos:** *Estudio descriptivo, observacional, retrospectivo y transversal del periodo 2012 al 2022.* **Resultados:** *Se incluyeron 435 pacientes con MaV, con edad mediana de presentación de 1 mes de vida. Los síntomas y signos más reportados fueron aumento de volumen (97.2%), cambio en coloración de la piel (65.5%) y dolor (43.3%). Las MaV más comunes fueron linfáticas (36.7%), siguiéndoles las venolinfáticas (18.3%). La escleroterapia fue el tratamiento más frecuente (73.4%) y el tratamiento médico más utilizado fue sirolimus (18.5%), ambos con excelente/buena respuesta en > 85% de los pacientes.* **Conclusiones:** *En este estudio retrospectivo de niños con MaV encontramos que las más frecuentes son de bajo flujo y el tratamiento más usado escleroterapia y sirolimus. La respuesta terapéutica de la mayoría fue excelente/buena.*

***Palabras clave:*** *Malformaciones Vasculares. Pediatría. Equipo Interdisciplinario de Salud.*

## Introduction

Vascular anomalies are divided into tumors and vascular malformations (VaMs)[1-3]. Tumors originate from vascular proliferation; infantile hemangiomas are the most common and well-known[1]. VaMs arise from errors in embryonic vasculogenesis, are present at birth (although not always evident), and do not involute. They can affect capillary, venous, arterial, and lymphatic vessels. VaMs have a variable clinical spectrum, ranging from skin spots to complex lesions with significant symptoms and impact on quality of life[2].

The International Society for the Study of Vascular Anomalies (ISSVA) classification[3] divides VaMs into four groups: (1) Simple: A single type of vessel affected, (2) Combined: ≥ 2 types of vessels affected, (3) Large vessel or truncal, and (4) Associated with other anomalies or syndromic (Table 1).

The incidence of VaMs is 0.3-1.5% in the general population and 5-10% in the pediatric population[4]. There is no sex predilection, and they occur sporadically. VaMs can affect localized areas or might involve extensive or segmental body surfaces[2]. Treatment varies depending on the affected vessel, location, size, and associated affected structures and can be conservative or interventional. In recent years, signaling pathways involved in the pathophysiology of VaMs have been identified, which has led to new therapeutic modalities such as sirolimus[5].

The vascular anomalies clinic (VAC) at our referral institution was established in 2012 to provide comprehensive medical care to a specific patient population referred between institutions and internal services due to the complexity of their conditions. This study aimed to describe the demographic and clinical characteristics of the patients treated, the type of VaMs they presented with, the treatment received, and their response to treatment.

## Methods

The study design was descriptive, observational, retrospective, and cross-sectional. The institutional committees approved the study protocol with registration number INP2021/022.

Records of patients with VaMs treated at the institutional VAC from January 01, 2012, to February 28, 2022, were reviewed. The variables studied were sex, age, final diagnosis according to ISSVA, date of symptom onset, type, size, distribution, depth, topography, symptomatology of the VaMs, number of visits to the VAC, treatment received, response, and treatment-associated complications. Patients whose records had < 80% of the analyzed variables were excluded from the study. As VaMs have heterogeneous involvement, for their study, we divided the patients into three categories according to distribution: (1) localized, affecting a single circumscribed body area; (2) segmental, affecting a body segment; and (3) extensive, affecting > 1 body segment. The depth of the VaMs was categorized into three groups based on physical examination and imaging studies: (1) superficial in skin and soft tissues, (2) deep in muscle, joints, and/or bone, and (3) mixed if they affected both of the above. Treatment response was evaluated according to three parameters: (1) clinical: comparison of clinical photographs before and after treatment, (2) radiological: comparison of radiological studies, and (3) functional: semi-quantitative evaluation by the patient and/or caregivers regarding volume reduction, pain reduction, and other symptoms, increased mobility or functionality, among others. These three types of response were quantified in a range of 0-100%, and the result was classified according to the following parameters: excellent (75-100%), good (50-74%), moderate (25-49%), and poor/no response (0-24%).

Descriptive statistics were used for continuous quantitative variables using measures of central tendency,

**Table 1.** Classification of VaMs according to ISSVA (2018)

| Vascular simple malformations | |
|---|---|
| **Affected vessels** | **Nomenclature** |
| CM[a] | Cutaneo-mucosal CM (salmon patch, Port-wine stain)<br>With ocular anomalies and/or CM in leptomeninges (Sturge-Weber Syndrome)<br>With soft tissue or bone overgrowth |
| | Reticulated CM<br>With microcephaly or megalencephaly/polymicrogyria |
| | CM with arteriovenous malformation |
| | Cutis marmorata telangiectatica congenita |
| | Telangiectasias<br>Hereditary hemorrhagic telangiectasia |
| LM[a] | Common cystic LM<br>Macrocystic<br>Microcystic<br>Mixed |
| | Generalized lymphatic anomaly or kaposiform |
| | LM with massive osteolysis (Gorham-Stout Syndrome) |
| | LM of the central duct |
| | Primary lymphedema (various types) |
| VM[a] | Common VM |
| | Familial cutaneo-mucosal VM |
| | Glomovenous malformation |
| | Cutaneo-gastrointestinal VM (Blue rubber bleb nevus syndrome or Bean syndrome) |
| | Cerebral VM |
| | Familial intraosseous VM |
| | Verrucous VM |
| AVM or AVF[b] | Sporadic AVM/AVF |
| | AVM/AVF in Hereditary hemorrhagic telangiectasia |
| | AVM/AVF with CM |
| **Combined vascular malformations** | |
| **Type of affected vessels** | **Nomenclature** |
| CM + VM[a] | Capillary-Venous Malformation |
| CM + LM[a] | Capillary and Lymphatic malformation |
| CM + AVM[b] | Capillary and Arteriovenous Malformation |
| ML + VM[a] | Lymphatic-Venous Malformation |
| CM + LM + VM[a] | Capillary-Venous and Lymphatic malformation |
| CM + LM + AVM[b] | Lymphatic and Arteriovenous Malformation |
| CM + VM + AVM[b] | Capillary-Venous and Arteriovenous Malformation |
| CM + LM + VM + AVM[b] | Lymphatic-Venous and Arteriovenous Malformation |

*(Continues)*

**Table 1.** Classification of VaMs according to ISSVA (2018) *(continued)*

| Vascular malformations associated with other anomalies | |
|---|---|
| **Type of affected vessels** | **Associations and nomenclature** |
| CM + VM ± LM[a] | With limb overgrowth (Klippel-Trenaunay Syndrome) |
| CM + AVF[b] | With limb overgrowth (Parkes-Weber Syndrome) |
| VM limb[a] | With bone hypotrophy (Servelle-Martorell Syndrome) |
| CM limb[a] | With congenital limb hypertrophy |
| VM[a] | With/without spindle cell hemangioma and enchondroma (Maffucci Syndrome) |
| LM + VM + CM ± AVM[a,b] | With congenital lipomatous overgrowth, epidermal nevus, skeletal anomalies (CLOVES Syndrome[c]) |
| MC + VM ± LM[a] | With asymmetric somatic growth, connective tissue nevus (Proteus Syndrome) |
| AVM + VM[b] | With macrocephaly and lipomatous growth (Bannayan-Riley-Ruvalcaba Syndrome) |
| CM lower lip + LM head and neck[a] | With asymmetry and partial/generalized overgrowth (CLAPO Syndrome[d]) |
| **Provisionally Unclassified Vascular Anomalies** | |
| Intramuscular hemangioma<br>Angiokeratoma<br>Sinusoidal hemangioma<br>Acral arteriovenous tumor<br>Multifocal lymphangioendotheliomatosis with thrombocytopenia<br>Soft-tissue hamartoma associated with PTEN mutations<br>Fibroadipose vascular anomaly | |

ISSVA: international society for the study of vascular anomalies; CM: capillary malformation; LM: lymphatic malformation; VM: venous malformation; AVM: arteriovenous malformation; AVF: arteriovenous fistula. [a]Low flow; [b]High flow; [c]Congenital lipomatous overgrowth vascular malformations epidermal nevi and scoliosis/skeletal/spinal anomalies; [d]Capillary vascular malformation lymphatic malformation asymmetry and partial/generalized overgrowth.

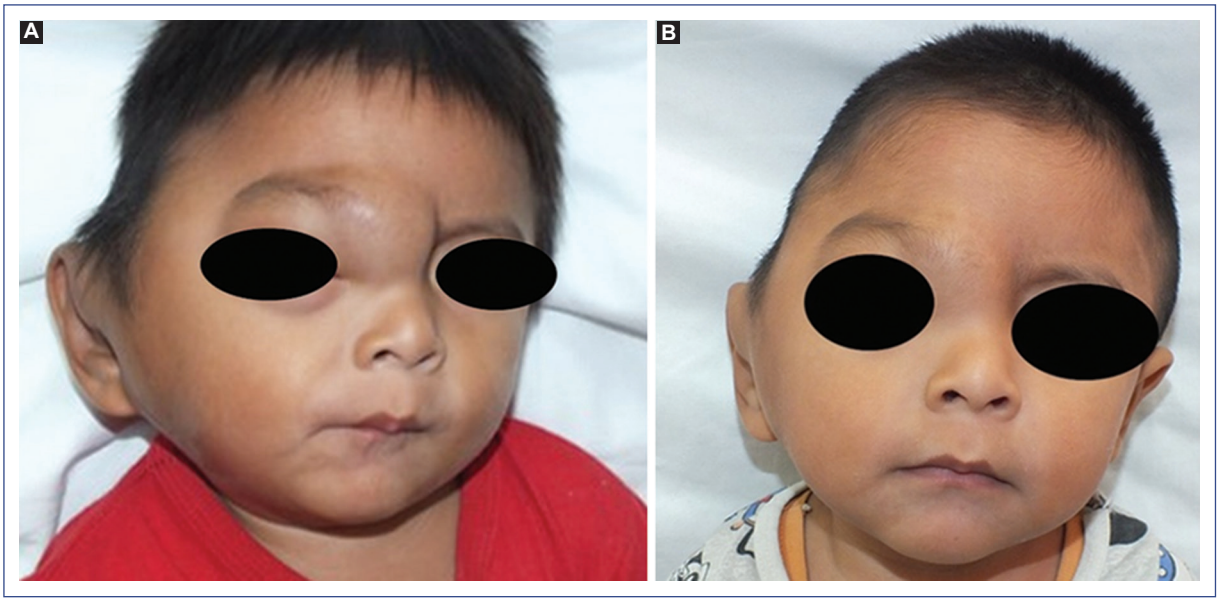


**Figure 1. A:** a 3-year-old patient with lymphatic malformation in the glabellar, periocular, cheek, and right auricular regions. **B:** after treatment with bleomycin sclerotherapy and sirolimus treatment.


**Figure 2.** **A:** a 12-year-old patient with periorbital and intraconal lymphatic malformation. **B:** after treatment with sirolimus.

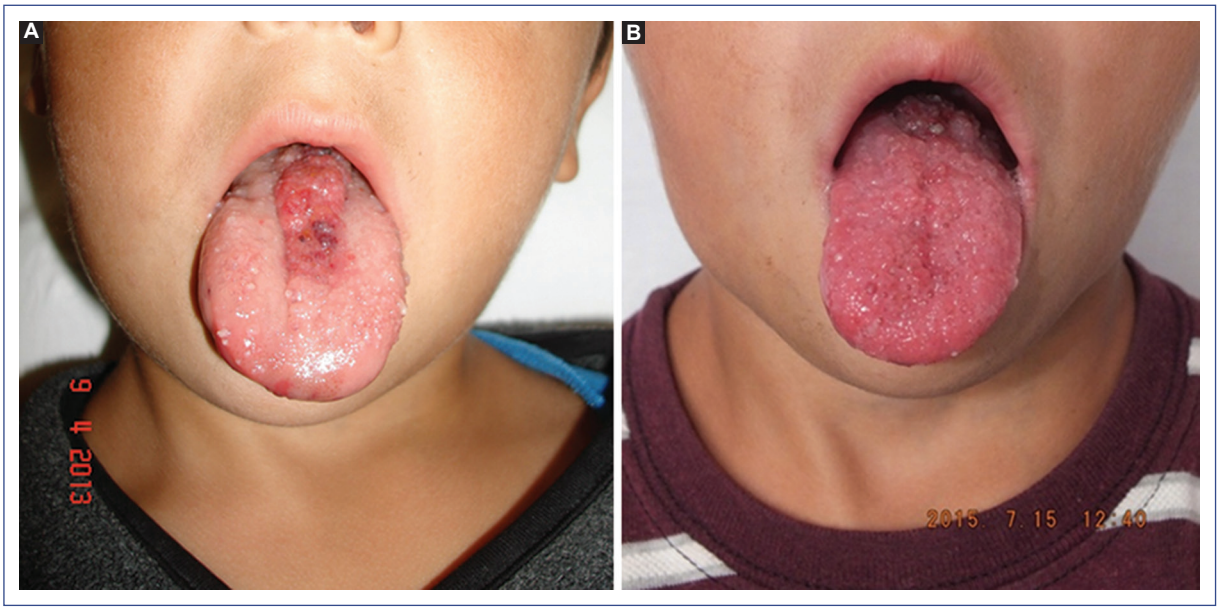


**Figure 3.** **A:** a 6-year-old patient with venolymphatic malformation in the tongue and neck. **B:** after treatment with alcohol sclerotherapy.

as well as dispersion measures and proportions were used for qualitative variables.

## Results

A total of 435 patients from 23 states were included in the study. The most frequent distribution was localized (351, 80.6%) and superficial involvement (195, 44.8%). The predominant topography was head and neck (212, 48.7%) (Figs. 1-3), followed by extremities (182, 41.8%) (Figs. 4 and 5). In general, the main signs and symptoms were increased volume (425, 97.2%), change in skin color (285, 65.5%), and pain (189, 43.4%) (Table 2). The age at which the signs and symptoms initially manifested

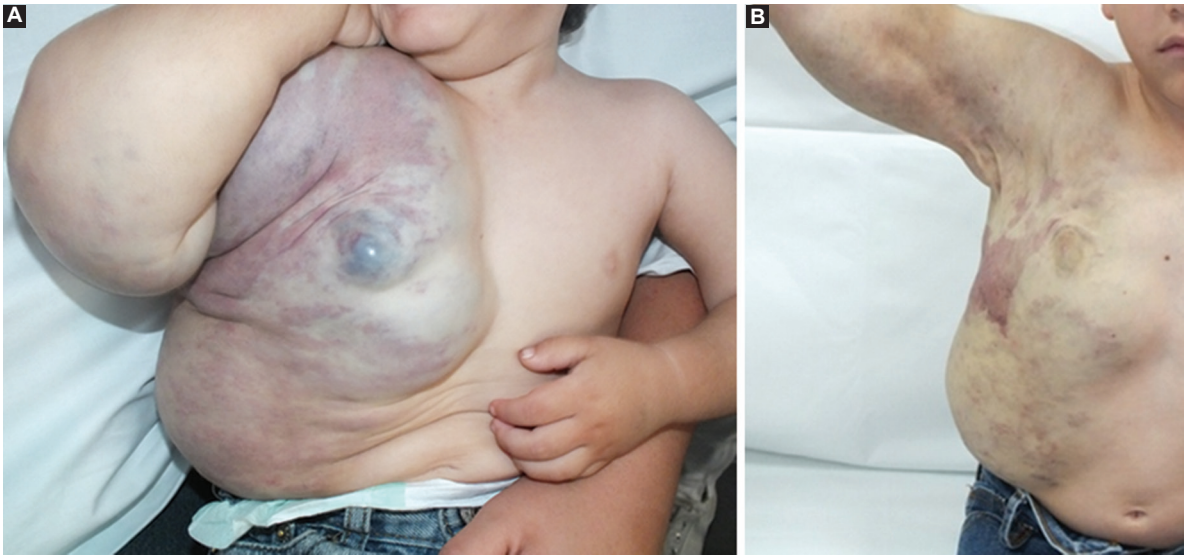


**Figure 4. A:** a 3-year-old patient with venolymphatic and capillary malformation in the right hemibody and arm. **B:** after treatment with surgery and sirolimus.

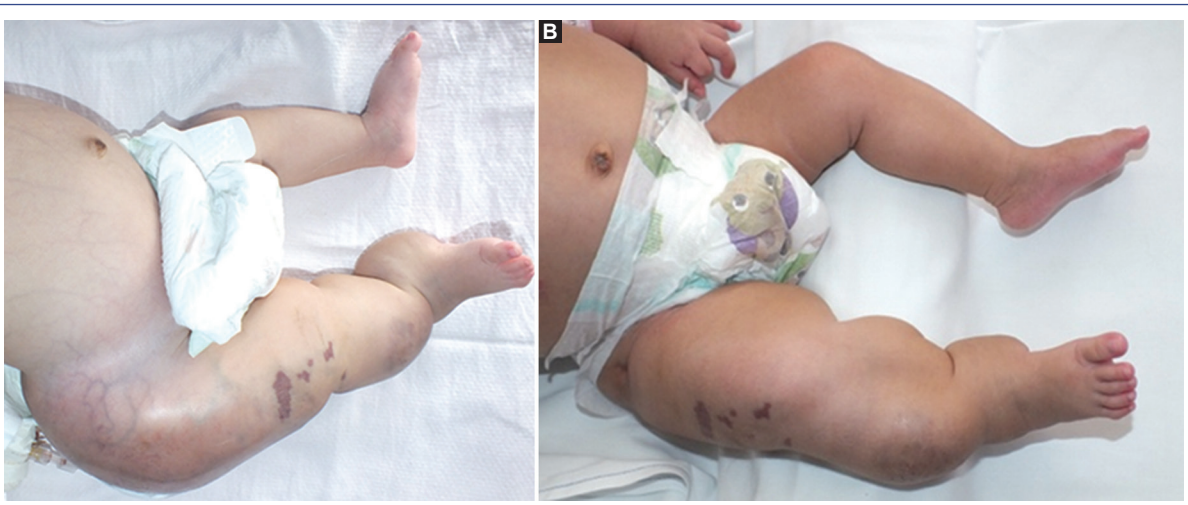


**Figure 5. A:** a 3-month-old patient with Klippel-Trenaunay syndrome in the right lower limb. **B:** after treatment with sirolimus.

varied widely from birth to 15 years (median of 1 month); it was not reported in 9 (2%) patients.

Manifestations in specific areas were reported. In patients with head and neck involvement, these were dysphagia, otalgia, odynophagia, loss of teeth, stridor, apnea, language disorders, and inability to eat (Fig. 1). In VaMs affecting the ocular area, eyelid edema, proptosis, visual field, or visual acuity alteration were found (Fig. 2). Localization in the extremities was accompanied by paresthesia, dysesthesia, soft-tissue hypertrophy, pruritus, cellulitis, infection, and pathological fractures (Figs. 4 and 5). Cavity involvement caused pleural effusion, airway compression, hematochezia, melena, and anemia.

The final diagnoses established in the VAC according to the ISSVA 2018 classification were 20 different ones (Table 3). Simple VaMs predominated in 300 patients (68.9%): lymphatic followed by venous and arteriovenous

**Table 2.** Demographic and clinical characteristics of 435 patients

| Category of characteristic | Specific characteristic | n = 435 (%) |
|---|---|---|
| Federal entity of origin | Mexico City | 144 (33.1) |
| | State of Mexico | 125 (28.7) |
| | Puebla | 35 (8.0) |
| | Guerrero | 25 (5.7) |
| | Other[a] | 106 (24.3) |
| Sex | Female | 223 (51.2) |
| | Male | 212 (48.7) |
| Body Distribution | Localized | 351 (80.6) |
| | Extensive | 54 (12.4) |
| | Segmental | 30 (6.8) |
| Depth | Superficial | 195 (44.8) |
| | Mixed | 156 (35.8) |
| | Deep | 84 (19.3) |
| Topography | Head and neck | 212 (48.7) |
| | Face | 143 (32.8) |
| | Neck | 92 (21.1) |
| | Perioral region | 25 (5.7) |
| | Orbital region | 18 (4.1) |
| | Scalp | 2 (0.4) |
| | Airway | 13 (2.9) |
| | Limbs | 182 (41.8) |
| | Lower limbs | 124 (28.5) |
| | Upper limbs | 87 (20.0) |
| | Trunk | 106 (24.3) |
| | Intracavitary | 13 (2.9) |
| | Intra-abdominal | 7 (1.6) |
| | Intrathoracic | 5 (1.1) |
| | Pelvis | 1 (0.2) |
| | Genitalia | 17 (3.9) |
| Symptoms and Signs | Volume increase | 425 (97.2) |
| | Skin color change | 285 (65.5) |
| | Pain | 189 (43.3) |
| | Functional incapacity | 159 (36.5) |
| | Bleeding | 46 (10.5) |
| | Other manifestations[b] | 63 (14.4) |

[a]Oaxaca 18 (4.1) Veracruz 14 (3.2) Michoacán 10 (2.2) Hidalgo 8 (1.8) Chiapas 8 (1.8) Morelos 7 (1.6) Tlaxcala 7 (1.6) Guanajuato 7 (1.6) Querétaro 6 (1.3) San Luis Potosí 3 (0.6) Jalisco 2 (0.4) Baja California Sur 2 (0.4) Baja California 1 (0.2) Nayarit 1 (0.2) Sinaloa 1 (0.2) Tamaulipas 1 (0.2) Zacatecas 1 (0.2) not referred 8 (1.8); [b]Airway compression 16 (3.6) Dysphagia 8 (1.8) Proptosis 5 (1.1) Soft-tissue hypertrophy 4 (0.9) Infection 4 (0.9) Pruritus 3 (0.6) Cellulitis 2 (0.4) Apnea 2 (0.4) Dyspnea 2 (0.4) Language disorders 2 (0.4) Feeding incapacity 2 (0.4) Odynophagia 2 (0.4) Paresthesia 2 (0.4) Otalgia 1 (0.2) Sialorrhea 1 (0.2) Loss of teeth 1 (0.2) Stridor 1 (0.2) Eyelid edema 1 (0.2) Visual field/acuity alteration 1 (0.2) Dysesthesia 1 (0.2) Pathological fractures 1 (0.2) Pleural effusion 1 (0.2).

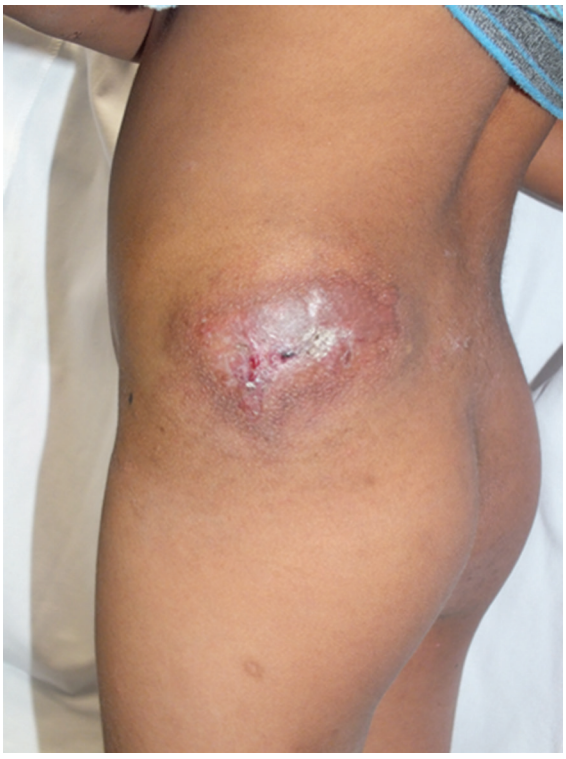

**Figure 6.** A 5-year-old patient with an arteriovenous malformation in the left hip.

(Fig. 6). The next group was combined VaMs in 109 patients (25.0%), and of these, venolymphatic malformations were the most frequent (Fig. 3). Seven types of VaMs associated with other anomalies were identified; Klippel-Trenaunay syndrome was the most common in 15 (3.4%). Within the group of provisionally unclassified vascular anomalies, we found three patients diagnosed with fibroadipose vascular anomaly (FAVA). Regarding clinical follow-up, the patients had 931 consultations at the VAC, with a median of 2 per patient (range 1-12).

A total of 339 patients (77.9%) received treatment, with radiological interventions being the most frequent in 281 (82.8%), followed by medical or symptomatic treatment in 167 (49.2%), and surgical treatment in 63 (18.5%) (Table 4). One hundred and 25 patients (36.8%) received more than one therapeutic modality during the studied period, with a median of two modalities per patient (range 2-4).

Sclerotherapy was performed in 249 (73.4%) patients, with a median of 2 (range 1-15) procedures per patient, for a total of 698 procedures. The main conditions treated with this modality were lymphatic malformations (LMs) in 101 patients (40.5%), venolymphatic malformations in

**Table 3.** Diagnoses established in patients according to International Society for the Study of Vascular Anomalies 2018[1]

| Category of VaM according to ISSVA | Specific type of VaM | n = 435 (%) |
|---|---|---|
| Simple | Lymphatic Malformation | 160 (36.7) |
| | Venous Malformation | 78 (17.9) |
| | Arteriovenous Malformation | 46 (10.5) |
| | Capillary Malformation | 10 (2.2) |
| | Blue Rubber Bleb Nevus Syndrome | 4 (0.9) |
| | Gorham-Stout Syndrome | 1 (0.2) |
| | Generalized Lymphatic Anomaly | 1 (0.2) |
| | Total | 300 (68.9) |
| Combined | Lymphatic-Venous Malformation | 80 (18.3) |
| | Capillary-Venous Malformation | 16 (3.6) |
| | Capillary-Venous-Lymphatic Malformation | 9 (2.0) |
| | Capillary-Lymphatic Malformation | 2 (0.4) |
| | Lymphatic-Arteriovenous Malformation | 2 (0.4) |
| | Total | 109 (25.0) |
| Associated with other anomalies | Klippel-Trenaunay Syndrome | 15 (3.4) |
| | Servelle-Martorell Syndrome | 2 (0.4) |
| | Proteus Syndrome | 2 (0.4) |
| | Bannayan-Riley-Ruvalcaba Syndrome | 1 (0.2) |
| | CLOVES Syndrome[a] | 1 (0.2) |
| | CLAPO Syndrome[b] | 1 (0.2) |
| | Total | 22 (5.0) |
| Provisionally unclassified | Fibroadipose vascular anomaly | 3 (0.6) |
| | Total | 3 (0.6) |

[a]Congenital lipomatous overgrowth vascular malformations epidermal nevi and scoliosis/skeletal/spinal anomalies; [b]Capillary vascular malformation Lymphatic malformation Asymmetry and Partial/generalized Overgrowth; [1]International Society for the Study of Vascular Anomalies. Issva.org. 2018 [Internet]. [cited 2023 May 29]. Available from: https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf.

51 patients (20.4%), and venous malformations in 50 patients (20.0%) (Fig. 3). According to the individual characteristics of each patient's VaMs and institutional availability, various drugs were used for sclerotherapy: bleomycin, polidocanol, absolute alcohol, 50% glucose solution, or OK-432. The functional therapeutic response was excellent in 59.6% of patients and good in 30.7% (Table 5). Complications were reported in 11 patients (4.4%) and were fibrosis (3), necrosis (2), unsightly scar (2), soft-tissue infection (1), facial paralysis (2), and rash (1).

Embolization was performed in 32 patients (9.4%), with a median of 1 (range 1-5) procedure per patient, for a total of 52 procedures. The agents used were hystoacril, polyvinyl alcohol, and coils. Seven patients were treated exclusively with embolization; the response was excellent in 25% of patients and good in 50% (Table 5). Complications occurred in 4 patients (12.5%): cerebrovascular disease, caudate nucleus infarction, left hemifacial paralysis, and retractile scar.

Surgical treatment was performed on 59 patients (17.4%), mainly with LM in 19 (32.3%). Of these, 14 patients received only surgical treatment, and an improvement classified as excellent was reported in 90-100% (Table 5). Six patients (10.1%) presented complications: nociceptive pain syndrome (1), functional

**Table 4.** Treatments used in 339 treated patients

| Category | Treatment | n = 339 (%) |
|---|---|---|
| Interventional Radiology | Sclerotherapy | 249 (73.4) |
| | Embolization | 32 (9.4) |
| | Total | 281 (82.8) |
| Medical | Sirolimus | 63 (18.5) |
| | Symptomatic/adjunct[a] | 47 (13.8) |
| | Non-steroidal anti-inflammatory drugs | 30 (8.8) |
| | Paracetamol | 12 (3.5) |
| | Anticoagulants | 5 (1.4) |
| | Antibiotics | 4 (1.1) |
| | Omeprazole | 3 (0.8) |
| | Propranolol | 2 (0.5) |
| | Systemic corticosteroids | 1 (0.2) |
| | Total | 167 (49.2) |
| Surgical | Surgery | 59 (17.4) |
| | Electrofuguration/ radiofrequency | 4 (1.1) |
| | Total | 63 (18.5) |

[a]Compression stockings 43 (12.6) splint 1 (0.2) insole 1 (0.2) laser 1 (0.2) drying fomentations 1 (0.2).

incapacity (1), adhesions (1), soft-tissue infection (2), and esthetic alteration (1).

Medical treatment was given to 165 (48.6%) patients, with sirolimus being the most common in 63 (18.5%), and as adjuvant or symptomatic treatment, the use of compression stockings in 43 (12.6%) (Table 4). Sirolimus treatment was indicated in patients with VaMs related to mutations in the mTOR pathway, mainly simple (lymphatic) in 17 patients (26.9%), combined low-flow (venolymphatic) in 22 (34.9%), and associated with other anomalies such as Klippel-Trenaunay syndrome in 8 (12.6%) (Table 6 and Fig. 5). In four patients, it was discontinued due to adverse effects associated with the medication: mucositis (2), infection (2), and increased triglycerides (1), and in nine patients due to loss of follow-up. In patients who received sirolimus alone, the functional response was excellent in 31.8% and good in 54.5%. In 29 patients treated with sirolimus after receiving other therapeutic modalities, the functional therapeutic response was excellent in 41.6% and good in 37.5% (Table 5).

According to the type of VaMs, we found that patients with simple and combined VaMs received sclerotherapy more frequently (239, 58.4%), while those with VaMs associated with other anomalies received mainly medical treatment (16, 69.5%) and symptomatic treatment (16, 69.5%) (Table 6).

## Discussion

VaMs can present with a variable clinical spectrum depending on the type of vessel affected, location, size, and depth. Due to the complexity of VaMs, the initial diagnosis is sometimes difficult, and they can be confused or misnamed, which delays appropriate treatment and does not allow for an accurate prognosis for patients[6-8]. Primary care physicians must know each VaMs type's correct classification and clinical characteristics to allow for a correct diagnostic approach and timely referral[8]. Non-invasive diagnostic tests (doppler ultrasound, magnetic resonance imaging) and sometimes invasive tests (arteriography or biopsy) are generally required to classify VaMs correctly. Once an accurate diagnosis is established, the required management can range from expectant observation to multidisciplinary interventional treatment, depending on the VaMs type[6]. For these reasons, it is recommended that a step-by-step diagnostic approach and comprehensive management to be established, ideally by a collaborative multidisciplinary team such as VACs[6,7,9]. The VAC in our institution was established in 2012 in response to institutional needs as a referral center for patients with complex VaMs. It holds weekly sessions with a fixed multidisciplinary team and support specialists.

Referred patients are assessed by one of the services, usually dermatology, and are scheduled with initial radiological studies (ultrasound or magnetic resonance imaging) at the VAC. Once there, a complete physical examination is performed again, and radiological studies are analyzed (new studies are indicated if necessary). A diagnosis is made according to the ISSVA criteria, and a treatment is proposed to the patient and their parents. Follow-up is done again at the VAC to assess the response to radiological or surgical treatment. In the outpatient clinic, the relevant services are provided depending on each case and the type of treatment.

Ten years after the start of the VAC, we conducted this study seeking to describe the clinical characteristics of the Mexican pediatric population with VaMs

**Table 5.** Therapeutic response to each treatment group

| Treatment modality | Response | Clinical n (%) | Radiological n (%) | Functional n (%) |
|---|---|---|---|---|
| | | n = 114 | n = 77 | n = 114 |
| Sclerotherapy | Excellent | 65 (57) | 40 (51.9) | 68 (59.6) |
| | Good | 36 (31.5) | 24 (31.1) | 35 (30.7) |
| | Moderate | 6 (5.2) | 7 (9) | 10 (8.7) |
| | Poor/none | 3 (2.6) | 6 (7.7) | 1 (0.8) |
| | | n = 4 | n = 3 | n = 4 |
| Embolization | Excellent | 1 (25) | 1 (33.3) | 1 (25) |
| | Good | 2 (50) | 1 (33.3) | 2 (50) |
| | Moderate | 0 | 0 | 1 (25) |
| | Poor/none | 1 (25) | 1 (33.3) | 0 |
| | | n = 10 | n = 4 | n = 10 |
| Surgical | Excellent | 9 (90) | 4 (100) | 9 (90) |
| | Good | 0 | 0 | 0 |
| | Moderate | 0 | 0 | 0 |
| | Poor/none | 1 (10) | 0 | 1 (10) |
| | | n = 22 | n = 8 | n = 22 |
| Sirolimus | Excellent | 4 (18.8) | 1 (12.5) | 7 (31.8) |
| | Good | 14 (63.6) | 3 (37.5) | 12 (54.5) |
| | Moderate | 1 (4.5) | 1 (12.5) | 0 |
| | Poor/none | 3 (13.6) | 3 (37.5) | 3 (13.6) |
| | | n = 24 | n = 17 | n = 24 |
| Previous treatment + sirolimus | Excellent | 5 (20.8) | 3 (17.6) | 10 (41.6) |
| | Good | 12 (50) | 10 (58.8) | 9 (37.5) |
| | Moderate | 2 (8,3) | 1 (5.8) | 1 (4.1) |
| | Poor/none | 5 (20.8) | 3 (17.6) | 4 (16.6) |

treated so far, as well as their clinical evolution and response to the treatments employed.

We found that simple VaMs were the most frequent, including LMs, followed by combined venolymphatic, venous, and arteriovenous malformations. This is similar to what has been previously reported in the literature, where simple malformations are the most common; however, in other studies, venous malformations predominate[6,7], which may be because the population treated in our VAC is pediatric, and LMs frequently become evident after infectious processes, unlike venous malformations, whose clinical course is more chronic and slower.

The most frequent location in our study was the head and neck, followed by the extremities (mainly lower), which is consistent with the literature[7]. Airway involvement was infrequent; however, early identification is vital to avoid complications. All patients studied manifested symptoms or signs (100%), specifically increased volume, change in color, and pain, coinciding with the clinical presentation described in the literature[7,10].

At the VAC, the most commonly used interventional radiology treatment was sclerotherapy in 56.6%, mainly for LMs, followed by venolymphatic and venous malformations. In similar studies, the most frequently used treatment was also sclerotherapy in

**Table 6.** Treatments indicated for each group of patients with vascular malformations

| Category of VaM | Treatment modality | n (%) |
|---|---|---|
| Simple VaMs (n = 300) | Sclerotherapy | 170 (56.6) |
| | Observation (none) | 73 (24.3) |
| | Symptomatic treatment | 50 (16.6) |
| | Medical treatment | 39 (13.0) |
| | Surgery | 38 (12.6) |
| | Embolization | 27 (9.0) |
| Combined VaMs (n = 109) | Sclerotherapy | 69 (63.3) |
| | Medical treatment | 28 (25.6) |
| | Observation (none) | 19 (17.4) |
| | Surgery | 15 (13.7) |
| | Symptomatic treatment | 14 (12.8) |
| | Embolization | 3 (2.7) |
| VaMs associated with other anomalies (n = 23) | Medical treatment | 16 (69.5) |
| | Symptomatic treatment | 16 (69.5) |
| | Sclerotherapy | 8 (34.7) |
| | Surgery | 6 (26.0) |
| | Observation (none) | 4 (3.6) |
| | Embolization | 2 (8.6) |
| Provisionally unclassified (n = 3) | Sclerotherapy | 2 (66.6) |
| | Medical treatment | 1 (33.3) |
| | Symptomatic treatment | 1 (33.3) |

VaMs: vascular malformations.

36-49%, coinciding with the type of VaMs treated with this modality[7,11]. Sclerotherapy sessions were performed every 1-2 months, with two sessions per patient. In similar studies, an average of 2-3.7 procedures per patient is reported. In our study, approximately 90% of patients who received this therapeutic modality had an excellent and good response, similar to previous reports. Sclerotherapy is considered a useful procedure to improve the symptoms and size of VaMs with a lymphatic and/or venous component in those who undergo it before reaching puberty[12]. Possible side effects of sclerotherapy include allergic reactions to sclerosants, pain, neurological alterations derived from the procedure, embolic complications, necrosis, pigmentation at the puncture site, or induration[12,13]. In our patients, complications associated with sclerotherapy occurred in 8.0% and were mainly fibrosis, esthetic alteration, and infection, coinciding with the literature[7].

Embolization is used more frequently in high-flow malformations; it is considered helpful to reduce bleeding in case of severe symptoms or before a surgical procedure. To achieve therapeutic success, it is necessary to completely embolize the central vascular nidus[14]. In this study, 78.1% of patients treated with embolization had an arteriovenous malformation[14,15]. Only one intervention per patient was required, in general, and complications occurred in 12.5%: cerebrovascular disease, caudate nucleus infarction, left hemifacial paralysis, and retractile scar. Various complications have been described in the literature, including those reported in our patients. However, because the drugs and techniques are different, it is difficult to assess their actual frequency[15].

Surgical interventions were the least frequent treatment in our clinic (17.4%); however, surgery is the most frequent therapeutic modality in centers where debulking and amputations are performed[6].

Some VaMs are caused by mutations in the *PIK3CA*, *RAS*, and *GNA* gene families. Mutations in *PIK3CA* are involved in some syndromes with overgrowth and various types of simple or combined low-flow malformations. Mutations in genes in the RAS pathway (*KRAS, MAP2K1, BRAF*) are mainly associated with high-flow or arteriovenous malformations (Fig. 6)[5]. All these genes encode membrane-associated proteins that control endothelial cells' proliferation, differentiation, and organization and are closely linked to the mTOR pathway. Identifying these mutations and affected pathways has allowed the repositioning of therapeutic options. One of them is sirolimus, a specific mTOR inhibitor that has shown efficacy in VaMs and has become the first-line treatment, alone or as an adjuvant, in patients with extensive LM, VM, or combined low-flow malformations and those associated with overgrowth[5,16]. The recommended dose is 0.8 mg/m$^2$ until 10-15 ng/mL levels are reached[17]. Adverse effects reported with the use of this medication include mucositis, gastrointestinal problems, soft-tissue infections, alteration of laboratory parameters of liver and lipid profiles, pneumonia, and, to a lesser extent, bone marrow suppression and recurrence of basal cell carcinoma[6,18]. Currently, in our VAC, we have treated 56 patients with sirolimus, showing an

excellent and good response in > 75%, and only 4 patients have had to discontinue treatment due to mild adverse effects.

Pulsed dye laser and intravascular lasers are other therapeutic options that can be used to treat VaMs[6]; however, our institution does not have other modalities.

The benefits of specialized multidisciplinary clinics have been well described, including enhancing the patient experience, improving population health, and reducing *per capita* costs[9]. We have observed these benefits throughout the years that VAC has been operating. First, patients can be evaluated by multiple specialists simultaneously, which streamlines time and costs for the institution and the patients themselves[6,9]. Moreover, this space allows for the discussion of each patient's case by the group of specialists together, taking into account previous diagnostic studies and clinical characteristics, aided by existing literature, instead of each specialist evaluating and concluding an opinion on their own. This allows for an accurate diagnosis and an appropriate treatment plan for the patient and their family. In addition, the latter have the opportunity to ask questions and resolve their doubts before the entire group of specialists[6]. Since the VAC was initiated in our institution, we have become a national referral center and a support center for specialists in other regions. We have had internal challenges, such as logistical issues for scheduling appointments, administrative support, and a lack of human and financial resources. However, our biggest challenge is that there is no VAC in our country to provide care for adult patients with VaMs, so on reaching the majority age, patients are referred to various tertiary-level care institutions. However, in many cases, follow-up is lost.

This study has limitations, such as loss of information in the medical record or lack of patient follow-up. In addition, the VAC does not treat patients with isolated capillary malformations or vascular tumors, so we did not include these conditions. Finally, there are no validated measures or tools to assess treatment response or effectiveness in patients with VaMs due to their wide range of clinical manifestations and inter-individual variability[6], so we used semi-quantitative categories to describe the therapeutic response.

However, this study of 435 pediatric patients with VaMs is the largest in our country and one of the largest in the global literature. We describe the frequency of VaMs, associated clinical manifestations, treatment, and clinical evolution of a cohort of patients with follow-up over 10 years, generating relevant information to guide medical care of these patients. We confirm the importance of comprehensive and multidisciplinary care for patients with VaMs and hope that more institutions will use this experience to form multidisciplinary clinics to diagnose and treat patients with these complex conditions that significantly affect their quality of life.

## Conclusion

The most common VaMs in this retrospective study in a multidisciplinary clinic for the care of children were lymphatic, venolymphatic, and venous malformations; the age at presentation is very early. The most frequent associated symptoms were increased volume, change in skin color, and pain. Sclerotherapy and sirolimus were the main treatments, with a good and excellent response.

## Funding

The authors declare that they have not received funding.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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