

Multisystem vascular dysplasia: Osler-Weber-Rendu disease: unraveling the cause of the bleeding

Displasia vascular multisistémica: enfermedad de Osler-Weber-Rendu: desenmarañando la causa de la hemorragia

Neftalí Alexander Granados Flores[1]
José Alfonso Rumoroso García[2]

https://doi.org/10.53903/01212095.229

Key words (MeSH)
Telangiectasia, hereditary hemorrhagic
Arteriovenous malformations
Rare diseases

Palabras clave (DeCS)
Telangiectasia hemorrágica hereditaria
Malformaciones arteriovenosas
Enfermedades raras

Summary

Osler-Weber-Rendu disease (OWR), also known as multisystem vascular dysplasia or hereditary hemorrhagic telangiectasia, is a rare autosomal dominant disorder, characterized by the development of vascular dysplasias (VD) such as telangiectasias and arteriovenous malformations of mucocutaneous or visceral location, which show a tendency to bleeding, and can affect any organ or system, with epistaxis being the most frequent initial clinical presentation. Although the definitive diagnosis is based on genetic studies, due to their low availability and high cost, they have led to the use of imaging methods to identify findings that guide clinical suspicion. Three cases are presented with a diagnosis of OWR and imaging findings of hepatic, gastrointestinal and pulmonary DV levels.

Resumen

La enfermedad de Osler-Weber-Rendu (OWR), también conocida como displasia vascular multisistémica o telangiectasia hemorrágica hereditaria. Es un trastorno autosómico dominante raro, caracterizado por el desarrollo de displasias vasculares (DV), como telangiectasias y malformaciones arteriovenosas de localización mucocutánea o visceral, las cuales muestran tendencia al sangrado, que pueden afectar cualquier órgano o sistema, con la epistaxis como la presentación clínica inicial más frecuente. Aunque el diagnóstico definitivo se basa en estudios genéticos, su baja disponibilidad y alto costo han llevado al uso de métodos de imagen para identificar los hallazgos que guían la sospecha clínica. Se presentan tres casos con diagnóstico de OWR y los hallazgos por imagen de DV hepática, gastrointestinal y pulmonar.

Introduction

In 1864, Henry Gawen Sutton reported the first case of this disease, but it was not until 1896 that Henri Jules Marie Rendu recognized it as an entity different from the hemophilias. William Osler and Frederick Parkes Weber in 1907 described the syndrome in greater depth and published the first series of cases, which is why this pathology was baptized with the triple eponym (Osler-Weber-Rendu [OWR]) as it is known to date. The American physician Frederick M. Hanes is credited with the first use of the term "hereditary hemorrhagic telangiectasia" in 1907 to refer to this entity (1-3).

This syndrome shows no sex predilection and consists of a rare autosomal dominant neoformative angiopathy (prevalence of 1.5-2/100,000 individuals in the general population; although higher figures have been reported by Afro-Caribbean residents of Curaçao and Bonaire) (2-5).

It is characterized by the development of vascular dysplasias (VD) represented by anomalous vascular communications, such as mucocutaneous telangiectasias (histologically showing dilated capillaries lined with flat endothelial cells) and/or arteriovenous malformations (AVM) that have a mixture of thick-walled and thin-walled vessels (2). They can affect any part of the body, but are most frequently found in the nasopharynx, central nervous system, lungs, liver, spleen, urinary tract, gastrointestinal tract, conjunctivae, trunk, upper extremities and fingers (1, 4).

Two forms of OWR have been differentiated in relation to the involvement of the *HHT1* and *HHT2* genes. The *HHT1* variant (mutations in the endoglin gene) on the long arm of chromosome 9 (9q33- q34.1). *HHT2* (mutations in the *ALK1* gene) on the long arm of chromosome 12 (12q11-q14) (1, 6); the latter with an increased risk of developing hepatic AVM (2).

[1]Médico Radiologist, Salvadoran Institute of Social Security. San Salvador.

[2]Medical radiologist specializing in sectional body imaging. National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ). Mexico.

The clinical diagnosis is based on the identification of the Curaçao criteria, classified according to the number of them present, as follows: definite (three or more), possible (two) and improbable (one) (6, 7) (Table 1).

Table 1. Curaçao Criteria

Criteria	Description
Epistaxis	Spontaneous or recurrent
Telangiectasias	Multiple and in characteristic sites: lips, oral cavity, fingers and nose
Visceral lesions	Gastrointestinal telangiectasias, pulmonary, hepatic, cerebral or spinal AVMs
Family history	First degree relative with OWR

Although definitive diagnosis is based on genetic studies, their low availability and high cost have led to the use of imaging methods such as angiography, considered the gold standard for the identification of findings that guide clinical suspicion.

Telangiectasias affecting the nasopharynx cause epistaxis (95%), considered the most common and earliest symptom. The same percentage of patients present telangiectasias in hands, face and oral cavity (8-10). Gastrointestinal involvement (25 %) is more frequent in the stomach and duodenum, manifested by melena and anemia, especially in patients older than 60 years (1, 11); there may be pancreatic involvement in smaller proportion (10-15 %) or splenic (10 %).

Some years ago hepatic findings (8-78%) were considered rare, but with the advent of angiographic techniques by computed axial tomography (CT), their diagnosis is increasingly frequent. It is based on the identification of vascular shunting or vascular malformations which, given the double vascular system of this organ, can be presented and classified into three types:

- Arteriovenous (hepatic artery and suprahepatic vein), causing congestive heart failure (CHF).
- Arterioportal (hepatic artery and portal vein), causing portal hypertension.
- Portovenous (portal vein and suprahepatic vein), less frequent, causing hepatic encephalopathy (7, 11).

In CT the findings that may indicate hepatic involvement are:

1. Mosaic perfusion pattern, poorly defined areas, generally triangular, of high density in arterial phase with respect to the background hepatic parenchyma, which homogenize in venous phase.
2. Telangiectasias - seen as hypervascular nodules in arterial phase smaller than 10 mm, predominantly subcapsular location and low density in venous phase, sometimes they can confluence forming nodules larger than 10 mm, with persistent enhancement in arterial and venous phase.
3. Tortuous dilatation of the hepatic artery in isolation and/or associated with dilatation of its intrahepatic branches.
4. Aneurysms observed as tortuous or saccular fusiform dilatations.
5. Identification of short circuits, which can be arteriovenous (the most frequent) and are seen as filling of the suprahepatic veins in early arterial phase; arterioportal, as filling of the portal vein and its branches in early arterial phase; portovenous (rare), as dilatation of the portal (>13 mm) or one of its branches, with communication towards any of the suprahepatic veins in portal phase (7).

Magnetic resonance imaging (MRI) has the advantage that, apart from evaluating the described findings, it allows determining the affectation of the biliary tract (intra and/or extrahepatic stenosis, segmental dilatation and/or cysts) (7).

All these alterations lead to the so-called pseudocirrhosis, or Osler's cirrhosis, which occurs in 8% of patients (mean age 30 years, more frequently in women) (7). Its genesis lies in three basic alterations: high output CHF (due to increased ventricular filling pressures and pulmonary hypertension), portal hypertension and biliary necrosis (10) (Figure 1).

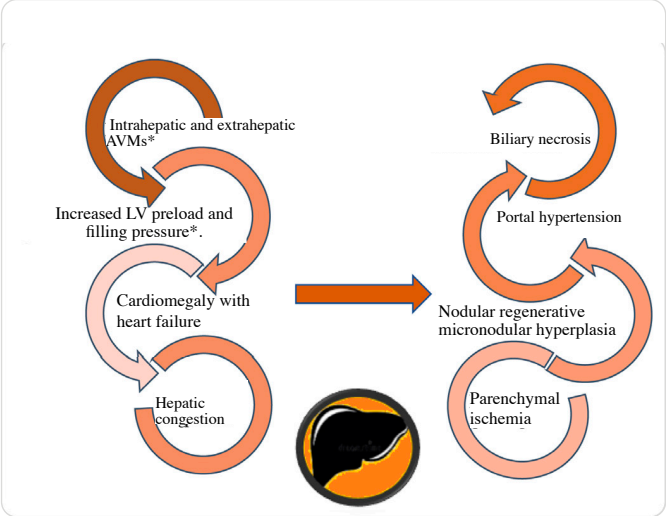


Figure 1. Pathophysiology of liver damage in OWR.
*LV: left ventricle. AVM: arteriovenous malformation.

Pulmonary involvement (20-50 %) presents with isolated AVMs, although most are multiple (60 %) and bilateral, especially in the lower lobes, and cause cyanosis, dyspnea, hypoxemia, hemoptysis, polycythemia, stroke and abscesses, due to the risk of developing paradoxical emboli (2, 7, 10, 11). There may be CT or chest radiographic findings consisting of a circumscribed nodular lesion, variable in shape (round, elliptical or sinuous), which after administration of contrast material show marked enhancement, revealing its vascular origin, and identify a nutrient artery and a draining vein. Pulmonary angiography helps to verify the arterial-venous circuit and to plan embolization.

As for treatment, embolization or surgical resection of AVMs is often necessary; treatment is not recommended in asymptomatic patients with hepatic involvement. In advanced stages with Osler cirrhosis, liver transplantation may be necessary.

Medically, it has been observed that angiogenesis is related to high levels of vascular endothelial growth factor, so that bevacizumab - an immunomodulator against this factor - has shown some efficacy (5); in cases in which medical treatment has failed and the patient is not suitable for transplantation, embolization/ligation of the hepatic artery can be considered as a purely palliative procedure (7).

Case report

Case 1

A 77-year-old male patient with a history of cirrhosis of cardiac origin and OWR since 1996. The following examinations were performed: endoscopy, which reported angioectasia of 1 cm in diameter in the gastric fundus; ileocolonoscopy, which showed angioectasias of less than 5 mm; colonoscopy, with finding of two vascular ectasias of 5 mm in the cecum; capsule endoscopy: diffuse angioectasias, small, limited to the small intestine, not candidates for enteroscopy. The lesions were treated with argon plasma electrocoagulation. Due to intermittent episodes of cognitive impairment related to hepatic encephalopathy, she was put on the waiting list for liver transplantation. She continued with outpatient gastroenterology controls and imaging studies were performed as protocol: hepatic and splenic color Doppler ultrasound

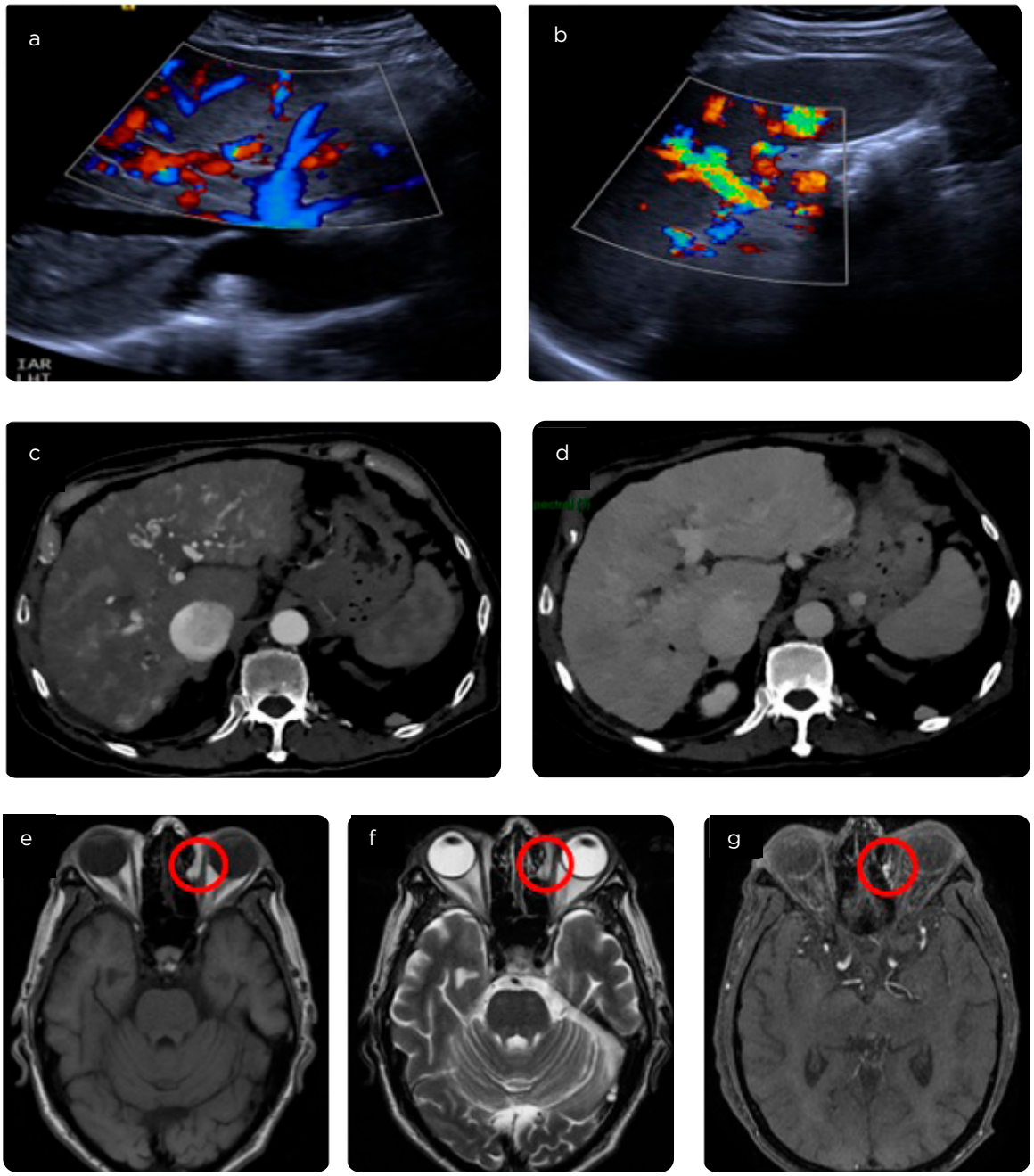


Figure 2. Abdominal USG: heterogeneous hepatic parenchyma due to cirrhosis, at color Doppler a) multiple tortuous vascular structures with erratic direction flow in relation to AVM, b) similar lesions in splenic parenchyma. c and d) Abdominal CT: cirrhosis and hepatic congestion; heterogeneous aspect with heterogeneous enhancement of pseudonodular aspect after administration of contrast medium in relation to its vascular origin. e and f) Brain MRI in sequences with T1 and T2 information: thickening in the lateral wall of the left anterior ethmoidal cells. g) After the contrast medium, enhancement of tortuous vascular structure in relation to AVM.

and CT. He presented episodes of moderate epistaxis, so he underwent an MRI, the finding of which was AVM in the lateral wall of the left anterior ethmoidal cells (figure 2).

Case 2

A 68-year-old female patient with a history of upper gastrointestinal OWR. She underwent endoscopy with findings of four since 2004, episodes of lower gastrointestinal bleeding in 2015 and epistaxis gastric focal areas of angioectasias to which ligation was performed. repeatedly, the last one in 2017. In 2019 she underwent a panendoscopy She was discharged, and in outpatient follow-up she underwent a CT scan that

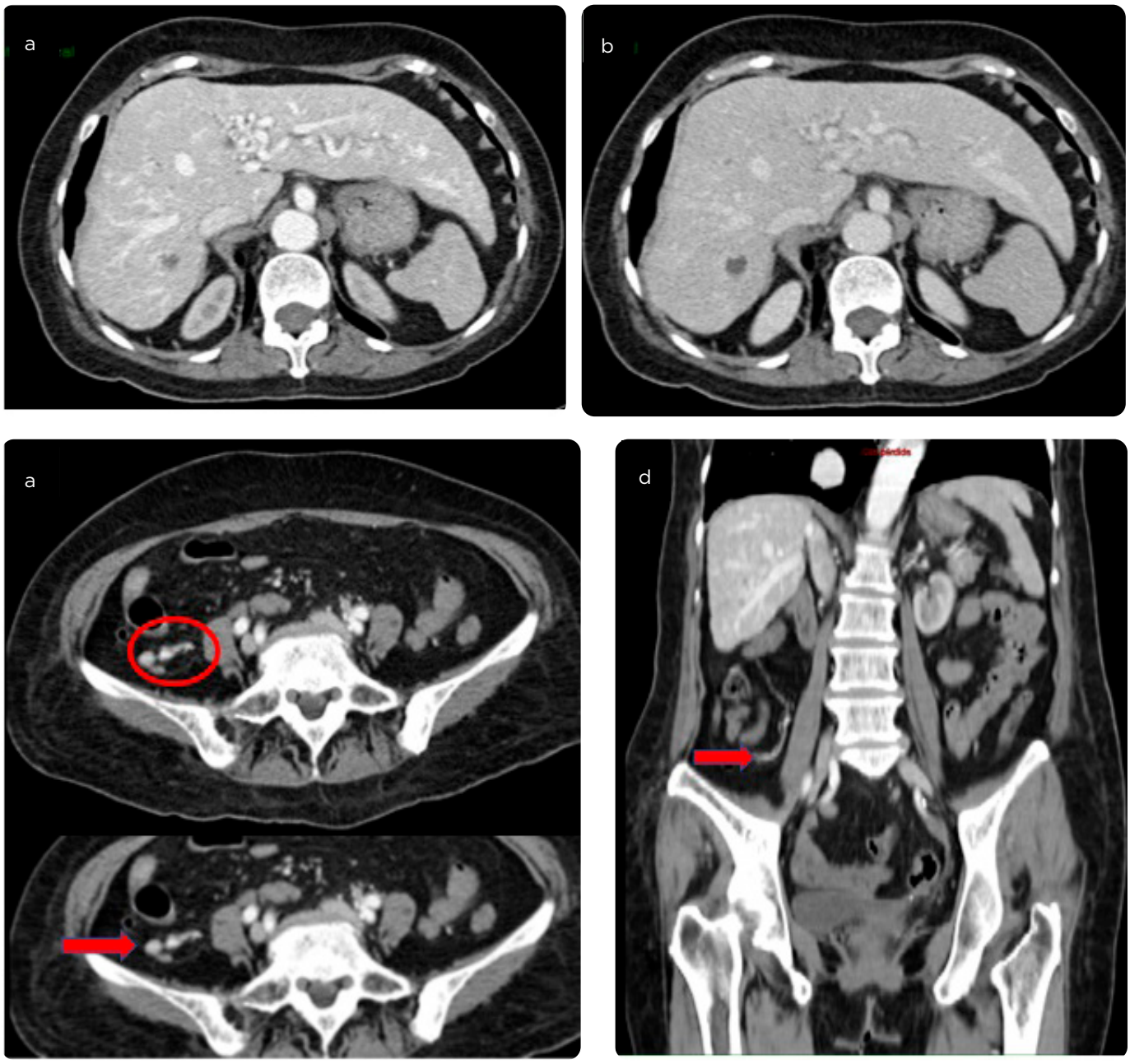


Figure 3. Abdominopelvic CT. a) Liver of heterogeneous density due to tortuous structures with multiple vascular collaterals in left lobe (segment II) identifiable in arterial phase. b) Images suggestive of AVM that persist in venous phase. c) In axial caudal sections in arterial phase, ingurgitation due to vascular dysplasia of the ileocolic artery is identified, finding also visible in coronal reconstruction d).

reported angioectasias in the gastric fundus, body and antrum and where CT scan that identified hepatic and gastrointestinal findings (Figure 3).

Case 3

A 61-year-old female patient diagnosed with OWR, who presented with pulmonary AVM previously treated with coils in 2011. She was re-evaluated for dyspnea, holosystolic murmur, desaturation and acrocyanosis. Transthoracic echocardiography showed images compatible with intrapulmonary shunt, due to recurrence of AVM (Figure 4). He was reintervened with Amplatzer vascular plug vascular occlusion devices in 2019 with resolution of shunt. She has presented with multiple episodes of epistaxis associated with heat or cold. An endoscopy taken in 2011 demonstrated mild gastric and duodenal angiodysplasias. At



Figure 4. CT angiography. a) Pulmonary arteries axial sections in pulmonary window, and b) soft tissues: arteriovenous fistula in superior segment of the lingula that depends on its segmental-subsegmental arterial branch with two venous drainage tracts (caliber up to 9 mm) that flow into the ipsilateral superior pulmonary vein. c) Selective angiography: embolizing material in the communication site, with partial opacification due to permeability. d) Abdominal CAT scan axial sections in arterial phase, and e) venous: serpentiginous and irregular linear areas in the hepatic segments IV-V-VII dependent on portal and venous tracts.

outpatient follow-up, an abdominal CT scan was taken with hepatic findings (Figure 4).

Discussion

All patients met the diagnostic criteria in force since 1999 for OWR, known as Curaçao criteria; they had presented at some point in their evolution epistaxis, considered the most frequent and initial symptom of the pathology; gastrointestinal, hepatic, splenic, pulmonary and paranasal sinus vascular anomalies were identified by endoscopic studies or imaging methods (USG, CT and MRI).

Although the literature describes them as common, no central nervous system (CNS) findings were documented (Table 2). The treatment of these patients was symptomatic treatment of the hemorrhage, together with prevention of possible complications by resection or sclerosis of the AVMs.

To reduce the embolic risk presented by pulmonary lesions larger than 3 mm in diameter, they should be embolized by interventional radiology, with close follow-up due to the increase in size or repermeabilization that may occur over time, as in the case of the third patient.

Table 2. Organs or systems with documented involvement

Organ or systems	Patients
Gastrointestinal (stomach, small and large intestines)	3
Liver	3
Spleen	1
Paranasal sinuses	1
Lung	1
100% of the patients presented epistaxis at some time during the pathological evolution	

Conclusion

When OWR is suspected, imaging studies allow the identification of VD in different organs and systems, which together with the clinical criteria of Curaçao help to establish an accurate and timely diagnosis. Likewise, diagnostic images help in the close follow-up of the disease for the prevention and management of complications, not only local, such as hemorrhage, but also systemic, such as cardiac and hepatic failure, which are determinant in the prognosis and survival of these patients.

References

1. Lidia Duque E, Nguyen Castro G, José Larquin C. Enfermedad de Rendu Osler Weber: presentación de un caso. Rev. Arch Med Camagüey. 2016;20(6).
2. Wirsching KEC, Kühnel TS. Update on clinical strategies in hereditary hemorrhagic telangiectasia from an ENT point of view. Clin Exp Otorhinolaryngol. 2017;10:153-7.
3. Orizaga-y-Quiroga TL, Villarreal-Martínez A, Jaramillo-Moreno G, Ocampo-Candiani J. Síndrome de Osler-Weber-Rendu y su relación con la dermatología. Actas Dermosifiliogr (Engl Ed). 2019;110(7):526-32. https://doi.org/10.1016/j.ad.2018.11.007
4. Bustamante F, Picón OT, Tenreiro A, Bustamante E. Síndrome de Rendu-Osler-Weber: presentación de un caso clínico. Avances en Biomedicina. 2016;5(2):104-10.
5. Lerut J, European Liver Transplant Association. Liver transplantation for hereditary hemorrhagic telangiectasia: Report of the European liver transplant registry. Ann Surg. 2016;244:854-62.
6. Sandoval DK, García E, Ramírez S, Torres KJ, Velandia MC, Villamizar JF, et al. Síndrome de Rendu Osler Weber en una adolescente en Colombia. Reporte de un caso de autopsia. Biosalud. 2018;17(1):83-9.
7. Quesada SG, Rodríguez AL, Domínguez M. Enfermedad de Rendu Osler Weber aproximación diagnóstica mediante TC y RM. Presentación Electrónica Educativa. Sociedad Española de Radiología Médica.
8. Cherem-Kibrit M, da Silva P, de la Vega G F, Gutiérrez R. Síndrome Osler-Weber-Rendu. Manejo endoscópico de un sangrado inusual. Endoscopia. 2021;32(2).
9. Kühnel T, Wirsching K, Wohlgemuth W, Chavan A, Evert K, Vielsmeier V. Hereditary hemorrhagic telangiectasia. Otolaryngol Clin North Am. 2018;51(1):237-54.
10. Bernardes C, Santos S, Loureiro R, Borges V, Ramos G. Bevacizumab for refractory gastrointestinal bleeding in Rendu-Osler-Weber disease. GE Port J Gastroenterol. 2018;25(2):91-5.
11. Ferri F, Ferri H. Osler-Weber-Rendu Syndrome. En: Ferri F, Ferri H. 2018 Ferri's Clinical Advisor. Elsevier; 2018.

Correspondence

Neftalí Alexander Granados Flores
Departamento de Radiología "Adán Pitol Croda"
Instituto Nacional de Ciencias Médicas y Nutrición (INCMNSZ)
Calle Huastecos 3, Pedregal de las Águilas Tlalpan, Ciudad de México
neftaligranados.dr@gmail.com

Received for evaluation: December 15, 2022
Accepted for publication: March 26, 2023