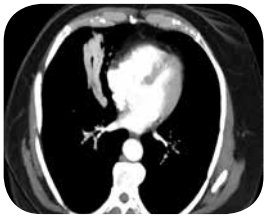

Diagnosis and Endovascular Treatment of Pulmonary and Hepatic Arteriovenous Malformations in Adult Patients with Hereditary Hemorrhagic Telangiectasia

Diagnóstico y tratamiento endovascular de las malformaciones arteriovenosas pulmonares y hepáticas en pacientes adultos con telangiectasia hemorrágica hereditaria

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Summary

Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome (ROWS) is an autosomal dominant vascular dysplasia with variable penetrance, characterized by arteriovenous malformations and mucocutaneous telangiectasias. The current diagnosis and prognosis is oriented to the early identification of risk factors, signs and symptoms, as well as in the recognition and characterization of vascular malformations in the different organs that are involved by the disease. The application of percutaneous techniques by an interventional radiology team is part of the approach in the treatment of patients with confirmation of arteriovenous malformations in lung and liver, such as in the cases that will be exposed in this revision. These treatment techniques have achieved the curative or palliative control of the different complications that could be generated by the different malformations.

Resumen

La telangiectasia hemorrágica hereditaria (THH) o síndrome de Rendu-Osler-Weber (SROW) es una displasia vascular autosómica dominante con penetrancia variable, caracterizada por malformaciones arteriovenosas y telangiectasias mucocutáneas. Actualmente, el diagnóstico y pronóstico está orientado a la identificación temprana de factores de riesgo, signos y síntomas, así como en el reconocimiento e identificación de las malformaciones vasculares en los diferentes órganos que se ven afectados por la enfermedad. La aplicación de técnicas percutáneas, por parte de un equipo de radiología intervencionista, hace parte del abordaje en el tratamiento de los pacientes a quienes se les han confirmado malformaciones arteriovenosas en pulmón e hígado, como en los casos que se expondrán en esta revisión. Con estas técnicas de tratamiento se ha logrado curar o paliar las complicaciones que se pudieran generar por las diferentes malformaciones.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is typically characterized by the triad of multiple telangiectasias, recurrent epistaxis, and family history (1-4). The disease originates from a mutation that leads to the formation of multiple arteriovenous malformations in the skin and mucous membranes, as well as in different organs, mainly described in the lung, liver and brain (5,6). The diagnosis and current treatment of the disease is interdisciplinary, and the general and interventional radiologists have a decisive role in the identification, evaluation and definitive treatment.

1. General vision of the disease

HHT is a genetic disorder that is characterized mainly by telangiectasias in skin and mucous membranes associated with the appearance of multiple

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visceral vascular malformations of high flow, caused by mutations of proteins involved in processes of angiogenesis, proliferation, differentiation and cell migration (7-9).

It has an estimated prevalence of 10-20 cases per 100,000 inhabitants, mainly affects white individuals and has no sex differences (10-12). However, more recent studies have reported an increase in the prevalence of 1 among 5,000-8,000 inhabitants (13).

Its pathophysiology follows several stages, beginning with the focal dilation of postcapillary venules surrounded by a mononuclear leukocyte infiltrate. These vessels continue to increase in size at the expense of their diameter and thickness of the wall, until they acquire their characteristic tortuosity and connection through capillaries with dilated arterioles. Subsequently, these capillaries will disappear leading to direct arteriovenous communication, this being larger in arteriovenous malformations (14-16).

Since 2000, the Curaçao criteria, published in 2009, were established as the diagnostic criteria of the HHT. Currently there are no clinical studies that validate these criteria. Experts agree that they are particularly useful in the discrimination of affected and unaffected older adults, and in ruling out the diagnosis in young adults.

The Curaçao criteria take into account the following clinical and imaging findings:

- Spontaneous and recurrent epistaxis.
- Multiple telangiectasias in characteristic sites, such as lips, oral cavity, fingers, nose.
- Visceral vascular malformations, such as telangiectasias or gastrointestinal, pulmonary, hepatic, cerebral or spinal arteriovenous malformations.
- Family history in the first degree with the disease according to the above criteria.

A definitive diagnosis of HHT is considered when three or more criteria are met; possible when two criteria are met and unlikely when less than two criteria are met (17-19).

2. Diagnosis and treatment of pulmonary arteriovenous malformations

Arteriovenous malformations are the most common pattern of pulmonary involvement in HHT, with an appearance rate between 15-50% of cases and are considered as a marker of the disease (20-23).

The conformation of the arteriovenous malformation consists of an afferent artery, arteriovenous communication and an efferent vein. The role of the radiologist is to perform an adequate anatomical description to determine the type of approach and planning of endovascular treatment (24-27).

The afferent vessel can be single or multiple, short or long and usually comes from the pulmonary circulation; although in some cases it can vary and come from the systemic circulation by bronchial or intercostal branches. The arteriovenous communication can be seen as an aneurysmal sac, a serpentiginous vascular network or tortuous and dilated communications between the artery and the vein, an important finding taking into account the risk of accidental migration of the device and embolization to left cavities. Its single or multiple efferent portion usually has communication with the pulmonary veins or their branches, or it may have direct connection with the inferior vena cava or even with the left atrium (28,29).

According to its angiographic aspect, malformations can be classified as simple and complex. The first show an afferent artery originating in a single segment of the pulmonary artery, which feeds through a smooth aneurysmal communication to a single pulmonary drainage vein. The second type has multiple afferent arteries that originate from several segmental arteries and feed several drainage veins through septate aneurysmal communication or small vessels (30-32).

It has been observed that arteriovenous malformations are multiple and, although they appear throughout the lung, they predominate in their bases; however, it has been possible to establish two predominant types of pulmonary distribution, one discrete and the other diffuse.

The most relevant is the diffuse pattern, of which multiple definitions have been proposed and in function of unifying concepts, the clinical classification divides it into:

- Subsegmental diffuse: it has compromise of each subsegmental artery of at least one lobe.
- Segmental diffuse: it has commitment of each segmental artery of at least one lobe
- Mixed segmental / subsegmental: it is a combination of segmental and subsegmental arteries compromise of at least one lobe.

It is important to identify the predominant pattern, given that complications are more frequent in diffuse patterns, specifically in the diffuse subsegmental pattern, and a neurological morbidity that reaches up to 70% has been reported (33,34).

The diagnosis of pulmonary involvement due to the disease can begin with a chest X-ray, which has limited sensitivity for the detection of vascular lesions, particularly the smallest ones; However, arteriovenous (AV) malformations can be observed as well-circumscribed, rounded, lobulated, non-calcified lesions with band-shaped shadows, which are the reflection of the ramifications of afferent vessels and dilated drainage vessels (35).

Currently, chest tomography and transthoracic echocardiography with contrast medium are the diagnostic tools of choice that allow optimal screening and evaluation.

Transthoracic echocardiography with contrast medium is a minimally invasive technique with high sensitivity (97%) and high negative predictive value (99%). The objective is to observe the location of microbubbles in the cardiac cavities after the intravenous injection of agitated saline solution, so if they are observed immediately, it suggests an intracardiac short circuit; but if they appear after 2 to 5 heartbeats, suggests a pulmonary shunt from right to left. In general, a test that shows bubbles in the left atrium is considered positive.

Historically, pulmonary angiography had the gold standard for the diagnosis of pulmonary vascular malformations. Currently, computed tomography (CT) of the chest is preferred with contrast medium as the gold standard, given the advantages it provides in terms of high anatomical resolution, precise localization, definition of the type of malformation and because of its usefulness in planning the embolization,

follow-up of reperfusion and growth of lesions, a frequent finding in these patients. Additionally, it is useful in the detection of subphrenic, hepatic and / or pancreatic visceral involvement (36).

For the endovascular treatment of pulmonary vascular malformations, the use of transcatheter embolization is recommended, as it has demonstrated its efficacy and high safety profile with a low rate of complications.

The indication for performing treatment using this technique is based on the diameter of the afferent artery, which should be ≥ 3 mm. However, embolization of the 2-mm arteries must be evaluated in each particular case and may be appropriate given similar outcomes to larger ones, according to experts' opinion (37,38).

Likewise, it is recommended the follow-up of patients who underwent the procedure with chest CT, in order to detect the reperfusion, growth or new appearance of pulmonary arteriovenous malformations, as well as to verify the success of the endovascular therapy evaluated by the location of the afferent artery distal to the aneurysmal sac and the position of the microspirals, indicating a complete retraction of the embolized malformation (39,40).

It is recommended that follow-up with CT be between 6 and 12 months after embolization and then every 3 years; however, for patients in whom the distribution pattern of diffuse subsegmental vascular lesions was identified, their follow-up must be annual.

Among the complications due to transcatheter embolization, device migration, air embolism, stroke, pulmonary infarction and hemoptysis should be considered, all related to malformations and observed during a follow-up of 5 to 10 years (41,42).

In our hospital we have had experience in the diagnosis and treatment of this type of patients, so we studied the case of a female patient of 65 years of age, to whom, as an incidental diagnosis, pulmonary arteriovenous malformation with subsequent molecular diagnosis of HHT was found. Upon physical examination, she only showed desaturation in the ambient air. She did not report dyspnea and had no relevant history. The diagnosis was made by scanography (Figure 1).

She underwent endovascular treatment, to which her blood oxygen saturation was increased, from 75% before entering the procedure to 93% on the first day postprocedure and in the subsequent evaluation in 3 and 6 months (Figure 2).

3. Diagnosis and treatment of hepatic arteriovenous malformations

Liver involvement due to HHT syndrome is due to a wide spectrum of vascular malformations, ranging from small telangiectasias to large arteriovenous malformations. Vascular malformations appear in 32% to 78% of patients with HHT, but only approximately 8% of cases are symptomatic (43,44).

The currently known intrahepatic malformations were grouped into three types of short circuits:

» Short circuit hepatic artery to hepatic veins, known as arteriosystemic.

» Short circuit hepatic artery to portal vein, proper description of the arterioportal short circuit.

» Portosystemic short circuit, characterized by a communication between the portal vein and the hepatic vein or the inferior vena cava.

The clinical manifestation is variable. Among its possibilities there can be high-spending heart failure with symptoms of dyspnea on exertion, ascites and edema, as in the case of arteriosystemic-type shunts; with portal hypertension and risk of varicose hemorrhage, corresponding to the presentation of arterioportal shunts; and other less frequent ones, such as biliary ischemia, pseudocirrosis with nodular transformation of the hepatic parenchyma without fibrous septa, focal nodular hyperplasia, hepatic encephalopathy and abdominal angina resulting from mesenteric ischemia, by steal through the hepatic artery (45,46).

Within the modalities available for the diagnosis of hepatic involvement due to the disease is ultrasound in its Doppler modality, which has advantages in the evaluation of the artery caliber, the pattern and spectral flow analysis, though it is a technique that needs of an optimal examiner's training.

Therefore, it is useful that from the beginning patients are classified according to severity, in order to help in making therapeutic decisions (47-49). The severity can be determined with Doppler ultrasound as shown in Table 1.

Table 1. Gravity scale of hepatic vascular malformations in hereditary hemorrhagic telangiectasia

Level	Criteria
0+	• Diameter of HA> 5 but <6 mm, and / or • VPF> 80 cm / s, and / or • RI <0.55, and / or • Peripheral hepatic hypervascularization
1	• Dilation of HA, only extrahepatic> 6 mm, and • VPF> 80 cm / s, and / or • RI <0.55
2	• Dilation of HA, extra and intrahepatic (double channel sign) and • VPF> 80 cm / s • Possibly associated with moderate abnormality of hepatic and / or portal vein flow.
3	• Complex changes in the hepatic artery and its branches (tortuous and entangled) with marked flow abnormalities associated with: - Moderate dilation of the hepatic and/or portal veins, and/or - Abnormality of hepatic and/or portal vein flow
4	• Decompensation of arteriovenous shunt, such as: - Marked dilation of the hepatic and/or portal vein. - Marked flow abnormalities in both arteries and veins.

Abbreviations: HA: hepatic artery; RI: resistance index; VPF: velocity of portal venous flow.
Source: Taken and translated from Searchini et al. (50).

CT of the abdomen allows the detection of malformations in 67-74% of the cases, which can be classified according to size, for example, in the large ones a marked and early enhancement of the portal system can be found during the arterial phase, while in the small ones, a wedge-shaped peripheral hepatic area with increased attenuation can be observed, associated with an early portal filling in the arterial phase followed by normalization in the portal phase attenuation (51-53).

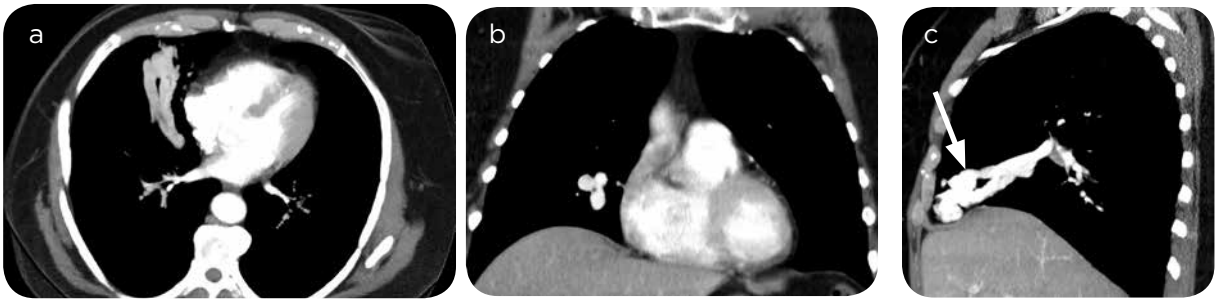

Figure 1. Chest scan with contrast medium. a) Axial with MIP reconstructions, b) coronal reconstruction, c) sagittal reconstruction (arrow). Large arteriovenous pulmonary malformation, located in the middle lobe.

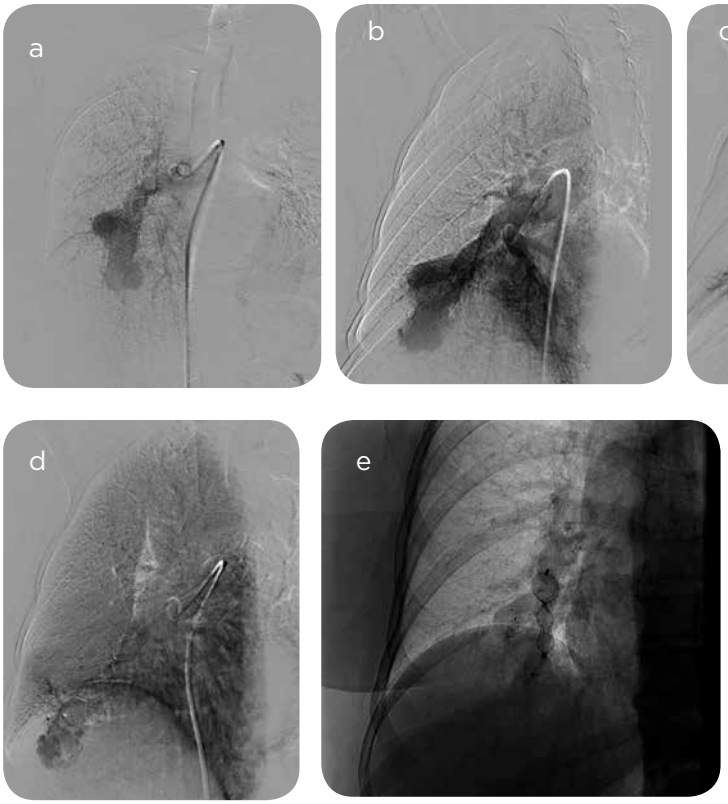

Figure 2. Images of pulmonary arteriography and occlusion of vascular malformation. Angiography images with digital subtraction. a) Preliminary image: the vascular malformation in the middle lobe is identified. b-d) Sequence of the endovascular treatment with placement of the Amplatzer type II device initially, and type IV in the artery of lesser contribution, with their respective satisfactory angiographic controls. e) Final control image: the occlusion devices are observed.

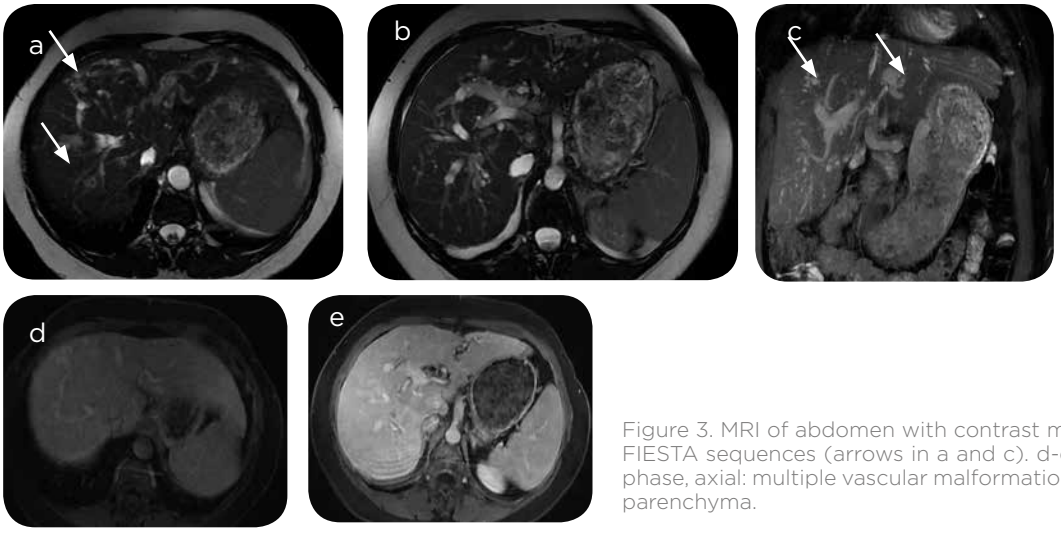

Figure 3. MRI of abdomen with contrast medium. a-c) axial and coronal FIESTA sequences (arrows in a and c). d-e) T1 + Gd dynamic in arterial phase, axial: multiple vascular malformations are observed in the hepatic parenchyma.

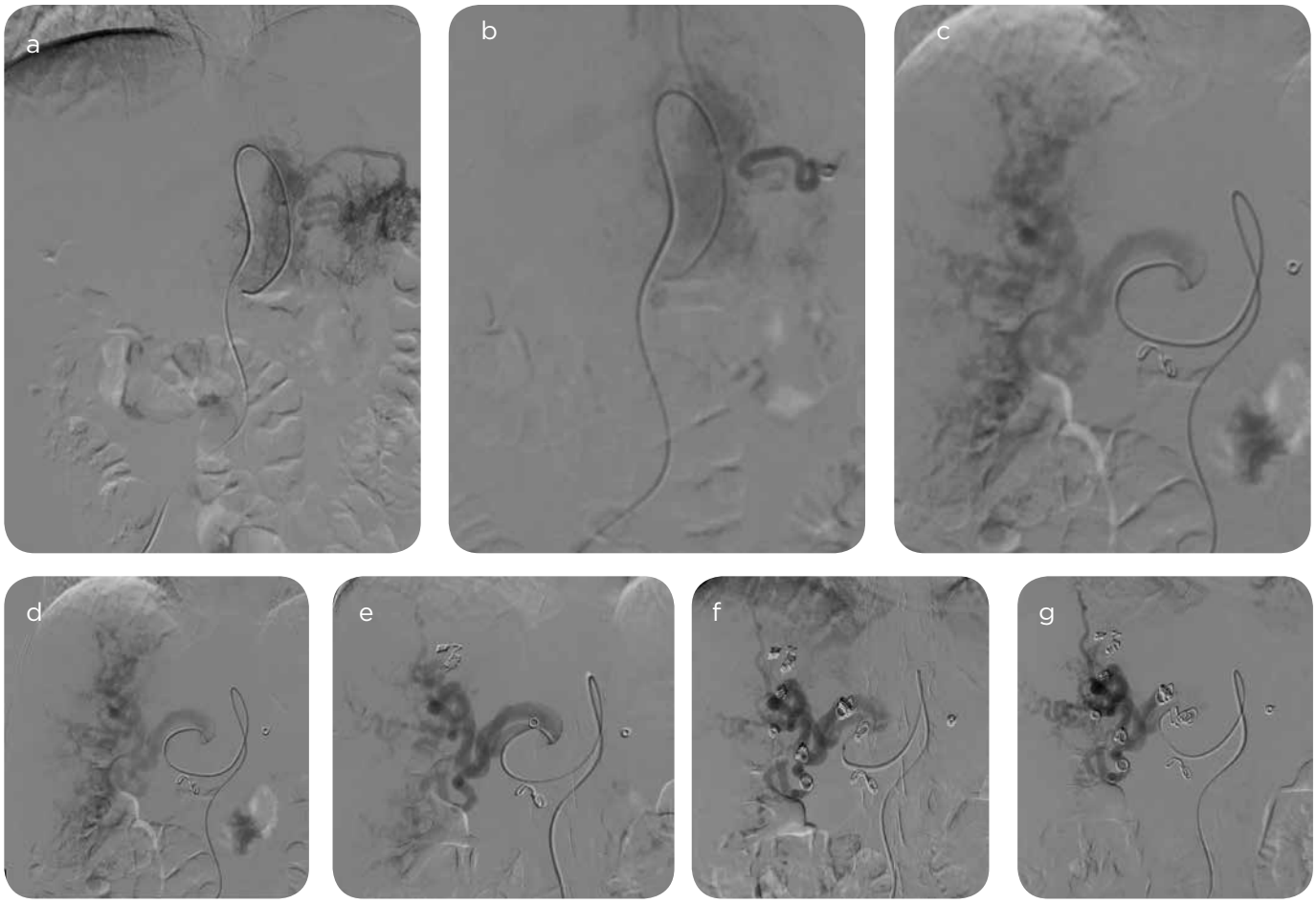

Figure 4. Hepatic arteriography. Angiography images with digital subtraction. Multiple vascular malformations are observed. Endovascular treatment and selective embolizations with 32 metallic spirals and the angiographic controls after the placement of these.

Depending on the type, hepatic arteriovenous malformations can be arterioportal short circuits, which are typically subcapsular, with early and prolonged enhancement of the portal vessels during the early arterial phase, a feature that under normal conditions does not occur. You can also find dilations of the hepatic artery and the portal vein associated with collateral vessels and splenomegaly.

In another type of short circuit, such as arteriosystemic, it has been seen that they can be isolated and / or associated with the arterioportal type, and their findings by scanning include simultaneous opacification of the hepatic artery and veins during the early arterial phase. Finally, the short circuits that represent a greater challenge for the radiologist are those of portosystemic type, due to the subtlety of the findings in the portal and venous phases. During the portal-venous phase, the dilated portal veins are in communication with a hepatic or systemic vein, or the dilated hepatic artery can also be visualized, either with dilatations of the hepatic or portal veins; or the presence of large confluent vascular masses (54-57).

Selective angiography of the hepatic artery has traditionally been considered the gold standard; it is an invasive diagnostic technique, so it is currently less used for diagnosis; nevertheless, angiographic studies allow the recognition of the characteristic features of the vascular malformations of the syndrome, within which the enlargement of the hepatic artery and its ramification to a dilatation with disseminated intrahepatic telangiectases and arteriovenous communications have been described, or also, other vascular abnormalities can be observed in the other hepatic and collateral vessels; as a stenosis of the celiac trunk and the splenic artery, and malformations in the mesenteric arteries, and even in the right renal artery. It should be remembered that the portosystemic type circuits are angiographically hidden lesions.

MR angiography allows the visualization of the map of anomalous vessels; however, it can be said that the findings found are similar to those obtained with tomographic studies (58).

The only treatment considered as curative for patients with liver involvement by HHT is orthotopic liver transplantation. The main indications for carrying it out include ischemic biliary necrosis and high-spending heart failure and intractable portal hypertension. Although favorable results have been obtained in the majority of transplant patients, the reported postoperative mortality can not be ignored in the long term, given that it reaches up to 10% in these patients (59,60).

The other available therapeutic options are only recommended for symptomatic patients with HHT 3 and 4 on the gravity scale by Doppler ultrasound and for those with liver involvement.

For patients with complicated hepatic vascular malformations, who do not respond to intensive medical treatment, who present a progressive worsening of their baseline clinical status or who are not candidates for liver transplantation, invasive palliative treatments have been proposed, such as transarterial embolization of arteriovenous fistulas. hepatic The above procedure should be used with caution, due to the risk of fatal outcomes or development of post-embolization complications and should be avoided in patients with biliary signs and / or symptoms (61,62).

In our hospital we had a female patient of 62 years of age, with HHT and hepatic manifestation, who was documented an arterioportal fistula, with hepatopetal flow and discrete splenomegaly (Figure 3).

Given the imaging findings and pathological history, the patient underwent endovascular treatment (Figure 4).

5. Conclusions

In recent years, the quality and life expectancy of patients with HHT syndrome has improved significantly thanks to the multidisciplinary approach to which they have been subjected, which allows a better understanding and treatment of the disease. Its approach includes, among other important points, an adequate assessment by diagnostic and interventional radiologists, who will contribute not only to the adequate diagnosis of visceral compromise, but also to the possibility of performing minimally invasive treatments; methods that will involve an important part of the definitive and / or palliative treatment of arteriovenous malformations in different organs.

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