A Case of Hereditary Hemorrhagic Telangiectasia Presenting with Asymptomatic Liver Lesions and a History of Early-onset Myocardial Infarction and Multiple Intracranial Aneurysms

Maki Sakuma¹, Takeshi Inagaki¹, Reiko Arakawa²,³, Norihiro Kato²,³ and Takashi Okafuji⁴

Abstract:
Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder of the vasculature, characterized by epistaxis, telangiectasia and arteriovenous malformations in multiple organs. We herein report a 49-year-old woman with a history of early-onset myocardial infarction and intracranial aneurysms, in whom we incidentally detected multiple hepatic vascular abnormalities. We subsequently diagnosed her with HHT after discovering gastrointestinal telangiectases and a pulmonary arteriovenous fistula along with a history of recurrent epistaxis. Whole-exome sequencing revealed a novel pathogenic variant in SMAD4, a relatively rare causative gene for HHT. This case highlights the fact that HHT patients may present with asymptomatic liver lesions.

Key words: hereditary hemorrhagic telangiectasia, Osler-Rendu-Weber disease, intrahepatic shunts, myocardial infarction, intracranial aneurysms, SMAD4

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Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder diagnosed when at least three of the four Curaçaó criteria are satisfied: epistaxis; mucocutaneous telangiectasia at characteristic sites such as lips, oral cavity, fingers or nose; visceral lesions such as telangiectases or arteriovenous malformations (AVMs) in the gastrointestinal tract, liver, lungs, brain or spinal cord; and a family history of HHT (1). Most patients with a clinical diagnosis of HHT show a pathogenic variant identifiable in the ENG, ACVRL1(ALK1), or (less frequently) SMAD4 genes (1).

The diagnosis of HHT may be difficult, as the symptoms are non-specific and age-dependent. Asymptomatic liver lesions of HHT are particularly challenging cues to a diagnosis, as benign lesions often depend on radiological interpretation alone, which may lead to a suspected diagnosis of such vascular abnormalities as atypical hemangiomas or peliosis hepatis, among others.

We herein report a case of HHT presenting with multiple asymptomatic liver lesions with a history of early-onset acute myocardial infarction (MI) and two intracranial aneurysms, confirmed to have a pathogenic variant in SMAD4.

Case Report

A 49-year-old woman was referred to our hospital following an incidental finding of a low-density area on computed tomography (CT) of the liver suspected to represent peliosis hepatis. She had a history of acute MI treated with percutaneous coronary intervention at 49 years old and had a large left internal carotid aneurysm and right middle cerebral artery aneurysm that had been treated at 45 years old. Her blood count was within normal limits, and no elevation in
Contrast agent-enhanced CT and magnetic resonance imaging (MRI) revealed an early and persistently enhancing hypervascular nodule in S7, as well as multiple telangiectases and early enhancing portal and hepatic veins, indicating arteriportal and arteriovenous shunts respectively (Fig. 1). We found no signs of portal hypertension, including portosystemic venous shunts or splenomegaly, but the portal vein was dilated. The nodule in S7 was initially interpreted as a variant of peliosis hepatis. Follow-up ultrasound showed no marked increase in the size of the nodule.

One year later, the patient was referred to us again with anemia (hemoglobin [Hb], 6.0 g/dL). Gastrointestinal endoscopy showed negative findings, but capsule endoscopy identified multiple angiodysplasias in the small intestine. Double-balloon endoscopy was scheduled but not conducted, as the anemia improved, and the lesion was not hemorrhagic at the time of treatment. After another 2 years, anemia recurred (Hb, 8.9 g/dL), and gastric angiodysplasias were discovered on endoscopy (Fig. 2a). The lesion was treated with argon plasma coagulation. The presence of multiple arteriovenous abnormalities raised the possibility of hereditary
hemosiderotic telangiectasia (HHT). Several years later, a small pulmonary arteriovenous fistula (AVF) (Fig. 2b) was incidentally discovered, heightening the suspicion of HHT.

Detailed inquiries revealed that she had experienced recurrent spontaneous epistaxis beginning in her teens. No telangiectasia of the skin was evident, and she showed no family history related to HHT aside from the sudden death of her mother from an unknown cause when she was 29 years old. Her 2 children, at 26 and 30 years old, had not experienced any episodes of recurrent epistaxis.

The patient satisfied two of the Curaçao criteria: epistaxis; the presence of visceral lesions—gastrointestinal telangiectases, pulmonary AVF and hepatic telangiectases—which amounted to a diagnosis of “probable HHT”. To help establish a definitive diagnosis, whole-exome sequencing was performed. A novel pathogenic mutation in SMAD4 (NM_005359.6:c.486dupT (NP_005350.1:p.Val163Cysfs*3)) was identified, representing a single-nucleotide insertion in exon 4 at genomic locus GRCh37.Chr18:48581182. This insertion resulted in nonsense-mediated decay of the transcript. No pathogenic mutations were seen in ENG or ALK1.

The pulmonary AVF showed a feeding artery 1.5 mm in diameter, for which embolization was considered unnecessary. Echocardiography did not show any cardiac overload due to liver shunt. We contacted the hospital conducting the follow-up of the intracranial aneurysms and confirmed that she did not have cerebral AVMs. Since an SMAD4 mutation can cause juvenile polyposis and colon cancer (1), gastrointestinal endoscopy was performed, but the result was negative. We contacted the hospital in which her MI had been treated to investigate whether or not the MI was related to HHT and were informed that the occluded coronary artery seemed neither atherosclerotic nor embolic. The cause of MI appeared young and has a high penetrance, but the symptom is non-specific and fluctuates in severity. Gastrointestinal angioectases are also not very specific, as age-related an-giodysplasia appears identical on endoscopy (2). The relatively specific visceral lesions are often asymptomatic. When found, suspicion of HHT is relatively straightforward in cases of cerebral and pulmonary arteriovenous malformations, but the liver lesions are more difficult to interpret radiologically without prior knowledge of the diagnosis, just as the initial radiological interpretation of our case was peliosis hepatis.

Our case was unique in that the patient presented with an asymptomatic liver lesion are likely to pose a diagnostic challenge. The liver lesion in our patient was described as a hypervascular nodule in the presence of multiple telangiectases and early enhancing portal and hepatic veins, indicating arterioportal and arteriovenous shunts respectively in a non-cirrhotic liver. In HHT, nodular lesions >10 mm in size can develop after the coalescence of multiple telangiectases, termed “large confluent vascular mass”, and intrahepatic shunts (mostly arterio-portal and arterio-venous shunts) may also exist (3, 4). The liver radiology in our case was consistent with HHT, but the differential diagnoses included atypical hemangioma accompanying arterio-portal shunts as well as peliosis hepatitis, a rare condition characterized by blood-filled cavities distributed in the liver parenchyma. HHT may complicate peliosis hepatitis, as described in one case report (5). The radiological characteristics of possible HHT liver lesions and peliosis hepatitis are shown in Table 2 (3-5). In cases where the liver findings are indeterminate, clarifying the history of epistaxis and family history would be valuable, and if such a history is negative, contrast agent-enhanced chest CT may be able to detect pulmonary AVM/AVFs, which would support the diagnosis.

Table 1. Age Dependency of the Manifestations of HHT.

<table>
<thead>
<tr>
<th>HHT manifestation</th>
<th>frequency</th>
<th>common onset/development</th>
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<tbody>
<tr>
<td>Epistaxis</td>
<td>90%-97%</td>
<td>before 20</td>
</tr>
<tr>
<td>Skin telangiectasia</td>
<td>80%</td>
<td>before 30</td>
</tr>
<tr>
<td>Gastrointestinal telangiectasia</td>
<td>15%-30%</td>
<td>fifth decade</td>
</tr>
<tr>
<td>Pulmonary AVM</td>
<td>50%</td>
<td>puberty</td>
</tr>
<tr>
<td>Cerebral AVM</td>
<td>50%</td>
<td>childhood</td>
</tr>
<tr>
<td>Hepatic AVM</td>
<td>30%-70%</td>
<td>fifth decade/poorly documented</td>
</tr>
</tbody>
</table>

HHT: hereditary hemorrhagic telangiectasia, AVM: arteriovenous malformation

Our patient was referred on suspicion of peliosis hepatitis with a history of multiple vascular diseases without identifiable risk factors. She subsequently demonstrated gastrointestinal angioectases and pulmonary arteriovenous fistula. Although she only satisfied two of the diagnostic Curaçao criteria, the multiplicity of vascular abnormalities justified exome sequencing, which identified a novel SMAD4 pathogenic variant.

The diagnosis of HHT may be difficult for several reasons. The age-dependency of manifestations as summarized in Table 1 is a major feature of the disease that hinders an early diagnosis (1). Spontaneous and recurrent epistaxis appears young and has a high penetrance, but the symptom is non-specific and fluctuates in severity. Gastrointestinal angioectases are also not very specific, as age-related angiodysplasia appears identical on endoscopy (2). The relatively specific visceral lesions are often asymptomatic. When found, suspicion of HHT is relatively straightforward in cases of cerebral and pulmonary arteriovenous malformations, but the liver lesions are more difficult to interpret radiologically without prior knowledge of the diagnosis, just as the initial radiological interpretation of our case was peliosis hepatitis.

Discussion

Our patient was referred on suspicion of peliosis hepatitis with a history of multiple vascular diseases without identifiable risk factors. She subsequently demonstrated gastrointestinal angioectases and pulmonary arteriovenous fistula. Although she only satisfied two of the diagnostic Curaçao criteria, the multiplicity of vascular abnormalities justified exome sequencing, which identified a novel SMAD4 pathogenic variant.

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Our case was unique in that the patient presented with a history of early-onset MI and multiple intracranial aneurysms, which seemed out of the ordinary. Some epidemiological studies have shown an elevated incidence of arterial
aneurysms and dissections in HHT patients, especially with SMAD4 pathogenic variants (6), suggesting a propensity for HHT patients to develop vascular disorders other than AVMs and telangiectases. We summarize the evidence of the two conditions below.

**MI**

HHT patients are estimated to develop MI at a frequency of 0.9% (7), which is lower than the value in the general population. However, HHT patients may be at an increased risk of early-onset nonatherosclerotic MI through two HHT-related mechanisms. First, a retrospective study showed an increased incidence of SCAD among HHT patients (7). Second, embolic MI secondary to pulmonary AVMs has been described in case reports (8).

**Intracranial aneurysms**

Ishii et al. summarized 11 patients with HHT who showed concurrent intracranial aneurysms (9), and in an attempt to characterize connective tissue disorders in SMAD4-positive HHT patients, Wain et al. (6) reported brain aneurysms in 3% (1/34).

The literature does not provide strong evidence that a causal relationship exists between MI and intracranial aneurysm, but a genetic background of HHT, especially SMAD4, may reasonably be considered to impair the structure of the arteries. We believe that considering HHT as a differential diagnosis for vascular lesions of unknown origin is wise.

HHT has a prevalence of 1 in 5000 and is considered a rare and underdiagnosed disease with a higher mortality rate than seen in the general population (10). However, diagnosed patients who are appropriately screened for comorbidities and managed using up-to-date guidelines do not show marked differences in survival rates (10). An early diagnosis is important for patients, and clinicians should always inquire about a history of recurrent epistaxis when a patient presents with multiple hepatic telangiectases and evidence of intrahepatic shunts, multiple gastrointestinal angiodysplasias, or AVMs. If a positive history is detected, the guideline recommends genetic testing to achieve an early diagnosis in patients who do not satisfy the diagnostic criteria, as well as in asymptomatic young relatives of HHT patients (10). Once diagnosed, patients should undergo guideline-recommended screening programs to avoid preventable complications, as performed in the present case.

As medicine continues to advance, we expect more HHT manifestations to be detected incidentally, and we hope that our case report will contribute to the better management of such patients.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

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**References**


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**Table 2. CT Characteristics of HHT Lesions and Peliosis Hepatis.**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioportal shunts (52%)</td>
<td>Early and prolonged enhancement of the portal vein during the early arterial phase, which frequently becomes isodense with the aorta.</td>
</tr>
<tr>
<td>Arteriovenous shunts (15%)</td>
<td>Opacification of the hepatic veins during the early arterial phase.</td>
</tr>
<tr>
<td>Portosystemic venous shunts (rare)</td>
<td>Dilated portal veins communicating with large systemic or hepatic veins during the portal venous phase.</td>
</tr>
<tr>
<td>Parenchymal hepatic telangiectasia (63%)</td>
<td>Round, highly enhanced lesions persisting to the late arterial phase with a diameter less than 10 mm and a prevalently peripheral arrangement.</td>
</tr>
<tr>
<td>Large confluent vascular masses (25%)</td>
<td>Round, highly enhanced lesions as telangiectasia but with a diameter exceeding 10 mm.</td>
</tr>
<tr>
<td>Peliosis hepatis</td>
<td>Typically a hypoattenuating mass in the arterial phase, which progressively becomes hyperattenuating with centripetal or centrifugal enhancement in the portal venous phase. A variable enhancement pattern is seen depending on the state of cavities (thrombosed or hemorrhagic).</td>
</tr>
</tbody>
</table>

CT: computed tomography, HHT: hereditary hemorrhagic telangiectasia


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