Fatal hypoxic hepatitis in a patient with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's disease)

J. Henrion[1], P. Deltenre[1], M.-O. Peny[2], Ph. Dumoulin[3], Y. Laurent[4], R. Brenard[5]

(1) Unité d'Hépatogastroentérologie ; (2) Service d'Anatomopathologie ; (3) Service de Radiologie ; (4) Service de Réanimation, Hôpital de Jolimont, Haine-Saint-Paul, B-7100, Belgium ; (5) Service d'Hépatogastroentérologie, Grand Hôpital de Charleroi, Site St Joseph, Gilly, B-6060, Belgium.

Abstract

Hypoxic (ischemic) hepatitis generally requires the concurrence of an underlying condition which chronically exposes the liver to some degree of hypoxia (for example, congestive heart failure) combined with a triggering event (for example, arrhythmia) which further decreases the oxygen supply. We report a case of hypoxic hepatitis in which hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's disease) constituted this underlying condition and gastrointestinal hemorrhage was the triggering event. To our knowledge, this is the first reported case of hypoxic hepatitis in hereditary hemorrhagic telangiectasia with the exception of therapeutic ligation or embolization of the hepatic artery so as to decrease shunting of liver blood. Hemodynamic mechanisms are proposed to explain this particular outcome. (Acta gastroenterol. belg., **2010**, 73, **61-64**).

Key words : Hypoxic hepatitis, Ischemic hepatitis, Hereditary hemorrhagic telangiectasia, HHT, Rendu-Osler-Weber's disease

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber's disease, is an autosomally dominantly inherited condition characterized by muco-cutaneous telangiectases and visceral arteriovenous malformations. In most cases, the disease follows a rather benign course (1). Nevertheless, it is estimated that around 10 % of affected patients will die prematurely or will suffer major disability from HHT largely because of cerebral or pulmonary arteriovenous malformation (2). In case of severe venous malformations of the liver, some patients may develop life threatening conditions requiring liver transplantation such as high output heart failure, peri-biliary necrosis or abscess (3). We report the case of a patient who died from fulminant hypoxic (ischemic) hepatitis. To our knowledge, this is the first reported case of hypoxic hepatitis in the setting of HHT.

Case report

On February 12, 2008, a 57-year-old woman was admitted to the intensive care unit (ICU) for circulatory shock. She died nine hours later. On admission, serum ASAT were 100 times the upper limit of normal (3050 IU/mL, N < 31).

She was suffering from HHT. The diagnosis of HHT had been recognized when she was 43 on the basis of 3 cardinal criteria (4) : 1/ familial history (her mother and at least one maternal aunt had the disease), 2/ frequent epistaxis, 3/ telangiectases of nasal, oral and gastroduodenal mucosa and chronic anemia necessitating regular blood transfusions and continuous martial therapy. The presence of ALK1 gene mutation (HHT type 2) confirmed the diagnosis in 2007 (Service de Génétique Moléculaire, Groupement Hospitalier Edouard Herriot, Lyon, France). Cardiac work-ups were performed in March 2006 and April 2007. A slight mitral murmur (degree 2/6) was noted and considered to be unremarkable. Heart rate, arterial pressure and electrocardiogram were normal. Doppler ultrasonography showed normal contractility without left ventricular hypertrophy or pulmonary artery hypertension. Cerebral MRI and pulmonary angioscanner did not show any vascular malformations in April 2007.

In terms of liver involvement, the patient was seen for the first time at the outpatient liver clinic in December 2006. There was no clinical hepatomegaly or vascular thrill. Liver function tests were normal with the exception of slightly elevated GGT (106 IU/L, N < 50) and alkaline phosphatase (559 IU/L, N < 300). Liver ultrasonography showed heterogeneity of liver parenchyma with hypoechoic zones. An angioscan of the liver showed major heterogeneity of liver parenchyma with multiple peripheral zones enhancing rapidly and intensively at the artery phase of contrast injection (Fig. 1A). This pattern corresponded to multiple arteriovenous shunts and was previously referred to as *peripheral hypervascularization* (5). Avascular zones were also observed probably corresponding to areas of defective hepatic perfusion (Fig. 1A). Rapid opacification of the hepatic veins (Fig. 1B) and dilation of the hepatic artery (Fig. 1C) were also observed. Nasal and gastrointestinal blood loss was continuous during the years 2006 and 2007. Intensive martial therapy including biweekly injections of Venofer®

Correspondence to : Jean Henrion, Hépato-Gastroentérologie, Hôpital de Jolimont, Haine-Saint-Paul, B-7100, Belgium. E-mail : jeanhenrion@yahoo.fr

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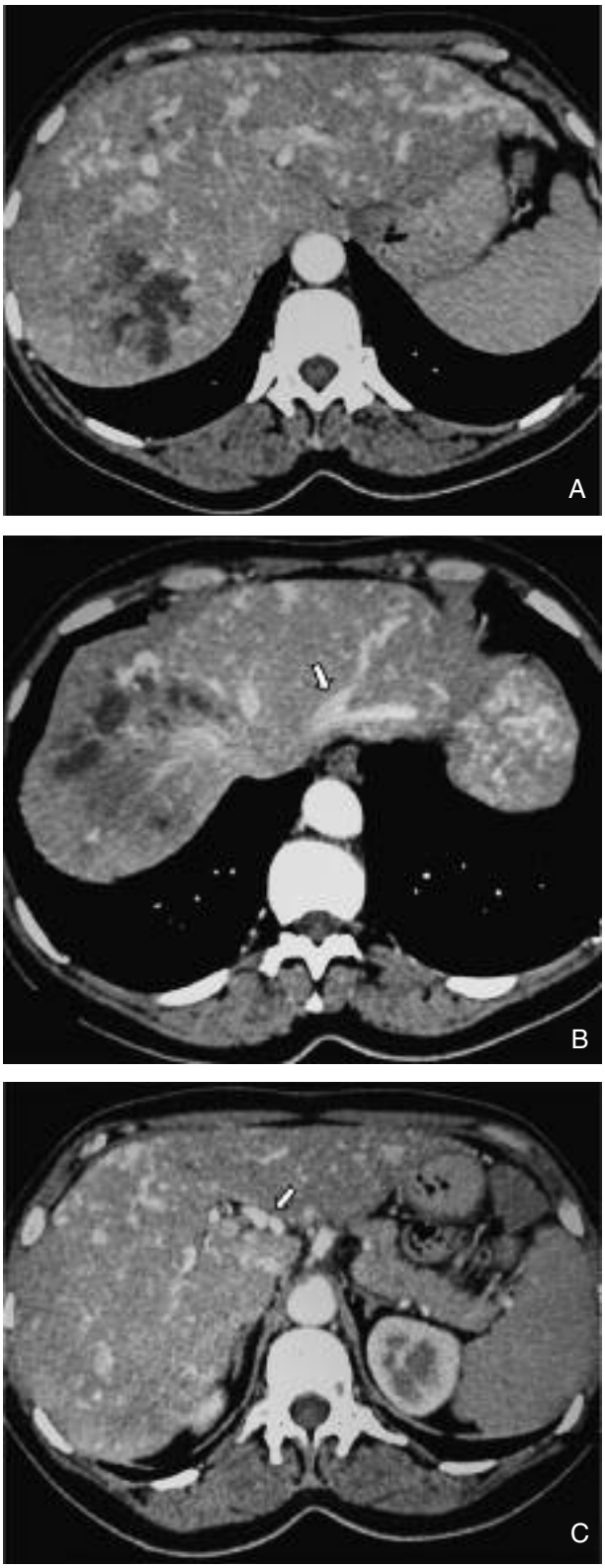

Fig. 1. — Angioscan of the liver. A/ Peripheral hypervascularization ; B/ Early opacification of hepatic veins (arrow) indicating anastomoses between the hepatic artery and hepatic veins; C/ Dilated hepatic artery (arrow).

enabled maintaining the hemoglobin level at about 10 g/dL. On two occasions, more than 30 gastric and intestinal vascular lesions were coagulated during endoscopy. On February 5, 2008, just a week before final admission to ICU, the patient was seen at the cardiology clinic. Mild pretibial edema, an early sign of cardiac failure, was noted for the first time, cardiac murmur was unchanged, heart rate was 96/min, arterial pressure was 120/70 mmHg and electrocardiogram was normal. Heart contractility was considered as normal upon Doppler ultrasonography. The pressure gradient between the right ventricle and right auricle was 19 mmHg. Hemoglobin level was 10.7 g/dL.

During the 3-day-period prior to final admission to the ICU, the patient passed dark stools. The day preceding admission, she felt weak and on the morning of admission, she became lethargic. Then, she collapsed. Upon admission to the emergency room, she was conscious but combative and confused. Blood pressure was 70/50 mmHg, heart rate 117/min and jugular veins were turgescent. Central venous pressure had risen to 21 cm H_2O. Glycemia was extremely low at 20 mg/dL, hemoglobin was 11.5 g/dL, blood urea 120 mg/dL, creatinine 1.96 mg/dL, INR 2.5, bilirubin 3.8 mg/dL, LDH 2070 IU/L (N < 250), ASAT 3050 IU/L (N < 31), ALAT 1135 IU/L (N < 34), pH 6.9, Pa CO_2 16.8 mmHg, Pa O_2 424 mmHg (under nasal oxygenotherapy), O_2 saturation 98% and lactic acid 23 mEq/L. Acetaminophen dosage was negative. Gastric endoscopy showed the presence of fresh blood. Transthoracic cardiac ultrasonography showed a hyperkinetic ventricle, tricuspid insufficiency and elevated pressure gradient between the right ventricle and the right auricle of 38 mmHg. Given the central venous pressure which had risen to 21 cm H_2O, pulmonary artery pressure was estimated abnormally high at 55 mmHg. Thoracic-abdominal angioscan was performed. Due to cardiac failure, only large pulmonary artery trunks could be opacified. Absence of nephrography on tardive sequences was also proof of severe cardiac failure. Shock state was treated by vascular filling, blood transfusion and intensive inotropic treatment combining noradrenalin and dobutamine. The patient died

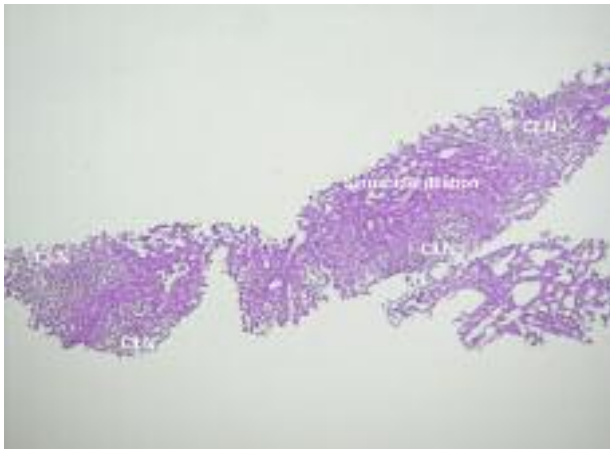

Fig. 2. — Liver histology (H&E, ×10) showing centrilobular liver cell necrosis (CLN) and dilated sinusoids.

from protracted shock 9 h after admission to the hospital. Blood samples taken during her stay in the ICU showed a rapid decrease in LDH, ASAT and ALAT levels. Transcutaneous needle sampling of liver tissue performed immediately postmortem showed extensive central liver cell necrosis and dilated sinusoids suggestive of hypoxic hepatitis (Fig. 2).

Discussion

In order to explain the dramatic course of this case, it was initially hypothesized that gastrointestinal hemorrhage led to circulatory shock with collapse on the day of admission and to hypoxic hepatitis and acute liver failure. In fact, the scenario was different. We assume that liver failure was present prior to the onset of circulatory shock. Circulatory shock was not the cause of hypoxic hepatitis, but rather, was the consequence of acute liver failure due to hypoxic hepatitis. Indeed, several points indicated that the collapse which motivated urgent admission to the hospital was not the leading event explaining the occurrence of hypoxic hepatitis : 1/ the patient had passed dark stools for three days, but this was not an infrequent event for her and was usually well supported; 2/ hemoglobin level at admission to the ICU was 11.6 g/dL, no different from the level observed a few days earlier when the patient was well (10.7 g/dL) ; 3/ the course of hypoxic hepatitis was already in a late phase upon admission. Serum bilirubin was 3.8 mg/dL, INR 2.5 and serum ASAT levels were already on a decreasing curve. If the patient's collapse which motivated urgent admission had been responsible for the occurrence of hypoxic hepatitis, the course of the liver injury would have been in its early phase, with increasing levels of serum aminotransferases ; 4/ finally, hepatic encephalopathy was already present the day before the onset of circulatory shock. Considering these points, we assume that the shock state leading to urgent admission was not of hemorrhagic origin but was the terminal event in rapid acute liver failure. A shock state in the course of acute liver failure has been reported in up to 36% of cases (6).

Hypoxic hepatitis occurs when the liver is deprived of oxygen and is unable to compensate by protective mechanisms. Three mechanisms of liver hypoxia are possible: 1/ a decrease in oxygen delivery by ischemia, hypoxemia or anemia ; 2/ passive congestion of the liver by increased central venous pressure as observed in congestive heart failure, cor pulmonale or pericarditis ; 3/ inability of liver cells to use oxygen due to cellular dysfunction or microvascular alterations as observed in the case of septic or toxic shock (7). Protective mechanisms include an increase in hepatic blood flow and an increase in oxygen extraction. The increase in hepatic blood flow may result from the increase in cardiac blood flow, as in anemia and hypoxemia (7,8) or may be due to an autonomic mechanism referred to as the *"hepatic artery buffer effect"* corresponding to dilation of hepatic arteries when the portal blood flow is decreased (9). As for the increase in hepatic oxygen extraction, it is made possible due to anatomic particularities of liver sinusoids (multiple fenestrations and absence of lamina basal) enabling liver cells to extract more than 90 % of delivered oxygen in situations such as cardiac failure and hypoxemia (10). In a clinical setting, the onset of hypoxic hepatitis generally requires the concurrence of both an underlying condition chronically exposing the liver to some degree of hypoxia and an acute event triggering hypoxic hepatitis when protective mechanisms are overrun. For example, in congestive heart failure, which is by far the most frequent underlying condition, the liver is chronically exposed to hypoxia by ischemia (due to a decrease in cardiac blood flow) and by passive congestion (due to an increase in central venous pressure). In this setting, hypoxic hepatitis will occur following an acute event, most often arrhythmia or pulmonary edema, that further decreases the oxygen supply and overruns the protective mechanism, in this case an increase in oxygen extraction (7,11). This acute event may, on occasion, be so brief that it remains unrecognized (12) and a shock state is observed in only half of hypoxic hepatitis cases (7).

How does this general scheme apply to our patient and how does it explain the onset of hypoxic hepatitis ? Clinical signs of liver involvement are not prominent in cases of HHT and are observed in around 10% of cases (13). In contrast, vascular malformations are observed in up to 84 % of HHT cases in color Doppler ultrasonography or angioscan (14). When liver involvement is clinically manifest, four presentations are possible depending on the type of vascular malformation : 1/ high output cardiac failure (the most frequent presentation) in case of anastomoses between the hepatic artery and hepatic veins; 2/ portal hypertension (ascites, variceal bleeding) in the case of an arterioportal fistula or nodular transformation of the liver (pseudocirrhosis) ; 3/ ischemic biliary injury due to shunting of the arterial blood flow supplying the biliary tree ; 4/ hepatic encephalopathy as a result of portal-to-hepatic vein shunting (15,16). In this setting, at least three mechanisms may cause chronic hypoxic injury of the liver. The first is the massive shunting of liver arterial blood flow depriving the liver of arterial oxygen. The second is high output cardiac failure due to massive blood return to the heart. Hyperdynamic circulation is observed in most patients with liver vascular malformations due to HHT and cardiac failure may be observed in around 50% of these cases (15). High output cardiac failure results in increased central venous pressure leading to passive congestion of the liver and impairment of portal blood flow. The third and probably least frequent mechanism of chronic hypoxic injury to the liver in HHT is the possible presence of anastomoses between the portal and hepatic veins. In case of marked shunting from the portal vein, only the hepatic artery supplies blood to the liver. To counterbalance these chronic mechanisms of hypoxia and avoid the additional detrimental effect of a concomitant hypoxic event, the

liver in HHT is unable to satisfactorily defend itself. Indeed, cardiac output is already massively increased and the hepatic artery buffer effect is of no help because of massive shunting of arterial blood flow. Moreover, liver extraction of oxygen cannot be truly increased in the face of massive shunting. In this situation, it may be hypothesized that a brief, even unnoticed, fall in cardiac output may disturb this fragile balance and result in liver hypoxia sufficient for inducing hypoxic hepatitis. In the case of our patient, the triggering event was probably gastrointestinal hemorrhage which was more severe than usual, requiring additional work load that the heart was unable to provide. Minor clinical signs of cardiac failure (pretibial edema) were for the first time present shortly before admission to the ICU and biventricular cardiac failure was clear-cut on admission as illustrated by elevated central venous pressure (despite hemorrhage) and a defect in pulmonary and renal perfusion on angioscanner.

In view of compromised oxygen supply to the liver in HHT, it might seem surprising that hypoxic hepatitis has not been reported more often in these patients. It is possible that this terminal event remained underrated in HHT patients dying from liver or cardiac failure and was included in the more general terms of "acute liver failure". It is also interesting to point out that extensive liver cell (and/or biliary) necrosis has been regularly reported as a consequence of therapeutic ligation, banding or embolization of the hepatic artery performed in the aim to decrease massive blood shunting. The interruption of artery blood flow resulted in several fatal outcomes and it is currently recommended that this treatment be avoided (13). The occurrence of hepatic necrosis after interruption of hepatic artery blood flow supports the presence of shunting from the portal vein to hepatic vein (15). Indeed, when the portal blood flow is not compromised, ligation or embolization of the hepatic artery does not lead to extensive liver cell necrosis.

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