Journal of Clinical Case Reports
ISSN: 2165-7920

Wong, J Clin Case Rep 2013, 3:2
DOI: 10.4172/2165-7920.1000252

Case Report Open Access

Hereditary Hemorrhagic Telangiectasia: Patient with Pulmonary Hypertension and Hepatic Encephalopathy

Chit Wai Wong*

Department of Medicine and Geriatrics, Caritas Medical Centre, Hong Kong

Abstract

Hereditary hemorrhagic telangiectasia (HHT) is usually under recognized. It is a rare genetic disorder characterized by telangiectasia and epistaxis. Visceral involvement by HHT is common but frequently asymptomatic and remains undiagnosed. However, once the visceral manifestation of the disease occurs, it can result in significant morbidity and mortality. This case report demonstrates the rare complications of pulmonary hypertension and hepatic encephalopathy in HHT.

Case Report

A 78 year-old lady had diagnosis of hereditary hemorrhagic telangiectasia (HHT). She had telangiectasia over mucosa of nasal septum, tongue and both forearm, and frequent recurrent epistaxis for more than 20 years. She had iron deficiency anemia and endoscopy in 2003 revealed multiple angiodysplasia in the stomach. Endoscopic argon plasma coagulation of angiodysplasia in stomach had been performed but was incomplete. She was put on iron supplement with hemoglobin level maintained at around 10 g/dL.

She had developed progressive shortness of breath for a year and was diagnosed to have pulmonary hypertension in late 2010. Transthoracic echocardiography showed a dilated right ventricle with tricuspid regurgitation, an estimated right ventricular systolic pressure of 80 mmHg, normal left ventricular systolic and diastolic function, no left atrial enlargement, and no valvular lesion. Contrast-enhanced CT of the chest and high-resolution imaging showed prominent and dilated pulmonary artery and its lobar branches, no filling defect within the pulmonary arteries, or significant pulmonary disease, but suspicion of vascular malformation or aneurysm (7 mm enhancing nodule in contact with pulmonary artery) in the left upper lobe of the lung. However, bubble contrast echocardiography failed to identify the intrapulmonary shunt. Human immunodeficiency virus, antinuclear antibody and rheumatoid factor serologies were negative.

There was incidental finding of a liver nodule (3 cm×2 cm×2 cm) with suspicion of focal nodular hyperplasia on CT scan performed in pulmonary hypertension workup. Contrast-enhanced CT of the abdomen repeated in September 2011 showed no interval change of the liver nodule over 9 months, and there was no cirrhosis like change or splenomegaly. Serum hepatitis B surface antigen and anti-hepatitis C virus antibody were negative.

She was admitted to medical ward in June 2012 with congestive heart failure, presented with dyspnea and peripheral edema. Transthoracic echocardiography showed satisfactory left ventricular contraction with ejection fraction of 87.64%, and dilated right ventricle with tricuspid regurgitation. She was managed with furosemide and with improvement.

However, she developed sudden onset of mental dullness a few days later. She was afebrile and the physical examination including cardiovascular system, chest and abdomen were unremarkable, and there was no focal neurological sign. Blood (results including complete blood count Hb 11.1 g/dL, WBC 8.7×10^9/L, PLT 210×10^9/L) renal function test (Urea 9.9 mmol/L, Creatinine 49 μmol/L), liver function test (Bilirubin 25 umol/L, ALP 88 U/L, ALT 13 U/L, Albumin 30 g/L), electrolytes (Sodium 141 mmol/L, Potassium 4.1 mmol/L, Calcium 2.19 mmol/L) and glucose (5.9 mmol/L) showed no significant abnormality. Blood gas result (pH 7.43, pCO_2 58.5 mmHg, pO_2 61 mmHg, Bicarbonate 40.2 mmol/L) showed no significant difference over the previously one year. However, there was elevated serum ammonia level to 54 μmol/L. Chest X-ray was clear and CT brain showed only old lacunar infarcts. She was managed as hepatic encephalopathy with lactulose and fleet enema. Her mental status improved shortly afterward.

Unfortunately, patient developed severe pneumonia a week later. Chest X-ray showed both lung haziness and white cell count elevated to 26.5×10^/L. It was also complicated with acute upper gastrointestinal bleeding and another episode of hepatic encephalopathy (Ammonia 181 μmol/L, Bilirubin 16 μmol/L, ALP 178 U/L, ALT 31 U/L, Albumin 20 g/L). Although active management including potent antibiotics, proton pump inhibitor intravenous infusion and blood transfusion were given, her condition continued to deteriorate and died a month after admission.

Retrospective review of contrast-enhanced CT of abdomen done in 2011 showed evidence of liver involvement by HHT. There is markedly dilated common hepatic artery and intrahepatic arterial branches (Figure 1). Besides, there is early filling of hepatic vein during arterial phase which is consistent with the presence of arteriovenous shunt (Figure 2).

Discussion

This case report illustrates a patient with HHT and the clinical manifestations caused by several organs involvement: epistasix, angiodysplasia in the gastrointestinal tract with iron deficiency anemia, hepatic involvement with hepatic encephalopathy, and pulmonary hypertension.

HHT is a systemic fibrovascular dysplasia, which is characterized by mucocutaneous telangiectasia and Arteriovenous Malformation (AVM) in visceral organs, predominantly the lung, liver, gastrointestinal

***Corresponding author:** Chit Wai Wong, MBBS, MRCP (UK), FHKAM, FHKCP, Department of Medicine and Geriatrics, Caritas Medical Centre, Hong Kong, E-mail: wong.chitwai@gmail.com

Received December 15, 2012; **Accepted** February 11, 2013; **Published** February 13, 2013

Citation: Wong CW (2013) Hereditary Hemorrhagic Telangiectasia: Patient with Pulmonary Hypertension and Hepatic Encephalopathy. J Clin Case Rep 3: 252. doi:10.4172/2165-7920.1000252

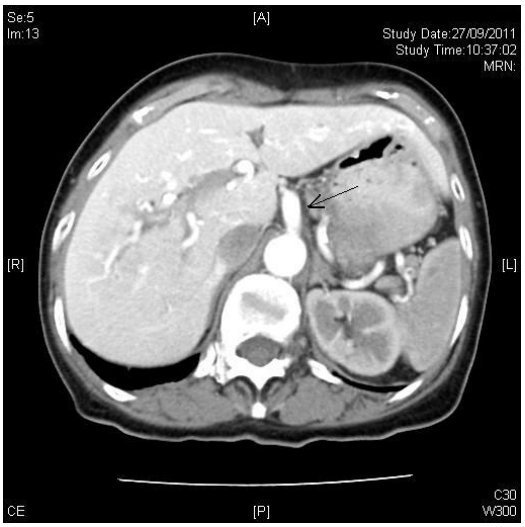

Figure 1: Contrast-enhanced CT of abdomen arterial phase images. Marked dilated common hepatic artery and intrahepatic branches.

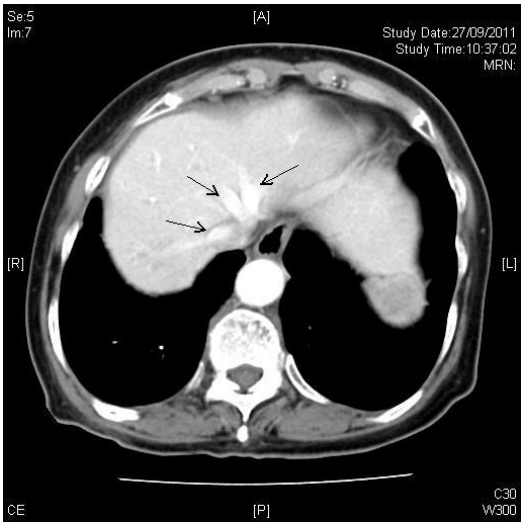

Figure 2: Contrast-enhanced CT of abdomen arterial phase image. Early filling of right, middle and left hepatic veins.

tract and brain. Although there is significant percentage of patients with HHT have these organ involvements, most of these patients are asymptomatic. Clinical manifestation is related to the complication of the underlying vascular abnormality such as shunting of blood, thrombosis and embolus. Diagnosis of HHT is based on the Curacao criteria: spontaneous recurrent epistaxis, mucocutaneous telangiectasia, visceral involvement (gastrointestinal telangiectasia; lung, liver, brain and spinal AVM), and an affected first degree relative [1]. The diagnosis is definite if 3 criteria are present, possible or suspected if 2 criteria are present and unlikely if fewer than 2 criteria are present. In this patient, she meets 3 criteria (recurrent epitaxis mucocutaneous telangiectasia, multiple angiodysplasia in the stomach and hepatic vascular malformation) and the diagnosis of HHT is definite.

HHT is an autosomal dominant disorder. It is caused by mutations of genes. Most important ones are the Endoglin (*ENG*) gene in chromosome 9 and the activin-receptor-like kinase type 1 (*ALK1*) gene in chromosome 12, which allows further classification into HHT type 1 (mutation in ENG gene) and type 2 (mutation in *ALK1* gene), with type 2 being most frequent [2]. Both genes are essential for maintaining vascular integrity. Due to late onset penetrance, sign of disease may not be present until after age of 30 or 40 [3]. Furthermore, the vascular abnormalities tend to increase in number and grow in size with age. As a result, the clinical manifestation appears progressively during life time and is not uncommon to have first noted at advanced age as in this patient.

Approximately 44% to 75% of HHT patients have lung involvement [4]. AVM in lung causing pulmonary arterial blood bypasses the alveoli to pulmonary vein directly without being oxygenated which leads to hypoxemia. Other clinical consequences of pulmonary AVMs include brain abscess and stroke. It is because bacteria and blood clots can bypass the capillary network of the lung and migrate directly to the brain without being "filter out". Furthermore, it may cause hemoptysis if bleeding from AVM occurs. Screening for pulmonary AVM is strongly recommended because pulmonary AVM can be safely treated with transcatheter embolotherapy, which in turn can limit the potential significant complications of pulmonary AVM arise [5].

Pulmonary hypertension is a rare pulmonary vascular manifestation of HHT. It has two distinct types. Most commonly, it associates with systemic arteriovenous shunting, mostly the liver AVM [6,7]. This, in turn, leads to increased systemic blood volume, increased pulmonary blood flow, high cardiac output and finally, left heart failure. This precipitates the development of pulmonary hypertension over time, though the precise mechanism is not completely understood [7]. Less commonly, the pulmonary hypertension in HHT can be an isolated condition with similarity to idiopathic Pulmonary Arterial Hypertension (PAH) [8]. It is clinically and histologically indistinguishable from idiopathic PAH. It is characterized by the obliteration of small pulmonary arteries leading to increased pulmonary vascular resistance and thus marked elevation of pulmonary arterial pressure. It is associated with mutations in the *ALK1* gene and thus is more common in type 2 HHT [8]. Although the clinical presentations of these two types of pulmonary hypertension in HHT are non-specific and similar, they can be readily differentiated by right side cardiac catheterization. In pulmonary hypertension associated with liver AVM, there is high cardiac output, elevated pulmonary wedge pressure and normal pulmonary vascular resistance. On the contrary, in PAH, the pulmonary wedge pressure is normal and the pulmonary vascular resistance is increase. Management of pulmonary hypertension in association with liver AVM is primarily by medical therapy, which includes correction of anemia, salt and fluid restriction, diuretics and digoxin etc, according to the clinical condition [6]. Treatment with transarterial embolization or ligation of liver AVM can cause significant complications such as hepatic or biliary necrosis [6], and should be used with caution. In HHT patients with pulmonary arterial hypertension, the use of special treatments (prostanoid analogs, sildenfil or bosentan) as for idiopathic pulmonary arterial hypertension, remain to be determined [5]. Nevertheless, treatment of pulmonary AVM by vaso-occlusion is contraindicated in patients with known pulmonary hypertension. It is because pulmonary AVM may contribute to lower the pulmonary artery pressure and pulmonary vascular resistance, so once it is occluded, the underlying pulmonary hypertension may be further worsened [5,9].

Although liver involvement occurs in up to 74% of patients [10], symptomatic involvement is infrequent. It occurs predominantly in females and is associated with mutation in the *ALK1* gene (HHT type

2) [11]. Clinical manifestations depend on the type of hepatic shunt present. Shunt between the hepatic arteries and hepatic veins may result in high output heart failure and pulmonary hypertension, and is the most common hepatic manifestation in HHT. Arterioportal shunt may leads to portal hypertension and is the next most common symptomatic hepatic involvement. Portovenous shunt may allow portal waste products without being metabolized by the liver, causing irritation to brain and results in hepatic encephalopathy. It is rare and there is only a few case of portovenous shunt with hepatic encephalopathy reported [12,13]. It is difficult to demonstrate portovenous shunt by imaging than the other two types of shunt, though it has been demonstrated histolgically [13]. The three types of shunt can occur concomitantly but usually one of them is predominant. The predominant type of shunt may change over time with spontaneous exacerbations and remissions. Doppler ultrasonography and multiphasic CT of liver are the useful noninvasive examination for identifying the hepatic shunt [10,12]. However, the imaging and clinical finding usually do not correlate in symptomatic patients [14]. In patient with symptomatic liver involvement, treatment is mainly by medical therapy for high output heart failure, complications of portal hypertension and hepatic encephalopathy. If the condition continues to deteriorate, hepatic artery embolization or ligation of the vascular abnormalities can be considered but needs caution, and the liver transplant is the last resort. Unlike pulmonary AVM, screening for liver AVM is not proposed as there is no prophylactic intervention recommended for asymptomatic liver involvement [15].

Incidental finding of focal nodular hyperplasia in liver can have clinical implication. Focal nodular hyperplasia is frequently associated with liver involvement by HHT and is of hundredfold more common in HHT as compared to general population. Its formation is the result of increased hepatic blood perfusion by abnormal blood shunting, which in turn leads to hepatocellular regenerative activity [13,16].

Pathophysiology of HHT can explain the clinical picture of pulmonary hypertension and hepatic encephalopathy in this patient. Investigations have ruled out chronic lung disease, pulmonary embolism and structural heart disease as the secondary causes of pulmonary hypertension. Pulmonary hypertension in this patient can be related to the presence of arteriovenous shunt in the liver, which is evidenced by the presence of early filling of hepatic vein in the arterial phase of contrast-enhanced CT study, causing high output cardiac failure and hyperdynamic pulmonary hypertension. Rarely, the pulmonary arterial hypertension with resemblance to idiopathic pulmonary arterial hypertension might result in similar picture as in this patient. Nevertheless, the right side cardiac catheterization is required to differentiate between the pulmonary hypertension associated with liver arteriovenous shunt and pulmonary arterial hypertension. Liver involvement by HHT in the absence of chronic liver disease can explain the hepatic encephalopathy though the portovenous shunt is difficult to show. Hope through this case report can alert us about the visceral involvement by HHT.

References

1. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, et al. (2000) Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 91: 66-67.
2. Abdalla SA, Letarte M (2006) Hereditary hemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 43: 97-110.
3. Porteous ME, Burn J, Proctor SJ (1992) Hereditary hemorrhagic telangiectasia: a clinical analysis. J Med Genet 29: 527-530.
4. Sabbà C, Pasculli G, Lenato GM, Suppressa P, Lastella P, et al. (2007) Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 5: 1149-1157.
5. Cottin V, Dupuis-Girod S, Lesca G, Cordier JF (2007) Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler disease). Respiration 74: 361-378.
6. Garcia-Tsao G, Korzenik JR, Young L, Henderson KJ, Jain D, et al. (2000) Liver disease in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 343: 931-936.
7. Bhatia S, Morrison JF, Bower TC, McGoon MD (2003) Pulmonary hypertension in the setting of acquired systemic arteriovenous fistulas. Mayo Clin Proc 78: 908-912.
8. Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, et al. (2001) Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 345: 325-334.
9. Haitjema T, ten Berg JM, Overtoom TT, Ernst JM, Westermann CJ (1996) Unusual complications after embolization of a pulmonary arteriovenous malformation. Chest 109: 1401-1404.
10. Memeo M, Stabile Ianora AA, Scardapane A, Buonamico P, Sabbà C, et al. (2004) Hepatic involvement in hereditary hemorrhagic telangiectasia: CT findings. Abdom Imaging 29: 211-220.
11. Kuehl HK, Caselitz M, Hasenkamp S, Wagner S, El-Harith el-HA, et al. (2005) Hepatic manifestation is associated with ALK1 in hereditary hemorrhagic telangiectasia: identification of five novel ALK1 and one novel ENG mutations. Hum Mutat 25: 320.
12. Naganuma H, Ishida H, Niizawa M, Igarashi K, Shioya T, et al. (1995) Hepatic involvement in Osler-Weber-Rendu disease: findings on pulsed and color Doppler sonography. AJR Am J Roentgenol 165: 1421-1425.
13. Wanless IR, Gryfe A (1986) Nodular transformation of the liver in hereditary hemorrhagic telangiectasia. Arch Pathol Lab Med 110: 331-335.
14. Wu JS, Saluja S, Garcia-Tsao G, Chong A, Henderson KJ, et al. (2006) Liver involvement in hereditary hemorrhagic telangiectasia: CT and clinical findings do not correlate in symptomatic patients. AJR Am J Roentgenol 187: W399-W405.
15. Buscarini E, Plauchu H, Garcia Tsao G, White RI Jr, Sabbà C, et al. (2006) Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. Liver Int 26: 1040-1046.
16. Wanless IR, Mawdsley C, Adams R (1985) On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology 5: 1194-1200.