

An Unusual Case of Klippel-Trénaunay-Weber Syndrome Presenting with Portosystemic Encephalopathy

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Abstract

We report a unique male patient presenting with portosystemic encephalopathy (PSE) due to intrahepatic portohepatic venous (PHV) shunts. He was diagnosed as having Klippel-Trénaunay-Weber syndrome (KTWS) based on the findings of a hemitruncal port-wine stain with subcutaneous arteriovenous fistulae and varicose veins in the legs. However, limb-hypertrophy, which is one of the most cardinal manifestations of KTWS, was absent, and in KTWS, PSE is quite a rare clinical manifestation. Hence, the clinical picture of this patient was unusual. Our clinical observation suggests that KTWS can be one of the underlying disorders causing PSE.

Key words: Klippel-Trénaunay-Weber syndrome, portosystemic encephalopathy, port-wine stain, portohepatic venous shunt, arteriovenous fistula

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Introduction

Klippel-Trénaunay-Weber syndrome (KTWS) is a rare disorder, characterized by arteriovenous (AV) fistulae in addition to the triad (port-wine stain, hypertrophy of bone and soft tissue, and varicose veins or venous malformations) of the Klippel-Trénaunay syndrome (KTS) (1, 2). Portosystemic encephalopathy (PSE) is a reversible cerebral disorder associated with neuropsychological dysfunctions that may develop in patients with portosystemic venous shunts secondary to chronic liver disease, surgery, or rarely, a congenital intra- or extrahepatic portosystemic venous shunt. In KTWS, PSE is quite a rare clinical manifestation and to date, only one KTS patient with hyperammonemia due to an extrahepatic portosystemic venous shunt has been reported (3).

Rendu-Osler-Weber syndrome (ROW), which is a hereditary disorder characterized by angiodysplastic lesions ranging from cutaneous and mucous membrane to visceral organs, is known to be sometimes accompanied by PSE owing to intrahepatic portosystemic venous shunts (4). Here, we report a unique patient presenting with PSE due to the intra-

hepatic portosystemic venous shunts, who was diagnosed as having KTWS because of a hemitruncal port-wine stain with subcutaneous AV fistulae and varicose veins in the legs. The patient has multiple complicated intrahepatic vascular abnormalities and telangiectatic lesions on mucous membrane, and this case was therefore difficult to distinguish from ROW.

Case Report

The patient was a 54-year-old Japanese man, who started to notice general fatigue in September 2003. One month later he became very forgetful and experienced tremors in both hands. On November 2, he became delirious and had urinary incontinence. He visited a local hospital where disorientation and flapping tremor in both hands were noted. Laboratory examination revealed a high plasma level of ammonia (267 $\mu\text{m}/\text{dL}$, normal $<70 \mu\text{m}/\text{dL}$). After that, his consciousness level fluctuated from alert to drowsy or delirious. He was thought to have hepatic encephalopathy and was referred to our hospital in December 2003. He had not experienced gastrointestinal bleeding, intracranial hemorrhage, or

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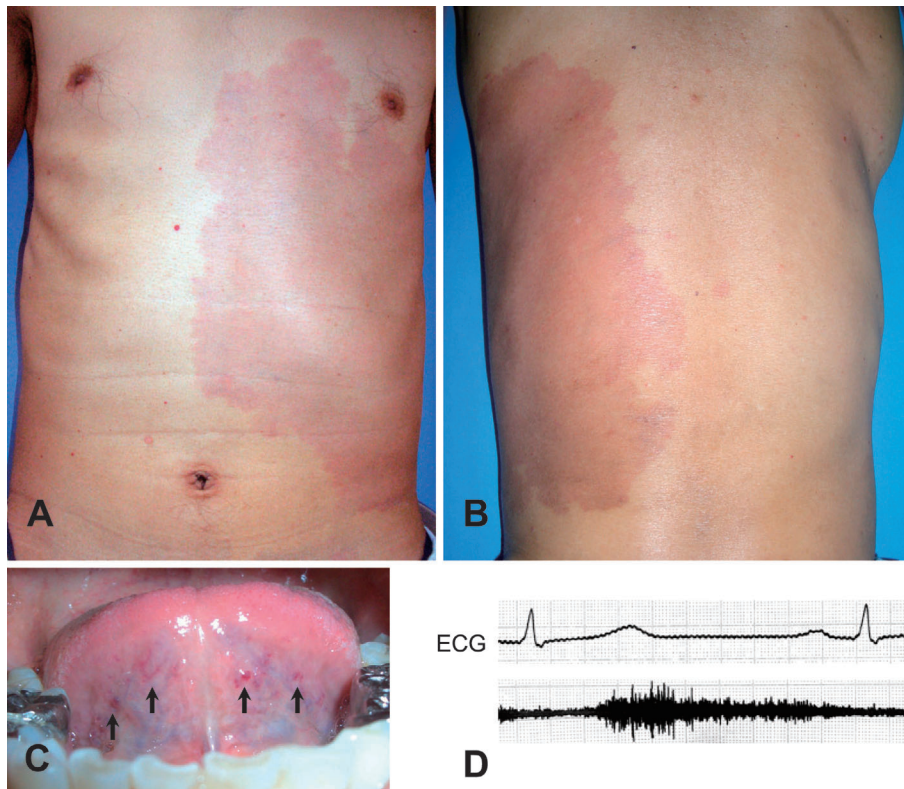


Figure 1. Hemitruncal port-wine stain (A, B), tongue telangiectases (C, arrows), and phonocardiogram at the port-wine stain (D). Phonocardiogram, recorded at 5 cm outside the midclavicular line in the 6th intercostal space, shows the presence of a continuous murmur. ECG: electrocardiogram. 1 cm/0.1 sec.

recurrent epistaxis. Nobody in his family had recurrent mucocutaneous hemorrhages suggestive of ROW or a port-wine stain.

On admission, he was alert and a widespread port-wine stain was seen on the left trunk (Fig. 1A, B). Some cherry-red spots (telangiectases) were present on the tongue (Fig. 1C). Varicose veins were found in the calves, but were not severe. A continuous murmur was audible over the port-wine stain (Fig. 1D). There were no signs of hepatosplenomegaly, palmar erythema, or vascular spiders on the chest, and limb-hypertrophy was also absent. Laboratory examination demonstrated leukocytopenia (white blood cell: $2,630/\mu\text{L}$) and mild thrombocytopenia ($11.4 \times 10^4/\mu\text{L}$, normal $12\text{--}41 \times 10^4/\mu\text{L}$). Red blood cell (RBC) count and hemoglobin were normal. There was no fragmented RBC. Serum levels of total protein and albumin were slightly low (6.5 g/dL, normal 6.8–8.3 g/dL, 3.5 g/dL, and normal 3.8–5.0 g/dL, respectively). Serum lactic dehydrogenase (LDH) and alkaline phosphatase (ALP) were increased (299 IU/L, normal <220 IU/L, and 504 IU/L, normal <360 IU/L, respectively). Serum aspartate aminotransferase was slightly high (42 U/L, normal 12–37 U/L), but alanine aminotransferase and γ -glutamyl transpeptidase were within normal limits. Total bilirubin level was high (2.71 mg/dL, normal 0.2–1.0 mg/dL) with an elevation of indirect bilirubin (2.12 mg/dL). Total cholesterol, cholinesterase, zinc sulfate turbidity test, and thymol turbidity test were all within normal ranges. Serum

haptoglobin was quite low (less than 5 mg/dL). Plasma ammonia was normal (49 $\mu\text{g/dL}$) when fasting but rose to 108 $\mu\text{g/dL}$ after dinner. Prothrombin time was elongated (16.9 sec, normal 10–12 sec) and a low level was seen in the hepaplastin test (67.2%, normal >70%). Fibrin degradation products (FDP) D-dimer was 1.3 $\mu\text{g/mL}$ (normal 0.2–1.3 $\mu\text{g/mL}$). Serum HBs antigen and HCV antibody were negative. Serum hyaluronic acid was elevated to 293 ng/mL (normal <50 ng/mL). Fisher-ratio was low (0.8, normal 2.4–4.4). Indocyanine green 15-minute retention rate was markedly elevated to 46.0% (normal <10%).

A contrast-enhanced abdominal CT showed a slightly atrophic hepatic right lobe and multiple portohepatic venous (PHV) shunts (Fig. 2A, C, D), but there was no extrahepatic portosystemic venous shunt within the abdominal cavity. In addition, multiple subcutaneous AV malformations were demonstrated on the left thoracoabdominal wall (Fig. 2B, C, D). There was no overt sign of splenomegaly, intrahepatic tumor, or ascites. No pulmonary AV fistula was seen on thoracic CT. Brain MRI showed a high signal in the bilateral basal ganglia on T1-weighted image (Fig. 3). An electroencephalogram showed diffuse slow α waves. Gastrofiberscopic examination disclosed no esophageal varices. Echocardiography revealed no congenital cardiac anomaly or valvular disorders, and there was no sign of congestive heart failure.

Selective hepatic arteriography showed widened and tortu-

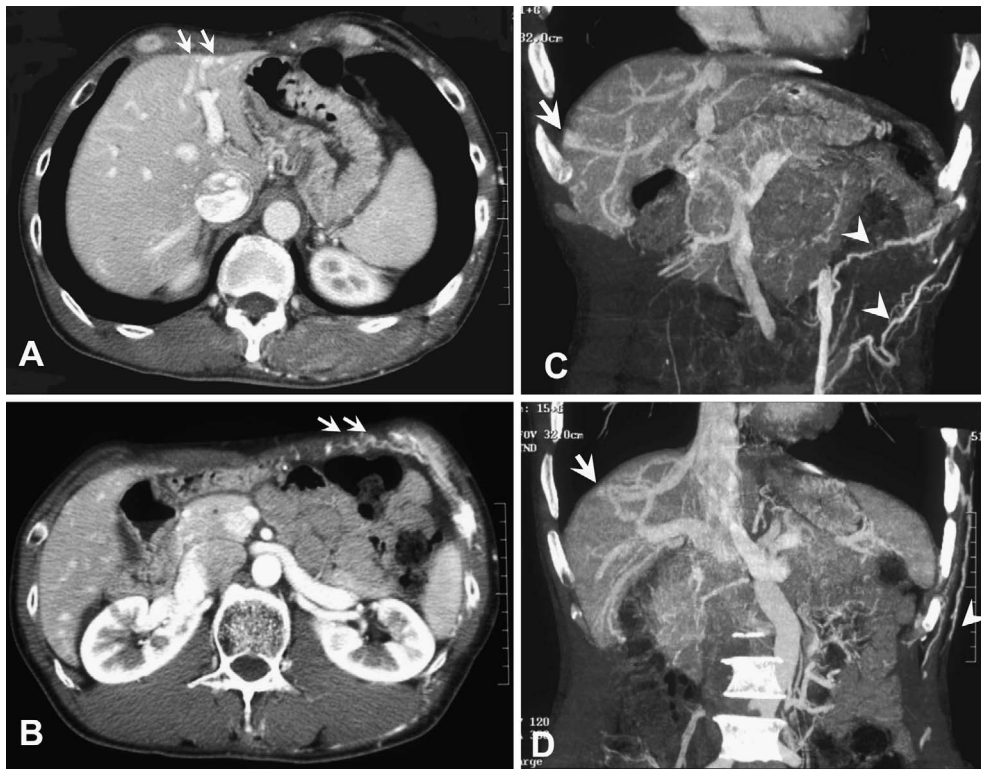


Figure 2. Enhanced abdominal CT scans. The abdominal CT scans show multiple intrahepatic PHV shunts (A, arrows) and multiple abnormal vessels in the subcutaneous soft tissues on the left abdominal wall (B, arrows). Coronal reconstructed CT images show intrahepatic PHV shunts (C, D, arrows) and multiple abnormal vessels on the left abdominal wall (C, D, arrowheads).

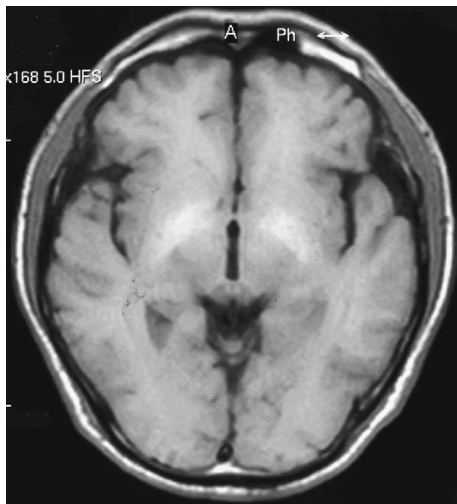


Figure 3. Brain MRI shows a high signal in globus pallidus on T1-weighted image.

ous hepatic arteries. Transarterial portography revealed multiple PHV shunts in the periphery of the hepatic right lobe (Fig. 4A). Balloon-occluded middle hepatic venography also showed multiple PHV shunts and hepatic venovenous shunts (Fig. 4B). Left 11th intercostal arteriography revealed an abnormally tortuous artery and AV malformations (Fig. 4C). Hence, a diagnosis of PSE due to PHV shunts was made in this patient. Since he began to take lactulose (60-90 mL/

day), no recurrence of encephalopathy has been seen.

Discussion

Commonly the diagnosis of KTWS can be made when any two of the triad of features of KTS and AV malformations are present (5). While the limb is most commonly affected, the trunk, usually the hemitrunk, is also involved (6, 7). In our patient, a hemitruncal port-wine stain and subcutaneous AV malformations were apparent. While limb-hypertrophy was absent in our patient, varicose veins, which were not severe, were found and thus, he was diagnosed as having KTWS. However, hypertrophy of bone and soft tissues is present in the majority of patients with KTS/KTWS (7), and no KTS/KTWS case with PSE has been reported except for a 6-year-old patient with hyperammonemia and an abnormal finding on brain MRI, as seen in our patient, due to a large extrahepatic portosystemic venous shunt (3). Hence, the present patient's clinical picture may be unusual compared to those in typical KTS/KTWS patients. Laboratory data of this patient showed impairment of hepatic synthetic function and mild cholestasis with leukocytopenia, thrombocytopenia, and hemolysis. Furthermore, an elevation of serum hyaluronic acid was found and therefore, the presence of mild liver cirrhotic changes or liver fibrosis with hypersplenism was suspected. However, the etiology of liver damage in this patient was not fully understood. In KTS/

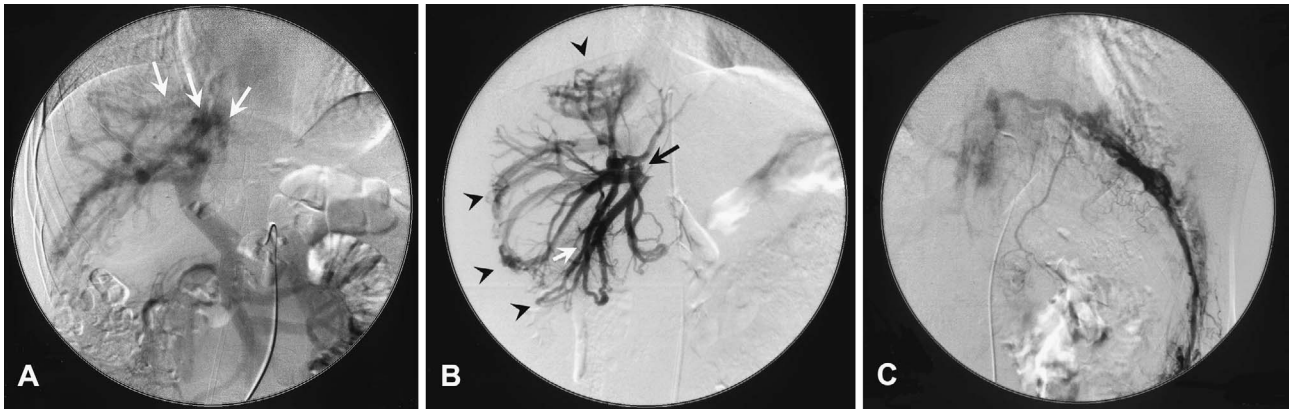


Figure 4. Abdominal angiogram (A, B), and left 11th intercostal arteriogram (C). Digital subtraction transarterial portogram (A) demonstrates intrahepatic PHV shunts. Arrows denote hepatic veins directly connected with portal veins. Balloon-occluded middle hepatic venography also shows intrahepatic PHV shunts (B). The black arrow indicates the middle hepatic vein, the white arrow a branch of the portal vein, and the black arrowheads multiple PHV or hepatic venovenous shunts. The left 11th intercostal arteriogram shows an abnormally tortuous artery and AV malformations (C).

KTWS, concomitant liver involvement is rare and only a few cases with multiple focal nodular hyperplasia, which is possibly associated with irregular arterial supply in the liver, have been reported (8). On the other hand, in ROW, the prevalence of liver involvement is relatively high, ranging from 8 to 31 percent of ROW patients (9, 10). Although ROW patients with liver involvement are generally asymptomatic (11), congestive cardiac failure, portal hypertension, PSE, cholangitis, and atypical cirrhosis, probably caused by hepatic vascular malformations, have been reported (11, 12). Hence, also in the present patient, the abnormality of the laboratory data mentioned above may be associated with hepatic vascular malformations.

The diagnosis of ROW is based on a combination of 4 clinical criteria: the recognition of mucocutaneous telangiectases, the occurrence of spontaneous and recurrent episodes of epistaxis, the presence of visceral involvement, and a family history of this disease (13). While in the present patient the mucocutaneous telangiectases and visceral involvement (multiple PHV shunts) were present, he had neither bleeding episodes nor a family history of ROW. In particular, recurrent epistaxis is known to be usually the first symptom and to be present in over 90% of patients with ROW (14), while so far there has been no report of ROW patients with a port-wine stain. Hence, it was less likely that our pa-

tient was suffering from ROW.

The etiology of KTWS remains obscure. While this syndrome is generally thought to occur sporadically, in some cases clinical manifestations of the syndrome have been found in family members, suggesting an autosomal dominant inheritance (15, 16). It has been postulated that this syndrome may be due to a somatic mutation for a factor critical to vasculogenesis and angiogenesis in embryonic development (6). Recently the vascular growth factor VG5Q was implicated in the etiology of KTS (17), with the observation that five of 130 KTS patients were constitutionally heterozygous for the sequence change E133K. However, it is now controversial whether this VG5Q E133K is indeed a causative gene mutation (18). Therefore, a molecular diagnosis of this syndrome is not yet available.

In addition to the triad of clinical features, various complications associated with the vascular pathologic condition can occur in KTS, including thrombotic episodes in the limbs, cellulitis, multiple pulmonary emboli, and localized consumptive coagulopathy (7). Gastrointestinal and genitourinary bleeding has also been reported in several cases (19, 20). Thus, the clinical manifestations in KTS/KTWS are heterogeneous and we conclude that KTS/KTWS can be one of the underlying disorders causing PSE.

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