CASE REPORT

Liver Cirrhosis Induced by Porphyria Cutanea Tarda: A Case Report and Review

Kwang Gyun Lee*, Jong Jin Hyun*, Yeon Seok Seo*, Bora Keum*, Hyung Joon Yim*, Yoon Tae Jeon*, Hong Sik Lee*, Hoon Jai Chun*, Chang Duck Kim*, Ho Sang Ryu*, and Soon Ho Um*[†]

*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University College of Medicine, [†]Liver Cirrhosis Clinical Research Center, Korea University Anam Hospital, Seoul, Korea

Porphyria cutanea tarda (PCT) is a metabolic disorder that results in a decrease in uroporphyrinogen decarboxylase activity. It is characterized by photosensitivity, bullae formation, and skin pigmentation. There are four types of PCT: acquired, familial, toxic, and hepatoerythropoietic. Uroporphyrin levels are elevated in the urine of PCT patients. PCT can be differentiated from other porphyrias by its clinical characteristics and the porphyrin levels in the serum, erythrocytes, urine, and feces. This metabolic disorder can lead to liver dysfunction as well as histological changes such as fatty infiltration or hepatic fibrosis. PCT rarely manifests as liver cirrhosis. We report herein a case of PCT-induced liver cirrhosis that progressed to hepatic failure. (**Gut Liver 2010;4:551-555**)

Key Words: Porphyria cutanea tarda; Uroporphyrin; Metabolic disorder; Liver cirrhosis

INTRODUCTION

Porphyria is caused by reduced activity or defects of any one of various enzymes that take part in heme biosynthesis.^{1,2} Porphyria cutanea tarda (PCT), the most common form of porphyria,¹ is a metabolic disorder that is caused by reduced activity of the enzyme uroporphyrinogen decarboxylase (Uro-D) in the liver.^{3,4} The main symptom of PCT is a skin manifestation. Changes in the liver parenchyme, such as fatty changes or iron infiltration, is also often seen in PCT patients, but cirrhotic change is rare.^{1,5} We report herein a case of a patient

with liver cirrhosis accompanied by ascites and jaundice, all of which were attributable to PCT.

CASE REPORT

A 30-year-old man presented to the emergency department of our hospital with a 1-month history of generalized weakness, jaundice, and bullae formation. The bullae developed mainly on his hands and feet, and were accompanied by intense itching. Over the previous 15 years, the patient's skin has been darkened and he complained of an itching sensation and erythema on sun-exposed areas, mainly the face, back of the hands, neck, and dorsum of the feet. The patient had been consuming about 120 g of alcohol per week for the past 5 years and taken herbal medicine 1 month prior to his admission. There was a family history of photosensitivity on his mother's side: in his grandmother, mother, and uncle. His vital signs upon admission were stable and he was mentally alert. Physical examination revealed icteric sclera and skin, and there were hyperpigmented spots and blisters over his face and on the back of his hands and feet (Fig. 1). Hepatosplenomegaly and shifting dullness were noted on abdominal examination. The results of blood tests were as follows: hemoglobin, 12.0 g/dL; white blood cell count, 4,600/mm³; platelet count, 85,000/mm³; prothrombin time, 17 seconds (normal range, 13 to 15 seconds); aspartate aminotransferase, 83 IU/L; alanine aminotransferase, 51 IU/L; and total bilirubin, 17.8 mg/dL. Viral and autoimmune markers were all negative. Porphyrin was detected in the

Correspondence to: Soon Ho Um

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Anam-dong 5-ga, Seongbuk-gu, Seoul 136-705, Korea

Tel: +82-2-920-5019, Fax: +82-2-953-1943, E-mail: umsh@korea.ac.kr

Received on January 29, 2010. Accepted on February 16, 2010.

DOI: 10.5009/gnl.2010.4.4.551

Fig. 1. Bullae, erosions, crusts, and hyperpigmented and depigmented scars are evident on the skin. (A) Foot. (B) Hands.

Fig. 2. Computed tomography scan of the abdomen showing a cirrhotic liver with hepatosplenomegaly, liver surface nodularity, and ascites.

Fig. 3. Subepidermal blister formation is seen on skin biopsy (H&E stain, $\times 100$).

patient's serum. Serum iron and zinc-protoporphyrin levels were normal. On a 24-hour urine analysis, porphobilinogen (PBG) was negative and delta-aminolevulinic acid (δ -ALA) level was normal, but uroporphyrin ($431,000 \mu\text{g/L}$) and coproporphyrin ($270 \mu\text{g/L}$) levels were elevated. No mutations in the Uro-D gene or hemochromatosis (HFE) gene were observed. A computed tomography (CT) scan of the abdomen revealed surface nodularity of the liver, ascites, and splenomegaly (Fig. 2). Biopsy of the skin revealed blister formation on the subepidermal area (Fig. 3), and biopsy of the liver demonstrated cirrhotic changes and brown porphyrin pigmentation (Fig. 4). Birefringent crystals were noted when the liver tissue was observed under a polarizing microscope (Fig. 5). The patient was diagnosed as having liver cirrhosis caused by PCT and

was given 200 mg of hydroxychloroquine twice a week for 8 months. However, after repeated episodes of progression and improvement, he eventually underwent liver transplantation.

DISCUSSION

PCT is a metabolic disorder that is induced by functional inhibition of Uro-D in the liver. It is not a rare disorder, with a incidence of about 1 in 10,000.^{6,7} During heme synthesis, the enzymatic step that converts uroporphyrinogen III to coproporphyrinogen is inhibited in PCT.²

PCT can be divided into four types according to its

Fig. 4. Cirrhotic parenchyma and brown-colored porphyrin pigmentation are noted on liver biopsy (A, Trichrome stain, $\times 200$; B, H&E stain, $\times 500$).

Fig. 5. Birefringent crystals are seen under polarizing microscopy of liver tissue (A, $\times 200$; B, $\times 500$).

characteristics. The sporadic or acquired form (type I), the most common type of PCT, is characterized by decreased enzymatic activity of hepatic Uro-D during the active disease state. This type of PCT is commonly induced by alcohol, estrogen, iron, drugs, hepatitis C virus, human immunodeficiency virus, systemic lupus erythematosus, or chemical materials. The hereditary form of PCT (type II) is an autosomal dominant disorder with genetic mutations of the Uro-D gene, and is associated with a family history, although most of the gene carriers are asymptomatic.¹ Recent reports suggest that there is a relationship between HFE gene mutation and PCT types I or II.^{8,9} The toxic form of PCT, or type III, is characterized by its sporadic nature with a familial history. Hepatoerythropoietic porphyria (HEP), the fourth type of

PCT, is caused by a homozygous defect of Uro-D. Patients with HEP may have a severe mutilating type of porphyria that presents in childhood.^{1,2,10}

In our case, mutations in the Uro-D or HFE genes were not detected despite the patient having a family history of photosensitivity. Therefore, our case could be classified as PCT type III. Although Uro-D gene mutation is not necessary for a diagnosis of PCT, its presence is important for differentiating between PCT types I and II.²

PCT is diagnosed by clinical symptoms, biopsy results, and biochemical tests. It is important to detect porphyrin in the urine, and a large amount of porphyrin produces pink fluorescence under Wood's lamp. The level of porphyrin in the urine, and especially uroporphyrin and heptacarboxylic porphyrin, is elevated more than 10-100

times in patients with PCT.^{10,11} Urinary levels of δ -ALA and PBG are within normal limits, and porphyrin can be detected in the feces, but this is not necessary for the diagnosis.¹² Several types of porphyria, such as hereditary coproporphyria (HC) and variegate porphyria (VP), may have skin manifestations that are similar to PCT, such as photosensitivity and blisters. However, those diseases can be differentiated from PCT based on the levels of urinary δ -ALA and PBG, which are raised in HC and VP but normal in PCT. Urinary uroporphyrin is not detected in patients with erythropoietic protoporphyria, and is elevated to a lesser degree in congenital erythropoietic porphyria (CEP) than in PCT, and the porphyrin of red blood cells (RBCs) is elevated in CEP, but not in PCT. In our case the levels of zinc protoporphyrin were normal, which is indicative of porphyrin in RBCs.^{13,14} The clinical symptoms caused by histopathological changes and abnormal liver function are present in most patients with PCT.

While the clinical manifestations of PCT present mainly in the skin, such as photosensitivity, bullae formation, or skin hyperpigmentation, and hepatic involvement of PCT is also common; most patients have abnormal liver function tests,¹⁵ and fatty degeneration and iron overload are seen in almost all of them.^{16,17} Brown-colored porphyrin pigmentation can also be observed in liver tissue from PCT patients under a microscope, and birefringent crystals can be noted in the liver parenchyme under a polarizing microscope.^{18,19} Although liver cirrhosis or hepatocellular carcinoma could be induced by PCT depending upon the degree of liver involvement,^{20,21} most patients with PCT show only mild elevation of aminotransferase levels.^{5,20} Decompensated cirrhosis requiring liver transplantation is very rare in this disease.⁷

PCT is often caused by porphyrinogen, and alcohol is one of the most important causative agents.²² Previous studies found that more than half of patients with PCT had a history of drinking.^{7,22} Alcohol activates aminolevulinic acid synthase, which is the first step in porphyrin synthesis, and it simultaneously induces PCT by inhibiting Uro-D.^{22,23} Our patient had a history of having continuously ingested alcohol and herbal medication when he was in an aggravated state of PCT. Therefore we suggest that alcohol abuse and intake of herbal medication may have been the porphyrinogen in this patient. The activation of uroporphyrin deposited in the skin by ultraviolet or visual light induces the production of oxidized reactive substances that excessively activate collagenase.²⁴ The activated collagenase causes deposition of collagen in the skin, and several skin manifestations, such as bullae formation, appear in the subepidermis.^{24,25} It is important for patients who are diagnosed with PCT to avoid

porphyrinogen and exposure to light. If there is an iron overload, phlebotomy is necessary to decrease the hepatic iron overload.^{26,27} Our patient had a low platelet count and no iron overload, and had a tendency toward bleeding, such as from the gum, so phlebotomy was not indicated. It is also necessary to administer an antimalarial agent to increase the excretion of porphyrin in the urine. Chloroquine (125-250 mg per os twice a week) or hydrochloroquine (200-400 mg per os twice a week) can be used.²⁸ However, hydrochloroquine was not effective in our case.

Serum and urinary hemoglobin, ferritin, and porphyrin levels should be checked regularly.²⁸⁻³⁰ Follow-up CT or abdominal sonography is necessary for assessing the presence of liver cirrhosis or hepatocellular carcinoma.^{29,31}

This disease is not uncommon, but physicians tend to overlook dermatologic symptoms or photosensitivity when evaluating patients with abnormal liver function tests. PCT should be considered as one of the potential causes of liver abnormality if photosensitivity and dermatologic symptoms are noted in patients with an abnormal liver function of an unknown etiology.

REFERENCES

1. Yachimski P, Shah N, Chung RT. Porphyria cutanea tarda. *Clin Gastroenterol Hepatol* 2007;5:e6.
2. Fritsch C, Lang K, von Schmiedeberg S, et al. Porphyria cutanea tarda. *Skin Pharmacol Appl Skin Physiol* 1998;11:321-335.
3. Moran MJ, Fontanellas A, Brudieux E, et al. Hepatic uroporphyrinogen decarboxylase activity in porphyria cutanea tarda patients: the influence of virus C infection. *Hepatology* 1998;27:584-589.
4. Martinez di Montemuros F, Tavazzi D, Patti E, Cappellini MD. Gene symbol: UROD. Disease: Porphyria, cutanea tarda. *Hum Genet* 2003;113:368.
5. Cassiman D, Vannootte J, Roelandts R, et al. Porphyria cutanea tarda and liver disease. A retrospective analysis of 17 cases from a single centre and review of the literature. *Acta Gastroenterol Belg* 2008;71:237-242.
6. Sarkany RP. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001;26:225-232.
7. Elder GH. Porphyria cutanea tarda. *Semin Liver Dis* 1998;18:67-75.
8. Young LC. Porphyria cutanea tarda associated with Cys282Tyr mutation in HFE gene in hereditary hemochromatosis: a case report and review of the literature. *Cutis* 2007;80:415-418.
9. Lamoril J, Andant C, Gouya L, et al. Hemochromatosis (HFE) and transferrin receptor-1 (TFR1) genes in sporadic porphyria cutanea tarda (sPCT). *Cell Mol Biol (Noisy-le-grand)* 2002;48:33-41.
10. Cohen DJ, McKay M. Porphyria cutanea tarda: a clinical review. *Compr Ther* 1996;22:175-178.
11. Bleasel NR, Varigos GA. Porphyria cutanea tarda. *Austra-*

- las J Dermatol 2000;41:197-206.
12. Nordmann Y. Biological diagnosis of porphyria cutanea tarda. *Ann Dermatol Venereol* 2000;127:860-861.
13. Counter SA, Buchanan LH, Ortega F. Zinc protoporphyrin levels, blood lead levels and neurocognitive deficits in Andean children with chronic lead exposure. *Clin Biochem* 2008;41:41-47.
14. Hershko C, Konijn AM, Link G, Moreb J, Grauer F, Weissenberg E. Combined use of zinc protoporphyrin (ZPP), mean corpuscular volume and haemoglobin measurements for classifying microcytic RBC disorders in children and young adults. *Clin Lab Haematol* 1985;7:259-269.
15. Murphy GM. The cutaneous porphyrias: a review. The British Photodermatology Group. *Br J Dermatol* 1999;140: 573-581.
16. Sampietro M, Fiorelli G, Fargion S. Iron overload in porphyria cutanea tarda. *Haematologica* 1999;84:248-253.
17. Hammerschmidt DE. Porphyria cutanea tarda. *J Lab Clin Med* 2000;136:490.
18. Siersema PD, Rademakers LH, Cleton MI, et al. The difference in liver pathology between sporadic and familial forms of porphyria cutanea tarda: the role of iron. *J Hepatol* 1995;23:259-267.
19. Cortes JM, Salata H. Hepatic pathology in porphyria cutanea tarda. *Liver* 1983;3:413-414.
20. Chevallier P, Bahadoran P, Buckley MJ, et al. Hepatic multi-nodular focal fatty metamorphosis in acquired porphyria cutanea tarda. Sonographic, CT, and MRI features. *Clin Imaging* 1998;22:418-421.
21. Gisbert JP, Garcia-Buey L, Alonso A, et al. Hepatocellular carcinoma risk in patients with porphyria cutanea tarda. *Eur J Gastroenterol Hepatol* 2004;16:689-692.
22. Elder GH. Alcohol intake and porphyria cutanea tarda. *Clin Dermatol* 1999;17:431-436.
23. Wolff Fernandez C, Krause Ianpaglia P, Franco Silva C, Armas Merino R. Effect of chloroquine treatment of porphyria cutanea tarda on the associated liver disease. *Rev Invest Clin* 2000;52:211-213.
24. Pizzino D, De Padova M, Labanca M, Varotti C. Pathology of the skin appendages in porphyria cutanea tarda. *G Ital Dermatol Venereol* 1988;123:607-608.
25. Krajnc I, Vizjak A, Hvala A, Jurcic V, Rozman B. The significance of histologic analysis of skin lesions in porphyria cutanea tarda. Light microscopy, electron microscopy, immunohistochemical and immunofluorescence analysis. *Wien Klin Wochenschr* 1998;110:651-654.
26. Mascaro JM, Herrero C. New reasons for an archaic treatment: phlebotomy in sporadic porphyria cutanea tarda. *Arch Dermatol* 2003;139:379-380.
27. Bygum A, Brandrup F. Iron overload in porphyria cutanea tarda. *Br J Dermatol* 2000;143:1116.
28. Wolff C, Armas R, Krause P, Parraguez A, Ramon Soto J. Treatment of porphyria cutanea tarda with chloroquine and its effect on associated liver disease: retrospective analysis. *Rev Med Chil* 1996;124:456-460.
29. Herrero C, Lecha M. Management of patients with porphyria cutanea tarda. *Photodermatol Photoimmunol Photomed* 1998;14:64-65.
30. Drago F, Battifoglio ML, Gelati G, Rebora A. Very low-dose chloroquine treatment for porphyria cutanea tarda. *Acta Derm Venereol* 1995;75:329-330.
31. Fracanzani AL, Taioli E, Sampietro M, et al. Liver cancer risk is increased in patients with porphyria cutanea tarda in comparison to matched control patients with chronic liver disease. *J Hepatol* 2001;35:498-503.