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CASE REPORT

Porphyria cutanea tarda as a complication of therapy for chronic hepatitis C

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Abstract

There is a strong association between porphyria cutanea tarda (PCT) and chronic viral hepatitis C. Therapy for chronic viral hepatitis C may improve PCT. However, there are only a few reports of the *de novo* development of PCT during therapy for chronic viral hepatitis C. We describe the development of PCT in a 56-year-old patient with chronic viral hepatitis C after 12 wk of peginterferon/ribavirin therapy. In addition, the patient was homozygous for the H63D hereditary hemochromatosis gene (*HFE*) mutation. The association of PCT with chronic viral hepatitis C and the possible role of hepatic iron overload and ribavirin-induced hemolytic anemia in the development of PCT during therapy for chronic viral hepatitis C are discussed.

Key words: Porphyria; Hepatitis C virus; Ribavirin; Pegylated interferon; Hemochromatosis

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INTRODUCTION

Porphyria cutanea tarda (PCT), the most common of the porphyrias, results from reduced activity of uroporphyrinogen decarboxylase (UROD), an enzyme in the heme biosynthetic pathway[1]. Clinical signs of PCT include photodistributed erythema, skin fragility, bullae, erosions and hypertrichosis. A strong association between PCT and hepatitis C virus (HCV) infection is well established[2]. Improvement of PCT during HCV treatment with interferon has been frequently described[3-6]. On the other hand, *de novo* occurrence of PCT during interferon plus ribavirin therapy for chronic viral hepatitis C has previously been described in only four patients[7-9]. Herein we describe the *de novo* development of PCT in a patient with chronic HCV infection undergoing combined peginterferon/ribavirin therapy, who was also found to be homozygous for the H63D mutation of the *HFE* gene.

CASE REPORT

Chronic hepatitis C (genotype 1a) was diagnosed in a 56-year-old man with a history of blood transfusions while serving in Vietnam. Past medical history included alcohol and cocaine dependency, as well as a history of treatment for rheumatoid arthritis, which was later characterized as osteoarthritis. He denied alcohol use for more than four years prior to initiation of ribavirin/interferon therapy. Prior tests for hepatitis B and HIV were negative. He did not smoke. Family history was noncontributory. At presentation, liver biopsy showed mildly active chronic hepatitis C with portal fibrosis (Batts and Ludwig grade 2 inflammation and stage 1 fibrosis). Hepatic iron deposition was not commented on. HCV-RNA PCR showed 102 500 copies and serum transaminases were mildly elevated (AST 53 IU/L and ALT 100 IU/L). The patient was treated with peginterferon-α2b (150 μg/wk) and ribavirin (1200 mg/day) for 44 weeks of a planned 48-week course. Treatment ceased early secondary to anemia and neutropenia. Viral clearance was achieved after 16 wk of treatment and HCV-RNA PCR remained negative at the

end of and 6 mo following treatment.

After 12 wk of therapy, the patient presented with multiple hand blisters and erosions in various stages of healing, consistent with PCT. Diagnosis of PCT was confirmed by detection of elevated urinary uroporphyrin (599 μg/24 h, N < 44) and heptacarboxyl-porphyrin (799 μg/24 h, N < 12) levels. Because of the patient's anemia (hemoglobin dropped from 15.7 g/dL pretreatment to 10.4 g/dL at onset of PCT), treatment of PCT with phlebotomy was deferred until completion of his peginterferon/ribavirin treatment. Clinical resolution of PCT occurred thereafter with repeated phlebotomy. Prior to initiation of phlebotomy, ferritin was markedly elevated (2920 ng/mL, N < 464) and the transferrin saturation was 81%. The patient was found to be homozygous for the H63D *HFE* gene mutation.

DISCUSSION

PCT arises from decreased activity of hepatic uroporphyrinogen decarboxylase (UROD), an enzyme in the heme synthetic pathway[1,10]. Although about 20% of cases involve mutations in the UROD gene (type Ⅱ PCT), nearly all other occurrences (approximately 80%) are considered to arise sporadically (type Ⅰ PCT)[1]. The genetic defects in type Ⅱ PCT alone are not sufficient to cause phenotypic PCT, for they reduce UROD activity by no more than 50%[10]. Other contributing factors, including those that may be associated with type I PCT, must be present for phenotypic expression. Whether sporadic or familial, the clinical manifestations of PCT are the same, including skin fragility, erythema, bullae, erosions, hypertrichosis and milia in sun-exposed areas of the skin[11]. These lesions result from the photosensitizing effects of porphyrins that accumulate in the skin or dermal blood vessels[12]. The pathogenesis of the enzymatic defect in sporadic PCT is unclear, but is postulated to involve increased oxidative stress in the liver, modulated by multiple exogenous and endogenous factors[12,13].

Well-recognized risk factors for PCT include HCV infection, hereditary hemochromatosis and other iron overload syndromes, as determined by mutations in the *HFE* gene, excessive alcohol use, HIV infection, and exposure to estrogen (including pregnancy) and polyhalogenated aromatic compounds[10]. The association of PCT with chronic HCV infection is particularly strong. The prevalence of HCV infection in patients with PCT was found to be about 50% in a recent systematic review and meta-analysis, though there was marked regional variation[2]. The underlying mechanism is unclear, despite this strong association of PCT with chronic HCV infection[11].

Mainstays of PCT management include phlebotomy, chloroquine and avoidance of sun exposure[12]. HCV-associated PCT has, similarly, been reported to improve following initiation of interferon monotherapy[3-6], though improvement with interferon administration is not universally described[14]. Likewise, we found a single report describing the onset of HCV-associated PCT 2 years following initiation of interferon monotherapy in a patient who also had non-Hodgkins lymphoma and dermatomyositis[15]. The skin lesions resolved with chemotherapy and the authors hypothesized that the lymphoma had triggered PCT.

In addition to the case we report here, *de novo* occurrence of PCT during interferon and ribavirin therapy for chronic HCV infection has been described in only 4 other cases[7-9]. Jessner *et al*[7] reported what they considered to be *de novo* occurrence of PCT after 4 months of therapy in a woman who had noticed occasional self-resolving small blisters prior to HCV therapy. A liver biopsy showed moderate iron deposition. She was found to have both type Ⅰ ("familial") PCT and heterozygosity for the C282Y HFE gene defect. Thevenot *et al*[8] described two patients without HFE gene defects who had onset of PCT one and two months, respectively, after initiating ribavirin and interferon therapy. One patient was noted to have a ferritin of 2408 ng/mL and the other patients' liver biopsy showed mild iron deposition in Kupffer cells. Mutation analysis of the UROD gene was not reported in either case. Finally, Frider *et al*[9] reported a 47-year-old patient who developed PCT after 44 weeks of ribavirin and interferon therapy. HFE genotyping revealed C282Y/H63D compound heterozygosity.

In all 5 reported cases of *de novo* PCT during ribavirin/interferon therapy, including that we describe here, the patients had clinical evidence of systemic or hepatic iron overload. Although the mechanism is unclear, iron overload is believed to play a significant role in the pathogenesis of PCT[16,17], possibly modulated by an iron-dependent reversible inactivation of hepatic UROD[16]. Supporting this are the oft-noted observations that the majority of patients with PCT exhibit some iron overload, iron depletion improves PCT, and iron administration produces relapse[13,16,17].

Possibly contributing to hepatic iron loading in the reported *de novo* occurrences of PCT was the administration of ribavirin. A well-recognized major side effect of ribavirin is dose-dependent reversible hemolytic anemia[18]. Although Thevenot *et al*[8] did not comment on anemia, Jessner *et al*[7] noted onset of anemia concomitant with diagnosis of PCT. In addition to anemia, hepatic iron stores have been found to increase following prolonged ribavirin administration[19,20], with a relatively greater concentration of iron demonstrated in hepatocytes *versus* Kupffer cells[20]. The additional hepatic iron loading attributable to ribavirin administration may reduce the level of UROD activity sufficiently for PCT to become manifest in otherwise susceptible individuals. Consequently, screening for treatable PCT-associated conditions, such as hemochromatosis, should be considered prior to initiation of peginterferon/ribavirin therapy for chronic HCV.

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