

# Blistering Disease During the Treatment of Chronic Hepatitis C With Ledipasvir/Sofosbuvir

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Hepatitis C virus-associated porphyria cutanea tarda can result from viral-induced inhibition of uroporphyrinogen decarboxylase and the subsequent accumulation of uroporphyrins and associated metabolites in urine.

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**P**orphyrin cutanea tarda (PCT) is the most common type of porphyria. The accumulation of porphyrin in various organ systems results from a deficiency of uroporphyrinogen decarboxylase (UROD).<sup>1-3</sup> Chronic hepatitis C virus (HCV) causes a hepatic decrease in hepcidin production, resulting in increased iron absorption. Iron loading and increased oxidative stress in the liver leads to nonporphyrin inhibition of UROD production and to oxidation of porphyrinogens to porphyrins.<sup>4</sup> This in turn leads to accumulation of uroporphyrins and carboxylated metabolites that can be detected in urine.<sup>4</sup>

Signs of PCT include blisters, vesicles, and possibly milia developing on sun-exposed areas of the skin, such as the face, forearms, and dorsal hands.<sup>4</sup> Case reports have demonstrated a resolution of PCT in patients with chronic HCV with treatment with direct-acting antivirals (DAAs), such as ledipasvir/sofosbuvir.<sup>1,3</sup> However, here we present 2 cases of patients who developed blistering diseases during treatment of chronic HCV with ledipasvir/sofosbuvir. Neither demonstrated complete resolution of symptoms during the treatment regimen.

## CASES

### Patient 1

A 63-year-old white male with a history of chronic HCV (genotype 1a), bipolar disorder, hyperlipidemia, tobacco dependence, and cirrhosis (F4 by elastography) presented with minimally to moderately painful blisters on his bilateral dorsal hands that had developed around weeks 8 to 9 of treatment with ledipasvir/sofosbuvir. The patient reported that

no new blisters had appeared following completion of 12 weeks of treatment and that his current blisters were in various stages of healing. He reported alcohol use of 1 to 2 twelve-ounce beers daily and no history of dioxin exposure. His medications included doxepin, hydralazine, hydrochlorothiazide, quetiapine, folic acid, and thiamine. His hepatitis C viral load was 440,000 IU/mL prior to treatment. Tests for hepatitis B surface antigen and HIV antibodies were negative. His iron level was 135  $\mu\text{g/dL}$ , total iron-binding capacity (TIBC) was 323  $\mu\text{g/dL}$ , and ferritin was 299.0 ng/mL. His *HFE* gene was negative for mutations. Following 4 weeks of treatment with ledipasvir/sofosbuvir, a hepatitis C viral load was not detected.

A physical examination on presentation revealed erosions with overlying hemorrhagic crusts on the bilateral dorsal hands (Figure). The differential diagnosis included PCT, pseudo-PCT, bullous pemphigoid, bullous arthropod bite reaction, and epidermolysis bullosa acquisita. A punch biopsy of the lesion on the right dorsal hand demonstrated re-epithelialization of a previously formed subepidermal bullae deemed compatible with PCT or pseudo-PCT. A 24-hour high-performance liquid chromatography quantitative urine porphyrin showed greatly elevated levels of urine porphyrins, including uroporphyrins and heptacarboxylporphyrins, and slight elevations of hexacarboxylporphyrins, pentacarboxylporphyrins, and coproporphyrins indicating a diagnosis of PCT.

At the 4-month follow-up, the patient reported no new blister formations. A physical examination revealed well-healed scars and several

FIGURE

**Erosions With Overlying Hemorrhagic Crusts**

clustered milia on bilateral dorsal hands with no active vesicles or bullae noted.

**Patient 2**

An African American male aged 63 years presented with a 1-month history of moderately painful blisters on his bilateral dorsal hands during treatment of chronic HCV (genotype 1a) with ledipasvir/sofosbuvir. His medical history included gout, tobacco and alcohol addiction, osteoarthritis, and hepatic fibrosis (F3 by elastography). The patient's medications included allopurinol, lisinopril, and hydrochlorothiazide. He reported no history of dioxin exposure. On the day of presentation, he was on week 9 of the 12-week treatment ledipasvir/sofosbuvir regimen. Laboratory results included an initial HCV viral load of 1,618,605 IU/mL. Tests for hepatitis B surface antigen and HIV antibodies were negative. His iron was 191  $\mu\text{g}/\text{dL}$ , TIBC 388  $\mu\text{g}/\text{dL}$ , and ferritin 459.0 ng/mL. After 4 weeks of treatment, the patient's hepatitis C viral load was undetectable.

A physical examination revealed several re-

solving erosions to his bilateral dorsal hands, some of which had overlying crusting along with one small hemorrhagic vesicle on the right dorsal hand. A punch biopsy of the hemorrhagic vesicle was performed and demonstrated a cell-poor subepidermal blister with festooning of the dermal papilla. A direct immunofluorescence study showed immunoglobulin (Ig) G fluorescence along the dermal-epidermal junction and within vessel walls in the superficial dermis. Weak IgM and C3 fluorescence also was noted within vessel walls in the superficial dermis. All of the patient findings and history were consistent with PCT, although pseudo-PCT also was a consideration. A 24-hour urine sample yielded negative results for porphobilinogen. Urine porphyrin test results were not available, leading to a presumptive histological diagnosis of PCT.

The patient completed 11 of the prescribed 12 weeks of ledipasvir/sofosbuvir. The blisters resolved shortly thereafter.

**DISCUSSION**

PCT has a well-established association with chronic HCV infection.<sup>4</sup> We present 2 cases of a blistering disease clinically and histologically compatible with PCT that developed in patients only after initiation of treatment for chronic HCV with ledipasvir/sofosbuvir. One case was confirmed as PCT on the basis of compatible histopathologic findings and a urine porphyrin assay that showed elevated levels of uroporphyrins and carboxylated metabolites. The second case was clinically and histologically suggestive of PCT but not confirmed by urine porphyrin testing. In both patients, after 8 to 9 weeks of a 12-week course of antiviral therapy, the blistering lesions were noted but appeared to be resolving, and no new lesions were noted after discontinuation of therapy. It appeared that the antiviral treatment temporally triggered the initiation of the blistering skin disease, and as the chronic HCV infection cleared after treatment, the blistering lesions also began to resolve.

Mechanistically, it is known that the virally-induced hepatic damage leads to inhibition of uroporphyrinogen decarboxylase, and the subsequent oxidation of porphyrinogens to porphyrins. Cofactors such as HIV infection also may contribute to development of PCT.<sup>5</sup>

De novo PCT has been documented during therapy using interferon and ribavirin.<sup>6</sup> The

hemolytic anemia and increased hepatic iron were implicated as potential etiologies.<sup>6</sup> Patients with HCV and PCT treated with the newer direct-acting antiviral therapies have been described to have experienced improvement in PCT symptoms.<sup>3</sup>

Although there were rare reports of deterioration in renal and liver function,<sup>7</sup> reactivation of HBV infection,<sup>8</sup> and Stevens-Johnson syndrome<sup>9</sup> with antiviral therapy, these complications were not observed in these patients. Both patients also had successful resolution of HCV infection, and by completion of the antiviral therapy, the blistering also resolved.

## CONCLUSION

PCT is an extrahepatic manifestation of HCV infection. Health care providers should be aware of the association of chronic HCV infection with PCT. The findings of PCT should not result in the delay or discontinuation of antiviral therapy.

## Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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