

# Hepatitis-Induced Porphyria: Are Direct-Acting Antiviral Agents the Way of the Future?

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## ABSTRACT

Porphyria cutanea tarda (PCT) is the most common porphyria and has a strong association with hepatitis C virus (HCV) infection and iron overload. Previous HCV treatment regimens, including interferon with or without ribavirin, may precipitate PCT relapse. Few case reports have shown that newer oral therapies, such as direct-acting antiviral agents, can successfully treat PCT parallel with HCV treatment. We present a case of a patient with non-iron-associated mixed porphyria that dramatically improved with direct-acting antiviral agent therapy for his HCV supporting the association of porphyria with chronic HCV.

## INTRODUCTION

Porphyrias are a family of diseases caused by altered enzymes related to heme biosynthesis, some of which are associated with skin manifestations, including porphyria cutanea tarda, erythropoietic protoporphyria, X-linked protoporphyria, congenital erythropoietic porphyria, and hepatoerythropoietic porphyria.<sup>1</sup> The skin lesions are precipitated by the photosensitizing effects of porphyrin buildup in the skin and dermal blood vessels.<sup>2</sup> Although porphyria cutanea tarda (PCT), caused by a deficiency in the enzyme uroporphyrinogen decarboxylase,<sup>3</sup> is the most common type to be associated with skin lesions, some present with a mixed picture.<sup>4</sup> Although there is a known strong association between PCT and hepatitis C virus (HCV) infection and iron (Fe) overload, with a seroprevalence of around 50%–70%,<sup>5,6</sup> there are only case reports of successful therapy with direct-acting antiviral agents (DAAs).<sup>7–9</sup> We report a case of a man with chronic HCV without Fe overload who presented with PCT-predominant mixed porphyria that subsequently improved on DAA therapy and after sustained virologic response 12 weeks after completion of therapy (SVR-12).

## CASE REPORT

A 58-year-old white man with a history of chronic HCV, genotype 1a, Crohn's disease, and stage IV renal cell carcinoma metastatic to the lung presented to the clinic for evaluation of his HCV. The patient described a painful, pruritic rash that started 6–8 weeks earlier. He denied jaundice, edema, and abdominal pain. Physical examination was remarkable for coalescent erythematous plaques with hemorrhagic crust, linear erosions, and tense bullae (Figure 1). Laboratory workup revealed aspartate aminotransferase 112 U/L, alanine aminotransferase 166 U/L, HCV ribonucleic acid 2,720 IU/mL, HCV genotype 1a, serum ferritin 35 ng/mL, iron saturation 9%, negative cryoglobulins and rheumatoid factor, serum porphyrins 6 and zinc protoporphyrin 69 µg/dL, urine heptacarb 74 µg/L, pentacarb 11 µg/L, uroporphyrin 91 µg/L, coproporphyrin I 329 µg/L, and coproporphyrin III 247 µg/L. Liver elastography showed F1-2 fibrosis (7.5 kPa) and no steatosis. Skin biopsy of the affected area revealed lichen simplex chronicus. The patient was initiated on glecaprevir/pibrentasvir for 8 weeks with marked improvement of his rash, normalized liver enzymes, and undetectable viral load during treatment and at SVR-12 (Figure 2).

## DISCUSSION

PCT, the most common of the porphyrias, is a blistering disorder that is characterized by increased skin fragility and marked photosensitivity. In our patient, although his skin biopsy was nondiagnostic, the diagnosis of a mixed PCT was based on elevated



**Figure 1.** Porphyria cutanea tarda before initiation of direct-acting antivirals.

laboratory values and skin findings. Although often associated with iron overload, the association of HCV infection and acquired PCT is well known, and there are no current guidelines regarding the treatment of PCT when associated with HCV infection. It is notable that although prevalence is high, only a minority of HCV-infected patients (1%–4%) develop overt PCT.<sup>10</sup> This suggests the necessity for potential susceptibility factors to precipitate PCT. These include heavy alcohol use, iron overload smoking, HCV, hemochromatosis gene mutation, estrogen use, human immunodeficiency virus infection, and inherited uroporphyrinogen decarboxylase mutations.<sup>11</sup>

In the past, treatment with interferon has not always successful with a sustained virologic response of 16–82%. It can also cause significant side effects and may exacerbate PCT relapse.<sup>12</sup> As such, it was advised to treat PCT independently of HCV with hydroxychloroquine or phlebotomy because PCT is more symptomatic and needs more urgent treatment. Furthermore, response to interferon-based therapy for HCV is better after decreased hepatic iron, which is elevated with active PCT.<sup>13</sup> The newer DAA treatments for HCV, however, are safer, require shorter courses (8–12 weeks), and are more effective than interferon-based therapies with sustained virologic responses of close to 95%.<sup>14</sup> In limited studies, DAA was not associated with



**Figure 2.** Skin findings after treatment of direct-acting antivirals.

PCT relapse and effectively treated PCT.<sup>7</sup> This could make treatment of PCT with hydroxychloroquine or phlebotomy unnecessary. Hydroxychloroquine, in particular, can carry significant side effects not seen with DAA.

Although our patient had a mixed type of PCT, he did not have Fe overload and showed drastic improvement of his cutaneous lesions after starting glecaprevir/pibrentasvir DAA therapy parallel to his HCV response with normalization of liver enzymes and undetectable viral load with SVR-12. This may suggest that the mechanism of PCT in HCV patients involves direct viral activity. As there are only a few cases reported in the literature to improve from DAA therapy, further studies are needed to determine whether DAA agents can be used as primary treatment for non-Fe overload HCV-associated PCT.

## DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. JJ John is the article guarantor.

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