

Three cases of incident lichen planus after direct-acting antiviral treatment for hepatitis C



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Key words: direct-acting antivirals; hepatitis C; lichen planus.

Hepatitis C virus (HCV) infection is associated with many extrahepatic manifestations, including skin diseases such as lichen planus (LP).¹ New direct-acting antiviral (DAA) agents are highly effective in treating HCV,² and many extrahepatic manifestations of HCV improve after treatment.³ However, limited data exist regarding outcomes of HCV-associated skin disease after DAA treatment. Case reports and series have documented HCV-associated cryoglobulinemic vasculitis,⁴ porphyria cutanea tarda,⁵ and oral and cutaneous LP⁶⁻¹⁰ improving or resolving after DAA treatment. Conversely, new-onset LP developing 3 months after HCV treatment with elbasvir-grazoprevir was recently described,¹¹ and a patient with pre-existing oral LP who had new cutaneous LP after treatment with ledipasvir-sofosbuvir was also reported.¹² We present 3 patients in whom new LP developed within months after treatment of HCV with DAA. With these cases, we highlight the need to further understand the connection between HCV and LP.

CASE 1

A 72-year old man with a history of HCV genotype 1a presented to the University of California, San Francisco (UCSF) Dermatology Clinic in April 2015 complaining of an itchy rash on his bilateral lower legs and torso. He had longstanding well-controlled HIV infection on abacavir, lamivudine, and raltegravir. He completed HCV treatment in December 2014 at an outside hospital with simeprevir-sofosbuvir, achieving sustained viral response (SVR). He had not received prior treatment for HCV.

In January 2015, scaly red-purple papules and plaques erupted on his lower legs (Fig 1). No oral or

Abbreviations used:

DAA:	direct-acting antiviral
HCV:	hepatitis C virus
LP:	lichen planus
SVR:	sustained viral response
UCSF:	University of California, San Francisco

genital lesions were noted. He did not respond to trials of triamcinolone 0.1% ointment and fluocinonide 0.05% cream, and a skin biopsy was obtained, confirming LP (Fig 2). Tacrolimus 0.1% ointment was prescribed. The lesions have since resolved.

CASE 2

A 61-year-old man presented to the UCSF oral medicine clinic in December 2015 after diagnosis of oral LP at an outside clinic. He had a history of genotype 1a HCV infection treated with sofosbuvir, ledipasvir, and ribavirin, achieving SVR in July 2015. He previously underwent 2 unsuccessful HCV treatments, not responding to pegylated interferon-ribavirin in the 1990s and pegylated interferon, ribavirin, and telaprevir in 2008. He was taking hydrochlorothiazide-lisinopril for hypertension, citalopram for depression, montelukast and albuterol for asthma, ranitidine for gastroesophageal reflux disease, and as-needed ibuprofen, cyclobenzaprine, and hydrocodone-acetaminophen for low back pain.

Weeks after DAA completion he had gingival pain and white lesions on his buccal mucosa. The patient's local dentist prescribed clotrimazole troches, but symptoms did not improve. His primary

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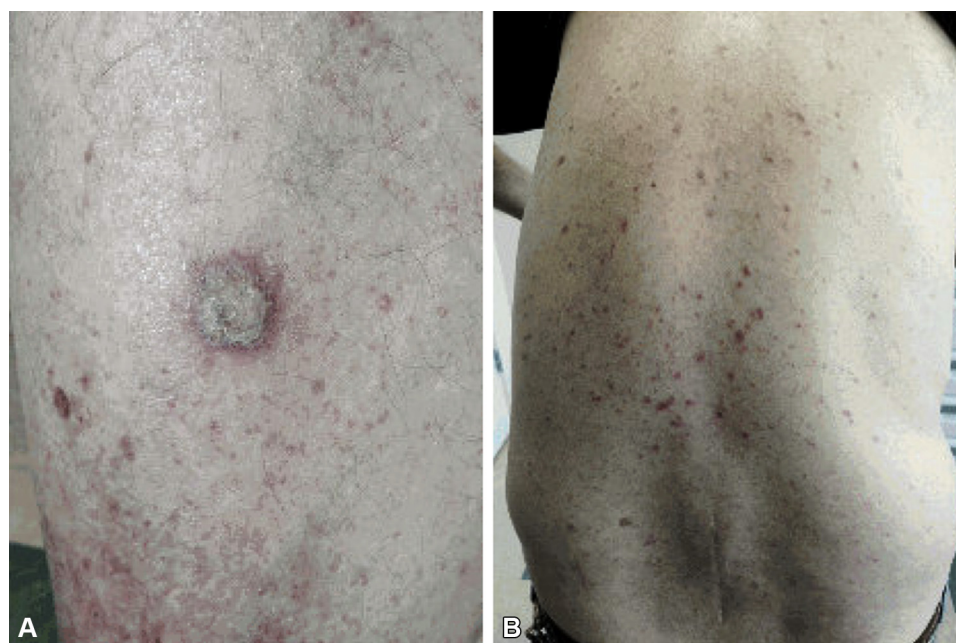


Fig 1. **A**, LP on anterior leg of patient 1. **B**, LP on back of patient 1.

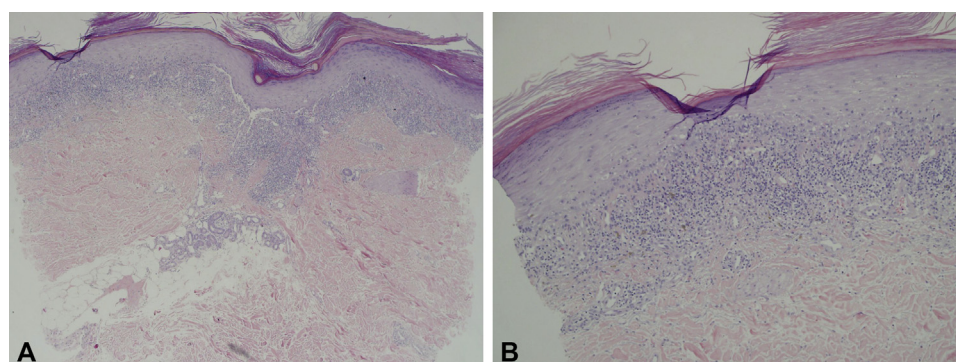


Fig 2. **A**, Biopsy from patient 1 exhibits a band-like infiltrate of lymphocytes in the papillary dermis, beneath a thickened epidermis with serrated and muted rete ridges and foci of hypergranulosis, and compact hyperkeratosis. The lymphocytic infiltrate obscures the dermoepidermal junction, where there is vacuolar change accompanied by dyskeratotic cells and focal separation of the epidermis at the junction. **B**, Photomicrograph of biopsy from patient 1.

care physician referred him to a local otolaryngologist, who performed a biopsy, which found a lichenoid infiltrate of lymphocytes and histiocytes present in the superficial submucosa, mild epidermal spongiosis, and scattered dyskeratotic keratinocytes. Eosinophils were not seen.

Exam at the time of presentation to UCSF Oral Medicine showed erythema and white striations on the bilateral buccal mucosa, posterior facial gingiva, and vestibule. No cutaneous or genital lesions were described. Dexamethasone elixir and clotrimazole troches, 10 mg, were prescribed, and the patient was lost to follow-up.

CASE 3

A 64-year-old woman presented to the UCSF Dermatology Clinic in December 2015 with several months of itchy rash on her buttocks and lower extremities. She had a history of cirrhosis secondary to genotype 1a HCV infection and failed pegylated interferon and ribavirin 15 years prior. She completed HCV treatment at an outside hospital approximately 1 year before with sofosbuvir, ledipasvir, and an experimental GS9451 HCV protease inhibitor with SVR.

Her examination found erythematous papules and plaques on buttocks, thighs, and lower legs.

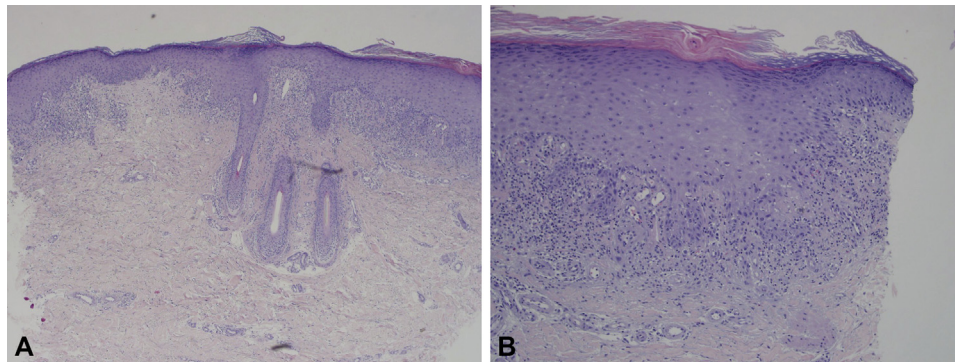


Fig 3. **A**, Low-power photomicrograph of biopsy from patient 3 shows a band-like infiltrate of lymphocytes in the papillary dermis, beneath a thickened epidermis with serrated rete ridges, foci of hypergranulosis, and compact hyperkeratosis. The lymphocytic infiltrate obscures the dermoepidermal junction, where there is vacuolar change accompanied by dyskeratotic cells. **B**, High-power photomicrograph from patient 3.

No oral or genital lesions were described. Biopsy findings were consistent with LP (Fig 3).

She was referred for phototherapy at an outside dermatologist and was lost to UCSF Dermatology follow-up, although according to recent records from hepatology, her LP has improved.

DISCUSSION

The relationship between LP and HCV infection is well described. Although conflicting conclusions exist in the literature, a 2010 meta-analysis analyzed 33 studies and found patients with LP were 5 times more likely to have HCV than controls.¹³ Although the etiopathogenesis remains poorly understood, hypotheses suggest basal keratinocytes present either a viral antigen or self-antigen that mimics a viral antigen to cytotoxic T cells, which causes tissue destruction.¹⁴ Nearby plasmacytoid dendritic cells also produce type-1 interferons, which further recruit cytotoxic T cells that target keratinocytes.¹⁴

Treatment with interferon-containing HCV regimens were frequently associated with flares of pre-existing LP or new diagnosis of LP,¹⁵ possibly because interferon signalling plays a direct role in LP pathogenesis.¹⁴ Ribavirin has also been associated with exacerbation of LP.¹⁵ However, none of our patients recently received interferon, and 2 of our patients had DAA treatments free of ribavirin.

In contrast to our patients, several cases published in the literature describe patients whose LP improved or resolved after treatment with DAA.⁷⁻¹¹ Perhaps the pathogenesis of LP in our patients differs from that of these patients, or perhaps the immunopathogenic drivers of LP in the setting of HCV lag behind treatment or are exacerbated by treatment in some cases. It is also possible our patients' LP was unrelated to HCV or its treatment.

Notably, all our patients are older, and advanced age increases the risk of LP. Our patients' LP lesions could also represent lichenoid drug eruptions, particularly patient 2, who was taking several medications (lisinopril, hydrochlorothiazide, ibuprofen, and ranitidine) implicated in lichenoid drug eruptions. Interestingly, all our patients had taken sofosbuvir as a component of their DAA regimens, raising the possibility of a lichenoid drug eruption to this medication. However, the case described by Kusari et al¹² was treated with a sofosbuvir-free regimen, and none of our patients exhibited histopathologic findings suggestive of lichenoid drug eruptions (eg, focal parakeratosis, abundant plasma cells, or eosinophils).

Larger, prospective studies of patients treated with DAA are needed to better describe the relationship between HCV treatment and incident LP, as well as the prognosis of pre-existing LP after DAA treatment. Our findings suggest patients treated with DAA may remain at risk for LP development.

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