BACKGROUND

Extrahepatic manifestations of chronic hepatitis C virus (HCV) infection frequently involve the skin. The impact of HCV treatment with direct-acting antivirals (DAAs) on skin disease is discussed controversially in patients with concomitant psoriasis. Here, we report a flare of psoriasis leading to resolution of skin manifestations with continued DAA treatment. Infection with the hepatitis C virus (HCV) can cause multiple extrahepatic manifestations such as glomerulonephritis, polyarteritis nodosa, and type 2 diabetes, mellitus, and cardiovascular disorders.¹ HCV-associated skin diseases comprise lichen ruber, vasculitis from mixed cryoglobulinemia, and also psoriasis.² Extrahepatic skin manifestations usually improve when patients with chronic hepatitis C achieve a sustained virologic response (SVR) on direct-acting antiviral (DAA) HCV treatment.³ Here, we report exacerbation of psoriasis on DAA treatment with elbasvir/grazoprevir (Zepatir®) which ultimately lead to resolution of psoriasis upon continuation of HCV therapy.

CASE PRESENTATION

In 2019, a 47-year-old Russian woman presented at our hepatology outpatient department for treatment of chronic hepatitis C. Her past medical history comprised surgery for ovarian cysts and a mild form of psoriasis diagnosed 4 years ago. However, psoriasis was asymptomatic for nearly a year prior to presentation and the patient did not show any psoriatic skin changes on the initial investigation.

The patient had chronic hepatitis C genotype 1b with a viral load of 288,376 IU/ml. Blood tests showed a slightly elevated GGT of 48 U/L (reference range <39 IU/ml),
while levels of aminotransferases ALT and AST as well as serum bilirubin were in the normal range. Major liver fibrosis was excluded by transient elastography which revealed a normal liver-stiffness of 4 kPa.

Presumably, infection had been acquired 15 years before owing to extensive oro-dental surgery. The patient had not received prior HCV treatment, and a 12-week therapy with fixed-dose oral elbasvir/grazoprevir (Zepatir®) was initiated.

At her first visit at treatment week 4, the patient presented with multiple, circumscribed, scaly, new psoriatic itching skin lesions on upper and lower extremities as well as the body-trunk (Figure 1A,B), which had appeared 1 week after start of DAA treatment initiation and gradually worsened over time. A specialist dermatologist confirmed the diagnosis of exacerbated psoriasis and classified disease activity as a Psoriasis Area and Severity Index (PASI) of 33. Topical therapy with vitamin D and beclomethasone was started. At this time, HCV RNA had already become undetectable (detection limit <12 IU/ml), and all liver enzymes were completely normalized.

Although we could not rule out exacerbated psoriasis to be side effect of elbasvir/grazoprevir and the pruritus was really disturbing, the patient insisted to continue DAA treatment. At the next visit (week 8) on continued DAAs, her psoriatic lesions persisted without any changes but slightly started to improve at the end of therapy (treatment week 12). Throughout treatment and at follow-up, HCV viral loads remained undetectable. Finally, the skin lesions started to resolve completely after 12 weeks of follow-up leaving behind only some increased scaling at Week 24 after the end of treatment (Figure 1C,D).

3 | DISCUSSION AND CONCLUSION

The underlying etiology of psoriasis is unknown; however, it is considered to reflect a chronic, cell-mediated, autoimmune skin condition, which can occur or exacerbate in association with chronic hepatitis C. In the past, chronic hepatitis C was treated with interferon-based therapies, which acts as immunostimulatory cytokine and can trigger and exacerbate any kind of autoimmune condition including psoriasis. Current treatment with DAAs is highly effective and has a good safety profile. Importantly, DAAs do not involve stimulation of the immune system, so induction of psoriasis exacerbation is an unexpected event. Thus, at first a rare side effect of elbasvir/grazoprevir therapy was considered as a potential cause of psoriasis exacerbation in our patient. However, stable skin manifestations when the patient continued on DAAs and the gradual resolution of skin lesions only after the patient had achieved a sustained viral response prompts towards an alternative underlying pathomechanism. In the literature, two alternative scenarios have been described for the course of psoriasis under DAAs: Heppt et al. reported two cases: the first one experienced psoriasis exacerbation,
and the second one suffered de novo induction of psoriasis during/after ledipasvir/sofosbuvir treatment. Of note, both patients had a history of prior interferon treatment, whereas our patient was treatment-naive. Beyond that, our patient received elbasvir/grazoprevir, that is, a different treatment regimen, which further supports our assumption, that aggravation of psoriasis was not a substance-related side effect. On the contrary, complete resolution of chronic psoriasis after ledipasvir/sofosbuvir treatment without exacerbation has also been reported. Here, our patient may provide a hint to improved understanding of such divergent observations in that we observed a sequence of events: first, a phase of psoriasis exacerbation during the active HCV elimination phase on DAA therapy followed by complete recovery once HCV was fully eliminated. In line with this hypothesis, Heppt et al. had interpreted the appearance of psoriasis on DAA treatment as manifestation of an immune reconstitution inflammatory syndrome in analogy to findings in HIV infected patients when the immune system has improved under antiretroviral treatment (ART) and HIV viral loads decline. Indeed, psoriasis can occur and exacerbate in up to 3% of HIV positive patients on antiretroviral therapy. However, in the patients reported by Heppt et al. aggravation of psoriasis had occurred when HCV viral loads had already become undetectable.

Our patient may elucidate this apparent discrepancy by demonstrating IRIS-like exacerbation with a flare of psoriasis when HCV viral loads were still further declining below the level of (quantitative) detection, while the final outcome was complete resolution of psoriasis, which was noted to begin at treatment week 8.

The immunological changes underlying apparent immune reconstitution in DAA treatment of chronic HCV infection remain unclear at present, particularly since after successful DAA treatment activated CD4+ regulatory T cells, suppressing inflammatory responses, persist for quite some time at increased levels as compared to healthy controls. On the contrary, activation of dendritic cells (DC) seems to play a role in the initial stage of psoriasis. DCs are antigen-presenting cells which populate the liver in high amounts. They are a potent source of type I interferon secretion in HCV infection and have sufficient potential to trigger activation of psoriasis during HCV infection. Interestingly, the frequency of DCs in peripheral blood was higher in patients who achieved a SVR than in those who failed. Thus, there seems to exist a reciprocal relationship between HCV clearance vs. numbers and functionality of dendritic cells including their production of inflammatory cytokines. Thus far, changes in DC refer to patients treated with IFN and ribavirin. Therefore, it remains unclear at present if the reciprocal relationship between treatment success and DCs still holds true also in DAA treatment.

Taken together, psoriasis and chronic HCV infection seem to share some immunological mechanisms, for example, elevated levels of TNF alpha, which still await further elucidation, especially with respect to the triggering factors. With improved insights, a typical sequence of events may become apparent with activation as the early step and complete resolution as the final outcome, as has been illustrated for psoriasis in our patient. Our observation may be important for the future management of patients with chronic Hepatitis C infection and can reassure physicians to proceed antiviral treatment besides psoriasis aggravation.

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CONFLICTS OF INTEREST
All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
LD was responsible for the conception of this work and drafted the report together with US. AH was involved in patient care together with LD and US. AH, BL, CPS, and US helped with data collection and critically revised the manuscript.

CONSENT
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DATA AVAILABILITY STATEMENT
Data sharing not applicable – no new data generated.

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