

# Development of Drug-Induced Inverse Psoriasis in a Patient with Crohn's Disease

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## ABSTRACT

Crohn's disease is difficult to manage and often requires multiple medications. While these drugs vastly improve quality of life, physicians must monitor for adverse events. We report a case of a flare of inverse psoriasis after 15 months of treatment with ustekinumab. This is the third reported case of a flare of drug-induced psoriasis after ustekinumab, and it is the first reported case with an inverse presentation; however, the clinical picture is confounded by concomitant use of hydroxychloroquine. Inverse psoriasis is a rare variant of drug-induced psoriasis of which physicians must be cognizant while treating patients with Crohn's disease.

## INTRODUCTION

Crohn's disease is difficult to manage and often requires multiple systemic medications to control over a lifetime. These medications can dramatically improve patients' quality of life, but they are also associated with a multitude of side effects, including cutaneous reactions. However, drug-induced rashes may be difficult to diagnose due to complicated medication histories.<sup>1,2</sup> Psoriasiform drug eruptions have been described with many of the new biologic agents used to treat Crohn's disease, including tumor necrosis factor (TNF)- $\alpha$  inhibitors.<sup>3</sup>

## CASE REPORT

A 56-year-old woman with a history of palmoplantar psoriasis, rheumatoid arthritis (RA), and esophageal, gastric, and ileocolonic Crohn's disease since 1981 was referred to dermatology after development of a rash in the intergluteal cleft and genital area. Her Crohn's disease had been well controlled by infliximab 5 mg/kg intravenous until secondary loss of response in the pretherapeutic drug monitoring era, and then by subcutaneous adalimumab 40 mg every 2 weeks. The patient was diagnosed clinically with palmoplantar psoriasis in 2009 while on adalimumab but had no confirmation biopsy; she required no medications to control her psoriasis. It is possible this was the patient's first incidence of drug-induced psoriasis. In 2011, she developed pan-esophageal inflammation, so adalimumab was discontinued and thalidomide 50 mg daily was prescribed with resolution of the odynophagia. In September 2015, she was started on ustekinumab 90 mg every 2 months due to worsening disease of the ileum, with hydroxychloroquine 200 mg daily added in December 2015 for joint pains. Her disease was well controlled, with a simple endoscopic score for Crohn's disease of 1 in 2013 and 4 in 2016. The patient's ustekinumab level in July 2017 was 1.4 without evidence of antibodies, and her dose of ustekinumab was raised to 90 mg monthly.

The patient noticed a rash along her buttocks in December 2016 that progressed until referral to dermatology in August 2017. The patient presented with large, well-demarcated pink plaques with minimal scale and a few satellite lesions with a collarette of scale along the vagina and extending into the perineum, buttocks, and perianal area (Figure 1). Large nodules considered to be benign and likely external hemorrhoids were also present in the perianal region. She had no visible skin rash elsewhere on her body at presentation.

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**Figure 1.** Psoriasiform rash at presentation.

Wet mount and potassium hydroxide (KOH) stain of scrapings of the lesion did not demonstrate hyphae. A biopsy of the plaque revealed psoriasiform epidermal hyperplasia, and the periodic acid Schiff stain was negative for fungal organisms. A biopsy of the nodules demonstrated no malignancy. The patient was diagnosed with drug-induced inverse psoriasis and started on tacrolimus cream daily and pulsed clobetasol cream as necessary on weekends. She presented for follow up in October 2017 and demonstrated improvement (Figure 2). Medications were not halted as her Crohn's disease was well controlled under the current medication regimen.

## DISCUSSION

Inverse psoriasis, an uncommon variant of psoriasis vulgaris, presents as well-demarcated, erythematous plaques of shiny



**Figure 2.** Psoriasiform rash after 2 months of treatment with topical tacrolimus and pulse clobetasol cream.

skin and minimal scale in flexural or intertriginous regions, while the more common plaque-type psoriasis is found on extensor surfaces.<sup>4</sup> Inverse psoriasis is often confused for intertrigo and can be diagnosed on clinical grounds and confirmed with biopsy.<sup>5</sup>

The gold standard of diagnosis for drug-induced psoriasis is induction of the rash with drug use and cessation of the rash with drug withdrawal.<sup>2</sup> However, drug withdrawal is not always possible. The disease may otherwise be diagnosed by gathering a detailed history of drug treatments, determining a relationship between the drug introduction and the onset of cutaneous symptoms, and identifying other possible triggering factors, as well as with histologic findings.<sup>2</sup>

Despite being an effective therapy for most patients with psoriasis, paradoxical psoriasis induction has been reported with the use of systemic immunotherapy drugs such as TNF- $\alpha$  inhibitors.<sup>6</sup> Plaque psoriasis is the most common subtype, while inverse psoriasis was reported in only 5% of cases in a recent case series.<sup>3</sup> Ustekinumab, a systemic immunotherapy drug that acts as an IL-12/23 monoclonal antibody, has been reported twice previously to induce flares of existent psoriasis and induce psoriatic arthritis.<sup>7,8</sup> Inhibition of IL-23 can induce a decrease in TNF- $\alpha$  and an unopposed increase in interferon- $\alpha$  in genetically predisposed individuals; this is postulated to provoke flares of psoriasis.<sup>8,9</sup> The latency period of these reactions ranged from 3 days to 22 months following first administration.<sup>7</sup>

Synthetic antimalarial drugs have a well-known history of inducing flares of psoriasis.<sup>10</sup> Hydroxychloroquine and other synthetic antimalarial drugs may induce psoriasis by interfering with the integrity of the epidermal barrier.<sup>11</sup> Proposed mechanisms include inhibition of epidermal transglutaminase enzymes or interfering with cholesterol metabolism, both of which are important for the structure of the epidermal barrier.<sup>11</sup> The rash occurs quickly, typically within 4–12 weeks after drug introduction.<sup>2</sup> Thalidomide was reported to induce psoriasis in 1 case report, with disease induction within 2 weeks.<sup>12</sup>

In our case, the patient developed an inverse psoriasiform rash confirmed with biopsy 12 months after initiation of hydroxychloroquine, 15 months following therapy with ustekinumab, and 5 years following therapy with thalidomide. The patient's Crohn's disease necessitated maintaining drug therapy. However, due to the recent introduction of psoriasiform rash-inducing medications, she was diagnosed with drug-induced inverse psoriasis. While the patient has a history of palmoplantar psoriasis, the inverse presentation and the time-course of the disease in relation to drug use made a drug-induced flare of inverse psoriasis more likely. Thalidomide is an unlikely culprit due to a 5-year history of treatment without adverse event, therefore either hydroxychloroquine or ustekinumab may have triggered the disease. We believe

ustekinumab to be the most likely cause, as it has been reported to induce flares of the disease anywhere from 3 days to 22 months following induction, while hydroxychloroquine-induced psoriasis typically presents within 4–12 weeks.

Inverse psoriasis is a rare presentation of drug-induced psoriasis. Physicians must be aware of this possible skin complication of many of the medications used in Crohn's disease. Future research should further elucidate the mechanism by which ustekinumab may cause this inverse psoriatic presentation.

## DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. H. Lev-Tov is the article guarantor.

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Informed consent was obtained for this case report.

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