

Clinical Pathologic Mismatch in a TNF-α Inhibitor-Associated Drug Reaction

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ABSTRACT

A 56-year-old Caucasian male with a history of chronic plaque psoriasis, primary sclerosing cholangitis status-post liver transplant on tacrolimus, and ulcerative colitis on infliximab developed a progressive erythematous eruption with associated fatigue, anorexia, myalgias, and arthralgias. On two separate occasions, his skin biopsy demonstrated a lichenoid interface dermatitis (LID). Despite multiple courses of oral prednisone, topical steroids, and a short course of hydroxychloroquine, his symptoms continued to relapse and remit. When a temporal association between increasing his infliximab dose and the global progression of his disease was identified, he was ultimately diagnosed with a TNF-α inhibitor-induced psoriasis flare.

Despite the patient's long-standing history of psoriasis, a plausible psoriasis rebound reaction after systemic steroids was not strongly considered in light of his histopathology. Though lichenoid interface dermatitis is a commonly reported histologic finding in patients on TNF-α inhibitors, it has scarcely been reported in patients with psoriasiform eruptions clinically.

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INTRODUCTION

There have been increasing reports of paradoxical inflammatory reactions induced by TNF-α inhibitors.[1] Clinically, cutaneous reactions induced by TNF-α inhibitors are variable and have been described as lichenoid, psoriasiform, or a combination, though histopathology in all cases is overwhelmingly characterized by a lichenoid interface dermatitis (LID), a distinct inflammatory pattern characterized by keratinocyte damage along the basal layer of the epidermis.[2] In other words, the clinical presentation in patients on TNF-α blocking agents may not correlate with the expected histopathologic pattern in its native disease form (eg, plaque psoriasis is characterized by a classic psoriasiform pattern and not a lichenoid or interface infiltrate).[3,4] We herein describe a patient to illustrate this unique diagnostic challenge.

A CASE REPORT

A 56-year-old Caucasian male with a history of chronic plaque psoriasis, ulcerative colitis, and primary sclerosing cholangitis (PSC) 2 years status-post liver transplant presented with a progressive erythematous eruption of three months duration. His medications included infliximab, alprazolam, metoprolol, amlodipine, mirtazapine, and tacrolimus. There were no recent medication additions or dose adjustments. Given PSC remission post-transplant, he had been on increasing doses of infliximab, ranging 5-10 mg/kg, for management of ongoing ulcerative colitis.

Two months prior, the eruption began on his hands and progressed to involve 50% of his body surface area (BSA). A pulsed 60mg prednisone taper resulted in complete resolution. Upon cessation, he experienced a rapid rebound of the dermatitis, prompting a second prednisone pulse with minimal improvement (Figure 1). Subsequent skin biopsy demonstrated an interface dermatitis with a diffuse perifollicular and perieccrine lymphocytic infiltrate (Figure 2). Anti-neutrophil antibodies (ANA) were negative and complement levels were normal. The working differential diagnosis included connective

FIGURE 1. Innumerable erythematous non-perifollicular clustered papules with fine white adhered scales on patient's right foot.

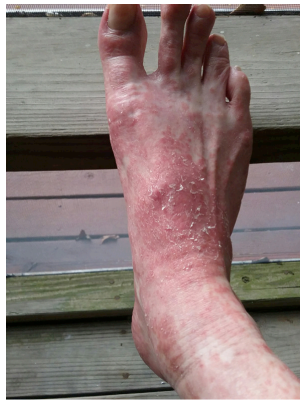
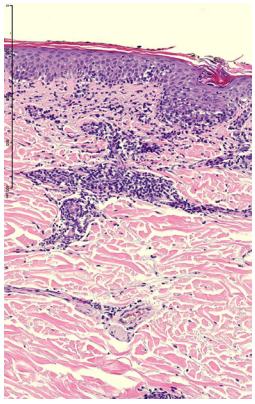


FIGURE 2. Diffuse erythema covering ~80% of patients body surface area with intertrigenous sparing.



tissue disease versus drug-induced lupus-like reaction. Despite a third prednisone pulse and topical steroids, he presented to the dermatology clinic with 80% BSA involvement (Figure 3). Further investigation demonstrated a temporal association after each infliximab infusion and a global progression as the dose per infusion increased. Additional serologies were negative for anti-double stranded DNA and anti-histone antibodies. Repeat skin biopsy confirmed a LID.

Over the next week, his condition rapidly progressed to erythroderma, diffuse non-scarring alopecia, and painful palmoplantar keratoderma. Systemically, he reported fatigue, anorexia, weight loss, myalgias, and arthralgias. These symptoms, combined with an interface dermatitis (histologically characteristic of connective tissue diseases), raised concern for an infliximab-mediated drug-induced lupus. A fourth prednisone pulse was initiated, and infliximab infusions were held. As before, he clinically resolved, however on completion of taper his rash flared, his alopecia worsened, and he developed Raynaud's phenomenon. Therefore, a decision was made to hold prednisone at a stable dose and add hydroxychloroquine.

Despite concurrent hydroxychloroquine for 2 months and interruption of infliximab for 3 months, his erythroderma persisted (Figure 4). Consequently, hydroxychloroquine was discontinued, cyclosporine was initiated (4mg/kg in two divided doses), and he was tapered off prednisone. This led to rapid, complete resolution of the rash and all associated symptoms. Ultimately, he was diagnosed with a paradoxical TNF-α induced drug eruption as opposed to a flare of underlying plaque psoriasis or a drug-induced connective tissue disease.

DISCUSSION

Dermatologic side effects are both significant and clinically relevant in patients treated with TNF-α inhibitors.[5] Cutaneous findings have been recorded in up to 60% of patients treated

FIGURE 3. Lichenoid/interface dermatitis on H&E stain. Focal basilar vacuolar degeneration, rare necrotic keratinocytes, reactive lymphocytic infiltrate.

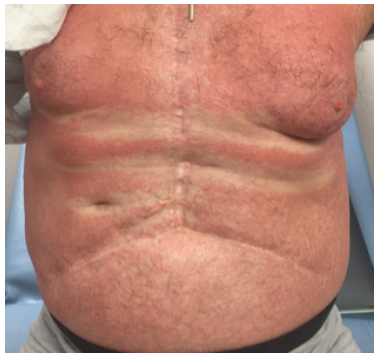
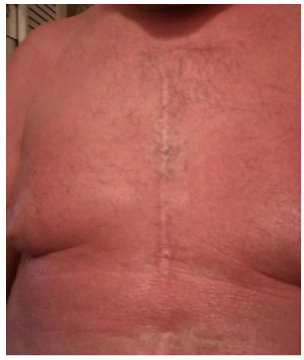


FIGURE 4. Patient progressed to complete confluent erythromderma covering almost 100% of his body surface area.



with TNF-α inhibitors for rheumatoid arthritis.[6] Paradoxically, despite psoriasiform and lichenoid eruptions often responding to TNF-α blockade, reports of drug-induced lichenoid and psoriasiform dermatitides have also been reported.[5] Often, clinical improvement can be provoked by discontinuing or switching the biologic agent, or with a short course of oral corticosteroids.[6]

Analogous to the multiplicity of clinical findings induced by TNF-α inhibitors, numerous histopathologic patterns have also been observed, however, lichenoid interface dermatitis (LID) appears to be a most common class-dependent finding.[7] Infliximab, adalimumab, and etanercept, all of which have FDA-approved dermatologic indications, have been associated with LID on histopathology.[3] Another notable and interesting feature of these drug reactions is the disconnect between the clinical exam and the histopathologic pattern.[3,4] For example, many patients with TNF-α-induced drug reactions have clinically "lichenoid" eruptions and, predictably, LID on histopathology. However, other distinct clinical presentations also show LID.

Case in point, our patient had a long-standing history of psoriasis, a plausible psoriasis rebound reaction after systemic steroids, and a clinical course consistent with an erythrodermic flare, however, none of the biopsies showed psoriasiform hyperplasia; rather, they consistently showed LID. While anecdotes exist, this histologic finding of LID among patients with clinically psoriasiform eruptions has scarcely been reported.[3,4]

The pathophysiology underlying LID in the setting of TNF-α blockade is poorly understood, but is thought to be T-cell-mediated.[8] It is speculated that suppression of TNF-α increases opposing inflammatory cytokines, creating a relative cytokine imbalance.[9] This results in a paradoxical autoimmune attack by T cells on the epidermis, which manifests as LID on histopathology.[9]

This clinicopathologic disconnect highlights an important barrier to proper diagnosis and management. For our patient, we suspect that titration to the maximum dose of infliximab created the precise inflammatory milieu to provoke his psoriasiform drug eruption and the LID seen on biopsy. This is supported by the finding that patients on high doses of TNF-α blockade experience the highest rate of presumably dose-dependent cutaneous side effects.[6] This phenomenon appears to be more common in patients with underlying psoriasis.[3] Unlike prior reports on this phenomenon, our patient failed to improve after discontinuation of the inciting agent, which we believe is due to steroid dependency stemming from multiple systemic steroid tapers throughout his course.[3,4] It is well-known that withdrawal of systemic steroids is a frequent precipitant of psoriasis flares; consequently, the most appropriate treatment for psoriasiform drug eruptions are steroid-sparing systemic anti-inflammatory agents.

The importance of this case is to highlight that LID should not be an unexpected histologic finding in patients on TNF-α inhibitors.[3,4] The paucity of literature on this phenomenon makes it particularly difficult to recognize, which risks improper diagnosis and a detrimental impact on patient care. Thus, we strongly recommend selecting treatment based on clinical presentation, rather than histopathologic findings.

DISCLOSURE

The authors have no conflicts.

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