Cutaneous Adverse Reaction to Infliximab: Report of Psoriasis Developing in 3 Patients

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Infliximab is a chimeric immunoglobulin G1κ monoclonal antibody against tumor necrosis factor α (TNF-α), a proinflammatory cytokine that participates in both normal immune function and the pathogenesis of many autoimmune disorders. Treatment with infliximab reduces the biologic activities of TNF-α and thus is indicated in the treatment of rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis.

To our knowledge, there have been 13 case reports of new-onset psoriasis, psoriasiform dermatitis, and palmoplantar pustular psoriasis that developed during treatment with infliximab. We report 3 additional cases of biopsy-proven new-onset psoriasis that developed while the patients underwent treatment with infliximab for inflammatory bowel disease.

Although the mechanism for the development of psoriasis in these patients is unclear, several possible explanations are proposed. With increasing use of infliximab and other TNF-α inhibitors in clinical practice, more cases of similar reactions to these drugs probably will be reported and are necessary to determine the importance of this eruption.

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Infliximab is a chimeric immunoglobulin G1κ monoclonal antibody (75% human and 25% mouse origin) against tumor necrosis factor α (TNF-α). It neutralizes the biologic activity of TNF-α by directly binding to soluble and transmembrane TNF-α molecules in the plasma and on the surface of macrophages and T cells in diseased tissue. The binding destroys these TNF-α molecules via antibody-dependent cellular toxicity and complement-dependent cytotoxic mechanisms. Thus, infliximab decreases the actions of TNF-α, which include induction of proinflammatory cytokines such as interleukins (IL) 1 and 6; enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes; activation of neutrophil and eosinophil functional activity; induction of acute phase reactants; and induction of tissue-degrading enzymes produced by synoviocytes and/or chondrocytes. Infliximab is indicated for the treatment of rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis.[1-7] Several studies also have demonstrated the efficacy of infliximab in the treatment of plaque-type psoriasis.[3-7]

Psoriasis vulgaris is a chronic cutaneous inflammatory disease displaying epidermal hyperproliferation with abnormal differentiation and inflammatory infiltration of the epidermis and dermis. These processes are mainly driven by activated T cells or antigen-presenting cells, which release various cytokines and chemokines. Signaling molecules include TNF-α, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and interferon γ (IFN-γ). TNF-α, in particular, has been shown to play a major role in this process. It has increased bioactivity in psoriatic lesions compared with uninvolved skin.

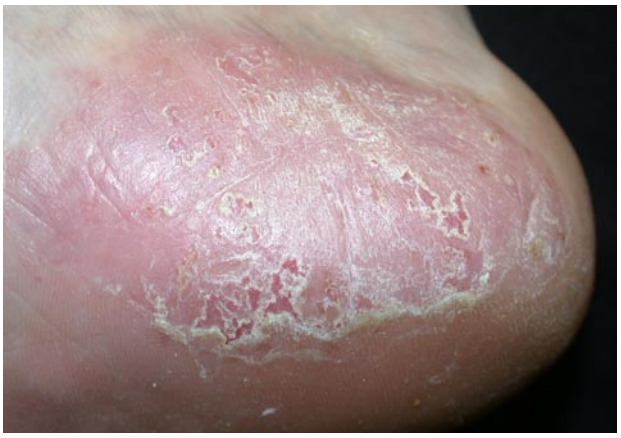

Figure 1. Well-demarcated, scaling, erythematous plaque on sole of foot.

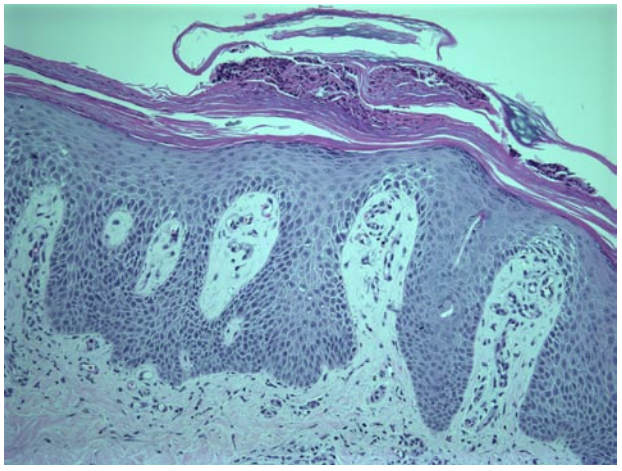

Figure 2. Hyperkeratosis, parakeratosis, psoriasiform hyperplasia with thinning of suprapapillary plate, and a perivascular mononuclear cell infiltrate (H&E, original magnification ×20).

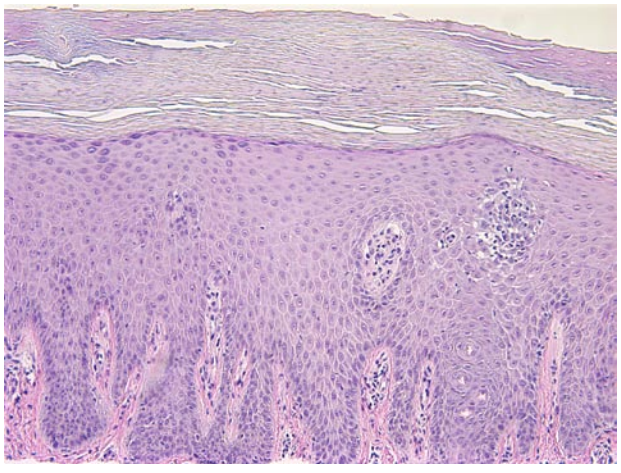

Figure 3. Orthokeratosis, parakeratosis, an intact granular zone, psoriasiform hyperplasia, dilated tortuous capillaries in thin papillae, and a sparse lymphocytic infiltrate around venules of the superficial plexus (H&E, original magnification ×20).

Normally, TNF-α is found throughout eccrine duct epithelium, but in psoriatic lesions it is found in the epidermis and dermal dendrocytes, which allows for an increased expression of other immunomodulatory cytokines such as IL-6, IL-8, and transforming growth factor α (TGF-α) in overlying keratinocytes. With inhibition of this cytokine, T-lymphocyte activation, T-lymphocyte infiltration, and keratinocyte proliferation would all theoretically be decreased in psoriatic plaques.[7,8] The 3 anti-TNF agents approved for use are monoclonal antibodies (infliximab and adalimumab) or soluble TNF-α receptor fusion proteins (etanercept). Currently, etanercept and infliximab are approved for the treatment of psoriasis.

We report 3 cases of biopsy-proven new-onset psoriasis that developed while the patients were undergoing treatment with infliximab for inflammatory bowel disease. There have been 13 previously reported cases of new-onset psoriasis, psoriasiform dermatitis, and palmoplantar pustular psoriasis that developed during treatment with infliximab.[1,9-15]

Case Reports

Patient 1—A 40-year-old woman had a prior medical history of irritable bowel syndrome and ulcerative colitis for 1 to 2 years. She had no prior medical history of psoriasis but had a family history for the disease. After 10 months of infliximab therapy for her ulcerative colitis at the standard dose (5 mg/kg intravenously [IV] on weeks 0, 2, 6; then 5 mg/kg every 8 weeks), she developed a scaly rash over her elbows, knees, hands, feet, and trunk. Physical examination revealed multiple well-demarcated, scaling, erythematous plaques on her elbows, knees, hands, feet (Figure 1), lower back, and chest. Her fingernails showed pitting and "oil spots." Histopathology demonstrated hyperkeratosis, parakeratosis, psoriasiform hyperplasia with thinning of the suprapapillary plate, and dilated capillaries in the dermal papillae. There was a perivascular mononuclear cell infiltrate and neutrophils in the stratum corneum (Figure 2). The infliximab was discontinued and she was treated with narrowband UVB with improvement of her skin lesions.

Patient 2—A 38-year-old man had a prior medical history of Crohn disease for 3 years. He had no prior medical or family history of psoriasis. After 42 months of infliximab therapy for Crohn disease at the standard dose (5 mg/kg IV on weeks 0, 2, 6; then 5 mg/kg every 8 weeks), he developed a scaly rash on his hands, feet, legs, and scalp. Physical examination revealed multiple hyperkeratotic scaling plaques of the palms, soles, trunk, extremities, and scalp.

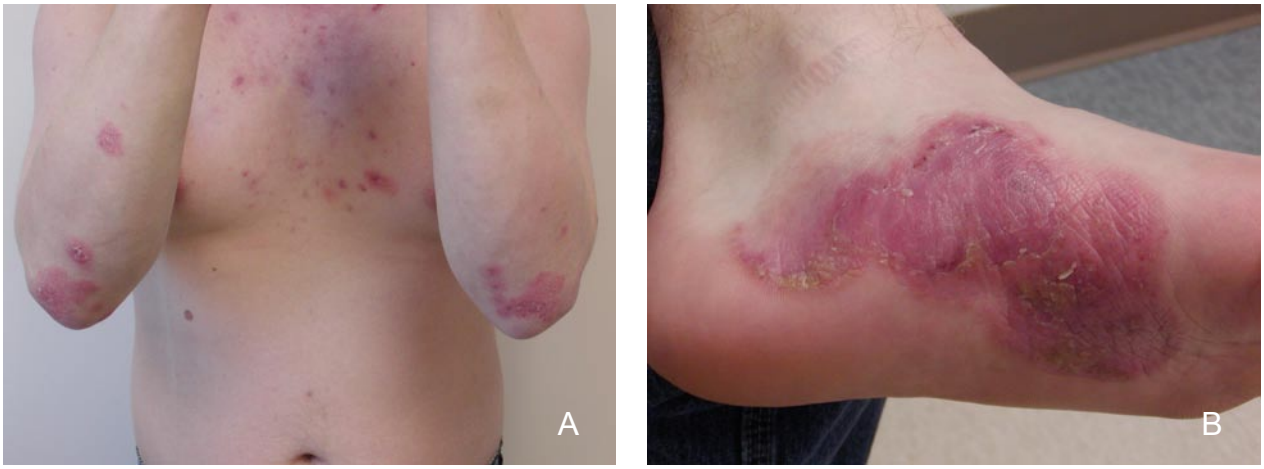

Figure 4. Psoriasiform scaling plaques on the elbows and chest (A) and the medial foot (B).

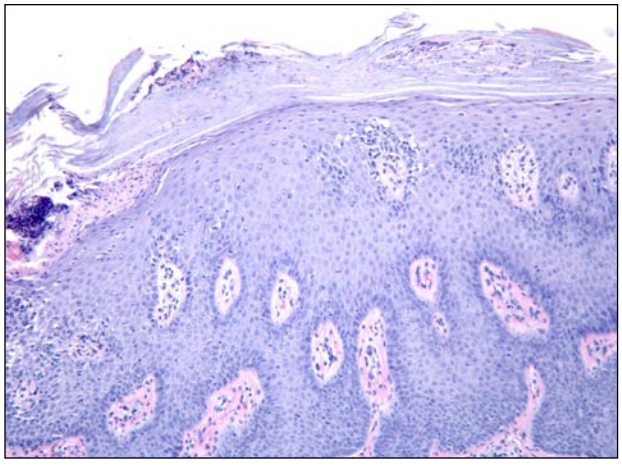

Figure 5. Hyperkeratosis with parakeratosis, psoriasiform hyperplasia, superficial perivascular lymphocytic infiltrate, and neutrophils in the stratum corneum (H&E, original magnification ×10).

Histopathology showed orthokeratosis, parakeratosis, an intact granular zone, psoriasiform hyperplasia, dilated tortuous capillaries in thin papillae, and a sparse lymphocytic infiltrate around venules of the superficial plexus (Figure 3). Periodic acid-Schiff stains were negative for fungus. Infliximab was continued and skin lesions improved with narrowband UVB treatment.

Patient 3—A 21-year-old man had a prior medical history of Crohn disease for 5 to 6 years. He had no prior medical or family history of psoriasis. After 4 months of infliximab therapy for Crohn disease at the standard dose (5 mg/kg IV on weeks 0, 2, 6; then 5 mg/kg every 8 weeks), he developed a rash on his legs that progressed to his knees, elbows, and scalp. Physical examination revealed psoriasiform scaling plaques on his medial feet, anterior shins, knees, chest, elbows, and scalp (Figure 4). Pustules were noted on the soles of his feet. No nail changes were seen.

Punch biopsy results from the right extensor forearm showed hyperkeratosis with parakeratosis, psoriasiform hyperplasia, superficial perivascular lymphocytic infiltrate, and neutrophils in the stratum corneum (Figure 5). Periodic acid-Schiff stain was negative for fungus.

Infliximab was continued and the patient's lesions improved with topical corticosteroid therapy.

Comment

Some reported adverse cutaneous reactions during infliximab therapy include folliculitis, alopecia, blistering eruption, xerosis, erythema multiforme, hyperhidrosis, pruritus, hyperkeratosis, hyperpigmentation, leukocytoclastic vasculitis, lichenoid dermatitis, lupuslike syndrome, perniosislike eruption, urticaria, rosacea, and granuloma annulare.[1,16]

To date, including our 3 cases, there have been 16 reports of new-onset psoriasis, psoriasiform dermatitis, and palmoplantar pustular psoriasis developing during treatment with infliximab (Table). The onset of eruption after initiation of infliximab ranged from 1 to 42 months, both sexes were affected (males and females in a 9:7 ratio), and the age range was 21 to 49 years. The patients underwent therapy for a number of underlying conditions, including rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn disease, and Adamantiades-Behçet disease. There have been other reported cases of new-onset and exacerbated psoriatic skin lesions during therapy with other TNF-α inhibitors (adalimumab and etanercept).[9-15,17]

The eruption seen in our patients while on infliximab therapy is clinically and histologically representative of psoriasis. Our patients showed well-demarcated, erythematous, hyperkeratotic scaling plaques in the typical psoriatic distribution with histologic findings of hyperplasia with some

Cases of New-Onset Psoriasis While on Infliximab Therapy*

Case	Age, y/ Sex	Diagnosis	Clinical Manifestation	Time to Onset, mo	Histopathology
Current report	40/F	UC	Plaques on elbows, knees, hands, lower back, and chest	10	Hyperkeratosis, parakeratosis, psoriasiform hyperplasia with thinning of suprapapillary plate, dilated capillaries in dermal papilla, perivascular mononuclear cell infiltrate, and neutrophils in the stratum corneum
Current report	38/M	CD	Multiple hyperkeratotic scaling plaques on palms, soles, trunk, extremities, and scalp	42	Orthokeratosis, parakeratosis, an intact granular zone, psoriasiform hyperplasia, dilated tortuous capillaries in thin papillae, and a sparse lymphocytic infiltrate around vessels of superficial plexus
Current report	21/M	CD	Psoriasiform scaling plaques on medial feet, anterior shins, knees, elbows, and scalp	4	Hyperkeratosis with parakeratosis, psoriasiform hyperplasia, superficial perivascular lymphocytic infiltrate, and neutrophils in the stratum corneum
Verea et al[1]	46/F	CD	Erythematous slightly scaling plaques on hands, elbows, legs, and buttocks	1	Acanthosis, papillomatosis, hyperkeratosis, parakeratosis, and focal areas of spongiosis in the epidermis, as well as exocytosis within its lower layers. An inflammatory infiltrate of lymphocytes and histiocytes with a lichenoid distribution in the dermis
Baeten et al[9]	45/M	AS	Dark erythema with squamocrustae, dried vesicles, and pustules on hands and feet	3	Enlarged epidermis with hyperorthokeratosis, parakeratosis, subcorneal pustules, and perivascular infiltrate with lymphocytes
Baeten et al[9]	44/M	AS	Dark erythema with squamocrustae, dried vesicles, and pustules on hands and feet	8	Enlarged epidermis with hyperorthokeratosis, parakeratosis, subcorneal pustules, and perivascular infiltrate with lymphocytes
Baeten et al[9]	44/F	AS	Dark erythema with squamocrustae, dried vesicles, and pustules on hands and feet	5	Enlarged epidermis with hyperorthokeratosis, parakeratosis, subcorneal pustules, and perivascular infiltrate with lymphocytes

Case	Age, y/ Sex	Diagnosis	Clinical Manifestation	Time to Onset, mo	Histopathology
Thurber et al[10]	36/M	UC	Psoriatic plaques and pustules on palms, soles, trunk, sacral area, and scalp. Nail pits on left index finger	6	Psoriasiform dermatitis
Dereure et al[11]	47/F	RA	Psoriatic lesions on anterior legs	2	Parakeratosis, acanthosis, hyperkeratosis, lack of granular layer, tortuous capillaries, and lymphocytic infiltrate in upper dermis
Kary et al[12]	38/M	RA	Psoriasis vulgaris	2	Confirmed histologically
Haibel et al[13]	32/M	AS	Psoriasis on palms, soles, and trunk	1.5	Unknown
Haibel et al[13]	27/F	AS	Palmoplantar psoriasis	10	Unknown
Grinblat and Scheinberg[14]	37/F	RA	Plaques over scalp, arms, and legs, and onychodystrophy	9	Hyperplasia of the epidermis, elongated papillae, parakeratosis, and corneum microabscesses
Sfikakis et al[15]	33/F	AS	Palmoplantar pustular lesions and plaques on arms, thighs, and trunk	9	Psoriasiform hyperplasia with intraepidermal pustules
Sfikakis et al[15]	49/M	ABD	Extensive plaques on scalp with silvery white scale	6	Parakeratosis, acanthosis, elongated rete ridges, and perivascular inflammatory infiltrate
Sfikakis et al[15]	43/M	ABD	Palmoplantar pustular lesions and plaques on elbows, knees, and scalp; onycholysis; and subungual keratosis	7	Not performed

*F indicates female; UC, ulcerative colitis; M, male; CD, Crohn disease; AS, ankylosing spondylitis; RA, rheumatoid arthritis; ABD, Adamantiades-Behçet disease.

thinning of the suprapapillary epidermis, parakeratosis, and elongation of the dermal papillae with dilated tortuous capillaries. These clinical and histologic features substantiate the diagnosis of psoriasis in these patients.

Both genetic and pathologic connections have been established between Crohn disease and psoriasis.[18] Patients with Crohn disease have a higher frequency of psoriasis than would be expected by chance alone. Both diseases are inflammatory conditions mediated by helper T1 cells producing cytokines such as TNF-α and IFN-γ that promote a cell-mediated immune response. The increased levels of TNF-α in psoriasis and Crohn disease lesions and the response of both diseases to TNF-α inhibitors demonstrates the importance of this cytokine in the pathophysiology of both diseases.[18]

TNF-α is a proinflammatory cytokine that induces a number of proteins, including nuclear factor-κB, IL-1, and IL-8. It also leads to the production of TGF-α, which may drive keratinocyte proliferation in psoriasis and induce

vascular endothelial growth factor, leading to the vascular changes seen in psoriasis. Increased TNF-α messenger RNA and protein have been seen in the serum, stool, and inflamed and normal intestinal mucosa of patients with Crohn disease. Signs of asymptomatic colon inflammation have been reported in patients with psoriatic arthritis and psoriasis.[18]

The TNF inhibitors infliximab, adalimumab, and etanercept are largely similar, though some differences are emerging. Certain inflammatory conditions seem to be more responsive to treatment with monoclonal antibodies (infliximab and adalimumab), and not to etanercept. The apparent lesser response of etanercept compared with infliximab might be explained by several factors, including differences in population of patients studied, route of administration (subcutaneous for etanercept, IV for infliximab), and ability to achieve cell lysis. Infliximab can trigger complement-mediated lysis of TNF-α–expressing cells in vitro, whereas etanercept does not cause cell lysis. Additionally, the infliximab–TNF-α complex is much more stable than the etanercept–TNF-α complex.[7] The slightly different spectrum of diseases effectively treated with the monoclonal antibodies (infliximab and adalimumab) suggests these medications may have additional mechanisms not possessed by soluble TNF receptors (etanercept).[19]

Although the mechanism for the development of psoriasis in our patients is unclear, several explanations are possible. It may be pure coincidence that our patients developed psoriasis while on infliximab therapy. Alternatively, they may have a high predisposition to develop psoriasis as a consequence of their underlying inflammatory bowel disease, as psoriasis has been shown to have a higher incidence in patients with Crohn disease. In either case, these psoriatic lesions may be unresponsive to infliximab and possibly other TNF inhibitors. In theory, some patients may not respond to TNF inhibitors because their psoriasis may not be driven by TNF-α but rather by some other signaling molecule. This possibility potentially could be explored by staining tissue samples for TNF-α.

TNF-α and its inhibitors have multiple biologic effects, some of which are paradoxical. Such effects may offer another explanation for the development of psoriasis in these patients.[1] It is possible that these eruptions are associated with the development of antibodies to infliximab, which may counter the therapeutic mechanism of action of the drug. Alternatively, repeated use of infliximab may cause up-regulation of TNF-α receptors, leading to psoriatic lesions. Finally, it is possible that these psoriatic eruptions are simply drug reactions.

Conclusion

Infliximab is a chimeric immunoglobulin G1κ monoclonal antibody against TNF-α. Because TNF-α is an inflammatory cytokine playing a role in both Crohn disease and psoriasis, it has been used to treat both diseases. It is interesting that the patients in this report presented with psoriasis, a cutaneous eruption in which TNF-α is thought to play an important role, while simultaneously being treated with a drug that is a potent inhibitor of TNF-α.

Including our 3 cases, there have been 16 cases of new-onset psoriasis developing in patients treated with infliximab. With increasing use of infliximab and other TNF-α inhibitors in clinical practice, more cases of similar reactions to these drugs probably will be reported and are necessary to determine the importance of this eruption.

At the time the manuscript was submitted in January 2005, only 13 other cases of new-onset psoriasis had been reported in patients treated with infliximab.

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