Psoriasis Induced by Tumor Necrosis Factor-α Antagonist Therapy: A Case Series

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ABSTRACT. ***Objective.*** Although tumor necrosis factor-α (TNF-α) antagonists are effective in the treatment of refractory psoriasis, some cases have suggested that psoriasis might be induced as a result of treatment prescribed mainly for rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease. To investigate anti-TNF-α induced psoriasis, we conducted a systematic analysis of the 6 cases we observed among our inflammatory patient cohort treated with anti-TNF-α (infliximab or etanercept).

Methods. We report 6 cases of psoriasis with onset during TNF-α antagonist therapy (infliximab and etanercept); characteristics and skin lesions are described.

Results. No patient had a personal or family history of psoriasis. The development of psoriasis was seen in all the types of inflammatory diseases we treated with TNF-α antagonists. There was great variation in the age of affected patients and in the onset of psoriasis after initiation of TNF-α antagonists. Both TNF-α antagonists studied were associated with development of psoriasis. In 2 cases psoriasis was associated with 2 different TNF-α antagonists in the same patient. In half our patients, skin lesions started in the inguinal and pubic regions, but palmoplantar pustulosis was also common. In half the cases, skin lesions responded favorably with topical agents despite continuation of TNF-α antagonist therapy.

Conclusion. In light of previously published cases describing psoriasis or psoriasiform lesions after TNF-α antagonist therapy, our series strongly confirms that TNF-α antagonists may induce psoriasis in some patients. Further studies are needed to identify risk factors for TNF-α antagonist induced psoriasis. (First Release Oct 1 2006; J Rheumatol 2007;34:380–5)

Key Indexing Terms:
PSORIASIS DRUG-INDUCED PSORIASIS TUMOR NECROSIS FACTOR-α ANTAGONIST
SPONDYLOARTHROPATHY RHEUMATOID ARTHRITIS

Tumor necrosis factor-α (TNF-α) antagonists have been approved for the treatment of rheumatoid arthritis (RA)[1], ankylosing spondylitis (AS)[2], and psoriatic arthritis (PsA)[3]. Both etanercept[4], a recombinant soluble human TNF receptor protein, and infliximab[5], a chimeric anti-TNF-α monoclonal antibody, have been used successfully and approved to treat psoriasis. The mechanisms of efficacy of TNF-α antagonists in patients with psoriasis may involve the reduction of inflammatory cytokines in psoriatic skin, leading to decreased infiltration of neutrophils, T cells, and dendritic cells and, finally, to decreased epidermal hyperplasia and cutaneous inflammation[6]. The programmed cell death of keratinocytes could be another mechanism for efficacy of TNF-α antagonists[7]. The adverse effects of TNF-α antagonists include skin abnormalities[8], which have been well documented in RA and consist chiefly of skin infections, eczema, and drug-related eruptions[9]. Vasculitis, cutaneous lupus erythematosus, and skin malignancies have been reported in a few patients. Several case reports of psoriasis developing during TNF-α antagonist therapy have been published[9-24], raising the possibility that TNF-α antagonists may induce or exacerbate psoriasis in some patients. To investigate this concept of anti-TNF-α induced psoriasis, we describe 6 cases of psoriasis with onset during TNF-α antagonist therapy, including 2 reports of psoriasis in which 2 different TNF-α antagonists were clearly associated.

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Accepted for publication June 21, 2006.

MATERIALS AND METHODS

Among the 400 patients followed in our service and treated with TNF-α antagonist therapy (etanercept or infliximab), we analyzed all the patients who developed skin lesions suggestive of psoriasis. Cutaneous diagnosis was clinically confirmed by experienced dermatologists. Inflammatory disease, concomitant immunosuppressive drugs, age of affected patients, type of reaction, skin lesions (pattern, localization), progress of cutaneous lesions, and therapeutic options were reviewed. Patient characteristics are summarized in Table 1.

RESULTS

Patient 1. A 70-year-old Caucasian woman with no personal or family history of psoriasis had severe RA since 1998. She

had erosive disease with positive tests for rheumatoid factor and anti-cyclic citrullinated peptide. In addition, she had chronic inactive hepatitis C infection that did not require antiviral therapy. In December 2000, severe RA symptoms despite methotrexate (10 mg/wk) prompted add-on therapy with infliximab (3 mg/kg at Weeks 0, 2, and 6, then once every 8 weeks). In May 2004, after the 25th infliximab infusion, erythematous, papular, scaly lesions developed in the inguinal folds and over the pubis, umbilical area, and legs. The lesions were suggestive of psoriasis. They improved with topical steroid treatment while infliximab therapy was continued. At last followup in March 2005 (30th infusion), the joint disease was well controlled and the skin lesions had cleared.

Case 2. A 53-year-old Caucasian woman had a 20-year history of spondyloarthropathy with severe Crohn's disease treated with ileal resection and azathioprine. She had no personal or family history of psoriasis. Infliximab (5 mg/kg) was added in November 2003, with good clinical response. In May 2004, 10 days after the sixth infusion, follicular skin lesions developed over the trunk, back, pubis, buttocks, and scalp. Histology showed parakeratosis, acanthosis, and a lymphocytic infiltrate in the upper dermis, ruling out an infection or Crohn's-related skin involvement and strongly suggesting psoriasis. The lesions persisted despite discontinuation of infliximab but cleared with topical betamethasone therapy. A new flare of spondyloarthropathy led to initiation of etanercept (25 mg subcutaneously twice a week) in November 2004. Thirty-six hours after the first injection, inflammatory lesions highly suggestive of psoriasis developed over the upper eyelids (Figure 1), neck, and inner thighs. The lesions resolved with topical steroid therapy while continuing etanercept. Her spondyloarthropathy failed to improve. Etanercept was stopped 2 months later due to the development of neurosensory symptoms, which are being assessed, and to lack of efficacy.

Case 3. A 32-year-old Caucasian woman had a spondyloarthropathy with Crohn's disease since 2000. She reported hidradenitis suppurativa but no personal or family history of psoriasis. In July 2004, severe symptoms despite sulfasalazine led to initiation of infliximab (5 mg/kg at Weeks 0, 2, and 6). Dramatic improvements occurred in the symptoms of spondyloarthropathy. However, 3 weeks after the third infusion, erythematous and scaly lesions developed over the palms and soles, which then spread to the torso. The lesions cleared after infliximab was discontinued.

In December 2004, a flare of arthritis prompted introduction of etanercept (25 mg subcutaneously twice a week). After the second injection, the skin lesions on the palms and soles recurred. Pitting of the nails was noted. Etanercept was discontinued and topical treatment given. The lesions cleared. Methotrexate was to be started shortly.

Case 4. A 56-year-old Caucasian woman with no personal or family history of psoriasis had HLA-B27-positive AS since 1976. She experienced onset of Crohn's disease 15 years later and has a history of total colectomy. Monotherapy with infliximab (5 mg/kg) was started in October 2003 to control the symptoms of AS. An excellent response was noted. In September 2004, 5 weeks after the seventh infusion, erythematous and scaly lesions highly suggestive of psoriasis developed over the pubis and vulva. The lesions responded well to topical steroids. Infliximab therapy was continued.

Case 5. A 39-year-old Caucasian man had severe HLA-B27-positive AS since 1988 that responded well to infliximab (5 mg/kg), which was started in June 2003. He had no personal or family history of psoriasis. In April 2004, vesicular and pustular lesions developed over the palms (Figure 2), and 2 months later, over the soles. Topical steroids were effective in controlling skin lesions, which cleared in November 2004. Infliximab therapy was continued.

Case 6. A 63-year-old Caucasian woman had severe RA since 1988. Her tests for rheumatoid factor were positive and she had had joint replacement therapy at the left hip and both shoulders. In February 2003, inadequate symptom control by methotrexate prompted add-on infliximab therapy (3 mg/kg). There was no personal or family history of psoriasis. Ten infliximab infusions were given, to no avail. In July 2004, she was switched to etanercept as monotherapy. Methotrexate was added 5 months later. In March 2005, the joint disease was partially controlled, but erythematous and scaly lesions typical of psoriasis developed over the legs and forearms. Topical vitamin D therapy (calcipotriol) without steroids was inadequately effective. Etanercept was discontinued. Thereafter lesions responded well to topical steroids.

DISCUSSION

We describe 6 cases of psoriasis with onset during TNF-α antagonist therapy drawn from a cohort of 400 patients. To our knowledge, 40 other cases, including 2 series[18,23], have been reported[9-24]. A recent online survey showed that 63% of rheumatologists responded affirmatively when asked if they had seen psoriasis or other skin reactions during anti-TNF-α treatment[25]. In our series, the following arguments strongly support a diagnosis of TNF-α antagonist-induced psoriasis: no personal or family history of psoriasis; no other triggering factors known to induce psoriasis, such as comedication, smoking, or infection; the timing of events; the clinical confirmation of psoriasis by experienced dermatologists; and the histological features of skin biopsy in Case 2. Moreover, in our Cases 2 and 3, recurrence of psoriasis when a second TNF-α antagonist was used was the equivalent of a positive challenge test[26]. To our knowledge, these are the first reported cases of recurrence of psoriasis after administration of a different TNF-α antagonist to treat spondyloarthropathy.

Three cases of exacerbation of psoriasis with a second TNF-α antagonist have been reported in RA[19,23]. They suggest a class effect of TNF-α antagonists, which is further supported by reports of psoriasis with all 3 available TNF-α antagonists[9-24]. The well documented association between

Table 1. Patient characteristics.

Patient	Age, yrs/Sex	Diagnosis	Disease Duration, yrs	Anti-TNF-α	Concomitant Medication	Latency, mo	Type of Eruption	Biopsy	Treatment	Therapeutic Option (anti-TNF-α)	Outcome
1	70 F	RA	6	INF	MTX	41	Erythematous, papular, scaly lesions on inguinal folds, pubis, umbilical area, legs	ND	Topical	Continuation	Recovery
2	53 F	SpA and Crohn's disease	20	INF	AZA	6	Follicular lesions on trunk, back, pubis, buttocks, scalp	Positive	Topical	Discontinuation	Recovery
				ETA		After 1st injection	Inflammatory lesions on upper eyelids, neck, inner thighs	ND	Topical	Continuation	Recovery
3	32 F	SpA and Crohn's disease	4	INF		2	Palmoplantar erythematous, scaly lesions, torso	ND	None	Discontinuation	Recovery
				ETA		After 2nd injection	Palmoplantar lesions, nail pitting	ND	Topical	Discontinuation	Recovery
4	56 F	SpA and Crohn's disease	28	INF		11	Erythematous, scaly lesions on pubis, vulva	ND	Topical	Continuation	Recovery
5	39 M	AS	16	INF		10	Palmoplantar vesicular pustular lesions	ND	Topical	Continuation	Recovery
6	63 F	RA	17	ETA	MTX	8	Erythematous, scaly lesions on legs, forearms	ND	Topical	Discontinuation	Recovery

RA: rheumatoid arthritis; SpA: spondyloarthropathy; AS: ankylosing spondylitis, INF: infliximab, ETA: etanercept; MTX: methotrexate; AZA: azathioprine; ND: not done.

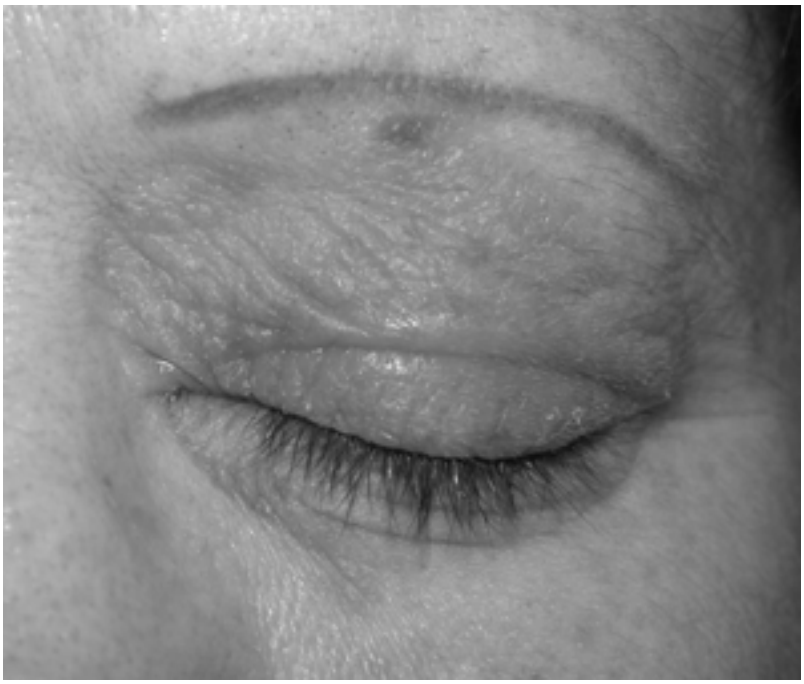

Figure 1. Inflammatory lesions on the eyelid during etanercept therapy.

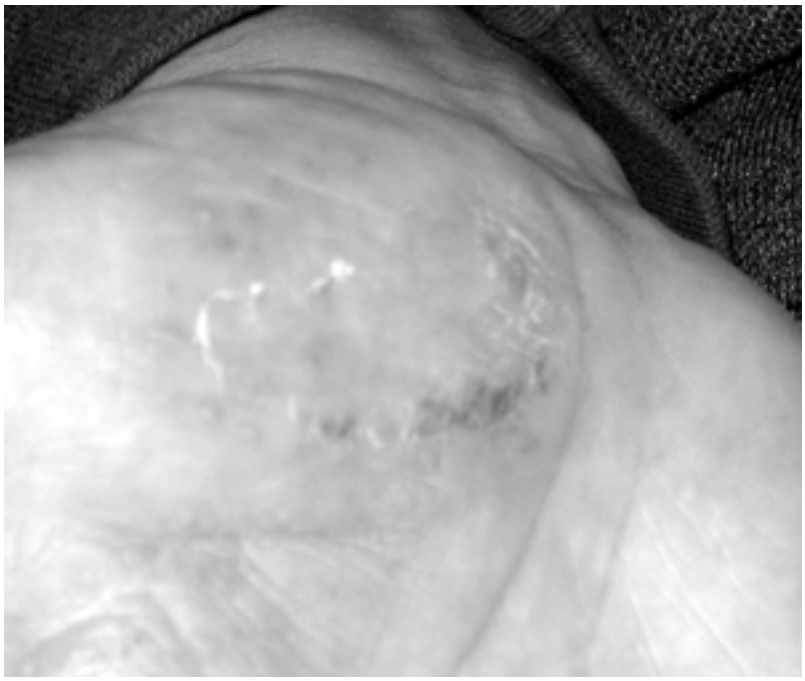

Figure 2. Papulopustular lesions over the palm during infliximab therapy.

psoriasis and spondyloarthropathies implies that patients with these joint conditions are at increased risk for experiencing psoriasis at some point, raising the possibility of coincidence when psoriasis starts during TNF-α antagonist therapy. However, psoriasis has also occurred during TNF-α antagonist therapy to treat patients with RA (our study[9,12,15,17-19,22,23]). No association between RA and psoriasis has been reported. Together, these data support a causal link between TNF-α antagonist therapy and psoriasis.

It is possible that, in some cases, lesions of psoriasis may not have been noticed by physicians before onset of anti-TNF-α and/or may not have been correctly diagnosed (for possible lesions in the past). Also, as suggested about a case of psoriasis exacerbation after a flu-like syndrome during TNF-α antagonist therapy, focal infections, a risk factor of induced psoriasis, may be overlooked[27].

Despite the limited number of published cases, a few features of TNF-α antagonist-induced psoriasis emerge from the available data. Cases have occurred in all the inflammatory diseases often treated with TNF-α antagonists: RA (n = 21), AS and other spondyloarthropathies (n = 9), Crohn's disease (n = 3), Behçet's disease (n = 2)[18], and ulcerative colitis (n = 2)[13,24].

Exacerbation of psoriasis (n = 3) in patients with recalcitrant psoriasis treated with TNF-α antagonist has also been reported[11,20]. The age of our affected patients varied from 32 to 70 years. The case of a 19-year-old man with Crohn's disease has been reported[24]. The male to female ratio, with available data, was 0.35. The number of TNF-α antagonist injections before psoriasis onset varied from 2 (with infliximab) to 25; moreover, in the literature, the time of first occurrence with the 3 TNF-α antagonists is very variable, ranging from second infusion to 1.5 years for infliximab, 4 days to 4 years for adalimumab, and 1 to 7 months for etanercept.

Importantly, psoriasis has occurred in patients receiving concomitant immunosuppressive drugs[18] such as methotrexate (our Cases 1 and 6 and cases reported elsewhere[12,19,23]), azathioprine (our Case 2), leflunomide[23], and leflunomide-methotrexate combination[15,23]. These immunosuppressive agents have been found effective in treating psoriasis. In half our patients, the skin lesions started in the inguinal and pubic regions. Palmoplantar pustulosis was common among previously reported cases (half of all cases collected), whether isolated or associated with psoriasis vulgaris or nail lesions (n = 5)[13,17,18]. No case of erythrodermic psoriasis or other severe pattern has been reported. Thus, it seems that TNF-α antagonist-induced psoriasis is different from ordinary psoriasis. Indeed, pustular psoriasis is usually quite rare compared with non-pustular forms, and the pubis is a rare site[28].

Resolution of skin lesions after discontinuation of TNF-α antagonist therapy has been reported. However, in nearly half our cases, the skin lesions cleared with topical agents without discontinuing TNF-α antagonist therapy. Indeed, considerable variation in disease progression of cutaneous lesions has been described: improvement after switch, improvement without discontinuation of TNF-α antagonist, recurrence after reinstitution of the same TNF-α antagonist (positive challenge test), and recurrence after reinstitution of a second TNF-α antagonist. Thus, despite the likely class effect of TNF-α antagonists, this wide variation in the progression of cutaneous disease suggests an individual susceptibility.

It is puzzling that medications used to treat psoriasis may induce psoriasis, suggesting a complex role for TNF-α antagonists in psoriasis. Further, human recombinant TNF has been found to be beneficial in patients with psoriasis[29]. Thus, for such patients, the action of TNF-α on psoriasis is perhaps different from other patients, i.e., without a pathologic function, or without a common pathologic role among several cytokines. However, rather than suppose a differing role (protective vs inducible) for TNF-α in psoriasis, it is likely, given the small category of patients concerned, that a subset of patients may be predisposed to TNF-α antagonist-induced psoriasis of a particular type, namely, palmoplantar pustulosis.

An infectious hypothesis has been proposed for this phenomenon, in particular in the context of palmoplantar pustulosis[10]. An autoimmune hypothesis has also been proposed[18], following the example of systemic lupus syndrome with, perhaps, immunologic differences, in particular in palmoplantar pustulosis. Indeed, several differences exist between psoriasis vulgaris and palmoplantar pustulosis. Histologically, in addition to neutrophils in the pustule and lymphocytes in the upper dermis, there are large numbers of mast cells and eosinophils[30]. Immunologically, polymorphism in the TNF-ß gene has been reported to be associated with palmoplantar pustulosis[31] rather than the TNF-α gene, whose promoter polymorphism has been reported to be associated with early-onset psoriasis[32]. Recently, patients with palmoplantar pustulosis, when compared with healthy patients, were reported to have lower expression of TNF-α in the eccrine palmar sweat gland and in the skin[19]. Thus, the normal function of TNF-α in the normal sweat duct could be disturbed by TNF-α antagonist. However, these hypotheses do not explain all the cases reported and there are many questions raised by reports on the efficacy of TNF-α antagonists in severe pustular psoriasis[33] or on exacerbation of psoriasis despite reduction of T cells in psoriatic plaque[20].

Our series of TNF-α antagonist-induced psoriasis, together with previous cases, strongly supports a link between TNF-α inhibition and development of psoriasis in some patients. Further work in collaboration with dermatologists is needed to identify risk factors for TNF-α antagonist-induced psoriasis, to advance knowledge of the pathophysiologic mechanism of this phenomenon, and to determine the best therapeutic strategy for this condition even if TNF-α antagonists can be continued. Thus, for example, it might be judicious to find out if the patient is a smoker or to screen for autoimmune thyroid disease[30] before introducing a TNF-α antagonist, given the relation between these factors and palmoplantar pustulosis[30].

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