Onset of psoriasis in patients receiving anti-TNF agents

A medical conundrum: onset of psoriasis in patients receiving anti-tumour necrosis factor agents

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> Life is a paradox. Every truth has its counterpart which contradicts it, and every philosopher supplies the logic for his own undoing.
> Elbert Hubbard

In the past decade, tumour necrosis factor (TNF) antagonists have been found to be remarkably effective for the treatment of immune-mediated inflammatory disorders such as rheumatoid arthritis and Crohn's disease.[1] These agents also dramatically lessen inflammation and improve the quality of life in patients with psoriasis and psoriatic arthritis.[2] The TNF-blocking agents have been relatively safe, although some concerns have been raised on the basis of a recent meta-analysis of trial data that identified an increased risk of serious infections and solid malignancy in a small percentage of patients treated with anti-TNF antibodies.[3] Of late, attention has also focused on a wide spectrum of skin lesions arising in patients treated with TNF antagonists.[4] The list is quite extensive, but some of the more common dermatological conditions include skin infections, skin tumours, discoid lupus, eczema, vasculitis and drug-related eruptions. Perhaps one of the most perplexing lesions are the psoriasiform eruptions that have been described in patients with rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and Behçet's disease during anti-TNF treatment, particularly because TNF is a pivotal molecule in the pathophysiology of psoriatic skin lesions.[5]

To date, 30 cases of psoriasiform skin eruptions have been reported in patients receiving TNF antagonists.[6–12] Table 1 summarises the demographics and information regarding diagnosis, type of TNF antagonist and details of the appearance and resolution of the skin lesions. Most of the patients had underlying rheumatoid arthritis, although this may simply reflect the fact that more patients with this diagnosis receive treatment with anti-TNF agents. Eight patients were receiving treatment for ankylosing spondylitis, two had inflammatory bowel disease and two had Behçet's disease. The mean age of patients was 49.8 years and disease duration ranged from 5 to 21 years. The most common skin eruption was pustular psoriasis; 10 patients had psoriasis vulgaris, whereas only one patient had the guttate variety, and another had both the guttate and vulgaris forms. Almost half of the patients were taking infliximab, eight were taking adalimumab and eight were taking etanercept. The onset of psoriasis occurred >12 weeks after the TNF antagonists were started in 21 patients, and psoriasis remained active in most of the patients maintained on TNF-blocking agents. When the TNF antagonist was stopped, psoriasiform lesions resolved in four patients and persisted in one. Only 12 patients were receiving concomitant disease-modifying anti-rheumatic drugs, which included leflunomide, sulfasalazine, methotrexate and azathioprine. In all, only eight patients had a personal or family history of psoriasis.

Several observations emerge from these data:

1. These lesions were consistent with psoriasis on the basis of a formal dermatological evaluation in some patients and histological confirmation in more than half of the patients.
2. Three forms of psoriasis were observed: vulgaris, palmopustular and guttate, hence emphasis on one form, such as palmopustular, may obscure more fundamental links that may shed light on pathogenesis.
3. Most patients had no personal or family history of psoriasis.
4. Psoriasiform skin lesions were noted in patients receiving all three TNF antagonists, which supports a class effect rather than a disease mechanism related to the structure or function of a single molecule.
5. Most of the patients had underlying rheumatoid arthritis or ankylosing spondylitis, but no reports of new-onset vulgaris or palmopustular psoriasis were identified in patients with psoriasis or psoriatic arthritis receiving anti-TNF agents. Certainly, a flare may not be reported in a patient with underlying psoriasis or psoriatic arthritis receiving TNF antagonists, but new-onset palmopustular eruptions would stand out.
6. Most of the psoriatic lesions appeared >12 weeks after anti-TNF treatment was initiated and the lesions persisted when the TNF antagonists were continued.

Table 2 gives the potential aetiologies for the psoriasiform lesions in patients receiving anti-TNF agents. The simplest explanation for the findings outlined above is that these patients were misdiagnosed and that they actually had psoriatic arthritis rather than rheumatoid arthritis, or that the patients with ankylosing spondylitis had axial psoriatic arthritis or psoriasis associated with ankylosing spondylitis. The patients with rheumatoid arthritis, however, had typical clinical and radiographic features of rheumatoid joint disease and almost all of them were rheumatoid-factor positive. The patients with ankylosing spondylitis met the New York criteria for ankylosing spondylitis, and only 25% of them had a history of psoriasis. Moreover, palmopustular eruptions have not been described in patients with psoriasis or psoriatic arthritis receiving anti-TNF agents. Nevertheless, the possibility that some of these patients may have underlying psoriatic arthritis cannot be excluded.

Another possibility is that the psoriatic lesions are a cutaneous manifestation of a bacterial infection. A large volume of evidence in the literature supports the role of bacterial infections and bacterial superantigens in the genesis or exacerbation of both psoriasis vulgaris and palmoplantar pustulosis.[13–15] None of the patients had a preceding bacterial illness, and clinical features of infection such as fever, leucocytosis or chills were not reported. Onset of guttate psoriasis, a form of the disease often triggered by a streptococcal infection, was observed in only two of the patients, and no preceding pharyngitis or upper respiratory tract infection was documented. In a Letter in this issue, Carter[16] raised the possibility that the palmopustular lesions are a manifestation of keratoderma blenorrhagicum triggered by persistent *Chlamydia trachomatis* or *Yersinia*. Although it is true that some manifestations of keratoderma blenorrhagicum are indistinguishable both clinically and histopathologically from palmopustular psoriasis, the

Table 1 Psoriasiform lesions in patients receiving anti-tumour necrosis factor agents

Underlying disease	
Rheumatoid arthritis	18
Ankylosing spondylitis	8
Crohn's disease	1
Ulcerative colitis	1
Behçet's disease	2
Disease duration (years)	5–21
Age (years)*	49.8 (11.6)
Sex*	F 17, M 5
Anti-TNF agent	
Adalimumab	8
Etanercept	8
Infliximab	14
Type of psoriasis	
Pustular psoriasis	19
Psoriasis vulgaris	10
Guttate psoriasis	2
Nail involvement	3/5 patients
Onset of psoriasis (weeks)	
Within 4	3
5–12	7
>12	20
Skin biopsy	15
Additional agents	
Leflunomide	5
Methotrexate	6
Azathiaprine	2
Sulfasalazine	1
History of psoriasis	6
Positive family history	2
Resolution of psoriasis	
Resolution off anti-TNF	4
No resolution off anti-TNF	1
Resolution on anti-TNF	2
No resolution on anti-TNF	23

F, female; M, male; TNF, tumour necrosis factor.
*Data available for only 22 patients.

absence of other features of reactive arthritis, such as eye disease, mucous membrane involvement and joint inflammation, coupled with no documented preceding infection in the urogenital or gastrointestinal tract, argues against keratoderma blenorrhagicum in most, if not all, the cases cited to date. Furthermore, only 3 of the 28 patients were reported to have nail lesions, a common feature seen in patients with keratoderma blenorrhagicum. The paradoxical concept that an effective treatment modality for a given disease can in turn trigger it in other patients is not unique to this condition. For example, TNF antagonists can lead to complete resolution of severe eczematous dermatitis in some patients, but can trigger flares of eczema in others.[17]

Acute generalised exanthematous pustulosis (AGEP), one form of pustular eruption after exposure to TNF antagonists, can be confused with palmopustular psoriasis.[18] These patients experience a sudden onset of widespread pustulosis, accompanied by neutrophilia and often fever. The lesions resolve rapidly after the drug is discontinued. Additionally, histopathological studies show a predominantly eosinophilic infiltration in the absence of the hallmark findings of psoriasis. Only two patients had widespread pustulosis. The first patient had a skin biopsy that was consistent with AGEP, but he went on to develop typical lesions of psoriasis vulgaris.[7] The second patient had an acute onset of widespread pustulosis accompanied by fever and pulmonary infiltrates, which we believed to be caused by an opportunist pathogen, but no confirmatory culture data were provided.[12] The skin lesions in the rest of the patients exposed to TNF antagonists were localised, did not resolve after withdrawal of the agent in most patients and had typical histopathological features of psoriasis. Another drug-induced skin eruption, interstitial granulomatous dermatitis, has been described after exposure to TNF antagonists, but these lesions appear as erythematous annular plaques on the trunk and extremities, and histopathological studies show mixed interstitial granulomatous infiltrates of lymphocytes, eosinophils and lymphocytes.[19] Patients with subacute cutaneous lupus can develop psoriasiform lesions: however, they often exhibit other features such as arthritis, photosensitivity and mucous membrane lesions.

The psoriatic phenotype may be a feature of different diseases. For example, psoriasis vulgaris and guttate psoriasis are phenotypically distinct and only guttate psoriasis has a strong association with preceding streptococcal infection, but both forms are linked to the PSORS1 region and HLA-CW6 on chromosome 6.[20] By contrast, palmopustular psoriasis is relatively rare, is more common in women, is generally more resistant to treatment and is not associated with genes at the PSORS1 locus. Thus, any mechanism for psoriasiform lesions after exposure to anti-TNF agents must take into account any change that can produce all three forms of psoriasis. TNF is a pivotal molecule in the cutaneous inflammatory response, and it is also a control point in the regulation of the immune response. Reduction in TNF levels may have effects on other cytokines or regulatory cells, and these responses are subject to genetic variation.[21] Therefore, psoriasiform lesions after anti-TNF treatment may represent an adverse drug reaction that is modulated by polymorphisms in genes that mediate cytokine production or T regulatory (Treg) function.

One plausible explanation for the onset of psoriasis is that the reduction of TNF levels may alter the dynamic interplay between TNF and interferon α (IFNα). Banchereau *et al*[22] have proposed a model in which a balance of TNF and IFNα sustains protective immunity, and an imbalance of these cytokines can promote an autoimmune response. Unopposed IFNα can activate pre-dendritic cells, resulting in the production of autoantibodies, a relevant mechanism in systemic lupus erythematosus and also possibly in lupus reactions that occur in patients receiving TNF antagonists.[23] In the case of psoriasis, a murine xenograft model showed that IFNα, derived from plasmacytoid pre-dendritic cells, was required to drive the development of psoriasis in vivo.[24] Unlike TNF, which is expressed by several cell types in the skin, IFN is localised to the plasmacytoid pre-dendritic cells, and its expression is tightly regulated and transient. One problem with this mechanism is that TNF is downstream of IFN in this murine model, hence TNF blockade should suppress psoriasis.[25] However, psoriasis can be triggered by multiple mechanisms in murine models such as knockout of junB,[26] or overexpression of STAT-3[27] or amphiregulin,[28] thus alternative pathways to psoriasis may explain the heterogeneous response in different people. Further support for the role of IFN in psoriasis comes from numerous case reports that document new onset of psoriasis in patients receiving IFNα for hepatitis or malignancy.[29–32]

Alternatively, change in T cell function could potentially trigger a psoriasiform response in patients after TNF inhibition. T cells are believed to play

Table 2 Potential aetiologies for psoriasiform lesions in patients receiving anti-tumour necrosis factor treatment

Underlying disease was PsA, not RA or AS
Systemic infection
Reactive arthritis
Drug-induced lupus
Adverse drug eruption
Acute generalised exanthematous pustulosis
Interstitial granulomatous dermatitis
Adverse drug reaction leading to altered immune response
Inflammation mediated by unopposed IFNα
Inflammation triggered by suppression of TNF in eccrine glands
Suppression of T regulatory cell function

AS, ankylosing spondylitis; IFN, interferon; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

an important part in the initiation and persistence of psoriasis.[33] A novel subset of Treg cells that express CD4 and CD25 are involved in suppression of autoimmunity in immunosuppressed mice.[34] These CD4, CD25 and Treg cells normally suppress autoimmune and inflammatory responses via cell–cell contact and through the release of transforming growth factor β and interleukin (IL) 10.[35] This subpopulation of Treg cells and natural killer cells constitutively express the cell receptor glucocorticoid-induced TNF receptor-related protein (GITR), and binding of this receptor by its ligand (GITR ligand; GITRL), on the surface of immature and mature dendritic cells, can abrogate suppression and result in T cell proliferation and IL2 secretion.[36] Keratinocytes also express high levels of GITR, and binding by GITRL results in decreased apoptosis after exposure to ultraviolet light[37] Therefore, a decline in TNF levels could foster psoriasis by two mechanisms. The plasmacytoid predendritic cells mentioned earlier strongly express the ligand for GITR and could provide an activation signal to Tregs and natural killer cells.[38] In addition, keratinocytes may receive an anti-apoptotic signal via the same type of interaction that would promote keratinocyte survival.

Finally, Michaelsson *et al*[12] recently suggested the possibility that local palmoplantar effects of TNF could play a part in the development of palmoplantar pustulosis in patients treated with anti-TNF agents. They reported that eccrine gland TNF expression was decreased in skin biopsies in 11 of 18 patients with palmoplantar psoriasis compared with decreased staining in only 2 of 13 controls. In this paradigm, suppression of TNF would favour the development of the palmopustular phenotype.

The most logical approach for patients receiving anti-TNF agents who develop psoriasiform lesions, would be to stop the TNF antagonist. However, this may result in a major flare of the underlying disease, which in many cases is more debilitating than the cutaneous disorder. Thus, it is imperative to exclude an infectious trigger, particularly if the patient continues to receive the TNF antagonist. The diagnosis of psoriasis should be confirmed clinically and histologically. A diagnosis for infection should include culture of the pharynx, urine analysis and urine culture for bacteria and chlamydia, and stool cultures in patients with gastrointestinal symptoms. If diffuse pustulosis is observed, the drug should be discontinued and a biopsy specimen of the affected skin examined for eosinophilic infiltration to confirm acute generalised exanthaematous pustulosis. The presence of the psoriasiform subset of subacute cutaneous lupus should be ruled out by measuring anti-Ro antibodies in the serum, particularly, in patients sensitive to the sun. Topical treatments have proved to be effective, and occlusive dressings can provide relief for palmopustular psoriasis. In the patients with severe psoriasis, a switch to another anti-TNF agent can ameliorate the skin disease, but it usually persists. Phototherapy and systemic agents such as methotrexate or ciclosporin may also be effective.

The studies outlined above document the presence of a paradoxical response to TNF blockade that seems counter-intuitive. How can inhibition of TNF suppress psoriasis in one patient and trigger its appearance in another? The answer to this question remains a mystery, but it is probably related to the immense complexity and variability of the human immune response and poorly understood genetic factors. A better understanding of the pathways that lead to psoriasiform lesions in patients receiving anti-TNF agents will probably provide novel insights into disease mechanisms that underlie psoriasis and other immune-mediated inflammatory disorders.

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