Lichenoid Reactions in Association with Tumor Necrosis Factor Alpha Inhibitors

A Review of the Literature and Addition of a Fourth Lichenoid Reaction

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ABSTRACT

In this manuscript, a clinical case of a patient treated with adalimumab for Behcet's disease develops lichen planopilaris. A variety of mucocutaneous lichenoid eruptions have recently been described in association with tumor necrosis factor alpha inhibitors. The authors briefly discuss the clinical and pathological presentation of lichen planopilaris as well as a potential pathogenesis of cutaneous adverse effects seen as the result of tumor necrosis factor alpha inhibitor therapy. They review all case reports of lichen planopilaris occurring on tumor necrosis factor alpha inhibitors and suggest its classification as a fourth recognized pattern on this therapy. (*J Clin Aesthet Dermatol.* 2015;8(6):45–49.)

The systemic adverse effects of tumor necrosis factor alpha (TNF) inhibitors are well known. Recently, attention has been directed to the potential and often paradoxical cutaneous adverse effects seen in association with TNF alpha inhibitors including lichen planus-like eruptions, psoriasis, alopecia areata, and lupus-like syndromes.[1,2] In addition, a variety of lichenoid reactions have been added to the emerging cutaneous adverse effects associated with TNF alpha inhibitors. Three patterns of lichenoid reactions have been reported—lichen planus (LP), maculopapular lichenoid reaction, and psoriasis-like with lichen planus histology. Lichen planopilaris (LPP) has been reported in few cases associated with infliximab and etanercept therapy.[3]

Of the TNF inhibitors, adalimumab is fully humanized and is purported to have a decreased risk for neutralizing antibody development. However, all of the TNF alpha inhibitors have been reported to stimulate an antibody response during therapy with no clear relationship to efficacy or adverse effects from developing antibodies while on these medications.[4] Many of the adverse reactions associated with this group of agents have appeared in the rheumatoid arthritis population, which may reflect increased coexistence of diseases characteristic to the rheumatoid arthritis population or a longer time frame of market availability of biologics for this patient population.

Garcovich et al[2] was the first to describe a patient who developed LPP after treatment with etanercept for psoriasis. Discontinuation of etanercept decreased the progression of LPP lesions; however, the patient's psoriasis flared several months later. Upon restarting etanercept, the patient gradually developed new LPP lesions.[2] Fernandez-Torres et al[3] also reported a case of LPP induced by inflixamab in a patient treated for psoriasis. Herein, the authors contribute an additional case report of LPP associated with adalimumab therapy for Behcet's disease and review the diversity of these lichenoid eruptions seen during TNF alpha inhibitor therapy (Table 1). They suggest LPP to be the fourth lichenoid reaction type that may develop during TNF alpha inhibitor therapy and caution clinicians to be aware of this eruption.

CASE REPORT

A 58-year-old woman with a nine-year history of

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TABLE 1. Overview of lichenoid reactions associated with TNF alpha inhibitors

STUDY	UNDERLYING DISEASE	DRUG	REACTION TYPE	TIME TO REACTION	TIME TO RESOLUTION	CESSATION OF TNF	OUTCOME	THERAPY FOR REACTION
Vergara et al[16]	Ankylosing spondylitis	Infliximab	LP	3 weeks	NR	No	Recovery	Topical steroids
Bovenschen et al[17]	Severe psoriasis	Etanercept	LP	5 weeks	NR	Yes	Recovery	NR
Battistella et al[18]	RA	Etanercept MTX	Linear LP	4 months	4 months	Yes	Recovery	Topical steroid continue MTX
Musumeci et al[19]	Severe psoriasis	Etanercept	LP with pterygium	8 months	1 month	No	Improved	Topical steroid
Moss et al[20]	Crohn's disease	Infliximab Azathioprine	Oral LP	3 weeks	1 month	No	Improved	Topical tacrolimus
De Simone et al[21]	Psoriasis and psoriatic arthritis	Adalimumab	Oral LP	1 month	1 month	No	Recovery	None
Asarch et al[1]	Severe psoriasis	Infliximab	Oral LP Acral LP Perianal LP	2 months	NR	Yes	Partial recovery	Cyclosporine, prednisone, topical triamcinolone
Asarch et al[1]	Severe psoriasis	Adalimumab	Oral LP Acral LP	5 months	NR	No	Recovery	Oral and topical steroid
Fernandez-Torres et al[3]	Severe psoriasis	Infliximab plus MTX	LPP	11 months	NR	No	Stabilization	Oral steroid
***Garcovich et al[2]**	Psoriasis with psoriatic arthritis	Etanercept	LPP	8 months	3 months	Yes	Recurred on rechallenge	NSAID, cyclosporine topical steroid
Abbasi et al[22]	Severe psoriasis	Etanercept	LPP	NR	NR	NR	Persisted	Class I topical steroid, topical tacrolimus

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Behcet's disease was initiated on adalimumab after failing other systemic therapies, including oral corticosteroids, colchicine, dapsone, mycophenolate mofetil, pentoxifylline, cyclosporin rinse, refecoxib, infliximab, and etanercept. The patient was on etanercept for two years. The patient immediately started adalimumab after discontinuing etanercept. After approximately one year of weekly adalimumab injections, the patient presented with a two-month history of progressive, patchy hair loss. On physical examination, she had approximately 10 patches of alopecia in the occipital and parietal regions, representing five percent of the scalp surface. The patches exhibited perifollicular erythema, scale, crust, and scarring. Routine chemistries, complete blood count, C-reactive protein, hepatitis serologies, and fungal culture were all within normal limits.

Horizontal and vertical sections of a scalp punch biopsy revealed a brisk lymphocytic lichenoid infiltrate within the infundibular and isthmic portions of the hair follicles. Also apparent were necrotic keratinocytes and concentric fibrosis. Peribulbar inflammation was absent.

She was diagnosed with LPP and started on topical clobetasol foam and methotrexate 7.5mg/week with folic acid. She had a decrease in perifollicular erythema and stabilization of alopecia after one year. She wished to continue adalimumab despite the development of LPP due to sustained symptomatic control of Behcet's disease achieved on the biologic.

DISCUSSION

Lichenoid eruptions in association with TNF alpha inhibitors were first reported by Vergara et al in 2002.[16] Since then, numerous cases of lichenoid eruptions, including cutaneous and oral LP, maculopapular, LPP, and

TABLE 1 continued. Overview of lichenoid reactions associated with TNF alpha inhibitors

STUDY	UNDERLYING DISEASE	DRUG	REACTION TYPE	TIME TO REACTION	TIME TO RESOLUTION	CESSATION OF TNF	OUTCOME	THERAPY FOR REACTION
Current study	Behcet's Disease	Adalimumab	LPP	12 months	12 months	No	Stabilized	MTX
Seneschal et al[23]	RA	Etanercept MTX	Psoriasis-like LP	2 months	NR	NR	NR	NR
Seneschal et al[23]	Ankylosing spondylitis	Infliximab MTX	Psoriasis-like LP	8 months	NR	NR	NR	NR
Seneschal et al[23]	RA	Etanercept	Psoriasis-like LP	18 months	NR	NR	NR	NR
Verea et al[24]	Crohn's disease	Infliximab	Psoriasis-like LP	6 weeks	NR	Yes	Stabilized	Topical steroids
Fendrie et al[25]	RA	Etanercept	Maculopapular	1.5 months	NR	Yes	Recovery	Topical and systemic steroids
Fendrie et al[25]	RA	Adalimumab	Maculopapular	3 weeks	NR	Yes	Recovery	NR
Fendrie et al[25]	RA	Lenercept	Maculopapular	2 months	NR	Yes	Recovery	Topical steroid
Beuthien et al[4]	RA	Adalimumab	EM-like	3 months	NR	Yes	Recovery	None
Vergara et al[16]	RA	Infliximab MTX	EM-like	NR	NR	Switch to etanercept	NR	Switched etanercept; EM-like again
Vergara et al[16]	RA	Infliximab azathioprine	EM-like	NR	NR	Yes	NR	Topical steroids
Vergara et al[16]	RA	Infliximab	EM-like	NR	NR	Yes	NR	Topical steroids

***Patient restarted etanercept and LPP progressed; biologic was permanently discontinued.**
NR=not reported, RA=rheumatoid arthritis, MTX=methotrexate

psoriasis-like LP, have been reported (Table 1). Lichen planopilaris is the most recent cutaneous lichenoid adverse reaction comprising a lymphocytic scarring alopecia that presents as hair loss and perifollicular erythema, which can be seen in association with cutaneous LP. Histopathologically, LPP is characterized by a lymphocytic, lichenoid interface dermatitis of the follicular infundibulum. Lichen planopilaris is a relatively rare cause of scarring alopecia in the United States accounting for approximately 1.15 to 7.59 percent of cases reported in four hair research centers.[5,6] Lichen planopilaris is difficult to treat and must be managed appropriately to prevent advancement of the disease and permanent fibrosis to the hair follicles. This report of LPP developing in a patient on adalimumab therapy not only adds to the spectrum of lichenoid disease found in association with this drug family, but also emphasizes the potential for irreversible side effects in select patients. This case also underscores how little we know about the mechanism of action or predictability of lichenoid reactions as the patient described herein had no adverse effects while on etanercept for two years, but developed LPP within 10 months of starting adalimumab therapy. Currently, there is no way to predict these reactions, and paradoxically, TNF alpha inhibitor therapies have been regularly reported as efficacious in many forms of LP.[7–9]

Erythema multiforme-like (EM) reactions have also been reported to develop in patients on TNF alpha inhibitors. This reaction type deserves mention in this review due to the shared dermatopathologic pattern seen with EM and lichenoid reactions. Development of these patterns after treatment with the same drug class suggests a shared immunologic response.

A variety of mechanisms have been proposed to explain

the development of cutaneous adverse effects observed in association with TNF alpha inhibitor therapy. The exact pathophysiology of LPP in association with TNF alpha inhibitors remains elusive. Type I interferon (IFN) is thought to play a role in the chronic inflammation of LP.[10] Some authors suggest that the suppression of TNF may lead to the development of opposing inflammatory cytokines, such as IFN, which may activate T cells and dendritic cells.[11]

TNF has recently been described to have two receptor types with variable roles in the immune system. Faustman et al[12] described two TNF receptor pathways: TNF receptor 1 and 2. TNF receptor 1 (TNFR1) is expressed on almost all cells of the body and plays a role in apoptosis while TNF receptor 2 (TNFR2) is confined to the immune system and helps control autoreactive CD4+ and CD8+ T cells. A possible pathway associated with LP may be one of imbalance. Suppression of TNF leaves IFN free to wreak havoc on the inflammatory process. Such an imbalance allows for increased levels of cytotoxic T cells.[1] Nonselective TNF inhibition allows an increase in autoreactive, cytotoxic CD8+ T cell activity and may explain the potential for development of LP.[2] Studies have examined the inflammatory infiltrate in case series of LP and observed a predominance of CD8+ T lymphocyte populations comprising the infiltrate. CD8+ cells have the ability to autoactivate against keratinocytes and therefore are thought to play a role in the development of LP.[13]

Recent microarray analysis and knock out mouse models for LPP demonstrate decreased expression of peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ is a transcription factor responsible for lipid homeostasis and downregulation of the inflammatory pathway in many cell types including the pilosebaceous unit. Loss of function of PPARγ is proposed to occur from genetic predisposition and or environmental triggers. Proinflammatory cytokines, such as IFN and TNF, can diminish PPARγ expression.[14] Therefore, unopposed IFN may lead to the downregulation of PPARγ and cause LPP to occur in patients on TNF inhibitors. PPARγ agonists, such as thiazolidinediones, may be a potential therapy for LPP. Several case reports utilizing this drug class have shown favorable results.[5,15] However, use of these agents in TNF-associated LPP has not been reported.

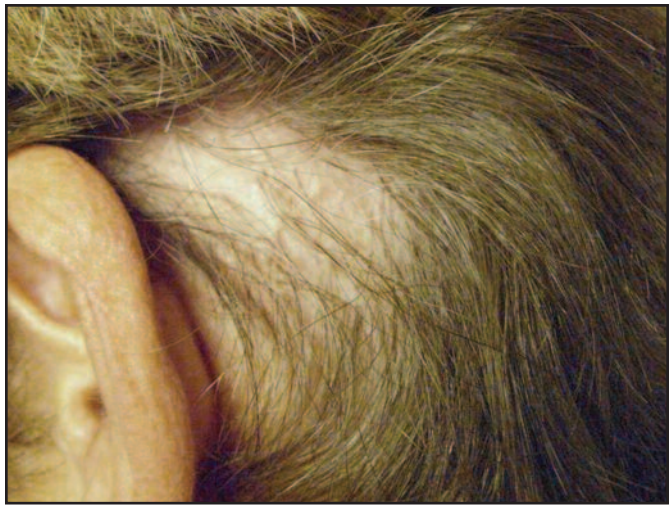

Figure 1. A patch of alopecia of the posterior auricular scalp demonstrating scale crust, scarring, and resolving perifollicular erythema.

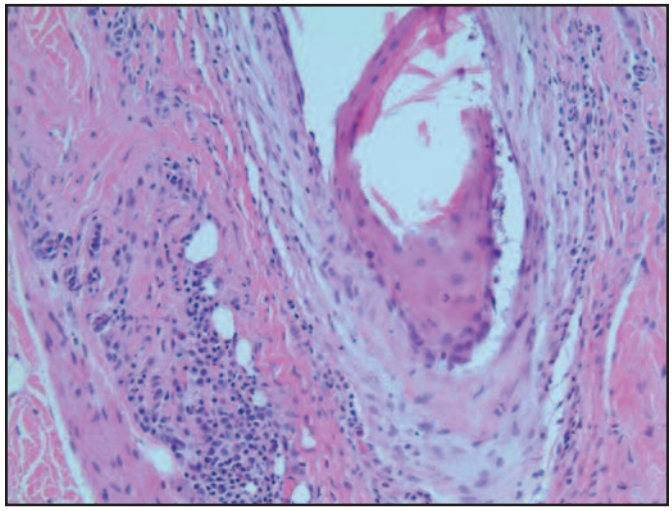

Figure 2. There is concentric fibrosis surrounding the upper follicle with an associated lichenoid infiltrate composed predominantly of lymphocytes.

CONCLUSION

This report of LPP developing in a patient undergoing treatment with adalimumab not only adds to the spectrum of lichenoid diseases found in association with this drug family, but also emphasizes the potential for irreversible side effects in select patients of permanent scarring alopecia. Currently, there is no way to predict these reactions, though TNF inhibitor therapies have been regularly reported as efficacious in many forms of LP. This reaction type may be more likely to occur in both genetically predisposed individuals and in those subjected to unknown environmental exposures. Recent consistent reporting of these reaction types suggests a possible new direction and understanding of lichenoid reactions. The next step in biologic therapy is to design pharmaceuticals with precise targets to prevent adverse reactions. Creation of highly specific binding TNF alpha inhibitors to TNFR1 would allow TNFR2 to regenerate oligodendrocytes and decrease the cytotoxic CD8+ profile, essentially preventing side effects, such as lichenoid reactions and demyelination of the central nervous system.[12] Until such a time, understanding the etiology and presentation of these lesions will allow physicians to better educate patients regarding potential side effects and perhaps unfold the pathogenesis of lichenoid reactions.

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