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Case report

TNF-inhibitor induced Lupus in a patient treated with adalimumab for rheumatoid arthritis

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Abstract

Anti-tumor necrosis factor induced lupus (ATIL) is a rare side effect reported in patients treated with anti-tumor necrosis factor medications such as infliximab, etanercept, and adalimumab. Of the three, this condition has been least commonly reported secondary to adalimumab. In this report, we present a case of ATIL in a patient treated for rheumatoid arthritis (RA) with adalimumab. This report will increase physician awareness of the warning signs, diagnostic options, and potential complications of ATIL. In this patient, adalimumab was discontinued and treatment was started, leading to improvement in the patient's status.

Abbreviations

ACR	**American College of Rheumatology**	ANA	**antinuclear autoantibodies**
ATIL	**Anti-TNF induced lupus**	dsDNA	**double-stranded DNA**
PYs	**patient years**	RA	**rheumatoid arthritis**
SLE	**systemic lupus erythematous**	TNF	**tumor necrosis factor**

Introduction

Anti-TNF medications were first introduced in 1998, providing a new treatment option for chronic inflammatory diseases. There are several agents currently available, such as infliximab (a chimeric monoclonal antibody), etanercept (a soluble receptor fusion protein), and adalimumab (a human monoclonal antibody). Adalimumab is also known as Humira (Abbott Laboratories, Illinois, USA). Although these agents have been reported by the FDA as safe and effective in the treatment of chronic inflammatory diseases, adverse events including autoimmune-related complications have been noted. In particular, anti-TNF induced lupus (ATIL) is increasingly being reported in the literature. The most common associated diseases with ATIL are RA and Crohn's disease and the most common causative agents are infliximab and etanercept. Adalimumab has also been noted to cause ATIL. However, adalimumab is one of the newer agents and thus, fewer patients have been exposed to the drug [1, 2, 3].

Case synopsis

A 66-year-old man with rheumatoid arthritis presented for evaluation of a rash. Prior to his presentation, he was seen several days earlier for the same rash and was initially treated with topical clindamycin solution and doxycycline 100mg BID for an eruption that was folliculocentric with papules and pustules. The eruption continued to progress during this initial treatment. Of note, the patient had recently been started on adalimumab for his rheumatoid arthritis and he first noticed the rash approximately 2 weeks after adalimumab was initiated. He denied that any other new medications had been started within recent months. He denied fever, chills, or weight loss but reported a flare in his significant joint pain, which was thought to be secondary to his chronic rheumatoid arthritis.

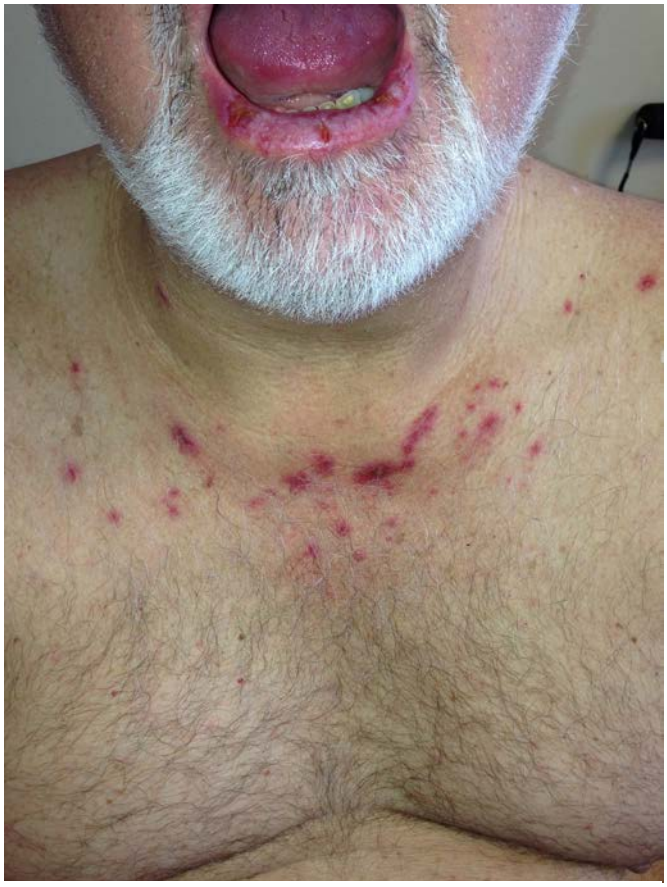
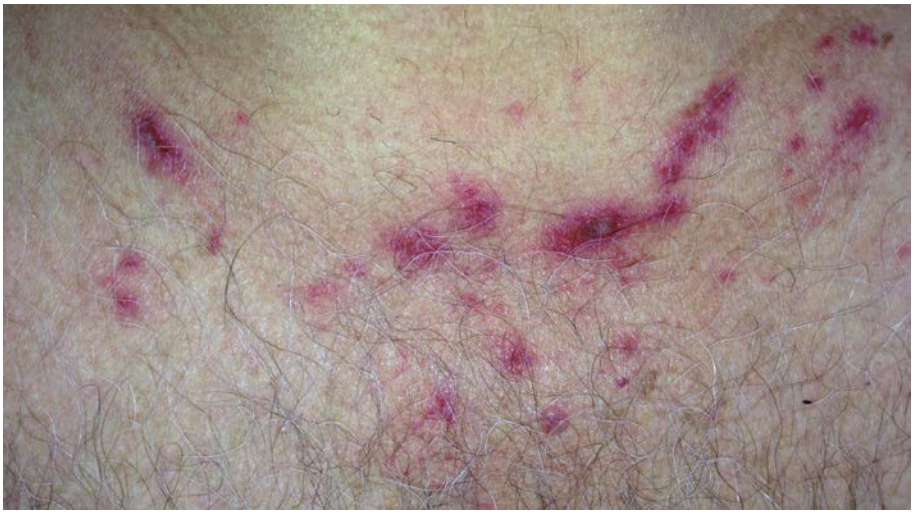


Figure 1. Multiple shallow erosions on the lower lip. Note, a 4mm ulceration was present on the hard palate (not seen). Distant view of erythematous papules on the patient's neck.

Physical Examination: On physical examination, there were erythematous papules with central erosions and crusting on the patient's neck, upper chest, back, and bilateral lateral extensor proximal arms. Multiple shallow erosions on the lower lip, and 4mm ulceration on the hard palate were also evident. Ocular and nasal mucosae were clear, and Nikolsky sign was negative.

Laboratory Findings: Although there are no specific laboratory tests currently validated for the diagnosis of anti-TNF-induced lupus (ATIL), patients can be evaluated with a punch biopsy and the same lab tests that are used in idiopathic systemic lupus erythematosus (SLE). Screening tests include autoantibody serologies, hematological profiles, and renal function panels [3]. Based on the reported literature recommendations, a laboratory workup was performed. In our patient, labs revealed: Positive ANA (1:160), low C3 (71.89) and C4 (4.39), elevated anti-histone (10.2; normal range 0 to 0.9) and positive anti-dsDNA (65, normal range 0 to 9). Myeloperoxidase Ab, P-ANCA, C-ANCA, atypical P-ANCA, anti-Smith antibody, anti-cardiolipin, anti-RNP, anti-SSA, and anti-SSB were negative.



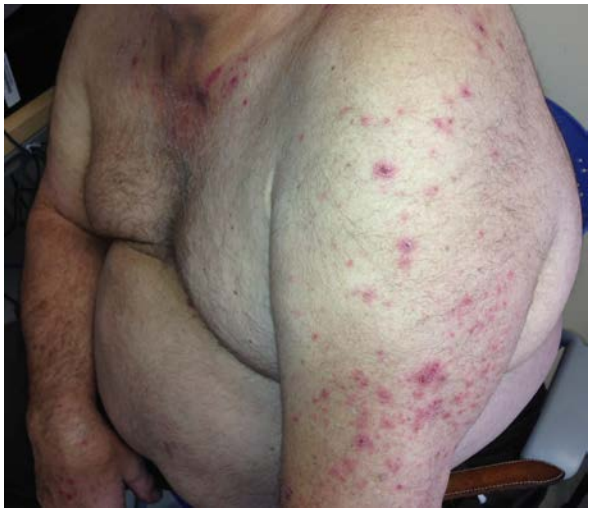


Figure 2. Close up view of erythematous papules with central erosions and crusting on the patient's neck and upper chest. **Figure 3.** Similar erythematous papules with central erosions and crusting were also found on the patient's back and lateral proximal arms, bilaterally.

Histopathologic Findings: Two 4mm punch biopsies were performed, which revealed a superficial and mid-perivascular infiltrate and an atrophic epidermis with a vacuolar interface dermatitis, parakeratosis, and necrotic keratinocytes. The histopathology found in this patient is consistent with other reported cases of ATIL and is also comparable to the changes seen in patients with non-drug-associated idiopathic SLE [3, 4, 5].

Clinical Course and patient outcome: There are no universally established guidelines for the management of ATIL. However, treatment options reported in the literature include discontinuation of the drug and initiation of corticosteroids, other immunosuppressive agents, or hydroxychloroquine. Of note, continued treatment with an alternative TNF-alpha inhibitor is not contraindicated in patients who develop one episode of ATIL [3, 6]. In our patient, adalimumab was discontinued and he was treated with a course of oral prednisone, topical clobetasol ointment for skin lesions, and triamcinolone dental paste for oral lesions. His skin and oral lesions slowly resolved over the following weeks.

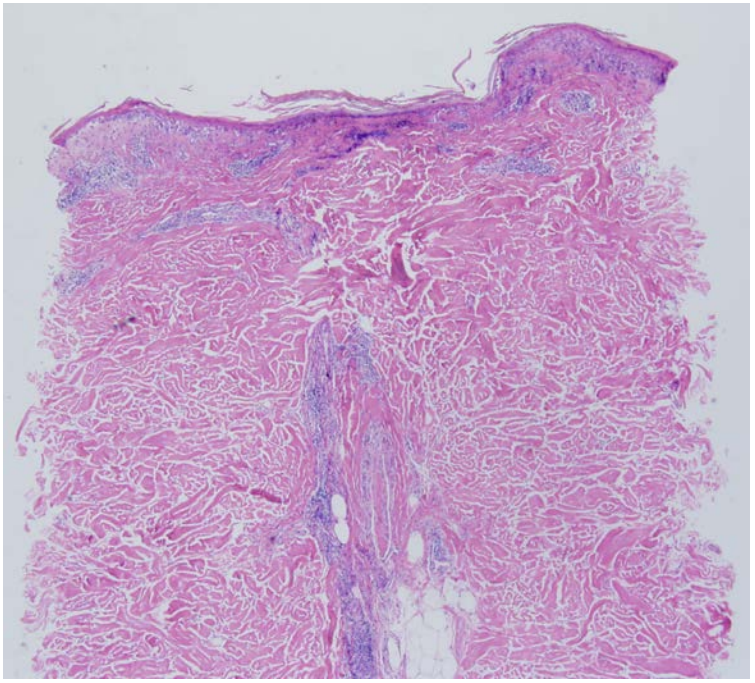
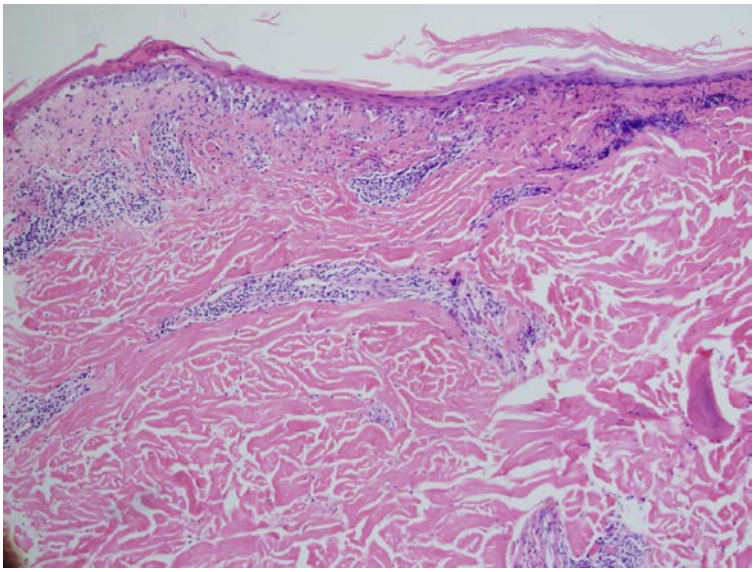
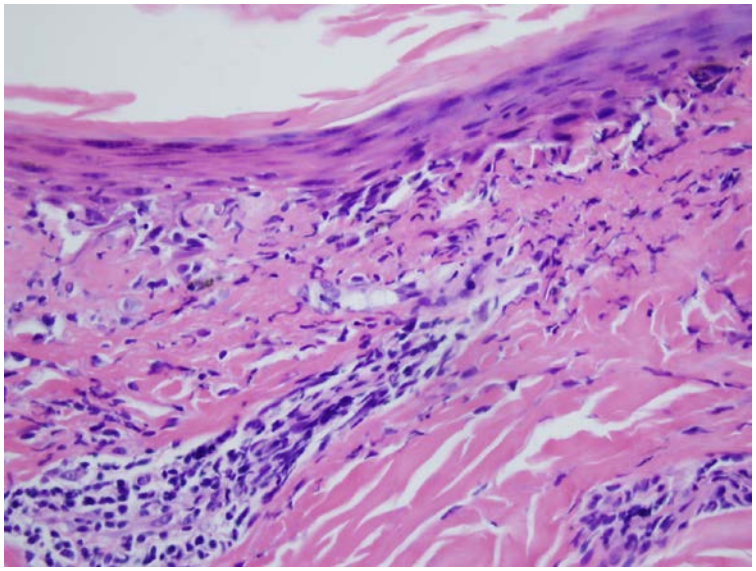


Figure 4. 4mm punch biopsy of lesion, showing an atrophic epidermis with a vacuolar interface dermatitis, parakeratosis, superficial and mid-perivascular infiltrate, and necrotic keratinocytes.





Figures 5 and 6. Close-up histopathologic images highlighting the vacuolar interface dermatitis and necrotic keratinocytes

Discussion

Epidemiology: Given that ATIL is rare and TNF-inhibitors are relatively new drugs, information on ATIL is limited to isolated case reports and case series. The true incidence of ATIL can only be estimated because of inadequate data, lack of double-blinded placebo-controlled prospective studies, and the difficulty in establishing definitive causality [7]. Various studies have produced a range of estimated rates. In a 2006 study, using safety data from trials of patients with RA treated with adalimumab, Schiff and colleagues reported a 0.08% and a 0.10% incidence of ATIL. In the same study, the estimated USA post-marketing rate for SLE in patients prescribed adalimumab was reported as 0.03/100 PYs, with an exposure of 78,522 PYs to adalimumab from December 2002 through June 2005 [8]. In 2007, Ramos-Casals et al found 92 reported cases of lupus following anti-TNF therapy, 15 of which were adalimumab-induced [1]. Adalimumab safety was also evaluated in a 10 year study that included 19,041 patients treated with adalimumab. In patients treated for RA, the study found 35 events in the lupus-like syndrome group with 12 (0.07/100 PYs) events considered serious adverse events [9].

Clinical Presentation: The onset of ATIL ranges from less than one month to more than 4 years after initiation of anti-TNF treatment [3]. Symptoms of ATIL vary from isolated cutaneous lesions to systemic manifestations. Cutaneous lesions of ATIL are similar to lesions present in idiopathic SLE and most often include malar rash, pruritic or photosensitive eruption, or purpura. Other cutaneous manifestations include discoid rash, mucosal ulcers, and alopecia [5, 10]. Systemic manifestations of ATIL include constitutional symptoms of fever, malaise and weight loss. Other findings include arthritis, myositis, serositis, and hematological abnormalities [10]. Our patient had baseline joint pain secondary to his RA, which appeared to have flared with the development of ATIL; in patients with existing joint pain, this may be difficult to definitively determine.

In a study of 83 patients who developed clinical signs of SLE secondary to ATIL, the frequency of malar rash was 36% and arthritis was 28%. Laboratory findings included positive ANA in 91% and positive anti-dsDNA in 64%. Other criteria found in less than 10% of cases included anti-Smith antibodies, oral ulcers, CNS involvement, and renal involvement [10]. In a retrospective French study of 22 patients with RA treated with TNF alpha inhibitors, 55% of patients developed ‘‘complete lupus’’, meeting at least 4 out of 11 of the American College of Rheumatology (ACR) criteria for idiopathic SLE. The most common non-cutaneous manifestations in these patients included arthritis, myositis with elevated muscle enzymes, serositis, and hematological abnormalities. No patients were reported to have renal or neurological disorders [5]. A study by Costa et al. found that ATIL manifested with arthritis in 51% of patients and cutaneous lesions in 72% of patients. In the same review, 90% of ATIL patients had a positive dsDNA and over 50% had extractable nuclear antigens and decreased serum complement levels. Other serious clinical complications of ATIL are rare but may include serositis with pleuritis or pericarditis, pleural or pericardial effusions, deep venous thrombosis, life-threating pneumonitis, and neuritis [4].

*Differential diagnosis***:** The differential diagnosis for this patient included drug-induced lupus related to adalimumab or an atypical drug eruption with mucositis related to adalimumab. Other possibilities include an atypical drug eruption related to another medication, drug-induced photo eruption, or connective tissue disease unrelated to the drug.

Diagnosis: Various criteria for diagnosis of ATIL have been suggested. The least stringent criteria for diagnosis requires one or more symptoms consistent with lupus erythematosus, concurrent exposure to a drug known to cause drug-induced lupus, no prior history of lupus erythematosus, and resolution of symptoms upon discontinuation of the drug. Isolated positive results for ANA or anti-dsDNA antibodies are not considered diagnostic [11]. More rigorous criteria for diagnosis requires a temporal relationship between symptoms and treatment and at least 4 out of the 11 ACR diagnostic criteria for SLE [5]. However, according to Costa et al., most patients described in case reports are diagnosed with drug-induced lupus on the basis of the temporal association between initiation of drug, onset of symptoms, and resolution upon withdrawal of the offending agent. This temporal association, though not a proof of causation, remains the best diagnostic evidence available. Despite the lack of specific laboratory tests and definitive diagnostic criteria, there are some lab abnormalities that may be suggestive of ATIL [4].

Table 1. Laboratory findings in idiopathic SLE, anti-TNFa induced lupus and drug-induced lupus erythematous

Laboratory test	Idiopathic SLE	Anti-TNF induced lupus	Drug-induced lupus erythematous
ANA			
(Vedove CD et al, 2012) [12]	>99%	>99%	>99%
(Ramos-Casals M et al, 2008) [10]	--	91%	--
(Ramos-Casals M et al, 2007) [1]	99%	79%	>95%
ENA			
(Vedove CD et al, 2012)	Up to 30%	Up to 10%	<5%
(Ramos-Casals M et al, 2008)	--	21.3%	--
(Ramos-Casals M et al, 2007)	--	--	--
Anti-histone Ab			
(Vedove CD et al, 2012)	Up to 50%	Up to 57%	Up to 95%
(Ramos-Casals M et al, 2008)	--	6.7%	--
(Ramos-Casals M et al, 2007)	50- 60%	ND	>95%
Anti-dsDNA Ab			
(Vedove CD et al, 2012)	50-70%	70-90%	<5%
(Ramos-Casals M et al, 2008)	--	64%	--
(Ramos-Casals M et al, 2007)	90%	72%	<5%
Anti-cardiolipin (aCL)			
(Vedove CD et al, 2012)	--	--	--
(Ramos-Casals M et al, 2008)	--	10.1%	--
(Ramos-Casals M et al, 2007)	15%	11%	5- 20%
Hypocomplementemia			
(Vedove CD et al, 2012)	51%	59%	<1%
(Ramos-Casals M et al, 2008)	--	33.7%	--
(Ramos-Casals M et al, 2007)	48%	17%	<5%
Leukopenia			
(Vedove CD et al, 2012)	--	--	--
(Ramos-Casals M et al, 2008)	--	19.3%	--
(Ramos-Casals M et al, 2007)	66%	14%	15%
Thrombocytopenia			
(Vedove CD et al, 2012)	--	--	--
(Ramos-Casals M et al, 2008)	--	6.0%	--
(Ramos-Casals M et al, 2007)	31%	6%	<5%

Abbreviations: Ab, antibody; ANA, antinuclear antibodies; dsDNA, double-stranded DNA; ENA, extractable nuclear antibodies; ND, no data; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

Conclusion

Anti-TNF induced lupus (ATIL) is a rare side effect reported in patients treated with anti-TNF agents. Increased use of TNF inhibitors in the treatment of chronic inflammatory diseases is increasing the incidence of this unique side effect. Although a definitive diagnostic criteria has yet to be established, we have presented a proven case of ATIL along with a review of the literature for the most common clinical manifestations, histopathologic findings, and laboratory features.

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