CASE REPORT

# Cutaneous benign T-cell lymphoid hyperplasia during adalimumab therapy in a patient with ankylosing spondylitis

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## ABSTRACT

The introduction of biological therapy, including anti tumor necrosis factor-alpha (TNF-α) represents a major step forward in the treatment of immune mediated inflammatory diseases. However, a number of adverse events have been reported. The potential increased risk of infection and malignancy are of significant concerns.

We want here to report a case of development of skin benign T- cell lymphoid hyperplasia during treatment of ankylosing spondylitis with adalimumab monotherapy.

## INTRODUCTION

Biologic immunomodulators are engineered to target specific mediators of inflammation and have been used in the treatment of many inflammatory conditions. TNF-α is a proinflammatory cytokine released by macrophages, monocytes, and T lymphocytes as well as many tissue-specific cell types including keratinocytes and dendritic cells.

Adalimumab (Humira) is a fully human monoclonal IgG1 antibody specific for TNF-α. It binds to both soluble and membrane bound TNF; it fixes complement and causes lysis of cells expressing membrane-bound TNF-α. Adalimumab is currently approved for psoriasis, psoriatic arthritis, adult and juvenile rheumatoid arthritis (RA), ankylosing spondylitis, hidradenitis suppurativa and inflammatory bowel diseases.[1, 2]

## CASE REPORT

A 68-year-old Kuwaiti male patient suffering from ankylosing spondylitis presented with asymptomatic skin lesions on the back for about three months. The patient was receiving anti-TNFα adalimumab subcutaneous injections 40 mg every other week for more than two years as the only medication to control ankylosing spondylitis (AS). The lesions consisted of multiple, smooth, glistening tumid, firm erythematous papules, nodules and plaques grouped on the trunk, axillae (Fig. 1 A, B, C). There were no clinically palpable lymph nodes. Mucous membranes were apparently free. Our clinical differential diagnosis was lupus erythematosus, cutaneous lymphoma and benign lymphoid hyperplasia. The patient was thoroughly investigated. Chemistry profile, complete blood count, film & urine analysis were all normal. Serology for Epstein Bar virus EBV was negative. Radiological evaluation revealed no abnormal findings regarding X-rays of skull, chest and cervical, thoracic & lumbosacral spines, ex-

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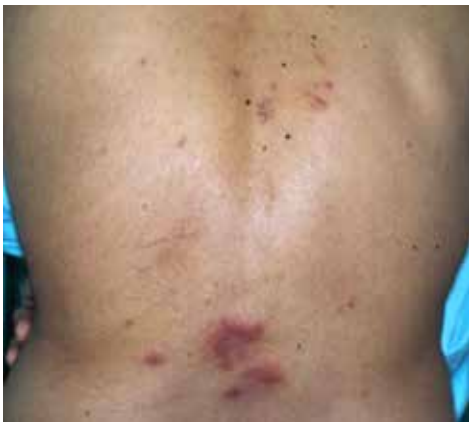
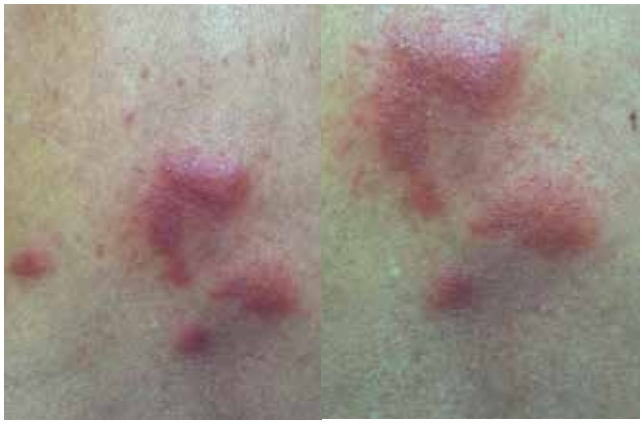
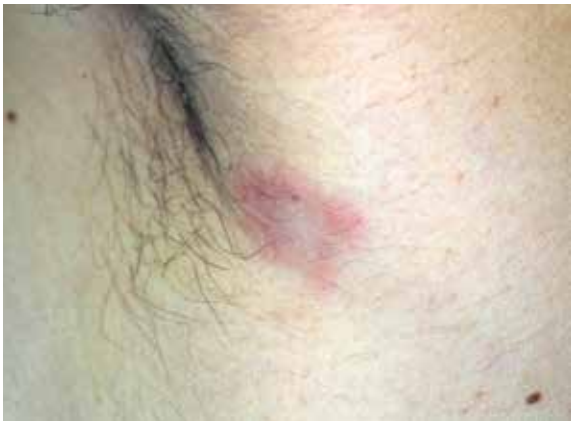


**Fig. 1 (A)** Papulonodules on the upper back, nodules & plaques on the sacral area.



**(Fig. 1 (B)** Reddish tumid grouped papules & plaques on lower back.



**(Fig. 1 (C)** Erythematous plaque with slightly elevated border & faint centre on the axilla.

cept features consistent with ankylosing spondylitis. Ultrasongraphy (abdomen, pelvis) showed no abnormal data. CT scan suggested no evidence of lymphadenopathy or involvement by lymphoma. Bone marrow was normocellular. ANA, anti-Ro, anti-La and serology for Borreliosis were negative. Lesional skin biopsy was taken and subjected to routine histopathology using H & E stain and immunohistologic study. The H & E stain showed diffuse dense band like and nodular mononuclear infiltrate involving predominantly the upper dermis even the papillary portion. The infiltrate was less dense in the lower dermis (Fig. 2 A, B, C). Peri-vascular and in between collagen bundles infiltration was evident (Fig. 2 D, E). Immunophenotyping illustrated that the infiltrate was mostly CD3 positive denoting T cell lymphocyte in origin (Fig. 3 A). The specimen showed positive staining for both helper (CD4) and suppressor (CD8) T cell lymphocytes (Fig. 3 B, C). The infiltrate was negative for both B cell lymphocytes (CD20) and CD30 immunostains (Fig.3 D, E).

Clinical, histopathology, immunophenotyping, ra-

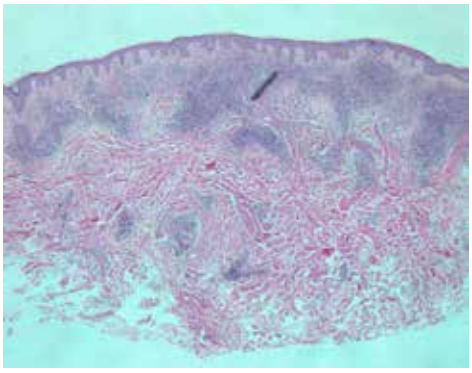


**Fig. 2 (A)** Dense mononuclear band like & nodular infiltrate involving upper, mid & deep dermis.

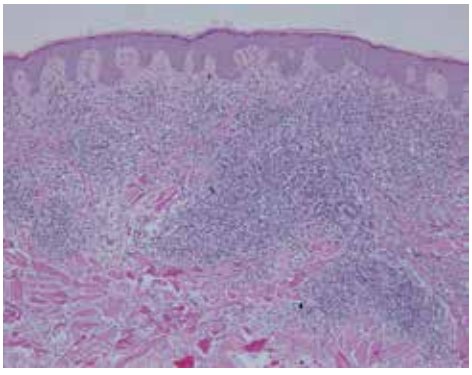


**Fig. 2 (B)** Dense mononuclear infiltrate involving upper, mid & deep dermis.

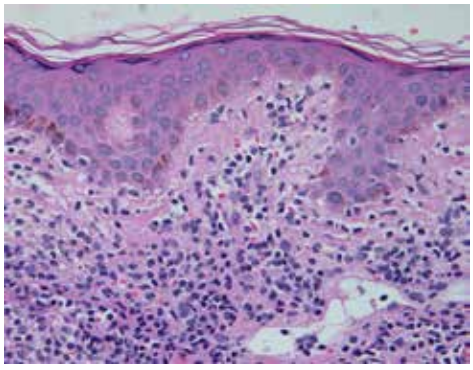


**Fig. 2 (C)** infiltrate affecting dermal papillae.

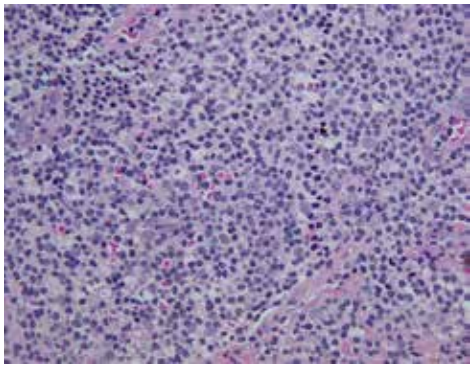


**Fig. 2 (D)** Dense deep dermal perivascular mononuclear infiltrate.

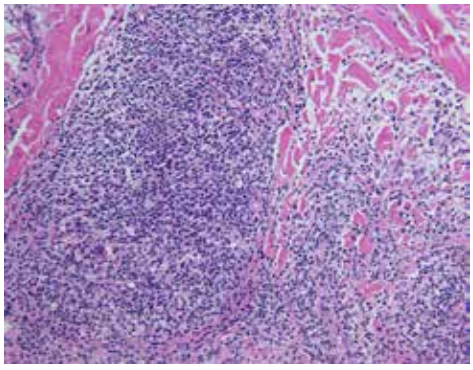


**Fig. 2 (E)** Dense deep dermal mononuclear infiltrate; in-between collagen bundles.

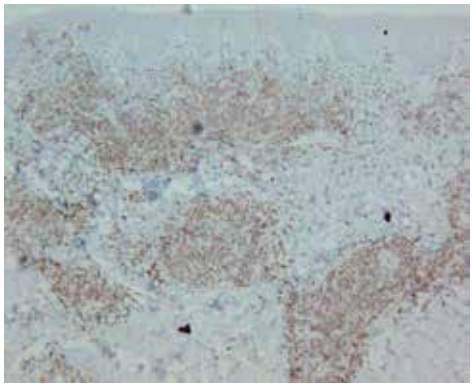


**Fig. 3 (A)** CD3:+ve

**Fig. 3 (B)** CD4:+ve

**Fig. 3 (C)** CD8:+ve

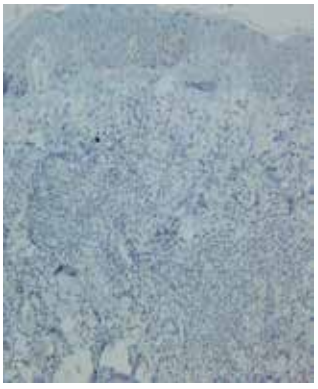


**Fig. 3 (D)** CD20:-ve

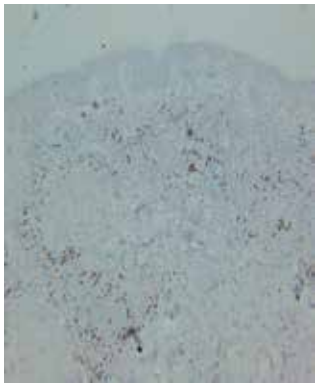


**Fig. 3 (E)** CD30:-ve

diologic & CT scan findings confirmed the diagnosis cutaneous benign T-cell lymphoid hyperplasia. The lesions responded to topical high potency steroids. Maintenance treatment was needed.

## DISCUSSION

TNF-α alpha promotes the inflammatory response that underlies many autoimmune disorders including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. Biological agents blocking TNF-α have been in use for the treatment of these autoimmune and inflammatory diseases since 1998.[3, 4]

There are currently two approved groups of biologic agents that target TNF-α: monoclonal antibodies {infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®) and certolizumab pegol (Cimzia®)} and the circulating receptor fusion protein {etanercept (Enbrel®)}.[1]

Numerous side effects, some of them serious, have been reported to these agents. Those consistent with immunosuppression include severe infections (tuberculosis), increased risk of lymphoma and solid tumors and the development of antinuclear auto-antibodies responsible for lupus. So, there are a number of safety considerations common to the entire class of TNF-α antagonist.[5] Different dermatological side effects have been reported with these agents including urticaria, eczema, lymphomatoid papulosis, erythema multiforme, lichenoid reactions, vasculitis, rosacea, pityriasis rosea, folliculitis, lupus, herpes zoster, fungal and bacterial infections, actinic keratosis, squamous and basal cell carcinoma. Paradoxically, there has been reported new-onset psoriasis in patients treated with TNF-α inhibitors, although the exact mechanism remains unclear.[6-9]

The term ''lymphoproliferative disorder,'' rather than lymphoma, is often used for lymphoid proliferations that share many features with conventional lymphomas but differ in that they may regress spontaneously when a causative infection is eradicated or an inciting medication is withdrawn. Immunosuppression-related (IR) lymphoproliferative disorder (LPD) is a well-recognized complication of immunosuppressive therapies. LPDs arising in association with prolonged use of immune-suppressive drugs for maintenance of transplanted organs and the treatment of autoimmune diseases are now a well-recognized phenomenon.[10-13] Methotrexate-LPDs are a subset of IR LPDs arising in patients receiving the drug for treatment of an autoimmune disease. The vast majority of cases develop in patients with RA, but occasional examples have occurred in those with psoriasis and dermatomyositis.[13-15]

Recently, it has become clear that these IR LPDs may rarely present within the skin[16,17] necessitating awareness and an appropriate level of suspicion on the part of dermatologists and dermatopathologists. We report a case of cutaneous benign T-cell lymphoid hyperplasia in a patient with AS that developed within 2 years of adalimumab therapy, suggesting a possible role of the drug in the development of this cutaneous reactive lymphoproliferative condition.

IR LPDs consists of several well-defined morphologic subtypes, many of which are histo-pathologically identical to well characterized lymphomas. The most common of these are diffuse large B-cell lymphoma (DLBCL), which accounts for 35% of cases; Hodgkin's lymphoma (HL), accounting for 25% of cases; and HL like infiltrates, which comprise approximately 8% of cases.[17] In our case the lesions comprised of mixed infiltrates of both T helper and suppressor lymphocytes. EBV is detected in only a subset of IR LPD[16,18,19] and our patient was EBV-negative.

It has been suggested that, in at least some cases, there may be stepwise progression from polymorphous early lesions to monomorphic, more overtly malignant lymphomas.[10,20] The development of lymphoma and exceptionally cutaneous T-cell lymphomas (CTCL) has been associated with the use of TNF-α blocking agent. However, the level of risk remains controversial. Mycosis fungoides-associated follicular mucinosis, Sezary syndrome, aggressive cutaneous T-cell lymphomas and CD30+ T-cell Lymphoma all have been reported during anti TNF-α therapy.[21-27] The pathophysiological mechanism of action of anti-TNF alpha in the development of tumours is not fully understood.TNF alpha inhibits nuclear factor-kappa B, which involves the production of many proapoptotic cytokines. Anti-TNF alpha would be expect-

ed to lead to under-production of metalloproteinases and cytokines implicated in the development of tumours and metastases.[5,28] In the current case, suggestion for cutaneous lymphoma was remote based on the morphological features of the biopsy specimen (Fig. 2 A-D). Furthermore, the co-expression of CD4 and CD8 confirms the diagnosis of an IR LPD. However, sequential biopsy specimens in such case are indicated to demonstrate any sort of histopathologic progression. Molecular biological techniques are not available in our department. Nevertheless, clonality cannot be used as single hallmark for pseudolymphomas as in a number of cases TCR gene rearrangements can be demonstrated despite the benign character.[10,20,29]

Withdrawal of the immunosuppressant and observation for 4 to 8 weeks was recommended by Salloum et al[30] as an initial treatment for IR LPDs. Nonetheless, in the current case, adalimumab withdrawal was not recommended as the benefit – risk ratio was high. The patient responded to topical high-potency steroids. However, careful follow up is prudent because a non resolving lesion should prompt concern for a malignant process.

In summary, we are the first to present a case of EBV-negative IR-LPD that developed after two years adalimumab monotherapy in a patient with AS. We believe it is likely that adalimumab contributed to the development of the disease. Withdrawal of the suspected implicated drug adalimumab may be indicated but the benefit was so strong. Thus, our patient should be continually monitored for signs of lymphoma as it has been reported following clearance of pseudolymphoma.

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