Lepromatous leprosy associated with the use of anti-TNF α therapy: case report

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ABSTRACT

TNF blockers have been used in the treatment of several types of chronic inflammatory arthritis, especially rheumatoid arthritis. However, many doubts regarding the safety and high risk of infectious diseases in these patients remain. The main objective of this report was to present a case of lepromatous leprosy in a rheumatoid arthritis patient using TNF blockers. The development of adverse events should be rigorously observed, especially those related to infectious agents. Thus, appropriate investigation of skin lesions in patients receiving anti-TNFα therapy is recommended, as the initial clinical manifestation may be unusual, particularly in endemic regions in Brazil.

Keywords: TNF blockers, rheumatoid arthritis, adverse events, leprosy.

INTRODUCTION

Tumor necrosis factor-alpha blocking agents are important and effective options in the treatment of several chronic inflammatory arthropathies (CIAs), especially rheumatoid arthritis (RA), that present inadequate response to methotrexate and/or other disease-modifying drugs (DMARDS). On the other hand, they are also associated with a higher frequency of serious adverse events, especially infectious and allergic complications.

It is known that TNF is important for granuloma formation and maintenance, and, therefore, anti-TNF therapy might cause disorganization of granulomas and cause reactivation of latent granulomatous infections, such as tuberculosis and leprosy.

Pharmacological and biochemical peculiarities of anti-TNFα agents can explain the differences among them, especially regarding safety.[1,2] Monoclonal antibodies, chimeric (infliximab - IFX) or human (adalimumab - ADA), neutralize soluble TNF-a, as well as that bound to the cell membrane with more avidity and for a longer time, while etanercept (ETN) binds only the soluble fraction, in a more reversible way, and for a shorter time. Additionally, IFX and ADA promote more apoptosis, as well as a dose-dependent reduction in the levels of interferon gamma (IFN-γ) in a dose-dependent fashion. On the other hand, ETN lacks those characteristics. The reduction in the concentration of IFN-γ can also be associated with failure to inhibit the intracellular growth of mycobacteria.[3,4]

Mycobacterium leprae causes a chronic disease with two clinical presentations: tuberculoid leprosy, represented by well-organized granulomas with few mycobacteria; and lepromatous leprosy, characterized by less organized lesions and with a greater number if bacilli. The clinical presentation is polymorphic, ranging from skin changes, with areas of desensitization and hypopigmentation, to more severe neural lesions or involvement of other organs, including bones and joints.

CASE REPORT

A.T.S., a 44 year-old male patient had had a diagnosis of RA for five years, characterized by symmetrical polyarthritis of small and large joints, associated with prolonged morning stiffness, negative rheumatoid factor and anti-citrullinated peptide antibodies (APF – perinuclear antibody), as well as erosive radiological changes in hips and wrists. The patient was initially treated with methotrexate and corticosteroids, but, due to persistent articular activity and worsening

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articular capacity (HAQ = 1.3), leflunomide was associated to the therapeutic regimen and, after failure of this combined therapy, IFX was instituted. He used methotrexate and IFX for 21 months with no reports of relevant adverse reactions, but maintaining moderate disease activity (DAS28 between 3.6 and 5.4). As the response to chimeric anti-TNF remained inadequate, it was decided to substitute it by ADA. Fifteen days after the introduction of the new medication, the patient developed non-pruriginous, non-desquamative erythematous maculae disseminated in the trunk and extremities (Figure 1), associated with fever, myalgia, and thickening of the ulnar nerve. Skin biopsy confirmed the diagnosis of lepromatous leprosy, according to the classification of Ridley and Jopling, with a bacilliferous index of +2/+4 (Figure 2). Epidemiology was negative for leprosy. Anti-TNF therapy was discontinued and specific treatment for leprosy was instituted (clofazimine, rifampin, and dapsone), scheduled to last 24 months. After 12 months of polychemotherapy, the patient showed improvement of the skin lesions, but remained with polyarticular activity (DAS28 = 6.4), even on high doses of corticosteroids (40 mg/day of prednisone).

DISCUSSION

Anti-TNFα therapy is associated with a wide variety of common or opportunistic infections, in addition to other manifestations related to allergic or immunologic phenomena. The frequency of the association between anti-TNF blockers and adverse cutaneous reactions diverge among the different studies.

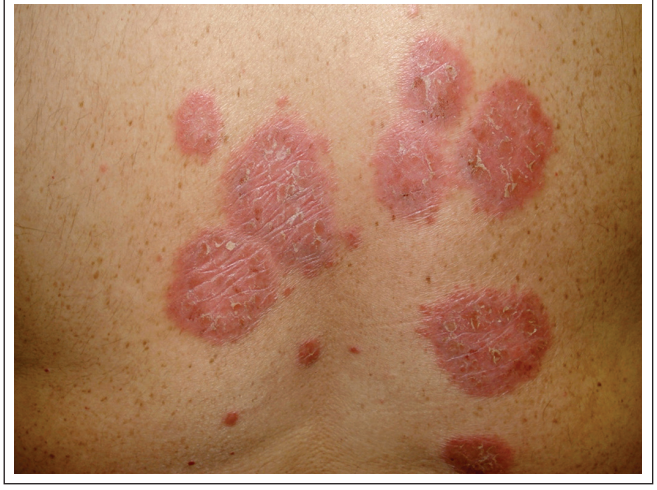

Figure 1
Erythematous maculae, with little desquamation, disseminated in the trunk.

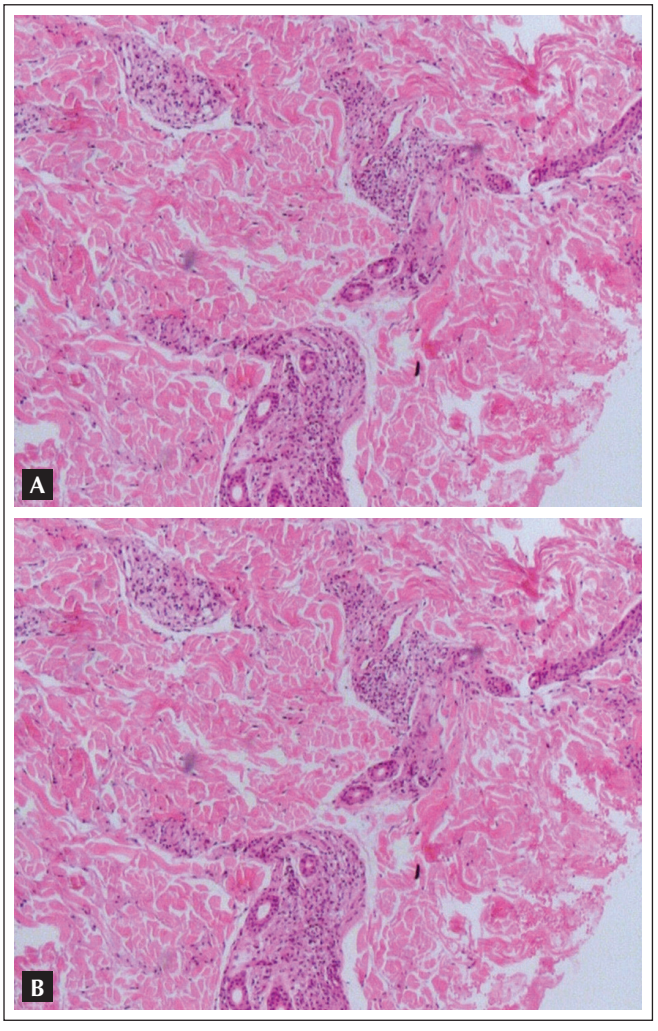

Figure 2
A: Perivascular lymphomononuclear infiltrate. Non-epithelioid differentiated macrophages. Abundant cytoplasm with opacified vacuoli. vacuolvacuolesacificados. **B**: Bacilli within the vacuoli. Ziehl Nielsen staining positive for intracytoplasmic acid-fast bacilli.

Wallis *et al*., studying the data in the reports of adverse events of the FDA (Food Drug Administration), observed an incidence of granulomatous disease of 238.6 and 73.5/100 thousand patients treated with IFX and ETN, respectively, during almost five years of observation. Among mycobacterial infections, the majority was caused by *Mycobacterium tuberculosis* (60.2%, for IFX, and 46.9%, for ETN), followed by other species (5.4%, for IFX, and 8.4%, for ETN). *Mycobacterium leprae* was identified as the causative agent in only 0.1%, all in the IFX group.[2]

In the United States, two patients with RA who developed lepromatous leprosy 12 and 24 months after the onset of treatment with IFX have been reported.[5] Recently, Oberstein *et al*. reported on a patient from the Amazon region with symmetrical polyarthritis and inadequate response to corticosteroids and MTX, who developed diffuse macular rash with biopsy compatible with tuberculoid leprosy after using ADA.[6] Our patient was treated with IFX for almost two years and he did not develop significant adverse reaction, but, two weeks after it was substituted for ADA, he developed cutaneous lesions characteristic of lepromatous leprosy. It is known that the natural history of leprosy is characterized by a slow course until the development of skin lesions; however, in this case, an intimate temporal correlation between the modification of the anti-TNF agent and the cutaneous lesion was observed. It is not possible to state with certainty whether changing the anti-TNF agent was responsible for triggering the disease or whether the patient had a latent infection and the change in the medication was only a temporal coincidence.

Once again, the immunogenic characteristics of TNF blockers (chimeric monoclonal *versus* human, for instance) can explain the reason for the late cutaneous manifestation of leprosy. Thus, since IFX is chimeric in nature and, consequently, more immunogenic, one could suppose that the presence of more human anti-chimera antibodies (HACAs) with potentially less concentration of the agent in the leprosy microenvironment would neutralize? the granuloma disorganization. Changing to a human agent might have led to greater TNF blockade, as this agent is not neutralized by anti-IFX antibodies or HACAs. These aspects (changing the anti-TNF agent and clinical type of leprosy) make this case unique.

Musculoskeletal manifestation can develop during leprosy reactions[7] and can mimic CIAs, which might delay the correct diagnosis. In leprosy, the involved joints are similar to those observed in RA (wrists, metacarpophalangeal, proximal interphalangeal, metatarsophalangeal, knees), associated with morning stiffness.[8] Rheumatoid factor can be present in these patients,[9] although, more recently, Ribeiro *et al*. have demonstrated a low prevalence of this autoantibody and anti-citrullinated peptides (anti-CCP) among us.[10]

The exact mechanism by which TNFα blockers cause the reactivation of latent granulomatous infections is not well known, but it has been speculated that disorganization of the granuloma would be directly related to TNF and to the imbalance between the production and the release of IFNγ and IFNa, as well as the complex interaction among circulating lymphocytes and epithelioid cells and local macrophages (innate and acquired immunity). Munk *et al*. demonstrated that elevated plasma concentrations of the soluble TNFα receptor I in leprosy patients could cause ineffective regulation of the inflammatory activity by inhibiting the *in vitro* cytolytic activity of TNF. This finding suggests that the regulatory activity of the soluble TNF receptor is partially hindered in patients with lepromatous leprosy, but not in other clinical types of the disease.[11]

In the three cases reported in the literature,[5,6] the differential diagnosis between RA and leprosy-related arthritis remained uncertain. On the other hand, in the case reported here, the patient had erosive and symmetrical polyarthritis of small and large joints five years before the development of leprosy, developing severe ankylosis of hips and shoulders, articular findings that are not observed in leprosy patients. These particularities can help to attain the differential diagnosis between the musculoskeletal manifestations of leprosy and RA. It is important to stress that, in general, the articular involvement improves after the treatment of leprosy, which was not observed in the case presented here.

CONCLUSION

Anti-TNFα therapy has been long and widely used in the treatment of patients with different CIAs who present inadequate response to methotrexate and other DMARDS. However, the risks should be weighted and discussed with the patient, especially the reactivation of latent granulomatous infections, such as tuberculosis and leprosy, which are endemic in Brazil. Thus, a wide, adequate, and careful evaluation before starting the therapy with TNFα blockers is recommended to minimize adverse reactions. Moreover, more attention should be given to cutaneous lesions that develop or exacerbate in these patients.

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