

Infliximab use and sequential occurrence of autoantibodies and neoplasia in a patient with spondyloarthritis

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ABSTRACT

The development of antinuclear antibodies after long-term use of anti-TNF therapy has been reported by several authors. The occurrence of lymphoproliferative neoplasms and, less commonly, solid tumors has also been reported. We present a case of simultaneous development of antinuclear antibodies and solid tumor in a patient with spondyloarthritis while on infliximab therapy. The implications and possible correlations with a solid tumor occurrence are reviewed and discussed.

Keywords: infliximab, antinuclear antibodies, neoplasia, spondyloarthritis.

INTRODUCTION

Drugs that act against tumor necrosis factor (anti-TNF) have been used in ever-increasing scale in rheumatic and autoimmune diseases. After a decade of use, a number of adverse effects was described, and variable efficacy responses were reported after its use for prolonged periods.¹

Recently, we treated a spondyloarthritis female patient with infliximab for a period of two consecutive years. After a year on the use of the medication a thyroid follicular neoplasm and, subsequently, antinuclear antibodies emerged.

The association of infliximab with antinuclear antibodies and the occurrence of neoplasms will be reviewed and discussed here.

CASE REPORT

SL, a 26 year-old white female, was evaluated two years ago, referring low back pain without sciatica. This condition had

begun about five years ago. She was examined by orthopedists that diagnosed a herniated disc at L4-L5, and was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy with no response. Subsequently, she was evaluated by a neurosurgeon that recommended neurolysis, which was not successful. On examination, the patient reported night pain, which was relieved when she interrupted sleep and walked for several minutes.

A new magnetic resonance imaging showed presence of bilateral sacroiliitis, and laboratory tests showed erythrocyte sedimentation rate (ESR) = 55 mm, C-reactive protein (CRP) = 18 mg/L, and she was tested positive for HLA-B27. Rheumatoid factor, anti-CCP, and antinuclear antibodies were negative. Patient was started on infliximab 3 mg/kg from August 2006. Soon after the first administration, there was a total improvement of pain. Infliximab therapy every eight weeks was than maintained.

In April 2008, the patient visited an endocrinologist due to weight loss. On that occasion, a thyroid nodule was identified, and a subsequent evaluation proved to be a papillary carcinoma.

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The patient underwent thyroidectomy and staging; received thyroid hormone supplementation and no further infusions of anti-TNF.

In August 2008, there was a resurgence of pain, now associated with peripheral joint pain. Seen by a colleague who requested further laboratory tests, elevated acute phase reactants was found and now with high titers of antinuclear antibodies (1/640) and anti-DNA antibodies at very high titers by enzyme-immunoassay 190 U (normal values below 40 U).

After assessing the benefits and possible risks of continued use of infliximab, anti-TNF therapy was reinstated, and the patient began receiving bi-monthly doses of medication, obtaining complete regression of articular and axial conditions. Administration of analgesics and NSAIDs was again attempted with no success at that time. About six months after therapy resumption, the patient is clinically well and with no complaints of rheumatic pain.

DISCUSSION

Tumor necrosis factor is a cytokine with important role in inflammatory diseases of rheumatic background. With the increasing use of these agents, a series of adverse events of infectious and cardiovascular nature, lymphoma, and demyelinating diseases have been described.²

Autoimmune manifestations ranging from asymptomatic laboratory changes to presence of systemic autoimmune diseases were also reported.^{3,4} A summary of autoantibodies and autoimmune manifestations in international records is shown in Table 1.

Our patient apparently developed antinuclear antibodies and anti-DNA antibodies after repeated infusions of infliximab. She did not meet criteria for classification of systemic

lupus erythematosus, belonging to the group of asymptomatic laboratory changes.

The most reported cases of lupus following the use of anti-TNFs recalls the drug-induced lupus condition with presence of arthritis, skin manifestations, and systemic symptoms. None of these symptoms was present in our case.⁵ Discontinue the use of this medication for this reason would not, in our view, be appropriate and also presents no evidence in literature. In cases where diagnosis of lupus could be established, approximately 90% were positive for antinuclear factor, and 60% for anti-DNA.⁶

Induction of autoantibodies in rheumatoid arthritis patients treated with anti-TNF is well documented in literature. Eriksson *et al.*⁷ found in 24% of 53 patients a prevalence of antinuclear antibodies at baseline, increasing to 77% in 30 weeks, and 69% in 54 weeks. Other studies confirm the observations of Eriksson *et al.*^{8,9}

In this regard, two elements must be mentioned: the first refers to the possibility that some cases are a type of "rhupus", with mixed components of rheumatoid arthritis and systemic lupus erythematosus, and the second refers to the fact that several cases lack previous immunological documentation.

The mechanism responsible for the emergence of autoantibodies is not well established, a possible element is the role of anti-TNF therapy as an adjuvant factor similar to that which can occur with exposure to sunlight and pregnancy.

The relationship between continuous use of anti-TNF and neoplasm remains controversial, perhaps less in the occurrence of lymphomas, often not statistically significant, and with less relevance regarding solid tumors. As for lymphomas, there may be a greater risk. However, in patients with rheumatoid arthritis, association with viral elements that could lead to the development of lymphoma may be

Table 1

Record of autoimmune diseases associated with the use of anti-TNF (October 2008)

	Total number of reported cases	Infliximab	Etanercept	Adalimumab
Vasculitis	118	51	60	5
Systemic lupus erythematosus/lupus-like	105	45	38	22
Psoriasis	50	33	17	10
Interstitial lung disease	34	20	11	3
Antiphospholipid antibody syndrome	42	14	16	2
Autoimmune eye disease	19	7	12	0
Sarcoidosis	10	2	8	0
Autoimmune hepatitis	7	7	0	0
Inflammatory myopathy	4	2	1	0

Adapted from Haraoui *et al.*⁵

established, as in the case of Epstein Barr virus. Disease severity is another element that can lead to an oligoclonal expansion of lymphocytes in premalignant stage. Regarding solid tumors, a possible association with its occurrence is still uncertain. Recent study shows that in 3,688 patients who received anti-TNF therapy, 30 cases of neoplasms occurred and, among these, two cases of lymphoma, four lung tumors, four breast cancers, three bowel cancers, one prostate cancer, and none of thyroid. Although it can not be totally excluded, it is unlikely that the occurrence of thyroid cancer is related to the use of infliximab.^{10,11,12}

Additionally, the natural history of cancer is peculiar, with low degree of invasion and spread, and the elements of total cure are associated in most cases after thyroidectomy. Any decisions on whether to proceed with treatment in cases similar to ours should arise from individual analysis.

We understand that, because the patient had ANA and anti-DNA negative before TNF and that it occurred after the use of infliximab, the potential risk for developing systemic lupus erythematosus might exist; however, after a year of treatment there was no occurrence of symptoms like rash, arthritis, serositis, and hypocomplementemia in clinical-laboratory follow-up. The optimal clinical response to inflammatory arthritis and the absence of options with other biologicals with different mechanisms of action for this disease have enabled our choice for maintaining infliximab.

In summary, we present a case of continuous use of infliximab with autoantibody formation (with no clinical rebound) and thyroid cancer. The drug was stopped after the appearance of autoantibodies and thyroid cancer and restarted after apparent cure of tumor disease.

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