



## Letters to the Editor

### Hepatosplenic gammadelta T-cell lymphoma and Sjögren's syndrome



#### *Linfoma T hepatoesplénico gamma-delta y síndrome de Sjögren*

Mr. Editor,

Individuals with primary Sjögren's syndrome (pSS) have over 40-fold increased risk of the development B-cell lymphoma.<sup>1</sup> The relationship of SS with T-cell lymphoma is, nevertheless, enigmatic. We herein describe a case of a patient with features compatible with SS who evolved to a hepatosplenic gammadelta T-cell lymphoma (GDTL).

The patient, a 25-year-old white female, had complained of fatigue, "dry eyes" (confirmed by an Ophthalmologist), parotid enlargement and xerostomia for the last four years. Physical examination in December 2008 revealed increased parotid glands and hepatosplenomegaly, but no peripheral lymphadenopathy. Pancytopenia was present (hemoglobin 7.9 g/dL, white blood cell 1000 cells/mm<sup>3</sup>, platelet count 107,000 cells/mm<sup>3</sup>). The erythrocyte sedimentation rate was of 37 mm in the first hour. Polyclonal hypergammaglobulinemia was present. The antinuclear antibody test was strongly positive (1/5120, speckled pattern), and anti-SSA antibodies were detected in high levels (124 units in an ELISA). The rheumatoid factor test was weakly positive (45 units). Abdominal ecography confirmed hepatosplenomegaly. A bone marrow biopsy (BMB) showed hypercellularity, without evidence of malignancy. Considering the clinical and laboratory findings suggestive of pSS, the patient was treated with prednisone and azathioprine.

After eight months, a notable improvement of clinical and hematological features was seen. Hepatosplenomegaly remained, however, and a new BMB plus splenectomy were carried out. At that time, hemoglobin was 10 g/dL, the leukocyte count was 21,900 cells/cm<sup>3</sup> (with 65 erythroblasts per 100 leukocytes), and the platelet count was 106,000/cm<sup>3</sup>. The spleen histology was inconclusive, and the BMB showed interstitial infiltration by atypical lymphoid cells. Immunohistochemistry of spleen and bone marrow revealed the following lymphocyte profile: CD3+, CD4–, CD5–, CD8–, Ki 67+ with a rate of 50% CD56+ focal. The karyotype showed, of importance, eight trisomy and absence of chromosome seven. Altogether, morphologic, phenotypic and genetic findings were compatible with a hepatosplenic GDTL. After eighteen months of standard chemotherapy, the patient died in September 2011.

Hepatosplenic GDTL is an aggressive and uncommon malignancy (<1% of lymphoid neoplasms). Intense gammadelta T-cell proliferation is characteristically seen in liver, spleen and bone marrow sinusoids.<sup>2</sup> The disorder usually affects young adults, and the outcome is poor.<sup>3</sup> Hepatosplenomegaly and severe cytopenias, both seen in our patient, are usual aspects;

lymphadenopathy is rare.<sup>4</sup> Of interest, hepatosplenic GDTL can mimic the hemophagocytic syndrome.<sup>5</sup> In 2009, a cutaneous GDTL was diagnosed in a patient with rheumatoid arthritis using etanercept.<sup>6</sup>

Current ACR classification criteria for SS include autoantibodies, ocular staining and salivary gland histology, suggesting that case definition requires two of the three.<sup>7</sup> pSS was initially a suitable diagnosis for our patient due to the presence of ophthalmic sicca, parotiditis, typical autoantibodies, polyclonal hypergammaglobulinemia, and peripheral pancytopenia. The first BMB showed no malignancy, and clinical features responded well to traditional immunosuppression.

The unexpected persistence of hepatosplenomegaly led to an immunohistochemistry diagnosis of hepatosplenic GDTL eight months ahead. Thus, it is conceivable that the patient firstly had pSS and later developed a GDTL. Although one cannot rule out the possibility that she presented GDTL with SS features since the beginning, the reported median survival time of six months for GDTL<sup>8</sup> turns it less plausible. Also, an atypical form of SS "secondary" to GDTL could be brought about. Necessary to say, the occurrence of SS and GDTL could have been only coincidental in our patient. For any of these circumstances, no similar clinical scenario combining SS features and GDTL has been described so far.

In summary, we describe a case of a young patient with features of SS who evolved, unusually, to a hepatosplenic GDTL. The interplay of SS with non-B lymphomas has yet to be clarified.

#### Conflict of interest

The authors have no conflict of interest to declare.

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## Transaminase Elevation Secondary to the Use of Adalimumab<sup>☆</sup>



### Elevación de transaminasas secundaria a uso de adalimumab

Dear Editor:

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by sacroiliac inflammation and inflammatory low back pain. It belongs to the spondyloarthritis group of disease, which has the common denominator of the presence of sacroiliitis, extra-articular manifestations and HLA-B27 positivity.<sup>1,2</sup>

Conventional treatment with disease modifying antirheumatic drugs (DMARDs) has limited efficacy, particularly in patients with axial involvement, due to which the use of biologic therapy with monoclonal antibodies against tumor necrosis factor (anti-TNF), including adalimumab, was introduced and which has led to<sup>3</sup> improved clinical responses. Among the adverse events of anti-TNF drugs, there are reported cases of elevated liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT),<sup>4</sup> and even<sup>5</sup> subacute liver failure.

We report the case of a 32-year-old man with AS of 2 years evolution, HLA-B27 positive, with a poor response to sulfasalazine 1 g/8 h, and NSAIDs, who had persistent severe pain in the lumbosacral region associated with stiffness and functional limitation. Physical examination revealed pain on the sacroiliac joints and arc movement limitation. MRI evidenced spinal osteitis, spinal cord edema and early changes of sacroiliac ankylosis.

AS was considered as in progression, with a high score on the BASFI and BASDAI scales, for which treatment with adalimumab was initiated at a dose of 40 mg every 15 days, achieving an adequate clinical response. During follow-up, progressive elevation of aminotransferases was documented, with bilirubin and alkaline phosphatase within normal limits. Since at that time the patient had received no other medication, possible hepatotoxicity adalimumab was suspected, so the biological therapy (Table 1) was suspended with a decline in the aminotransferase levels. A diagnostic test was done with the administration of another dose of adalimumab,

once aminotransferases normalized, with a new elevation thereof seen, confirming the case as drug-induced. The diagnostic approach was complemented with tests for viral B and C hepatitis virus, anti-smooth muscle, antimitochondrial antibodies and liver biopsy, ruling out an autoimmune origin.

Anti-TNF therapy may cause hepatotoxicity, which can range from alterations in liver function tests to cases of severe liver failure, through reactivation of viral hepatitis.<sup>6</sup> Hagel et al. published a case of a patient aged 44 with a history of psoriasis without liver disease, who developed subacute liver failure 4 months after treatment with adalimumab. After discontinuation of therapy and initiation of prednisone, a decrease in aminotransferase levels to normal was documented. The same authors reported mild elevation of aminotransferases, up to 3 times the reference value in 1%–4% of patients treated.<sup>5</sup> Van der Heijde et al., in 208 AS patients treated with adalimumab, reported at week 12 of follow-up, elevated aminotransferases in 6 patients, with ALT levels 3 times above the reference value, and subsequent normalization of levels in 4 of them without suspension. At 24-weeks of follow-up, only 6 patients (2.8%) had serious adverse events, including one case of elevated liver enzymes in need of liver biopsy in a patient with moderate alcohol consumption and concomitant treatment with indomethacin.<sup>7</sup>

A Japanese study documented hepatic adverse event in 31.7% of patients treated with adalimumab, including elevated aminotransferases, up to 2.5 times normal, and hepatic steatosis. In neither case was it considered a serious episode and did not require discontinuation of the drug. Cases of hepatitis B reactivation beginning with elevated aminotransferases have also been reported.<sup>2,8</sup>

Researchers of the CORRONA (Consortium of Rheumatology Researchers of North America) data collection program compared patients receiving anti-TNF therapy (infliximab, etanercept or adalimumab) and who had alterations in liver function tests, and found the following odds ratios for an increase of >2 times in liver function tests: infliximab 2.4 (95% CI: 1.53–3.76), adalimumab 1.72 (95% CI: 0.99–3.01) and etanercept 1.1 (95% CI: 0.64–1.88); however, they noted that the frequency of this disorder is rare.<sup>4</sup>

Our case presented elevated aminotransferases after initiation of adalimumab therapy, which resolved following discontinuation of the drug.

The elevation of aminotransferases is an effect that can occur in patients with AS receiving anti-TNF treatment, however, its progression to severe hepatitis is rare and in most patients is a temporary adverse event that resolves spontaneously and does not produce symptoms.

**Table 1**

Aminotransferases During Treatment With Adalimumab.

	Baseline	Week 4	Week 8	Week 12	Week 20	Suspension	Restart
AST	18 U/l	23 U/l	61 U/l	93 U/l	64 U/l	35 U/l	93 U/l
ALT	34 U/l	30 U/l	38 U/l	50 U/l	34 U/l	21 U/l	43 U/l

Normal value of AST up to 32 U/l and ALT up to 40 U/l.

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### Conflict of Interest

The authors have no conflicts of interest.