

- Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken). 2012;64:475–87.
8. Lu CL, Tang Y, Yang QP, Wang M, Zhao S, Bi CF, et al. Hepatosplenic T-cell lymphoma: clinicopathologic, immunophenotypic, and molecular characterization of 17 Chinese cases. Hum Pathol. 2011;42:1965–78.

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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.

## References

- Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis Jr JC, Dijkmans B, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2006;65:442–52.
- Kobayashi S, Harigai M, Mozaffarian N, Pangan AL, Sharma S, Brown LS, et al. A multicenter, open-label, efficacy, pharmacokinetic, and safety study of adalimumab in Japanese patients with ankylosing spondylitis. *Mod Rheumatol.* 2012;22:589–97.
- Lin J, Ziring D, Desai S, Kim S, Wong M, Korin Y, et al. TNF $\alpha$  blockade in human diseases: an overview of efficacy and safety. *Clin Immunol.* 2008;126:13–30.
- Sokolove J, Strand V, Greenberg JD, Curtis JR, Kavanaugh A, Kremer JM, et al., CORRONA Investigators. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2010;69:1612–7.
- Hagel S, Bruns T, Theis B, Herrmann A, Stallmach A. Subacute liver failure induced by adalimumab. *Int J Clin Pharmacol Ther.* 2011;49:38–40.
- Efe C. Drug induced autoimmune hepatitis and TNF- $\alpha$  blocking agents: is there a real relationship? *Autoimmunity Rev.* 2013;12:337–9.
- Van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2006;54:2136–46.
- Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract Res Clin Rheumatol.* 2006;20:757–90.

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## Acquired Madelung's Deformity in Rheumatoid Factor-positive Polyarticular Juvenile Idiopathic Arthritis<sup>\*</sup>



### *Deformidad de Madelung adquirida en la artritis idiopática juvenil poliarticular con factor reumatoide positivo*

Dear Editor:

Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of diseases that is characterized by presenting arthritis of unknown etiology before 16 years of age and includes the systemic, oligoarticular and polyarticular with positive and negative rheumatoid factor (RF) types.<sup>1</sup> Persistent joint inflammation in these diseases may eventually lead to premature skeletal maturation and this, in time, originate a discrepancy in extremities, small vertebral bodies, deviation of the tibio-astragalus joint and Madelung's deformity of the carpus.<sup>2</sup>

We report the case of a 34-year-old male diagnosed with RF positive polyarticular JIA at 15 months of age, based on symmetric polyarthritis affecting elbows, wrists, metacarpophalangeal and proximal interphalangeal joints on the hands, as well as the knees, ankles and metatarsophalangeal joints and subcutaneous nodules, positive for RF (353 IU/ml) and elevated acute phase reactants (erythrocyte sedimentation rate of 45 mm/h, C-reactive protein 6.5 mg/l). He had no other relevant family or personal history. He was treated with nonsteroidal antiinflammatory drugs, systemic and intra-articular corticosteroids, gold salts and methotrexate but, despite this, the disease remained active with persistent synovitis of both wrists, developing bilateral subluxation at that level and limitation of dorsiflexion and supination. Radiographs of both wrists showed shortening of the medial distal radius, exaggeration of the radial tilt and proximal migration of the bones of the first row of the carpus, adopting a V shape between the radius and ulna, consistent with Madelung's deformity (Fig. 1). The patient also developed "trigger fingers" in both hands and bilateral hallux valgus. At age 24, he began treatment with etanercept, achieving control of disease activity. Currently no synovitis of the wrists is

present, but the limited movement persists, though it does not prevent him from carrying out his usual activities.

Madelung's deformity is a rare congenital disorder characterized by asymmetric carpal growth and curvature of the distal radial physis, resulting in a decrease in grip force of the hand. The common mechanism in Madelung's deformity is a premature closure of the epiphyseal growth cartilage in the medial and anterior portion of the distal palmar radius. This results in a shortening of the radius and, therefore, an apparent ulnar overgrowth. It is frequently associated with genetic syndromes such as Leri-Weill dyschondrosteosis and Turner's syndrome.<sup>3</sup> Alterations similar to those produced in congenital Madelung's deformity have been described in other disorders, including trauma, tumors, infections, endocrine disorders and generalized skeletal dysplasias.<sup>3–5</sup> The deformity may also occur in patients with the acquired form related to JIA because early skeletal maturation induced by joint inflammation can cause early closure of the carpal physis.<sup>2,6</sup> There have been 2 cases of severe Madelung's deformity in patients with RF negative polyarticular JIA who also had Turner's syndrome,<sup>7</sup> but in our case there was no evidence of another associated genetic syndrome.

Among the clinical and radiological characteristics of Madelung's deformity, dorsal and medial curvature of the distal radius, an increase in the inclination of the joint surface of the distal radius, the triangulation of the carpus with proximal migration and volar migration of the semilunar bone, as well as the prominent ulnar head, are common.<sup>8</sup> This deformity is typically present bilaterally and manifested before 20 years of age. Patients have a limited pronation and supination of the affected carpus.<sup>3,5</sup> Severe cases develop progressive osteoarthritis and instability of the distal radioulnar joint, radiocarpal osteoarthritis and may complicate with rupture of the extensor tendons of the fingers.<sup>3</sup>

There are no specific guidelines for the treatment of this deformity and it is initially conservative, postponing surgical correction until skeletal maturity is achieved. Several techniques have been described for the correction of Madelung's deformity, but no clear evidence exists that supports the specific use of any of them. Common indications for surgery are pain, limitation in mobility and esthetic concerns.<sup>3</sup>

In conclusion, acquired Madelung's deformity may occur as a complication of JIA, worsening the functional capacity even more in these patients, making it important to consider it in the patient's clinical and radiological evaluation.

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