



Fig. 1. Cutaneous leishmaniasis lesion in carpus (Oriental sore).

and legs. Each lesion represents a bite. Visceral leishmaniasis can present with a febrile syndrome with constitutional symptoms and manifestations depending on the affected organs (spleen, liver, bone marrow, among others).²

Tumor necrosis factor- α is a cytokine implicated in the immune response against intracellular parasites. It has been involved in granuloma formation and in containing the protozoa.³

Since the introduction of anti-TNF- α agents, there have been several cases of leishmaniasis.⁴ According to the reports, it seems that the risk is greatest during the first year of treatment, and to a greater extent with infliximab than with the subcutaneous drugs.^{5,6} There have also been cases with other types of immunosuppressive agents, like azathioprine, methotrexate, cyclosporine, steroid and cyclophosphamide.⁷

In immunocompromised patients, the risk of reactivation, and thus, of active visceral leishmaniasis is increasing.^{4,7} In regions in which it is endemic, in an immunocompromised patient with fever, asthenia, splenomegaly and pancytopenia, this diagnostic possibility should be considered.⁴ In our case, the patient was receiving treatment with an immunosuppressive agent, and came from an area in which leishmaniasis is endemic. Thus, upon the first diagnostic suspicion, after the development of the skin lesion, the latter was biopsied and immunosuppressive therapy was discontinued.

References

- Lucientes J, Castillo JA, Gracia MJ, Peribáñez MA. Flebotomos, de la biología al control. *Revista Electrónica de Veterinaria REDVET*. Available in: <http://www.veterinaria.org/revistas/redvet/n080805.html> [accessed 14.10.13].
- David CV, Craft N. Cutaneous and mucocutaneous leishmaniasis. *Dermatol Ther*. 2009;22:491–502.
- Engwerda CR, Ato M, Stager S, Alexander CE, Stanley AC, Kaye PM. Distinct roles for lymphotoxin and tumornecrosis factor in the control of leishmania donovani infection. *Am J Pathol*. 2004;165:2123–33.
- Cascio A. Leishmaniasis and biologic therapies for rheumatologic diseases. *Semin Arthritis Rheum*. 2010;40:e3–5.
- Martin-Mola E, Balsa A. Infectious complications of biologic agents. *Rheum Dis Clin N Am*. 2009;35:183–99.
- Guedes-Barbosa LS, Costa IP, Fernandes V, Mota LM, Menezes I, Scheinberg MA. Leishmaniasis during anti-tumor necrosis factor therapy: report of 4 cases and review of the literature (additional 28 cases). *Semin Arthritis Rheum*. 2013;43:152–215.
- Van Griensven J, Carrillo E, Lopez-Velez R, Lynen L, Moreno L. Leishmaniasis in immunosuppressed individuals. *Clin Microbiol Infect*. 2014;20:286–99.

María José Moreno Martínez,^{a,*} Manuel José Moreno Ramos,^a Paloma Sánchez Pedreño^b

^a *Departamento de Reumatología, H.C.U. Virgen de la Arrixaca, Murcia, Spain*

^b *Departamento de Dermatología, H.C.U. Virgen de la Arrixaca, Murcia, Spain*

* Corresponding author.

E-mail address: mjmorenomartinez@gmail.com (M.J. Moreno Martínez).

2173-5743/

© 2016 Elsevier España, S.L.U. and Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. All rights reserved.

Autoimmune pitfalls in treatment with TNF α inhibitors



Los escollos autoinmunes en el tratamiento de pacientes con anti-TNF α

Dear Editor,

Systemic lupus erythematosus (SLE) may be induced by several drugs, including the anti-TNF α agents.

As time passes, and after an experience of almost 15 years with these drugs in a wide variety of rheumatic diseases, there are questions still unanswered.

In fact, despite the frequent and well-established development of autoantibodies, such as anti-nuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA), among patients treated with anti-TNF α agents, the occurrence of clinical SLE still remains a rare adverse event.^{1,2} Its aetiology, triggering factors and temporal association are still unknown. From case-reports published in

the literature and some data available from registries, it seems more common in rheumatoid arthritis patients under infliximab³. However, as new drugs are becoming available, new cases have been reported.⁴

In our cohort, from 401 rheumatic patients (with rheumatoid arthritis, spondylarthritis and psoriatic arthritis) exposed to anti-TNF α agents, only three of them developed drug induced lupus after a mean time of exposure of 4.11 ± 4.71 months.

The first case is a 52-year-old male patient suffering from ankylosing spondylitis for 7 years and treated with infliximab (450 mg, 8/8 weeks). After 20 months of treatment, he started complaining of asthenia, fever, dyspnoea and arthralgia. The chest X-ray showed bilateral pleural effusion. Laboratory investigation revealed normal blood cell count, raised erythrocyte sedimentation rate (ESR) (87 mm, normal <20 mm/h) and c-reactive protein (CRP) (76.6 mg/L, normal <0.3 mg/L). Additionally he had positive ANA (1/640, homogeneous pattern), positive anti-DsDNA (263 UI/mL, normal <200), complement consumption (C3 76 mg/dL, normal >83 and C4 11 mg/dL, normal >12). Anti-histone antibodies,

anti-cardiolipin antibodies and other anti-extractable nuclear antigens were negative. The diagnosis of infliximab-induced lupus was established and infliximab was discontinued. Prednisolone 1 mg/kg/day, was started; after four weeks all symptoms had resolved, and after two months, autoantibodies were negative and complement levels returned to normal. Three months later, he started etanercept (50 mg/week) without any adverse events.

The second case is a 60-year-old male patient, with an 8-year history of rheumatoid arthritis (RA), under adalimumab (40 mg every other week) in association with oral methotrexate (20 mg/week). Baseline laboratory investigations showed positive ANA (1/100, homogeneous pattern), in the absence of other clinical or laboratory manifestations suggestive of lupus, and negative anti-DsDNA. After 3 months of treatment, he presented arthralgia, asthenia, anorexia, malar rash and hand cutaneous vasculitis. Laboratory investigation showed normal cell blood count, positive ANA (1/320 homogeneous pattern), positive anti-DsDNA (326.2 UI/mL), complement consumption (C3 79 mg/dL, and C4 10 mg/dL). The other autoantibodies tested, namely anti-histone antibodies, were negative. Within four weeks of adalimumab suspension, rapid reduction of the clinical symptoms and biological parameters was seen and antibodies disappeared after three months.

The third case is a 44 year-old female patient, with an 11-year history of RA treated with adalimumab (40 mg every other week) in association with leflunomide (20 mg/day). At baseline, clinical manifestations suggestive of lupus were absent and ANA and anti-DsDNA were negative. After four years of treatment, she developed photosensitivity, malar rash, disseminated sub-cutaneous lupus rash, asthenia, low grade fever and arthralgia. Laboratory investigation revealed leukopenia ($3560/\text{mm}^3$), ESR 60 mm/h, CRP 55.6 mg/L, positive ANA (1/320, homogeneous pattern), positive anti-dsDNA (233 UI/mL) and positive anti-histone antibody. Complement levels were within normal range and the other antibodies tested were negative. Adalimumab was suspended and after 6 weeks all symptoms disappeared and autoantibodies turned negative. She started golimumab (50 mg/month) without recurrence.

Herein, we reported three rare cases of anti-TNF-induced lupus, two of them induced by adalimumab, which have been very rarely described in literature³.

The three cases described mirror the clinical heterogeneity that these patients can present. Since the raise of autoantibodies during the treatment can occur, and, anti-histone antibodies can be negative, the most important features to identify such patients are the clinical symptoms. It is advisable to stop the drug and, despite some controversy, the switch to other anti-TNF can be done without recurrence.⁵

References

1. Takase K, Horton SC, Ganesha A, Das S, McHugh A, Emery P, et al. What is the utility of routine ANA testing in predicting development of biological DMARD-induced lupus and vasculitis in patients with rheumatoid arthritis? Data from a single-centre cohort. *Ann Rheum Dis*. 2014;73:1695–9.
2. Atzeni F, Talotta R, Salaffi F, Cassinotti A, Varisco V, Battellino M, et al. Immunogenicity and autoimmunity during anti-TNF therapy. *Autoimmun Rev*. 2013;12:703–8.
3. De Bandt M, Sibilia J, Le Loët X, Prouzeau S, Fautrel B, Marcelli C, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther*. 2005;7:R545–51.
4. Brunasso AM, Aberer W, Massone C. Subacute lupus erythematosus during treatment with golimumab for seronegative rheumatoid arthritis. *Lupus*. 2014;23:201–3.
5. Santiago T, Santiago MG, Rovisco J, Duarte C, Malcata A, da Silva JAP. A case of infliximab-induced lupus in a patient with ankylosing spondylitis: is it safe switch to another anti-TNF- α agent? *Clin Rheumatol*. 2013;32:1819–22.

Rita Fonseca,* Eva Mariz, Miguel Bernardes, Lúcia Costa

Rheumatology Departmente, São João Hospital, Oporto, Portugal

* Corresponding author.

E-mail address: anaritapfonseca@gmail.com (R. Fonseca).

2173-5743/

© 2016 Elsevier España, S.L.U. and Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. All rights reserved.

A Case Report of Pseudoxanthoma Elasticum and Systemic Lupus Erythematosus: An Uncommon Association?*



Presentación de un caso de Pseudoxantoma elasticum y lupus eritematoso sistémico: ¿una asociación infrecuente?

To the Editor,

Pseudoxanthoma elasticum (PXE) is a rare hereditary disorder that affects connective tissue and consists of a progressive calcification of the elastic fibers of the skin, the Bruch membrane in the retina and cardiovascular system. Its prevalence in the general population is estimated to be 1:25,000–100,000 population, with a slight predominance of women.¹ It frequently presents as yellowish papular lesions, which can converge and form plaques with an irregular morphology and a “paved” aspect due to the fact that the skin becomes laxer and more redundant.

The association of this disorder with other systemic connective tissue diseases is rare. To date, there have been 6 cases associated with rheumatoid arthritis,^{2–5} 2 with systemic lupus erythematosus

(SLE)⁶ and another associated with ankylosing spondylitis.⁷ We describe a case of PXE in a patient with SLE.

The patient was a 46-year-old woman, an active smoker, who had been diagnosed with SLE at the age of 28 years. She began with a nephrotic syndrome secondary to World Health Organization class IV diffuse proliferative lupus nephritis, which was treated with mycophenolate mofetil. This achieved resolution of the nephrotic syndrome, and she had been asymptomatic since then. During a check-up, she mentioned the development of asymptomatic skin lesions on her neck and in axillae. Physical examination revealed papular lesions measuring around 3 cm \times 7 cm, distributed on both sides of her neck. They were yellowish and lax, like “goosebumps” (Fig. 1), and she had others that were similar but smaller in the axillae. A specimen was taken for a skin biopsy which showed the existence of a high number of fragmented elastic fibers in the dermis (Fig. 1), a finding compatible with PXE. The study was completed with an examination of the fundus which showed nothing abnormal and renal ultrasound which revealed no signs of disease.

Pseudoxanthoma elasticum is a hereditary connective tissue disease related to a mutation in the *ABCC6* gene located on chromosome 16p13.1, that encodes the multidrug resistance protein 6 (MRP6), which is one of the family of adenosine triphosphate-dependent membrane transport proteins, which are mostly expressed in the liver and kidneys. Two types of inheritance have been described: autosomal recessive in 90% of the cases and autosomal dominant, much rarer. Mutation in the *ABCC6* gene

* Please cite this article as: Muñoz Gómez MM, Novella Navarro M, Ramírez Gómez M, Navas-Parejo A. Presentación de un caso de Pseudoxantoma elasticum y lupus eritematoso sistémico: ¿una asociación infrecuente? *Reumatol Clin*. 2017;13:183–184.