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Brief Report

Primary Tuberculosis Infection in Patients Treated With Tumor Necrosis Factor-alpha Antagonists and a Negative Initial Screening☆

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ABSTRACT

Introduction: Despite screening for latent tuberculosis (TB), new cases of TB infection are detected in patients treated with anti-TNF-α and negative initial screening, some of them after long treatment, which points more to a new infection.
Objectives: To describe the cases that have presumably developed a primary tuberculous infection during treatment with anti-TNF-α drugs.
Methods: Retrospective audit (1999–2012). Inclusion criteria were: (a) anti-TNF-α treatment; (b) initial latent TB screening negative; (c) TB diagnosed during anti-TNF-α treatment; (d) suspected primary TB infection (diagnosis after at least 12 months on anti-TNF-α). Clinical, epidemiological, therapeutic and outcome variables were reviewed.
Results: Two cases of primary TB infection were found out of 771 anti-TNF-α treated patients (0.2%). One woman aged 41 suffered TB pneumonia after 35 months of treatment with adalimumab, and a male aged 37 who developed disseminated TB after 107 months of treatment with infliximab.
Conclusions: Although uncommon, during TNF antagonist therapy, TB risk persists despite negative initial screening, so clinicians should be aware of TB during the entire treatment.

Primoinfección tuberculosa en pacientes con anti-TNF-α y cribado inicial negativo

Palabras clave:
Tuberculosis
Anti-TNF-α
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Reactivación tuberculosis latente

RESUMEN

Introducción: A pesar de las medidas de cribado de tuberculosis (TB) siguen detectándose casos en pacientes tratados con anti-TNF-α y cribado inicial negativo, algunos tras largo tiempo de tratamiento, lo que apunta más a una nueva infección.
Objetivos: Describir los casos que presumiblemente han desarrollado primoinfección tuberculosa durante el tratamiento con fármacos anti-TNF-α.
Métodos: Revisión retrospectiva (1999-2012), seleccionando según los siguientes criterios: *a)* tratamiento anti-TNF-α; *b)* cribado de TB inicial negativo; *c)* TB diagnosticada durante tratamiento anti-TNF-α, y *d)* sospecha de primoinfección tuberculosa (tras mínimo 12 meses de anti-TNF-α). Se han revisado sus variables clínicas, epidemiológicas, terapéuticas y de desenlace.
Resultados: Dos casos de primoinfección tuberculosa de 771 pacientes tratados con anti-TNF-α (0,2%). Una mujer de 41 años y 35 meses de tratamiento con adalimumab y un varón de 37 años y 107 meses de tratamiento con infliximab. La mujer presentó una neumonía y el varón una TB diseminada.

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Conclusiones: Durante la terapia anti-TNF-α persiste el riesgo de TB a pesar de cribado inicial negativo, por lo que el grado de sospecha debe ser elevado durante todo el tratamiento.

Introduction

Biologic therapies with tumor necrosis factor-alpha antagonists (anti-TNF-α) have revolutionized the prognosis of rheumatic diseases. Their use, however, is accompanied by certain risks. One of the adverse effects to be taken into account is the increase in the number of infections,[1] especially of the opportunistic and granulomatous types, such as tuberculosis (TB). Although the risk is increased with all the anti-TNF-α agents, there are data that suggest a higher risk among patients who are treated with monoclonal antibodies when compared with those receiving the fusion protein.[2]

Since 2002, the United States Food and Drug Administration recommends screening for TB, and chemoprophylaxis in case of latent TB infection, before initiating anti-TNF-α agents. Prophylaxis is recommended in the following situations[3]: (a) recent exposure to confirmed TB; (b) a history of TB without proper treatment; and (c) positive Mantoux test and/or radiographic evidence of sequelae of TB. This measure has dramatically reduced the incidence of TB among patients receiving anti-TNF-α[4]; however, cases of TB continue to be detected, despite an initial negative screening test.[5] This could be due to either a reactivation of latent TB with a negative screening test (false negative) or a primary tuberculous infection. The time to development of active TB after initiation of anti-TNF-α therapy may prove to be the clue to whether reactivation or primary infection should be suspected, as reactivation can be expected to occur within a short time after initiation of immunosuppressive therapy. However, a tuberculous infection after a long period of treatment suggests a primary infection, although it has not yet been possible to establish a clear time limit to distinguish between the 2 origins.[6]

Given its relevance, the objective of this study is to review the cases of active TB in which the patients presumably developed a primary tuberculous infection during treatment with anti-TNF-α agents, despite an initial negative screening test.

Material and Methods

We performed a retrospective review of the registry of patients receiving biologic therapy in the rheumatology department of Hospital General Universitaria de Alicante, in southeastern Spain, which included a total of 771 patients treated between 1999 and 2012 (year of the study). We selected the medical records of patients who met the following inclusion criteria: (a) current or previous treatment with anti-TNF-α; (b) negative results in TB screening prior to treatment with anti-TNF-α; (c) active TB diagnosed during treatment with anti-TNF-α; and (d) suspected primary tuberculous infection; for this study, primary tuberculous infection was considered if the diagnosis had been made after treatment with the biologic agents for at least 12 months.[7] The TB screening protocol in our center consists of the Mantoux test (1 or 2 steps), chest radiography, and microscopic study of sputum and urine specimens, when appropriate. We reviewed the clinical variables (signs of underlying disease and of tuberculosis), epidemiological variables (treatment duration, study of contacts), therapeutic variables (treatments received and duration) and outcome variables (test results and response to treatment) of the patients who met the inclusion criteria.

Results

Of the 771 patients included in the registry, 7 had active TB. One had not undergone screening for TB prior to initiation of anti-TNF-α therapy, as this took place before the recommendations. The results of the Mantoux test were positive in 2; 1 of them received complete chemical prophylaxis (a short 3-month regimen of rifampicin and isoniazid) and the other, incomplete. In the remaining 4 patients, screening (including 2-step Mantoux test and chest radiography) was negative. Two of them developed TB during the first year of anti-TNF-α therapy and, therefore, were considered to have a reactivation of latent TB, with false negative results in the screening test. Finally, 2 patients (0.2% of the series) met all the inclusion criteria, and were considered to have primary tuberculous infections.

Case no. 1: The patient was a 41-year-old HLA-B27-positive woman diagnosed, at the age of 30 years, as having ankylosing spondylitis affecting the axial skeleton and recurrent acute anterior uveitis. Her response to nonsteroid anti-inflammatory drugs (NSAID) was suboptimal and treatment with adalimumab was begun in 2006, following screening for TB (at the time of the Mantoux test, she was only being treated with NSAID). In 2009, after 35 months of adalimumab, she presented with fever, dry cough, odynophagia, and headache, and was feeling generally unwell. Pulmonary computed tomography revealed a mass measuring 4 cm in the anterior segment of left upper lobe, with suprahilar and prevascular adenopathy (Fig. 1). On this occasion, she reacted to the Mantoux test with an induration measuring 20 mm 48 h later. Fiberoptic bronchoscopy was performed with transbronchial biopsy and the study of the specimen revealed a mucosa with chronic granulomatous inflammation plus necrosis, and the culture was positive for *Mycobacterium tuberculosis*. After tuberculostatic therapy with rifampicin, pyrazinamide and isoniazid, the patient's disease resolved.

In the study of her contacts, her father proved to be positive for latent tuberculous infection, but no infectious contacts were

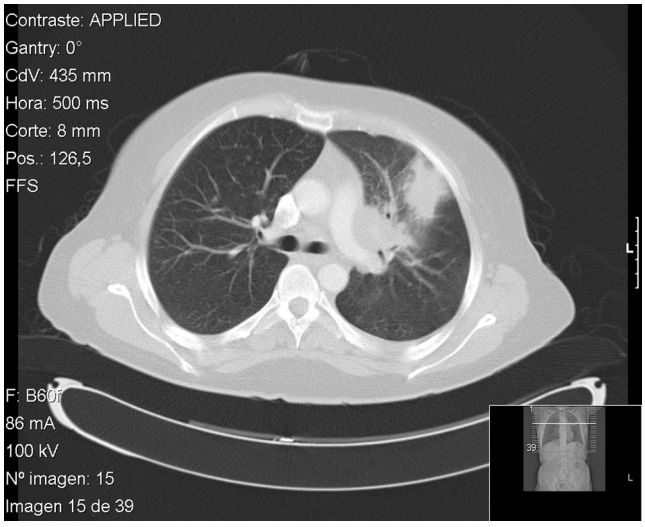

Fig. 1. Pulmonary computed tomography showing condensation in left upper lobe, in contact with the anterior costal pleura and accompanied by ipsilateral hilar adenopathy.