Short communication

Importance of tuberculosis screening before inhibiting tumour necrosis factor-alpha therapy

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ABSTRACT

Introduction: There has been an increase in the incidence of tuberculosis infection in recent years, due to the increasing use of drugs inhibiting tumour necrosis factor-alpha (anti-TNFα) in the treatment of inflammatory diseases.

Case report: We report the case of a male patient being treated with infliximab (anti-TNFα) who developed disseminated tuberculosis with ocular involvement.

Conclusion: It is very important to conduct a proper screening to detect patients at risk for tuberculosis before starting treatment with these drugs. For this purpose, the QuantiFERON®-TB Gold in Tube (Interferon Gamma Release Assay, IGRA) is presented as an alternative screening test with high sensitivity and specificity.

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Importancia del screening de tuberculosis previo al tratamiento con inhibidores del factor de necrosis tumoral alfa

RESUMEN

Introducción: En los últimos años se ha registrado un aumento en la incidencia de infección tuberculosa, debido a la utilización cada vez mayor de fármacos inhibidores del factor de necrosis tumoral alfa (anti-TNFα) en el tratamiento de enfermedades inflamatorias.

Caso clínico: Se describe el caso de un varón en tratamiento con infliximab (anti-TNFα) que desarrolla tuberculosis diseminada con afectación ocular.

Conclusión: Es de gran importancia la realización de un screening apropiado para detectar pacientes con riesgo de desarrollar tuberculosis antes de iniciar tratamiento con dichos fármacos. Con este propósito, el QuantiFERON®-TB Gold in Tube (Interferon Gamma Release Assay, IGRA) se presenta como una alternativa de alta sensibilidad y especificidad.

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**Introduction**

Antagonist of tumour necrosis factor-alpha (anti-TNFα) drugs is being increasingly used for treating inflammatory diseases. This has caused an increase in the incidence of tuberculosis infections. Accordingly, it is becoming more important to detect the latent infection before beginning treatment with these drugs. This paper reports a case of disseminated tuberculosis with ocular involvement in the context of treatment with infliximab.

**Case report**

A 35-year-old male, with ankylopoietic spondylitis in treatment with anti-TNFα infliximab (Remicade®, Merck Sharp and Dhome), was admitted to the Internal Medicine Service of our hospital for febrile syndrome analysis.

Before starting treatment with infliximab, the patient exhibited negative Mantoux. At admittance, he exhibited positive Mantoux after 72 h (1.2 cm) as well as positive Quantiferon®-TB Gold IT (12.86 U/ml). Bronchial and mediastinic adenopathy biopsies were performed and, with the histological diagnosis of tuberculosis, treatment was initiated with Rifater®, Sanofi Aventis (isoniazid, pyrazinamide and rifampicin) plus ethambutol. On day 12 the patient referred blurred vision in the right eye. Treatment was suspended due to suspected toxic neuropathy caused by ethambutol and assessment was requested to the Ophthalmology Service.

In the initial exploration, best-corrected visual acuity (BCVA) in the right eye (RE) was 0.5 (−1), and 1.0 in the left eye (LE). The anterior pole was normal, without exhibiting inflammatory signs. Intraocular pressure was within normal limits.

Fundoscopic exploration of the RE (Fig. 1) revealed normal papilla, with an epipapillary veil and choroidal inflammatory area with granuloma in the upper macula together with retinal neuroepithelium serous detachment, which was confirmed by optic coherence tomography (Cirrus OCT, Zeiss) (Fig. 2). The exploration also revealed an isolated cotton-like exudate in the temporal-superior arch. The LE was normal (Fig. 1).

The visual field (VF) exhibited central scotoma in the RE (Fig. 3), with the LE VF being normal.

Fluorescein angiography (FA) was performed and revealed hypo-fluorescence due to obstruction of the inflammatory area and choroidal area staining in late phases (Fig. 4).

After discarding ocular toxicity due to ethambutol it was decided to establish treatment with Rimstar®, Sandoz (ethambutol, isoniazid, pyrazinamide and rifampicin) for 3 months and subsequently with Rifinah®, Sanofi Aventis (isoniazid and rifampicin) for 9 months. In addition, 60 mg of prednisone per day was added to the treatment.

Ophthalmological assessments were performed at monthly intervals. At month 5, the BCVA of the RE was 1.0. Funduscopy (Fig. 5) revealed that the choroidal granuloma exhibited a scarred appearance and the serous detachment had disappeared as shown by the OCT (Fig. 6). In addition, the central scotoma had disappeared from the VF.

**Discussion**

Alpha tumour necrosis factor is a pro-inflammatory cytokine that is involved in the pathogeny of various chronic inflammatory diseases. It is an important component of the immune response by inducing the differentiation of monocytes into...
macrophages and also plays a key role in the formation and preservation of granuloma.\textsuperscript{1}

Anti-TNF\(\alpha\) drugs (infliximab and etanercept, among others) have brought on a revolution in the treatment of multiple inflammatory diseases such as ankylosing spondylitis. However, the increased risk of tuberculosis infection must be taken into account and latent or active tuberculosis screening must be performed. In 2007, Fonollosa et al.\textsuperscript{2} published the first reported case of tuberculose uveitis after treatment with etanercept. In addition, it must be mentioned that the majority of tuberculosis cases were associated to infliximab expressed with disseminated or extrapulmonary disease, as in the case of our patient.

Tuberculine or Mantoux test exhibits significant limitations such as false negatives due to technical causes, very recent infections, milia tuberculosis [50\%], AIDS, immunodepressed patients, immunosuppressant treatment, chronic kidney insufficiency, severe malnutrition, lymphoid organ disease, patients under 6 months of age or very old, or false positives due to BCG vaccination or infection due to non-tuberculous mycobacteria. It is recommended to carry out this

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig3.png}
\caption{Right eye visual field: central scotoma.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig4.png}
\caption{Right eye fluorescein angiography. Left: anerithra retinography. Centre: hypo-fluorescence due to obstruction of the inflammatory area. Right: choroidal area staining in late stages.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig5.png}
\caption{Right eye retinography at month 5: scar lesion secondary to choroidal granuloma.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig6.png}
\caption{Right eye optic coherence tomography (vertical section) at month 5: the neuroepithelium detachment and hyper-reflectiveness corresponding to the scar have disappeared.}
\end{figure}
test in 2 stages in order to improve its efficiency, maximizing the booster effect of the first test.

In the instant case, the patient exhibited negative Mantoux prior to infliximab treatment although the test was not repeated at a second stage.

Recent techniques for in vitro detection of tuberculosis infection, generally known as interferon gamma release assays (IGRA) were a significant development due to their high specificity. These techniques are based on the principle that the excited T-cells of infected individuals produce interferon gamma (IFNγ) in response to Mycobacterium tuberculosis antigens. The release of IFNγ can be measured by means of ELISA (QuantiFERON®-TB Gold in Tube) or ELISPOT (γ-SPOT.TB®). A high value of INFγ indicates tuberculosis infection.³

In this case, QuantiFERON®-TB Gold in Tube was positive although it was not carried out until the patient exhibited clinical signs of suspected tuberculosis.

In what concerns ocular tuberculosis, it is known that the majority of cases are due to haematogenous dissemination of the infection. In addition, it is advisable to take into account that the infection can arise even in the absence of pulmonary disease. Affected patients exhibit a broad range of clinical expressions,⁴ the most frequent being granulomatous uveitis and choroidal granuloma. The latter indicates haematogenous dissemination as in the present case. In addition, some forms of presentation are similar to intraocular idiopathic inflammatory conditions such as serpiginous choroidopathy, which produce confusion and difficulty for finalizing the diagnosis.

Accordingly, it is important to obtain an early diagnostic and to establish timely treatment to prevent significant complications that could even cause blindness.

Finally, the authors would like to emphasize the importance of carrying out an appropriate screening with all available tests (Mantoux, IGRA) in order to detect patients at risk of developing tuberculosis before establishing treatment with anti-TNF drugs.

Conflict of interest

No conflict of interest has been declared by the authors.

REFERENCES