CASE REPORT

Anal tuberculosis complicating anti-TNF α therapyNuria Luquín,¹ Mar Masiá,^{1,2} Raúl Noguera,³ Félix Gutiérrez²

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SUMMARY

A 42-year-old man receiving anti-tumour necrosis factor α (anti-TNF α) therapy with adalimumab due to psoriatic arthritis presented with a 2-month-old anal ulcer. An apical right lung infiltrate was found in his chest X-ray, although he had no pulmonary symptoms. Two biopsies of the ulcer were taken and reported as granulomatous, necrotising, with chronic inflammation (first), and as hyperplastic epidermis with lymphocytic infiltrate and the presence of plenty of plasmatic cells (second). Histochemical techniques, including Ziehl-Neelsen, Grocott and periodic acid-Schiff stains, and PCR for *Mycobacterium tuberculosis* on both biopsies were negative. Serology for HIV, syphilis and hepatitis were also negative. In the second biopsy culture, moderate colonies of *M. tuberculosis* finally grew. The patient started a four-drug antituberculosis regimen. Adalimumab was discontinued and etanercept introduced after 2 months of antituberculosis therapy. The patient remained on therapy for 9 months with complete ulcer resolution.

BACKGROUND

The risk of tuberculosis is increased with antitumour necrosis factor α (anti-TNF α) therapy, mainly in association with adalimumab or infliximab, both associated with a threefold to fourfold higher rate of tuberculosis development compared with etanercept.¹ Data from a large British study series of patients with rheumatoid arthritis on anti-TNF α therapy have shown a predominance of extrapulmonary disease, mainly affecting the lymph nodes, the gastrointestinal tract and the central nervous system, and a high frequency of disseminated tuberculosis, mostly in patients receiving adalimumab.¹ Anal and perianal tuberculosis are uncommon manifestations of extrapulmonary disease.^{2,3} To the best of our knowledge, its association with anti-TNF α therapy had not been previously described.

CASE PRESENTATION

A middle-aged man was referred to the infectious diseases unit with a 2-month history of anal ulcer and local pain at defecation. There were no accompanying gastrointestinal symptoms. He was born in South America, but had been living in Spain for over 10 years, and had not travelled abroad recently. He worked as a commercial agent and was a self-declared heterosexual. The patient had been diagnosed with psoriatic arthritis and had been receiving adalimumab every 2 weeks during the past 13 months, after two consecutive negative tuberculin tests and a negative QuantiFERON test.

Physical examination revealed a 2 cm diameter, white-bordered, pink-coloured anal ulcer at 3

Figure 1 Clinical presentation of tuberculous disease: ulcerated anal lesion.

o'clock (figure 1). There was a rolling, right inguinal lymphadenopathy 2–3 cm in diameter, which was not painful on palpation. No lesions were found on the penis.

INVESTIGATIONS

Routine blood tests were normal and serological test results for HIV, syphilis, *Entamoeba histolytica* and hepatitis B and C virus were negative. A biopsy of the ulcer revealed granulomatous, necrotising, chronic inflammation with no evidence of malignancy. Histochemistry, including periodic acid-Schiff (PAS), Grocott and Ziehl-Neelsen stains, did not detect fungi or acid-alcohol-resistant bacilli. PCR for *Mycobacterium tuberculosis* complex was negative. A second Mantoux and QuantiFERON test were now positive.

A chest radiograph revealed an apical right lung infiltrate, which was not present in the baseline X-ray. The patient denied pulmonary symptoms. An induced sputum sample was collected, with negative results for mycobacteria.

Another ulcer biopsy was performed, showing a cutaneous fragment with hyperplastic epidermis and lymphocytic infiltrate with numerous plasmatic cells. Special techniques (Ziehl-Neelsen, Grocott and PAS) and immunohistochemistry for *Treponema* were again negative. A fresh PCR for *M. tuberculosis* complex was also negative. Culture of this ulcer yielded moderate colonies of *M. tuberculosis*.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anal ulcer includes: malignant diseases, herpes simplex, syphilis, deep mycosis, lymphogranuloma venereum, cutaneous amoebiasis, Crohn's disease and ulcerative colitis.¹

TREATMENT

Adalimumab was discontinued and a four-drug anti-tuberculous regimen was started. Drug susceptibility

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testing revealed resistance to pyrazinamide, which was discontinued after 2 months of therapy.

OUTCOME AND FOLLOW-UP

The patient completed 3 months with isoniazid, rifampicin and ethambutol, and 6 months with isoniazid and rifampicin. Etanercept was introduced 2 months after antituberculous therapy initiation, because of uncontrolled articular disease despite the use of several alternative regimens. The ulcer resolved completely.

DISCUSSION

Despite the high frequency of active tuberculosis disease development in patients receiving anti-TNF α therapy,⁴ especially adalimumab, anal tuberculosis had not been described until now in association with biological therapies. Anal tuberculosis has been attributed to direct haematogenous spread from a lung focus, ingestion of sputum-containing bacilli from active pulmonary disease, or through regional lymphatic nodules from intestinal or urinary disease.⁵ The coexistence of pulmonary tuberculosis has been described in other series,^{6–9} although in our case it was an unexpected finding given the lack of respiratory symptoms. Interestingly, the patient had negative tuberculin and QuantiFERON tests before anti-TNF α therapy initiation, which turned out to be positive several months later. Reactivation of undiagnosed latent tuberculosis infection due to false-negative screening tests has been estimated to range from 0.2% to 4% in

rheumatic patients.^{10–13} However, because symptoms started 1 year after biological therapy initiation, and the two negative screening assays became subsequently positive, we considered the possibility that the patient could have acquired a new infection. Although pyrazinamide resistance is unusual, the frequency of primary isoniazid resistance in Spain reaches 5%,¹⁴ and susceptibility testing is therefore advisable when tuberculosis is diagnosed. Clinicians should be aware of tuberculosis development, which might have an atypical presentation, in anti-TNF α -treated patients, even in those with no initially demonstrated latent tuberculosis. Repetitive screening for tuberculosis might help in preventing some cases of disease development in patients receiving biological therapies.

Contributors FG suggested the case report. NL was involved in the patient's care and wrote the first draft of the manuscript. MM and FG revised and modified the manuscript. RN was the physician involved in the chronic patient's care and reviewed the manuscript. NL, MM, RN and FG approved the final version of the manuscript.

Competing interests None.

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Learning points

- ▶ Adalimumab is one of the monoclonal antibodies most frequently associated with tuberculosis disease development.
- ▶ Anal disease constitutes an unusual presentation of tuberculosis, and it can be associated with anti-TNF α therapy.
- ▶ *Mycobacterium tuberculosis* should be added to the list of organisms causing anal ulcers in patients receiving biological therapies.
- ▶ Patients with negative tuberculin and QuantiFERON tests before anti-TNF α therapy initiation should be re-screened and negative assays should not discourage tuberculosis disease investigation when suggestive symptoms are present.
- ▶ Antimicrobial susceptibility testing should always be performed to select the best treatment choice for each case in order to eradicate tuberculosis disease and avoid the emergence of new resistant cases.

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