Mycobacterium chelonae infection under adalimumab therapy for spondylarthritis

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ABSTRACT

Tumour necrosis factor (TNF)-α antagonists have been prescribed increasingly over the past few years to manage various inflammatory diseases. This widespread use was quickly followed by the heightened frequency of opportunistic mycobacterial infections including environmental non-tuberculous mycobacterial infections (ENTM). We describe a 66-year-old man taking adalimumab for spondyloarthropathy who developed an inflammatory infiltration in his right index finger. A non-necrotising granuloma with epitheloid and giant cells in the dermis and eosinophilic acid-fast bacilli, identified by using Ziehl-Neelsen staining suggested a mycobacterial infection. Cultures for mycobacteria grew positive on Loewenstein-Jensen medium and molecular identification confirmed M. chelonae *infection. The outcome was favourable after five months of clarythromycin.*

In this context of more frequent ENTM infections, chronic non-specific cutaneous lesions of the extremities should evoke systematically cutaneous ENTM infections. Skin biopsy with histological examination and oriented microbiological cultures and molecular identification are mandatory to confirm the diagnosis.

Introduction

Tumour necrosis factor (TNF)-α antagonists are being used more and more to manage various autoimmune and inflammatory diseases. However, the widespread use of these highly potent immunosuppressive therapies was quickly followed by the increased frequency of opportunistic mycobacterial infections, including tuberculosis but also environmental non-tuberculous mycobacterial (ENTM) infections (1). Herein, we report a cutaneous *Mycobacterium chelonae* infection developing under adalimumab.

Case report

A 66-year-old man followed for spondylarthritis was referred for an inflammatory infiltration of the right index finger. His spondylarthritis had been diagnosed in 1996 and was initially treated with low-dose oral corticosteroids and non-steroidal anti-inflammatory drugs. In 2004, recurrent episcleritis, and axial and peripheral involvement prompted prescription of infliximab (5 mg/kg, one infusion per month) with good efficacy. In February 2006, infliximab was switched to adalimumab (40 mg, every other week). In 2008, the patient developed cutaneous, painless, slow-growing, erythematous, infiltrated nodules, without ulceration or crusts, of the second phalange of the right index. The patient had not undergone recent surgery and did not recall any prior trauma or exposure to aquarium water. His physical examination was otherwise normal; spondylarthritis was well-controlled with adalimumab. He had no palpable lymph nodes or sporotrichoid dissemination of the lesions, and denied having night sweats, fever or weight loss.

One nodule was completely excised, embedded in full and multiple histological sections were examined. Light microscopy examination showed an inflammatory non-necrotising granuloma with epitheloid and giant cells in the dermis, surrounded by mononuclear cells mainly lymphocytes. Some areas contained a neutrophil rich infiltrate. Eosinophilic acid-fast bacilli, suggestive of a mycobacterial infection, were identified by using Ziehl-Neelsen staining. Direct tissue examination was negative but cultures on Loewenstein-Jensen medium grew mycobacteria within 20 days. Molecular identification using polymerase chain reaction amplification of the lesion confirmed *M. chelonae* infection. Adalimumab was discontinued and clarithromycin (2 g daily) alone was started. The clinical response was slow, with the first signs of regression observed at month 2. Two purple non-tender papules on the index finger had regressed at month 4. Treatment was stopped one month later. Only a pigmented scar remains visible after six months of follow-up. Because clinical remission of his spondyloarthropathy persisted, adalimumab was not reintroduced.

Discussion

We describe a new case of cutaneous infection caused by *M. chelonae*, an ENTM, under adalimumab that evolved

favourably under clarythromycin alone. To date, this is the third report of such an infection arising on adalumimab (2, 3).

ENTM are acid-fast mycobacteria. They have a worldwide distribution, are widespread in soil and water, include more than 30 species, and are classified according to their growth rate, pigmentation and genetic patterns (4). They are responsible for chronic infections of the skin and the soft tissues, but also of various organs, *e.g.* lungs, lymph nodes, joints or liver (1, 5, 6). Disseminated ENTM infection may occur, especially in immunocompromised hosts. The most common species in the western countries are *M. marinum* and the rapidly growing *M. abscessus, M. fortuitum, M. chelonae* (6). Almost all ENTM species have been incriminated in cutaneous lesions. Symptoms are non-specific and include sinus tracts, non-healing ulcers, subcutaneous abscesses, subcutaneous nodules of different sizes, and erythema associated with ulcers or chronically draining fistulas forming after surgery (5, 6). Lesions can be either isolated or multiple and often involve the extremities (5, 6). *M. chelonae* is more frequently isolated from the lower extremities and responsible for multiple lesions (5). Multiple lesions are often noted in immunocompromised (treatment or systemic comorbidity) patient. Single lesions are usually associated with a history of local trauma or surgery (5). We could not identify the inoculation site in our patient, whose lesions were restricted to one finger. Diagnosis is based on the combination of culture in a selective medium, histological examination and molecular biology techniques applied to a skin lesion biopsy. Each technique alone is not sufficient to make the diagnosis (4).

Reports of ENTM infections have increased over for the past years with the widespread use of TNF-α antagonists (1, 7). TNF-α and interferon-γ are the key proinflammatory cytokines involved in the immune response against mycobacterial infections. Thus, mycobacterial infections of the skin, but also lung, liver or eye have been reported in patients receiving infliximab, adalimumab or etanercept (2, 3, 8-14). To date, only one similar case was reported of cutaneous *M. chelonae* infection in a 68-year-old patient with rheumatoid arthritis who developed multiple subcutaneous nodules two months after starting adalimumab (2). The deleterious action of anti-TNF-α agents on anti-mycobacterial immunity and the risk of infection dissemination render mandatory the withdrawal of the biologic during antibiotic therapy until complete healing of the lesions, as for our patient (2). However, because our patient's mycobacterial infection resulted from accidental inoculation, and not reactivation, once lesion healing was complete, the mycobacterium could be considered eradicated and the TNF-α antagonist could be resumed, if necessary.

Optimal treatment of rapidly growing mycobacterial infections remains to be established, in the absence of randomised controlled trials. Clarythromycin monotherapy remains the treatment of choice for *M. chelonae* cutaneous infection, although its optimal dose and duration remain to be determined (4). Some authors recommend antibiotic susceptibility testing of all isolates and use of empirical therapy while awaiting results (5). The same authors recommended, for an isolated lesion, waiting for the susceptibility-test result before treating (5). Despite the clarythromycin efficacy in case reports, a combination of antibiotics has also been suggested, rather than monotherapy, to avoid resistance acquisition (5). Surgery is proposed in selected cases, especially for a single lesion (4, 5).

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