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CASE REPORT

Oral tuberculosis associated with a treatment with anti-rheumatic drugs

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BACKGROUND: The use of immunosuppressive medication is a dominant risk factor for infection in patients with rheumatoid arthritis (RA). Methotrexate (MTX) is one of the traditional disease-modifying antirheumatic drugs. Adalimumab [a human anti-tumor necrosis factor-α (anti-TNF-α) monoclonal antibody] represent an important advance in the treatment of RA and has been recently come in use. TNF-α plays a role in the host defense against *Mycobacterium tuberculosis* and notably in granuloma formation. Infections occur at a high rate among those who use one or the combination of the two medications.

METHOD: We examined a female patient that was referred to our department for evaluation and treatment of a granular lesion on the soft palate and uvula, complaining of mild dysphagia. The patient was treated for 4 months with MTX and adalimumab for RA before the oral lesion appeared.

RESULTS: The histopathological examination of a specimen of the oral lesion, taken by biopsy, showed a chronic inflammation characterized by tuberculous granulomas. Polymerase chain reaction test and culture of a new specimen was positive for *M. tuberculosis*.

CONCLUSIONS: The therapeutic use of MTX or/and adalimumab for the treatment of RA or few others diseases, can cause oral tuberculosis.

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Case report

A 43-year-old, female patient, was referred to the Oral Medicine and Maxillofacial Pathology Department of Aristotle University of Thessaloniki, Greece for evaluation and treatment of a granular lesion on the soft palate and the uvula, complaining of mild dysphagia. The lesion initially appeared 3 months ago, increased slowly in size. Her medical history revealed that, 2 years ago she had suffered from rheumatoid arthritis (RA). In January 2004, the patient had commenced the treatment for RA with adalimumab (Humira®; Abbot Laboratories, Abbot Park, IL, USA) in dose 40 mg subcutaneously every other week, with concomitant methotrexate (MTX) in dose 12.5 mg weekly, prescribed. Four months following onset of this regimen, the patient developed the palatal lesion. The lesion remained unhealed after antimicrobial chemotherapy (clarithromycin 250 mg twice daily, for 6 days) and use of prezolon (10 mg twice daily, for 21 days). Her rheumatologist prescribed the above regimen, as he considered to be an infection caused by common bacteria and in continuation, as allergic reaction probably to MTX.

Intraoral examination revealed a not well-defined, red, painful granular lesion in the soft palate (mostly in the right side) and uvula, measuring 2.5 × 3.0 cm in diameter, with multiple small ulcers on the surface (Fig. 1). Palpation showed a neck lymphadenopathy. Computerized tomography of the head and neck showed a local homogenous mass (Fig. 2).

Physical examination revealed a temperature of 37.5°C. Laboratory findings disclosed an elevation of erythrocyte sedimentation rate (ESR): 25 mm/h. The remaining laboratory values were within the range of normal. Electrolytes, liver and renal functions were normal. The patient was HIV-1 and HIV-2 negative. Chest radiography did not show any tuberculous focus or any other abnormal finding.

An incisional biopsy was performed. Microscopically, the specimen was composed of a chronic inflammation

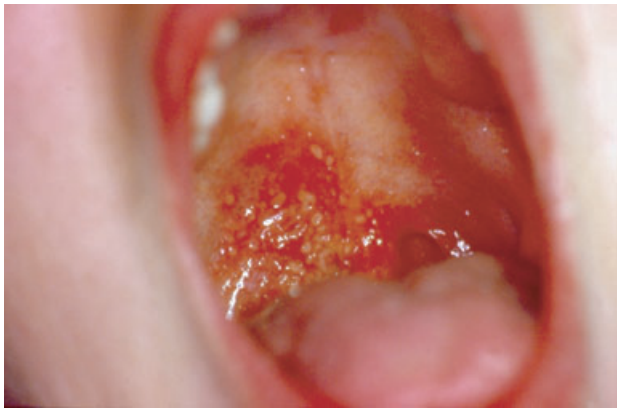

Figure 1 Clinical view of the oral tuberculosis lesions associated with antirheumatic therapy.

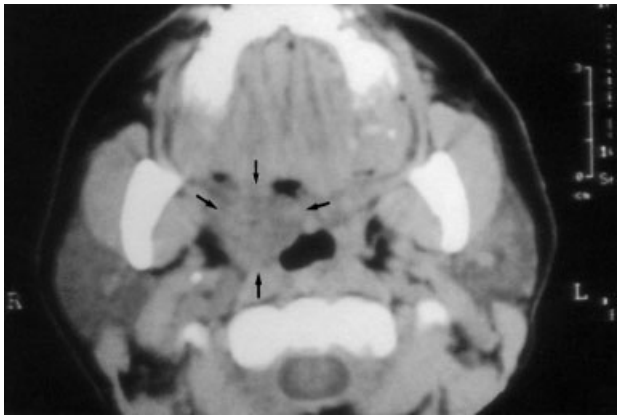

Figure 2 CT of the lesion demonstrating the unilocular homogenous well defined mass in the area of the right soft palate.

characterized by tuberculous granulomas consisting of epithelioid cells and Langhan's giant cells, surrounded by lymphatic infiltrations (Figs 3 and 4). These features were consistent with a diagnosis of tuberculosis (TB). Polymerase chain reaction technology was then conducted for specific sequences of the TB mycobacteria complex. *Mycobacterium tuberculosis* DNA was detectable. Furthermore, a new section of the tissue was taken and the culture of the specimen was positive for *M. tuberculosis*. A tuberculin skin test was strongly positive.

A diagnosis of TB associated with anti-rheumatic therapy was made, and as there was no known exposure to TB it has been considered as a progression of latent TB infection (LTBI) to TB disease.

The patient was referred to the pulmonary medical section for treatment. Antituberculotic therapy was administered. On a follow up, 40 days after the initial antituberculotic treatment and termination of antirheumatic treatment with adalimumab and MTX, the oral lesion was healed.

Comments

Infections are common in people with RA (1). The use of immunosuppressive medication is a dominant risk

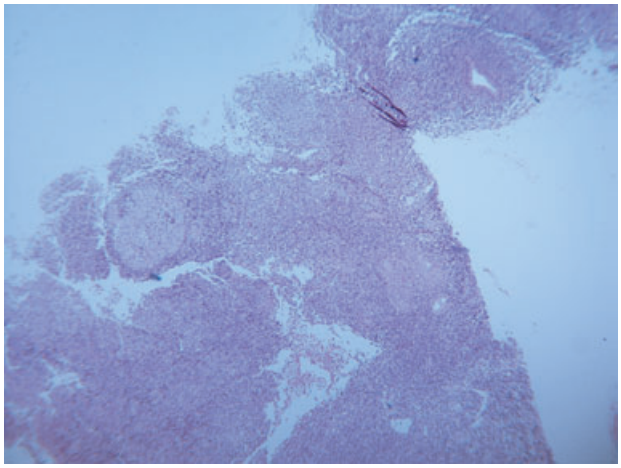

Figure 3 Low power view of tubercular granuloma (H&E ×40, original manifestation).

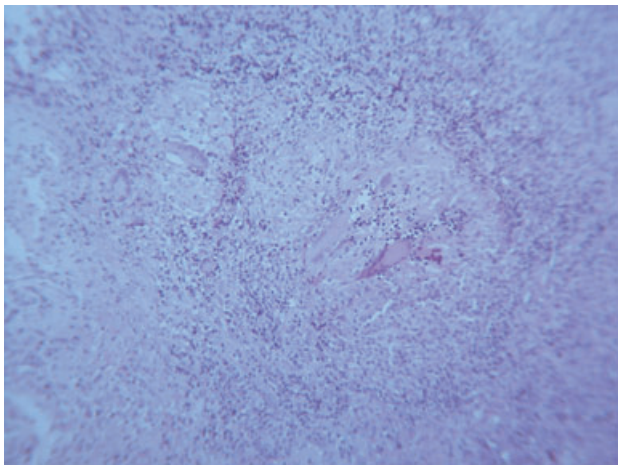

Figure 4 High power view of tubercular granuloma (H&E ×120, original manifestation).

factor for infection in those patients. MTX is one of the standard traditional disease-modifying antirheumatic drugs. Adalimumab [a human anti-tumor necrosis factor-α (anti-TNF-α) monoclonal antibody] represent an important advance in the treatment of RA and has been in use since 2003. TNF-α plays a role in the host defense against *M. tuberculosis* and notably in granuloma formation (2). Adalimumab can be given alone or with concomitant MTX. Infections, including mycobacterial diseases, occur at a high rate among those who use one or the combination of the two medications (1). TB disease is a potential adverse reaction from a treatment with adalimumab (3) or MTX (4). The majority of the cases represent progression of LTBI to TB disease, although the contribution of newly acquired *M. tuberculosis* infection to the total number of reports is unknown. The use of adalimumab and MTX has been associated with reactivation of TB (4, 5). Prior to the introduction of adalimumab and others TNF-α inhibitors, cases of TB had occasionally been observed by low-dose MTX therapy in patients with RA (5).

Through 2003, pre- and post-screening TB rates in clinical trials of adalimumab were 1.3/100 patient years and 0.08 (North America) and 0.13 (Europe) (6). Approximately 60% of TB patients develop extra-pulmonary disease in the range of 3–8 months (median time: 42 weeks) after the beginning of the treatment with adalimumab (7).

Adalimumab is under investigation in several other indications including ankylosing spondylitis, Crohn disease, psoriasis and psoriatic arthritis.

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