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A case of Brucella spondylitis in a patient with psoriatic arthritis receiving infliximab

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ABSTRACT

A 69-year-old woman with psoriatic arthritis treated with infliximab presented with low back pain of recent onset and fever. Serological, microbiological and imaging studies revealed Brucella spondylitis at the L5-S1 level. Immunosuppressive therapy was suspended and antibiotic therapy including doxycycline and rifampicin was administered for six months. The patient responded adequately with clinical and laboratory improvement and a considerable remission of spondylitis on repeat magnetic resonance imaging scan. The pathophysiology of tumor necrosis factor (TNF) α in Brucellosis and the role of anti-TNFα therapy are discussed.

Introduction

Brucellosis is a zoonosis still prevalent in a considerable part of the world including Greece. It is caused by intracellular bacteria belonging to the Brucella genus with tropism for the reticuloendothelial system. In humans the most frequent complication of brucellosis is osteoarticular disease with three distinct forms: peripheral arthritis, sacroiliitis, and spondylitis. Host immunity relies on intracellular destruction of endocytosed bacteria by phagocytes and infected phagocyte apoptosis rather than on specific antibody production of IgM, IgG and IgA class (1). Intracellular destruction and phagocyte apoptosis largely depend on the secretion of cytokines, such as interleukin (IL) 12, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and others. The potential effects of cytokine blocking *in vivo* and in particular TNF-α blocking in the course of human brucellosis are not clear. We report a case of a patient with psoriatic arthritis (PsA) on infliximab therapy who developed vertebral brucellosis and the role of TNF-α in its pathophysiology are discussed.

Case report

A 68-year-old woman with a 16-year history of PsA presented to our outpatient rheumatology clinic with worsening arthritis of hands, feet and knees bilaterally accompanied by psoriatic skin eruption on elbows, trunk and knees. Until then, she had sporadically received oral methylprednisolone and methotrexate, which had not been well tolerated due to nausea and elevated liver tests. No significant co-morbidities were reported in the history. On clinical evaluation the patient had synovitis of the small joints of hands and knees and psoriasis affecting a considerable area of trunk, upper and lower extremities. C-reactive protein (CRP) was 9 mg/L (normal <6 mg/L) and erythrocyte sedimentation rate (ESR) was 53 mm/h. Plain x-rays of the sacroiliac joints and spine showed no obvious lesions, while the x-rays of the hands showed joint space narrowing or even elimination, bone erosions and juxta-articular new bone formation affecting the majority of the joints of the hands bilaterally. Rheumatoid factor was negative. The patient was started on cyclosporine A (CsA) 200 mg/day (~2.5 mg/kg) and put on regular follow-up.

The patient showed a moderate skin and joint response, but on the fourth month she developed arterial hypertension and hypertrichosis. CsA was reduced to 100 mg daily and infliximab 5 mg/kg in a loading dose at 0, 2, 6 weeks and every 2 months thereafter was added to the therapeutic regimen. After almost 4 months she had a remarkable improvement of the skin and articular disease reflected in a CRP value of 2 mg/L and ESR 37 mm/h. Following another 2 months, on the fifth infliximab infusion, she reported low back pain despite the sustained improvement of the skin rash and the peripheral joints. Physical evaluation revealed only mild tenderness over lumbar spine. Inflammatory markers had moderately increased (CRP 33 mg/L; ESR 60 mm/h) and almost twofold serum elevations of liver enzymes were observed. Sacroiliac and lumbar spine x-rays were unremarkable. Axial involvement due to PsA was considered. Pending sacroiliac and lumbar spine magnetic resonance imaging (MRI), any modification in her immunosuppressive regimen was reserved until the completion of the work-up.

However, 10 days later, the patient presented complaining for worsening low back pain and fever reaching 39°C.

The patient was hospitalized and CsA was discontinued. Laboratory tests revealed elevated inflammatory markers (CRP 27 mg/L; ESR 110 mm/h) and liver biochemistry abnormalities (gamma glutamyl transpeptidase 101 UI/L, normal values <32 UI/L; alkaline phosphatase 140 UI/L, normal values <125 UI/L). Chest x-ray and purified protein derivative skin test were negative. Wright reaction and Rose Bengal plate tests were positive (titers 1/5120, 4+ respectively). Blood cultures drawn on fever spikes were positive for Brucella species. Moreover, serology revealed specific antibodies against Brucella species of the IgG, IgM and IgA class. An MRI examination revealed involvement of the L5, S1 vertebral bodies appearing with hypersignal in T2-weighted images, hyposignal in T1-weighted images and showing enhancement after intravenous contrast administration (Fig. 1A and 1B). In continuity with the vertebral lesion enhancing tissue was observed in the right prevertebral space (Fig. 1B and 1C). The L5-S1 disk showed normal morphology and signal characteristics (Fig. 1B). The appearance of the sacroiliac joints was unremarkable (Fig. 1D).

The patient was started on doxycycline 100 mg twice daily and rifampicin 900 mg/day, while infliximab infusions were suspended. Fever totally resolved in 4 days and the patient was discharged after 15 days on the same antibiotic regimen (2).

Two months after discharge, the patient's back pain had gradually ameliorated, while inflammation markers had decreased and liver enzymes normalized. Repeat MRI scan showed gradual and considerable decrease of the vertebral involvement and disappearance of the prevertebral enhancing tissue (Fig. 2). The patient went on an uncomplicated recovery in clinical and laboratory terms for the next four months, when a new MRI scan showed further improvement. Taking into account all clinical, laboratory and radiological evidence of brucellosis eradication, antibiotics were stopped after six months.

As far as PsA is concerned, a gradual relapse of the skin disease was already evident two months after CsA was stopped. As soon as the first clinical, laboratory and MRI re-evaluation, at two months, confirmed the effectiveness of the antibiotic treatment, CsA was initiated again at 100 mg daily. However, in the next months skin disease progressed even more, while a relapse of arthritis in the hands occurred soon after antibiotics were discontinued. Under these circumstances, infliximab was re-instituted 2 months after antibiotic discontinuation at a dose of 5 mg/kg every 2 months. It hardly needs mention that the patient has since been under close monitor, given that there is very little experience concerning re-institution of anti-TNFα agents after recovery from brucellosis. In a single case of brucellosis reactivation in a background of rheumatoid arthritis on infliximab, anti-TNFα therapy was re-started 9 months after completion of a successful antibiotic treatment without subsequent signs of relapse after two years of follow-up (3).

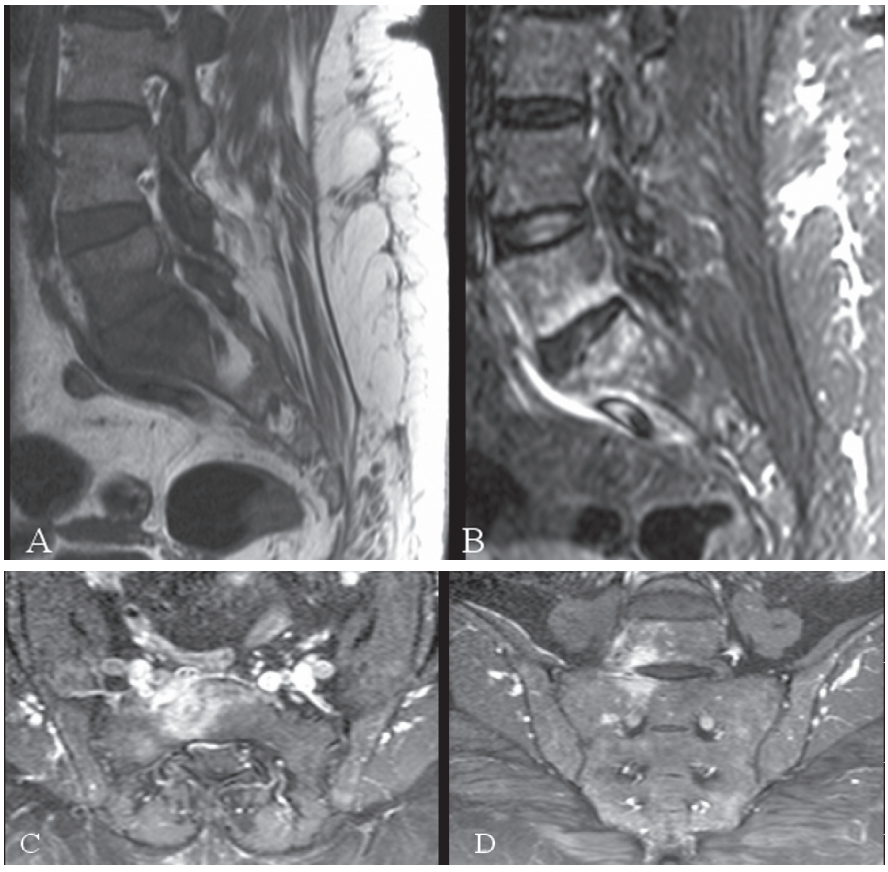

Fig. 1. Right parasagittal T1-weighted shows hyposignal of the L5, S1 vertebral bodies (**A**); right parasagittal T2-weighted shows hypersignal of the L5, S1 vertebral bodies (**B**); axial fat-suppressed contrast enhanced T1-weighted scan shows enhancement of the right part of the L5 and extension of the enhancing process into the right prevertebral space (**C**); coronal fat-suppressed contrast enhanced T1-weighted scan shows enhancement of the right part of the L5, S1 vertebral bodies. The sacroiliac joints are normal (**D**).

Discussion

Brucella is an intracellular microorganism that uses unique strategies to evade innate immunity mechanisms (1, 4). Adaptive immunity involves both antibody production and generation of Th1 responses. Antibodies can kill bacteria directly or indirectly through opsonization, but they cannot eradicate infection. More potent responses are raised from T cells. These cells secrete Th1-type cytokines, chiefly IFN-γ, which activates macrophages for more efficient phagocytosis and destruction of the microorganisms (5).

Although TNF-α is known to induce macrophage accumulation, activation and granuloma formation, it does not seem to be elevated in the serum of

humans with brucellosis (6). It appears that Brucella may interfere with TNF-α production by dendritic cells and impair antigen presentation to T cells, an effect that is reversed after exogenous addition of TNF-α (7). Furthermore, Brucella seems to halt the production of TNF-α by macrophages it has invaded, preventing autocrine macrophage stimulation, natural killer (NK) cell activation and the development of Th1 responses. This TNF-α suppression seems to be mediated through Brucella outer membrane protein 25 (Omp25) (8). Nevertheless, substances released from Brucellae and/or bacteria–infected macrophages result in the activation of a subclass of Tγ/δ cells which subsequently produce TNF-α, inducing macrophage and NK cell activation and specific Th1 and cytotoxic T-cell production, while they participate in the direct bacterial destruction. Thus, there seems to be a competition between Tγ/δ cell production of TNF-α favoring the host and TNF-α suppression in macrophages favoring the invader. The outcome of this antagonism may ultimately determine the elimination or chronicity of the infection (8) (Fig. 3). Early suppression of TNF-α actions through specific antibodies may thus promote the establishment of the infection. However, in an experimental model with mice, TNF-α inhibition with anti-TNFα antibodies prior to Brucellae inoculation resulted initially in more severe disease and smaller spleen enlargement than controls, but eventually the animals recovered from the infection as efficiently as normal controls did. Granulomas in liver were also formed (9). However, the pathogenesis of Brucella infection in mice is different from that in humans (8).

Greece is considered endemic for brucellosis as several of the countries in the Mediterranean basin. High rates are also reported for countries of the Middle East and Central Asia, as well as for some countries of Latin America. In contrast, North America, Western Europe and Australia report few cases of brucellosis (10). Registered cases of Brucella infection in Greece amounted to 222-545 yearly through the years 1997-2003 with an incidence of 20.9 new cases/year/10^6 people from year 2000 onwards, although some cases may have been missed to the authorities (1, 10, 11). Infection occurs through the gastrointestinal tract by consuming infected dairy products, through

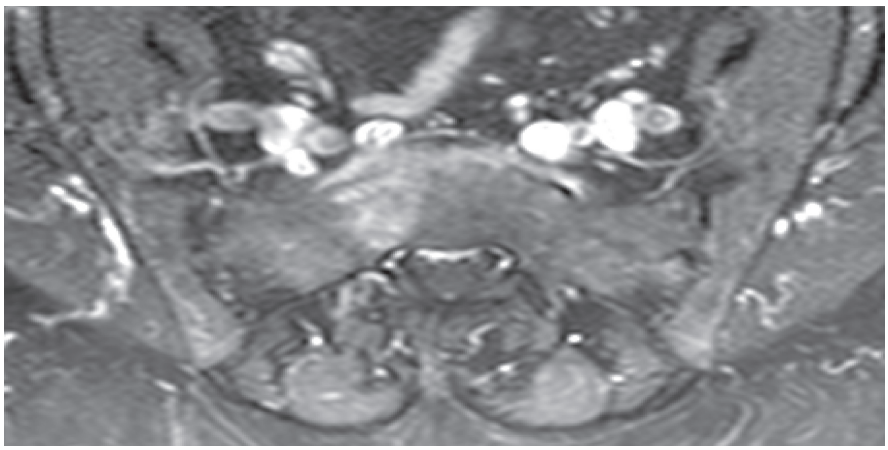

Fig. 2. Axial fat-suppressed contrast enhanced T1-weighted scan shows decrease of the L5, S1 enhancement and disappearance of the enhancing prevertebral process.

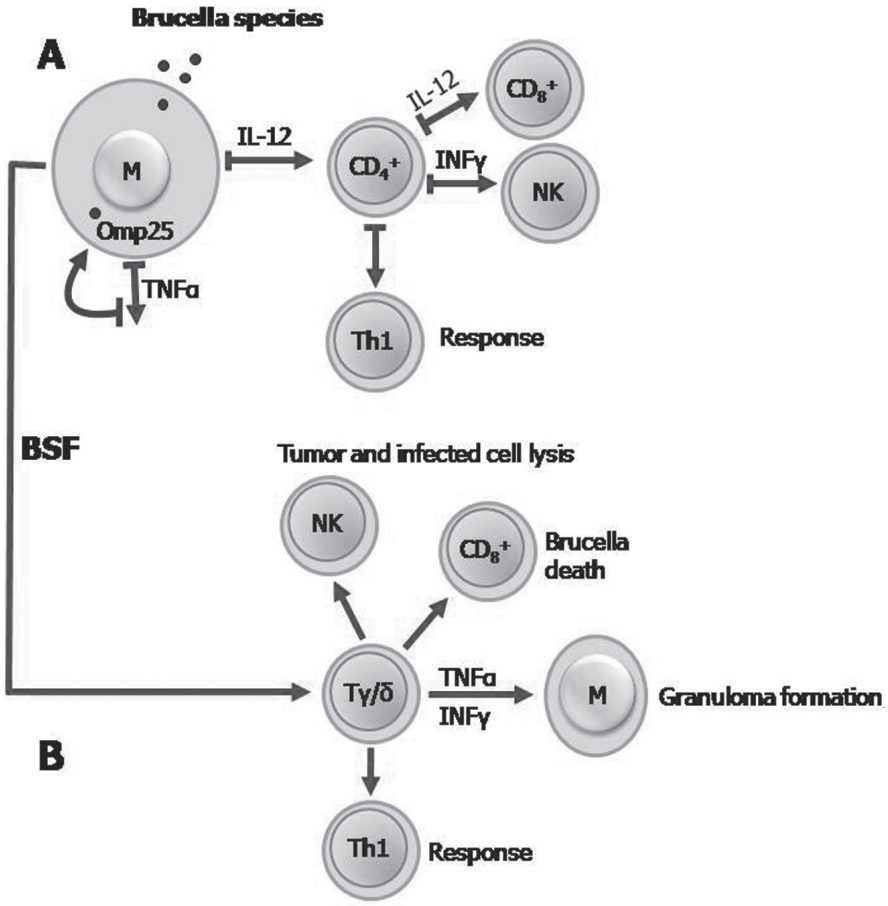

Fig. 3. Schematic representation of Brucella infection. Omp25 inhibits TNF-α release from infected macrophages, thus preventing autocrine stimulation and effective intracellular destruction of bacteria and pro-inflammatory cytokine release such as IL-12 essential for shifting the immune response forwards Th1 type. NK cell stimulation is also inhibited. All these events lead to Brucella survival (**A**). Brucella-derived molecules like BSF (Brucella suis fraction) released either from bacteria or infected cells stimulate a Tγ/δ cell subject for TNF production which may account for an alternative source of TNF-α, through which the above TNFα-depended immune processes may be mediated. Moreover, Tγ/δ cells engage in a direct cytotoxic activity against infected cells and/or bacteria (**B**).
M: macrophages; ⟼: suppression; →: activation; BSF: Brucella suis fraction.

skin ruptures or mucosal surfaces or by inhalation of infected aerosols during direct contact with infected animals or their parts (such as placentas, milk, meat, etc.) (12). Risk factors are (occupational) exposure to animals or their products, male gender (because of occupational exposure) and the period of year from December through May, *i.e.* following the parturition periods of sheep and goats (12).

As far as anti-TNFα agents are concerned, there has been a single report of re-activation of brucellosis in a rheumatoid arthritis patient on infliximab therapy (3). No other reports exist relating any of the three TNF-α inhibitors currently in use with Brucella infection in PsA or other rheumatic diseases. According to a Greek national registry for anti-TNFα use-related adverse events no additional case of brucellosis in the setting of anti-TNFα therapy for rheumatic conditions has been reported so far (personal communication).

In our patient there is no evidence in the history or the previous clinical evaluations of a smoldering Brucella infection. Moreover, the finding of specific Brucella antibodies of IgM class probably precludes a chronic infection. Most likely, she had recently acquired the infection through consumption of contaminated dairy products, since she had no history of contact with animals. Although, it is not routine in Greek or international rheumatology practice to screen patients for brucellosis prior to anti-TNFα initiation, as it is, for example, for tuberculosis, standard agglutination test would be a useful serologic assay every time brucellosis is suspected with a careful interpretation of the titer depending on history of exposure and prevalence of the infection in the area (1, 5).

Our patient presented with imaging findings of septic spondylitis and a differential diagnosis from SpA is mandatory. Spinal involvement in PsA mainly consists of sacroiliitis and spondylitis anterior (Romanus lesion). Romanus lesion starts as enthesitis at the insertion of annulus fibrosus and as the inflammatory process progresses involvement of the anterior corner of the vertebral bodies develops. On MRI "Romanus lesion" appears with hypersignal in T2, hyposignal in T1-weighted images and shows different degrees of enhancement after intravenous contrast administration. The lateralization of the involvement and the extension of the inflammatory process into the prevertebral space were helpful in the differential diagnosis between septic spondylitis and spondylitis anterior (13, 14).

This case reminds us that newly onset low back pain in a patient with long standing PsA under immunosuppressive treatment is quite unlikely to represent a commencing spinal involvement due to the disease process prompting for escalation of the immunosuppressive treatment. On the contrary, it could be the manifestation of an infectious or even malignant condition. In such cases careful approach is mandatory, because "light-hearted" escalation of the immune suppression might result in devastating consequences.

In conclusion, the role of TNF-α and the consequent effects of anti-TNFα therapy in humans infected with Brucella in the course of treatment still remain to be elucidated, since to the authors' knowledge this is the first case of brucellosis in a PsA patient on infliximab. Moreover, there have been no associations between psoriatic arthritis and Brucella spondylitis reported.

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