

***Salmonella enterica* Arthritis in a Patient with Rheumatoid Arthritis Receiving Anti-tumour Necrosis Factor Therapy**

M Bubonja-Sonje¹, D Rubinic², F Anic³, S Novak³, D Vuckovic⁴, M Abram¹

ABSTRACT

Anti-tumour necrosis factor (TNF) monoclonal antibodies have become an invaluable treatment against chronic inflammatory diseases such as rheumatoid arthritis (RA). However, due to increased risk of opportunistic infections, patients receiving anti-TNF therapy should be closely monitored for serious infections. Here, we describe a case of acute Salmonella enteritidis infection of a joint arthroplasty that previously was functioning well, in a patient receiving infliximab treatment for RA. After prolonged antimicrobial chemotherapy and interrupted infliximab treatment, reimplantation of a new prosthesis was successfully performed two years after Salmonella septic arthritis. Therefore, because of the possibility of extraintestinal salmonellosis, screening for fecal colonization could be advisable in patients undergoing anti-TNF treatment. Moreover, we emphasize the importance of appropriate counselling of these patients concerning food hygiene.

Keywords: Anti-TNF treatment, knee infection, *Salmonella enteritidis*

Artritis por *Salmonella enterica* en un Paciente con Artritis Reumatoide que Recibe Terapia con Factor de Necrosis Antitumoral

M Bubonja-Sonje¹, D Rubinic², F Anic³, S Novak³, D Vuckovic⁴, M Abram¹

RESUMEN

Los anticuerpos monoclonales del factor de necrosis antitumoral (FNT) se han convertido en un valioso tratamiento contra las enfermedades inflamatorias crónicas como la artritis reumatoide (AR). Sin embargo, debido al mayor riesgo de infecciones oportunistas, los pacientes que reciben terapia anti-FNT se deben monitorizar muy de cerca con respecto a la posibilidad de infecciones serias. Aquí describimos un caso de infección aguda por Salmonella enteritidis de una artroplastia de articulación que anteriormente funcionaba bien, en un paciente que recibía tratamiento con infliximab por RA. Después de prolongadas quimioterapias antimicrobianas y tratamiento interrumpido con infliximab, se realizó exitosamente la reimplantación de una nueva prótesis, dos años después de la artritis séptica por Salmonella. Por lo tanto, debido a la posibilidad de una salmonelosis extraintestinal, podría ser aconsejable el tamizaje de la colonización fecal en pacientes sometidos a tratamiento anti-FNT. Por otra parte, hacemos hincapié en la importancia de aconsejar apropiadamente a estos pacientes con respecto a la higiene de los alimentos.

Palabras claves: Tratamiento anti-FNT, infección de la rodilla, *Salmonella enteritidis*

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From: ¹Department of Clinical Microbiology, University Hospital Rijeka, Rijeka, Croatia, ²Lovran Clinic for Orthopaedic Surgery, Lovran, Croatia, ³Department of Internal Medicine, University Hospital Rijeka, Rijeka, Croatia and ⁴Department of Microbiology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia.

Correspondence: Dr M Bubonja-Sonje, Department of Clinical Microbiology, University Hospital Rijeka, Kresimirova 42, 51 000 Rijeka, Croatia. Fax: +385-51-658-841, e-mail: marina.bubonja@medri.uniri.hr

INTRODUCTION

The increased risk of serious infections in patients with rheumatoid arthritis (RA) is attributable to the disease process itself, as well as to the immunosuppressive properties of its treatment. Anti-tumour necrosis factor (TNF) therapy, used for immunomodulation in RA, is mostly associated with reactivation of opportunistic infections primarily caused by

intracellular bacteria such as *Salmonella*, *Mycobacterium*, and *Listeria* (1–4). The presence of a prosthetic implant may additionally change the likelihood of complications from an otherwise transient bacteraemia.

CASE REPORT

We describe a case of *S enterica* serotype enteritidis infection of a right total knee arthroplasty in a 62-year old patient. She was diagnosed with RA in 1986, and subsequently received long-term immunosuppressive treatment with methotrexate (15 mg weekly) and corticosteroids (5 mg prednisone daily). Total knee arthroplasty (TKA) was performed on the right knee in 2005. Treatment with infliximab was introduced in 2007. However, in May 2008, the sixth day after a 14-day administration of infliximab, she presented to clinic with sudden knee pain and infectious clinical symptoms. She reported five days of chills followed by high grade fever, and an acutely painful, swollen knee with stiffness and effusion. There was no history of trauma. Physical examination revealed important signs of inflammation in her right knee (tenderness to palpation, swelling, increased warmth and limited range of motion). Laboratory analysis showed elevated C-reactive protein (CRP) 132 mg/L, erythrocyte sedimentation rate 86 mm/h (Westergren) and white blood cell (WBC) count $8.9 \times 10^9/L$. Before antimicrobial therapy, joint aspiration was performed and synovial fluid, simultaneously with two samples for blood cultures, was sent to the microbiology laboratory. There were no crystals on microscopic examination and Gram stain of fluid was negative. Blood cultures were also negative, but synovial fluid grew pure culture of *Salmonella enteritidis*. Susceptibility testing showed sensitivity to most commonly used antimicrobials. The patient's past medical history included gastrointestinal salmonellosis approximately eight years before; she also had a history of recent travel to Turkey, a country with a high burden of salmonellosis. As the patient's condition did not improve significantly after five days of initial therapy, arthroscopic lavage and debridement were performed. Intravenous ceftriaxone was introduced and the patient got better. Infliximab treatment was stopped and therapy was not resumed. However, at the end of June 2008, after recurrence of the infection, open arthrotomy with irrigation and synovectomy with retention of prosthesis were done. Because of persistent knee pain and fistula formation, in April 2009, the joint had to be removed. While there were no further indications of infection, in February 2010 exchange arthroplasty was performed. The patient is now two years post second arthroplasty and continues to do well.

DISCUSSION

Prosthetic joint infection remains one of the most devastating complications after total joint arthroplasty, a common procedure in patients with RA. Although it is still controversial whether the use of TNF-alpha blocking agents *per se* increases the risk of infection or not (5–7), recently, a

prospective observational study showed small but significant overall risk of serious infections (8).

The present case report provides supporting evidence that patients receiving anti-TNF treatment have an increased susceptibility to *Salmonella* infections, which may develop at unusual localizations. *Salmonella* osteomyelitis is an uncommon disease, usually associated with sickle cell anaemia (9), other haemoglobinopathies (10), as well as with other disease states. Septic arthritis is a rare consequence of *Salmonella* bacteraemia, noted in less than 1% of cases. A few cases of extraintestinal *Salmonella* infections affecting bones and joints in anti-TNF treated patients have been previously reported (11–12). Since the joint infection is a rheumatology emergency that requires early diagnosis, it is appropriate to consider the possibility of septic arthritis in RA patients with knee arthroplasty who have undergone biologic therapy. The usual pathogenesis of *Salmonella* septic arthritis is thought to be haematogenous rather than direct inoculation into the joint; *Salmonella* septic arthritis has not been considered an intraoperative contaminant during joint replacement. In addition, infections that occur later than three months after joint arthroplasty are usually haematogenously acquired.

Although the patient described in this report did not present with any gastrointestinal symptoms, nor had positive fecal cultures, she had a history of enteric salmonellosis and recent travel to a high-risk endemic country, so haematogenous seeding of the knee still seems likely. Surgery was required to eradicate the infection but, finally, the patient had a successful clinical outcome of septic revision TKA.

Anti-TNF agents are remarkably effective in the treatment of chronic inflammatory rheumatic diseases. While they may be associated with an increased risk of opportunistic infections, these risks are not excessively high. Still, not all of the association between anti-TNF therapy and joint infection may represent a direct causal pathway. The infection risk is no reason to withhold therapy with TNF- α inhibitors; indeed, removal of anti-TNF therapy could lead to a worse functional status and increased risk of infection through that mechanism.

The risks of serious infections in patients undergoing anti-TNF treatment is overcome by testing for and treating existing latent infections, and adopting appropriate precautions prior to and during treatment with biological agents to minimize risk.

Screening for *Salmonella* fecal colonization could be advisable in these patients, and the diagnostic algorithm has to be designed for early diagnosis and treatment of possible salmonellosis. In addition, we emphasize the importance of appropriate counselling of these patients concerning food hygiene. In conclusion, there is need to summarize current knowledge which could provide evidence-based recommendations to reduce the salmonellosis risk among candidates for anti-TNF therapy as it has been done recently for tuberculosis risk (13).

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