

Ultrasound Detection of *Salmonella* Septic Arthritis in a Rheumatoid Arthritis Patient on Anti-TNF Treatment

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Abstract

We report a case of *Salmonella* septic arthritis detected by ultrasound in a 40-year-old man with rheumatoid arthritis while he was on anti-tumor necrosis factor- α monoclonal antibody certolizumab. An aspirate of his left elbow joint showed *Salmonella* enteritidis infection that was sensitive to ceftriaxone. This was preceded by a brief episode of loose stools following a visit to the Far East. He was treated with antibiotics and made a good recovery. There have only been a few case reports of *Salmonella* septic arthritis in a rheumatoid arthritis patient on anti-tumor necrosis factor treatment but none previously in association with certolizumab.

Keywords

musculoskeletal ultrasound, rheumatoid arthritis, *Salmonella*, septic arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, systemic disease that principally affects the synovium. Its prevalence is about 1% worldwide.¹ Women are affected 3 times more than men and onset is usually between 30 and 50 years.

Evidence has shown that early and aggressive management of RA with disease-modifying antirheumatic drugs (DMARDs) has proven beneficial in slowing disease progression.² NICE guidance supports the multidisciplinary team approach with physiotherapy, occupational therapy, podiatry, and psychotherapy.³ Pharmacological treatment includes analgesics, steroids, and DMARDs. With the advent of biologics, a new era of DMARD therapy has introduced various drugs such as anti-tumor necrosis factor (anti-TNF), anti-CD 20, anti-interleukin (IL)-6, and anti-IL-1. We currently have five anti-TNF drugs in the market to treat RA. These are infliximab, adalimumab, etanercept, certolizumab, and golimumab.

Anti-TNF drugs have a relatively good safety profile but are associated with several adverse events, which include the risk of malignancy, demyelinating disorders, lupus-like syndrome, congestive heart failure, and opportunistic infections.⁴ Patients with severe RA are prone to infections. We present a case of *Salmonella* septic arthritis in an RA patient treated with certolizumab.

Case Report

A 43-year-old British Indian business manager was treated for active RA. Over 3 years he had received sulfasalazine,

hydroxychloroquine, and methotrexate (MTX). Due to inefficacy and adverse effects, the DMARDs were stopped and certolizumab was commenced according to NICE guidelines with ongoing high disease activity. Within 1 month of commencing certolizumab, he traveled to Hong Kong during which he had a brief episode of gastroenteritis with fever. This was a self-limiting illness with spontaneous recovery within 2 days. Fifteen days later, he presented to our Rheumatology Department for a routine clinic visit. Clinical examination revealed typical rheumatoid changes with restricted range of movements of MCP, wrist, and elbow joints. His inflammatory markers were not significantly elevated in keeping with good RA disease control.

A musculoskeletal ultrasound examination performed at this clinic attendance, which did not reveal significant disease activity at the MCP, PIP, or wrist joints. However, in contrast, an ultrasound (US) examination of his left elbow revealed a moderated degree of synovial thickening a small amount of fluid, and positive power Doppler suggested an active inflammatory process. Clinical examination showed no joint tenderness, mild swelling, and restricted range of movement (extension limited to 150°), which was unchanged from previous clinic attendances. Given the monoarticular

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activity revealed on US examination, a decision was taken to aspirate this joint under US guidance despite the lack of clinical features of infection. His joint aspirate showed pus cells, macrophages, and neutrophils. Culture grew *Salmonella enteritidis* species sensitive to amoxicillin and ceftriaxone. As he was once again out of the country, he was treated with oral ciprofloxacin for a week and reviewed on his return to the United Kingdom. As the elbow effusion persisted, he was admitted for intravenous co-amoxiclav treatment. A magnetic resonance imaging (MRI) scan of the left elbow showed erosions, effusion, synovitis, but no osteomyelitis. His blood culture showed *Salmonella enteritidis*, and stool cultures were negative. Repeat aspirate showed no organisms within the joint fluid. He was discharged home a week later with a 2-week course of oral co-amoxiclav. On recent review he remains well with no recurrence of elbow effusion.

Discussion

A population-based study by Doran et al suggested that patients with RA were at increased risk of developing infections compared with non-RA subjects. This may be due to immunomodulatory effects of RA or due to agents with immunosuppressive effects used in its treatment.⁵

In further support of the notion of increased infection risk in patients with RA is the finding that up to 40% of patients with septic arthritis have RA.⁶ The annual incidence of septic arthritis in the general population is 2 to 5 per 100 000, and patients with preexisting RA were at an increased risk of septic arthritis (odds ratio = 4.0, 95% confidence interval = 1.9-8.3).⁷ One study suggested the annual frequency of septic arthritis to be 0.2% among patients with RA.⁸

Septic arthritis in patients with RA was initially described by Bywaters⁹ and by Kellgren and colleagues.¹⁰ Typically, septic arthritis presents with acute onset of severe joint pain, with very limited range of movements, accompanied by swelling and erythema at the affected joint. There are also systemic manifestations of infection including fever, elevated white blood cell count, and increased erythrocyte sedimentation rate. However, with RA the onset is more insidious and is mistaken for a flare of RA. The presentation may be with either a monoarticular or a polyarticular distribution. Polyarticular pattern may be seen in 10% to 20% of cases. The knee joint is involved in about 50% of cases. The presentation may be more subtle in patients on immunosuppressants (glucocorticoids, disease modifying drugs, and biologics).

Biologics such as adalimumab, infliximab, and etanercept have been in the scene for more than 10 years and have proven efficacy in RA. Certolizumab is a pegylated human monoclonal anti-TNF- α antibody and is one of the latest anti-TNF in the market. The RAPID 2 study showed that certolizumab pegol plus MTX was more efficacious than placebo plus MTX. The certolizumab combination rapidly and significantly improved clinical features, physical function, and inhibited radiographic progression.¹¹

The anti-TNF drugs are associated with unusual and atypical viral and fungal infections, tuberculosis, and bacterial infections. The meta-analysis of randomized clinical trials, the German and Spanish registries, and a re-analysis of BSR Biologics Register (BSRBR) data suggest that TNF inhibitor use is associated with an approximate doubling of risk of serious infection, particularly early on in the course of therapy.¹²⁻¹⁴ The RAPID study showed 7% serious infections. Two cases of tuberculosis were reported, but there were no opportunistic infections.¹¹

BSRBR data showed that patients on anti-TNF therapy were twice as likely to develop septic arthritis as controls (adjusted hazard ratio [HR] = 2.0, 95% confidence interval [CI] = 1.2-3.7). This risk was greatest during the first year of therapy, peaking at around 10 months after commencement. Among the responsible organisms found in 41% of cases, *Staphylococcus* was the most common organism in both cohorts (DMARD 55%; anti-TNF 50%), and several intracellular pathogens (including *Listeria* and *Salmonella*) were also reported with the anti-TNF cohort.

Salmonella are mobile gram-negative facultative intracellular anaerobes that cause a wide spectrum of disease ranging from gastroenteritis, enteric fever, and focal and disseminated infection. According to the World Health Organization, over 16 million people worldwide are infected with typhoid fever each year, with 500 000 to 600 000 fatal cases. Worldwide estimates of nontyphoid *Salmonella* range from 200 million to 1.3 billion, with an estimated death toll of 3 million each year.¹⁵ In the United States, the reported 2008 incidence was 16.2 cases per 100 000.¹⁶ Additionally, an estimated 500 people are infected with typhoid *Salmonella* annually. Most cases of documented typhoid disease are related to foreign travel to developing nations such as India (30%), Pakistan (13%), Mexico (12%), Bangladesh (8%), Philippines (8%), and Haiti (5%).¹⁷

Salmonella can be spread through contaminated raw eggs, in unpasteurized milk, and in undercooked meat. It rarely causes primary infection in the musculoskeletal system except in special circumstances such as following instrumentation, traumatic injury to the joint, or arthrocentesis. The risk of *Salmonella* septic arthritis is associated with infancy, elderly, or with diseases such as sickle cell anemia,¹⁸⁻²¹ acute lymphoblastic leukemia,^{22,23} thalassaemia,^{24,25} idiopathic thrombocytopenic purpura,²⁶ Crohn's disease,²⁷ systemic lupus erythematosus,^{28,29} HIV,³⁰ RA, and diabetes mellitus,³¹ or in special circumstances such as prosthetic joint,³²⁻³⁶ transplant,³⁷ or avascular necrosis. It can also cause osteomyelitis septic arthritis or postinfectious reactive arthritis.³⁸

BSRBR reported that the risk of septic arthritis with specific anti-TNF were etanercept HR 2.3 (CI = 1.2-4.4), infliximab HR 1.6 (CI = 0.8-3.2), and adalimumab HR 1.8 (CI = 1.0-3.5). Five cases of intracellular infection (2 *Listeria*, 3 *Salmonella*) and 11 cases of Streptococcal SA (including 4 *Streptococcus pyogenes*) were reported (all in the anti-TNF cohort). Katsarolis et al reported a case of septic arthritis due

to *Salmonella enteritidis* in a patient on infliximab for RA.³⁹ Antimicrobial chemotherapy with surgical intervention was necessary for eradication of the infection.

Wallis et al⁴⁰ have identified 11 cases of anti-TNF-associated *Salmonella* infection (7 cases with infliximab and 4 cases with etanercept) from the FDA's AERS. Two cases of *Salmonella* septic arthritis have been reported with etanercept and a further 2 cases have been reported with infliximab.^{39,41}

Three cases of *Salmonella* septicemia have been reported with anti-TNF therapy.⁴² Fu et al reported a case of disseminated *Salmonella typhimurium* infection in a psoriatic arthritis patient with infliximab treatment.⁴³ A case of disseminated *Salmonella paratyphi* infection in a RA patient treated with infliximab was reported.⁴⁴ Netea et al hypothesized that TNF neutralization with monoclonal antibodies may result in a decreased production of interferon (IFN)- γ , subsequently leading to a defective cellular immune response and decreased expression of Toll-like receptor 4. They concluded that as recognition of microorganisms by TLR-4 and activation of phagocytes by IFN- γ are crucial mechanisms for the defence against intracellular pathogens, their inhibition by anti-TNF leads to severe complication with *Salmonella* infections.⁴⁵

Quick diagnosis is essential to prevent joint destruction. Urgent aspiration of the affected joints is required, followed by antibiotic therapy. Because of the subtle presentation with RA and presence of some "sterile" joints, there is often a delay in the diagnosis of the septic arthritis in these patients. Blackburn et al⁴⁶ reported an average delay in diagnosis of 13.7 days. Radiologic investigations such as bone and gallium scans are often not helpful at the onset in distinguishing between infectious arthritis and inflammatory arthritis in patients with underlying inflammatory arthritis.⁴⁷

Grassi suggested that sonographic examination should be directed to the site of clinical symptoms, or where abnormalities or confusing findings are present on other imaging studies. In comparison with radiography, US has the potential advantage of depicting tendon lesions, enthesitis, fluid collection, synovial proliferation, cartilage damage, and even minimal interruptions of the cortical bone profile that are frequently missed by conventional radiography because of their size and localization.⁴⁸

In the same study, sonographic erosions that were not visible on radiography corresponded by site to MRI bone abnormalities. Hau and coworkers showed that ultrasonography provides better results than clinical examination alone.⁴⁹ Kraan and colleagues showed that ultrasonography and MRI both can detect subclinical synovitis with corroborative macroscopic and microscopic data from arthroscopy in clinically normal knees of patients with RA.⁵⁰ Karim and coworkers compared ultrasonography of the knee with the "gold standard" of arthroscopy, as well as clinical examination, to validate ultrasonographic images in terms of accurate representation of the pathology present

in the joint.⁵¹ They concluded that ultrasonography was valid and reproducible, as well as superior to clinical examination for detecting knee synovitis.

Makkuni et al emphasized on hygiene advice in patients on anti-TNF therapy. They felt counseling was very important as there were particularly no vaccines against *Salmonella paratyphi*.⁴¹ Inflammatory diseases and biologics both increase risk of unusual infections. Thus, one needs to be vigilant as patients receiving biological therapy may have an insidious course to any infective process and use US in the assessment.

Declaration of Conflicting Interests

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