Septic arthritis in the era of immunosuppressive treatments

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ABSTRACT

Immunosuppressants have been the mainstay of treatment for certain inflammatory joint conditions for many years. Developments in this field, namely biological treatments, have led to a change in the classical presentation of acute bone, joint and soft tissue infections. The normal findings of severe pain and tenderness on examination may be absent or simply mimic a typical exacerbation of the chronic joint condition. A minimally raised white cell count and elevated C-reactive protein in the absence of systemic signs of infection may be interpreted as further evidence for the diagnosis of an exacerbation of inflammatory arthritis. We present a unique case of recurrent polyarticular septic arthritis in a patient treated with immunosuppression for refractory rheumatoid arthritis. We hope this article will enable doctors to appreciate and recognise the changing face of septic arthritis in the modern era of immunosuppressant treatments.

KEYWORDS

Infectious arthritis – Immune system – Antirheumatic agents

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Generations of medical students and junior doctors have been taught that septic arthritis is an unmistakable condition with a readily identifiable natural history. However, the face of septic arthritis is changing with the increasing use of immunosuppressive medication. We present a case of recurrent polyarticular septic arthritis in a patient treated with immunosuppression for refractory rheumatoid arthritis and review some key lessons emerging from the contemporary literature.

Case History

A 65-year-old retired Caucasian woman with long-term rheumatoid arthritis and vasculitis (well controlled with leflunomide and prednisolone) presented to our emergency department with a 3-week history of worsening joint pain and stiffness bilaterally in her shoulders, elbows, hands, knees and feet. She had a temperature of 37.3°C, a blood pressure (BP) of 105/47mmHg, a heart rate (HR) of 95 beats per minute, a respiratory rate (RR) of 20 breaths per minute and oxygen saturation (SaO₂) of 95% on air.

Examination revealed effusions bilaterally in the patient’s shoulders and knees, and oedema in the hands and feet. She had a haemoglobin level of 9.1g/dl, a C-reactive protein (CRP) level of 368mg/l and a lactate level of 2.5mmol/l. She was admitted with a diagnosis of an acute exacerbation of rheumatoid arthritis, and treated with increased oral prednisolone and maintenance leflunomide.

Eleven days previously, the patient had been discharged from a Spanish hospital, where she had been treated for eleven days with high dose oral prednisolone for a similar presentation. During that admission, she had developed a sacral pressure sore that had subsequently become infected.

Eight hours following admission, the patient became haemodynamically unstable (temperature 38.5°C, BP 96/54mmHg, HR 110 beats per minute, RR 15 breaths per minute, SaO₂ 96% on 2l of oxygen). A sepsis screen showed consolidation in the middle zone of the right lung on chest x-ray; intravenous co-amoxiclav and fluids were commenced.

Forty-eight hours following admission, the patient became haemodynamically unstable again (temperature 38.7°C, BP 109/90mmHg, HR 125 beats per minute, RR 16 breaths per minute, SaO₂ 96% on air) with a CRP level of 292mg/l and a WCC of 11.8 × 10⁹/l. The possibility of septic arthritis was considered, prednisolone stopped and antibiotics were continued.

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urgent orthopaedic consultation requested. Both shoulders and knee joints were aspirated, and the sacral pressure sore was swabbed. These samples all isolated Staphylococcus aureus sensitive to fluclouxacinil and rifampicin. A diagnosis of septic polyarthritis secondary to the infected sacral pressure sore was made. Antibiotics were changed and the patient proceeded to emergency surgery.

Arthroscopic washout of both shoulders and knees was conducted with frank pus evacuated from all four joints. A 72-hour period on the high dependency unit followed but despite this, haemodynamic instability due to sepsis persisted and the patient returned to theatre for a second washout. Arthroscopic debrideemen and washout was conducted for both knees, shoulders and hips with frank pus evacuated from each. Despite a 4-day postoperative stay on the intensive care unit, the sepsis was overwhelming and the patient died 14 days later. Although it is difficult to ascertain whether this death was preventable, we are of the opinion that the delay to washout until 48 hours following admission coupled with the development of the sacral pressure sore contributed to the overwhelming nature of the septic shock in this case.

Discussion

How have immunosuppressive treatments evolved?
Immunosuppressive treatments have evolved significantly since 1949, when cortisone was shown to lessen the symptoms of rheumatoid arthritis. In the 1960s, azathioprine was shown to delay organ rejection and methotrexate was shown to suppress antibody formation in animals. Methotrexate was licensed by the US Food and Drug Administration in 1998 for treatment of rheumatoid arthritis. Leflunomide was shown to have significant immunosuppressive action in 1978 and remains in use today for the treatment of rheumatoid arthritis. Changes in treatment strategy have fuelled the development and use of biological agents. Infliximab (antibody against tumour necrosis factor alpha [anti-TNFα]), the first biological agent for the treatment of rheumatoid arthritis, was licensed in 2001. In 2013 in the UK, there are five available anti-TNFα agents, in addition to other therapies targeting interleukins 1 and 6 as well as B and T cells. Kinase inhibitors are currently in phase 3 clinical trials for rheumatoid arthritis.

How common are infections in immunosuppressed rheumatoid patients?
Rheumatoid arthritis affects approximately 400,000 people in the UK and generalised infections are common. However, it is unclear whether these infections are secondary to the immunosuppressive treatments or the disease itself. Extra-articular manifestations of the disease, reduced functional capacity, a raised erythrocyte sedimentation rate and seropositivity in rheumatoid arthritis are all predictors of increased risk of infection. Studies have shown early diagnosis and aggressive reduction in disease activity is fundamental to prevent long-term disability.

What are the common infections and pathogens?
In patients treated with biological therapies, pulmonary, opportunistic and septic arthritis are the most common infections. The French registry database has shown that increased bacterial infections (including Nocardia, atypical mycobacteria, Listeria and non-typoid bacteraemic salmonellosis), viral infections (herpes simplex, cytomegalovirus and varicella zoster) and fungal infections (pneumocystosis and Cryptococcus) are associated with the use of anti-TNFα agents. These infections have also been reflected in the UK registry data (British Society for Rheumatology Biologies Register), which shows these therapies double the risk of septic arthritis in rheumatoid arthritis patients. S aureus isolates were seen most frequently and a significant number were methicillin resistant. Among the anti-TNFα patients, uncommon septic arthritis causing organisms were reported including Listeria spp, Salmonella spp and Pseudomonas aeruginosa infection.

Conclusions
Acutely swollen joints can be a diagnostic challenge. Patients with longstanding severe joint arthropathy treated with immunosuppression may exhibit minimal systemic manifestations. The normal findings of severe pain and tenderness on examination may be absent or simply mimic a typical exacerbation of the chronic joint condition. A minimally raised WCC and elevated CRP level in the absence of systemic signs of infection may be interpreted as further evidence for the diagnosis of an exacerbation of inflammatory arthritis.

Septic arthritis should always be considered in any patients on long-term immunosuppression who present with acutely swollen joints. Joint aspiration and microbiological should be considered in all cases to actively rule in or rule out the diagnosis. The microbiologist must be aware of the patient’s immunosuppressed status so that more specific and/or longer term cultures for atypical organisms can be performed.

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