CASE REPORT

Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis

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A case of necrotising fasciitis in a patient receiving infliximab, an antitumour necrosis factor alpha (TNF- α) agent for rheumatoid arthritis, is presented. A widespread confluent, erythematous, pustular skin rash was the presenting sign. There was no fever throughout this admission. β -Haemolytic group A streptococcus was isolated from blood cultures and skin swabs. The adductor muscles and fascia around the site of a previous hip arthroplasty were necrotic on exploration. The case highlights the risk of severe sepsis in patients on anti-TNF- α treatment.

Tumour necrosis factor-alpha (TNF- α) has been identified as a major cytokine involved in the pathogenesis of rheumatoid arthritis. Infliximab (an anti-TNF- α agent) has been shown to reduce disease activity and progression of joint damage in rheumatoid arthritis.¹ However, there is a slight increased risk of infection with the use of infliximab. The Committee on Safety of Medicines advises caution with its use in light of the recent reports on reactivation of tuberculosis.² We report a case of a patient who developed fatal necrotising fasciitis after the use of infliximab.

CASE REPORT

A 54 year old man with rheumatoid arthritis presented to our outpatient clinic with a three day history of a painful, confluent, erythematous pustular rash over his trunk and limbs. He had felt generally unwell with lethargy and loss of appetite. However he denied any fever or night sweats.

He had a 12 year history of seropositive rheumatoid arthritis and had various disease modifying antirheumatoid drugs that failed to induce remission. These included sulphasalazine, azathioprine, cyclosporin, intramuscular gold, and methotrexate (up to 20 mg/week). His severe rheumatoid arthritis resulted in a left hip replacement, which was subsequently revised twice due to prosthesis failure. Due to his active, treatment resistant rheumatoid arthritis, infliximab was started. He was treated with 3 mg/kg infliximab, which was given at baseline, two, four, and eight weeks. This was repeated every eight weeks thereafter. He remained on intramuscular methotrexate (10 mg/week). Remission of his rheumatoid arthritis was induced with this regimen.

On examination he was afebrile (temperature 36.5°C). He had a pulse of 90 beats/min and blood pressure of 124/72 mm Hg. There was no lymphadenopathy. Examination of his respiratory and abdominal systems was unremarkable. Neurologically, there was reduced power in his left leg (grade 4/5) due to pain. There was no active synovitis.

Investigations

A skin biopsy of the rash showed an acute pustular dermatitis secondary to a drug reaction. Haematological investigation showed a haemoglobin concentration of 131 g/l, white cell

count $14.82 \times 10^9/l$, neutrophils $13.99 \times 10^9/l$, and platelets $295 \times 10^9/l$. A clotting screen gave a prothrombin time of 27 seconds, activated partial thromboplastin time (APTT) 38 seconds, and fibrinogen 9.33 g/l. Urea and electrolyte concentrations were normal and plasma glucose 6.1 mmol/l. Chest radiography was normal. Blood culture and skin swabs were taken.

Progress

Five hours later he became light headed and collapsed. He was now tachycardic (pulse of 140/min) and peripherally shut down but had a blood pressure of 120/70 mm Hg. He remained afebrile at 36.9°C. His left leg had become very tense, painful, and swollen. He had a metabolic acidosis with a pH of 7.21 and bicarbonate of 12.9 mmol/l. He was transferred to the intensive care unit.

He had worsening acidosis and hyperkalaemia (potassium 6.02 mmol/l). Further investigations showed a haemoglobin of 31 g/l, white cell count $2.04 \times 10^9/l$, platelets $70 \times 10^9/l$, prothrombin time 34 seconds, APTT 50 seconds, fibrinogen 5.87 g/l, and raised D-dimer (a fibrin degradation product) of 11.4 mg/l. These findings were consistent with a disseminated intravascular coagulopathy.

All his biochemical and haematological abnormalities were treated appropriately. He required inotropes and intubation. There was marked necrosis of his adductor compartment and fascia of his left thigh on exploration. He underwent debridement of his necrotic muscles but this was hampered by recurrent cardiac arrests. Despite resuscitation efforts, he died.

Microbiology results

His blood cultures and skin swabs grew haemolytic group A streptococcus. The isolation of this bacterium together with necrosis of subcutaneous tissue and severe systemic illness (sudden death, shock, disseminated intravascular coagulation, and system failure) conforms to the case definition of necrotising fasciitis.³

DISCUSSION

Infective side effects of anti-TNF- α treatment have been described in the literature but there has been no mention of fatal necrotising fasciitis. In an earlier trial with 73 patients there were six infective events in the infliximab treated group at four weeks. One of these had pneumonia which was possibly treatment related.⁴ The commonest infections involve the upper respiratory tract. In post-marketing surveillance, opportunistic infections such as tuberculosis, *Pneumocystis carinii* pneumonia, histoplasmosis, and aspergillosis have been reported.⁵

Abbreviations: APTT, activated partial thromboplastin time; TNF- α , tumour necrosis factor-alpha

Learning points

- Anti-TNF- α agents are useful in reducing disease activity and joint destruction in rheumatoid arthritis.
- Overall the data from drug trials shows that infliximab is safe when used appropriately.
- The use of infliximab is associated with the risk of severe sepsis.
- The absence of pyrexia or other signs of infection does not exclude the possibility of sepsis in patients treated with infliximab.
- Report all adverse events with the use of anti-TNF- α agents.

Treatment with low dose methotrexate on its own in rheumatoid arthritis does confer increased risk of infection. In an open study with low dose methotrexate, the incident infection rate during four years of follow up was 18%.⁶ The mean infection rate from eight double blind studies was 11.6%.⁶ Like infliximab, opportunistic infections have been reported.⁷ Late reactivation of spinal tuberculosis by low dose methotrexate therapy has also been reported.⁸ Therefore the use of infliximab together with methotrexate may further increase the risk of infection. In the second six months of follow up in the ATTRACT study, two people died in the group taking infliximab plus methotrexate. One had tuberculosis and the other had coccidiomycosis.⁹

In the infliximab trials, all patients received concomitant methotrexate.¹⁰ Overall, there was no significant difference between the rates of infection in the infliximab plus methotrexate than the placebo plus methotrexate groups. Data from 54 weeks of follow up showed the frequency of serious infections was 8% in infliximab compared with 6% in placebo treated groups.¹ However, upper respiratory infections, sinusitis, and pharyngitis tended to occur more frequently in the infliximab plus methotrexate compared with the placebo plus methotrexate group.¹

Although it is important to control rheumatoid arthritis, we must remember the role that TNF- α has in the host defence mechanism—for example, affecting lymphocyte activation, fibroblast proliferation, and cytokines such as interleukins 1, 6, and 8. Treated patients may not exhibit normal signs of infection such as fever because of the alteration of their immune response.

There is limited safety experience of infliximab treatment in patients who have undergone joint replacement such as the patient reported here. Our patient developed necrotising fasciitis around the site of his revised left hip prosthesis. There

is increased TNF- α expression around the site of a cementless prosthesis undergoing revision associated with osteolysis.¹⁰ The use of anti-TNF- α agents may alter the local cytokine profile around these sites and impair immune response to infection.

More information is required to assess the risks of infection particularly as infliximab will be used more frequently in the future. Although a causal relationship between the drug and the necrotising fasciitis is not proved, this association seeks to highlight the risk of severe sepsis with the use of anti-TNF- α agents. Physicians at all levels, not just rheumatologists, need to be aware of how symptoms of severe infection may be masked. All adverse events with the use of these agents must be reported to the Committee on Safety of Medicines via the “yellow card” system.

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