Unexpected outcome (positive or negative) including adverse drug reactions

A case of severe staphylococcal septicaemia: septic arthritis and a mediastinal abscess following leflunamide therapy for rheumatoid arthritis

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Summary

This highly unusual case illustrates how a potentially life-threatening complication may develop insidiously in the context of immunosuppression.

A 46-year-old woman presented with increasing malaise and a marked inflammatory response in the context of immunosuppressive therapy for rheumatoid arthritis. On the basis of microbiological findings, the patient was treated for systemic staphylococcal infection with a prolonged antibiotic course. In addition, incision and drainage procedures were performed on associated, non-resolving abscesses at various sites. One particular lesion in the breast was slow to heal and was monitored with ultrasound imaging. Subsequent cross-sectional imaging revealed that this was, in fact, a large mediastinal abscess, eroding the manubrium and lying within close proximity of the aorta. The patient was eventually referred to a cardiothoracic unit for complete evacuation of this lesion. Following a prolonged illness and treatment period, the patient recovered well and successfully resumed employment.

BACKGROUND

We feel that this case highlights the need for vigilance with regards atypical and insidious presentations of serious infections in rheumatoid patients treated with leflunomide. Securing such diagnoses requires an open, enquiring mind and targeted investigation.

Full recognition of the potentially devastating outcome of our patient's illness was only seen through the employment of cross-sectional imaging. This led to specialist cardiothoracic intervention – crucial to her ultimate recovery.

CASE PRESENTATION

A 46-year-old woman presented with a several week history of general malaise, low-grade fever and generalised arthralgia. Ten weeks prior to admission, she had been treated with the immune modulator leflunamide for seropositive rheumatoid arthritis. This was used in combination with steroid therapy. Having initially shown a good clinical response to the addition of leflunamide therapy, she developed a spontaneous rupture of her Achilles tendon and subsequently became increasingly unwell with symptoms of malaise, arthralgia and low-grade fever.

In addition to multiple joint pain and swelling, she developed an area of tenderness and swelling over her right chest wall. This was initially attributed to costochondritis and the use of crutches for her tendon injury.

Initial investigations revealed evidence of a marked inflammatory response with a C-reactive protein (CRP) of 479 mg/l, thrombocythaemia and a neutrophilia (12.7×10^9 l). In view of the significant elevation of CRP and fever, a decision was made to start antibiotic therapy. As

there was no haemodynamic instability she was treated with intravenous flucloxacillin and penicillin V for presumed soft tissue infection.

After 3 days of incubation, blood cultures grew staphylococcus aureus, sensitive to flucloxacillin. At this stage, the patient had developed multiple abscesses in her right and left thumbs and L hallux. These regions required incision and drainage and ongoing input from orthopaedic and plastic surgery teams. Cultures from all these areas grew staphylococcus aureus sensitive to flucloxacillin and erythromycin.

The area of tenderness and swelling in her chest wall also continued to increase in size, and, despite ultrasound imaging showing no evidence of a collection, an aspirate performed by the breast surgeons recovered turbid fluid. A CT scan was performed, and this was reported as showing a large inflammatory mass originating from the breast and extending to the anterior and posterior manubrium. Marked bony destruction of the manubrium permitted extension of the mass into the anterior mediastinum to lie just millimetres away from the aorta.

The cardiothoracic surgeons were contacted immediately. While awaiting a response and at the advice of microbiology, penicillin v was stopped, and fusidic acid was added to flucloxacillin to treat osteomyelitis. We were informed that the organism had been found to be susceptible to fusidin. In view of the severity of the condition, potential delay to definitive treatment, and following extensive discussion with the microbiology department, Rifampicin was also added to flucloxacillin for tissue penetration into a complicated abscess.

Due to proximity of this abscess to major vessels, the patient was transferred to a cardiothoracic centre. A debridement procedure was performed under general anaesthesia, and a suction drain was left in situ. Antibiotic therapy was continued for a further 2 weeks after surgery and discontinued as the patient improved.

INVESTIGATIONS

Please see above – CRP, blood cultures, wound cultures, CT scan. HIV testing not performed. Tuberculosis cultures negative – reported following treatment.

OUTCOME AND FOLLOW-UP

She recovered well despite the severity of her illness and returned to work as a receptionist several months later. Under rheumatology review, monthly gold therapy was initiated for her arthritis. Plastic surgery input continues for residual instability of the finger joints (following abscess formation). She is currently awaiting tendon surgery to both middle fingers.

DISCUSSION

Studies have demonstrated an increased infection-related mortality in rheumatoid patients.^{1 2} The addition of disease-modifying immunosuppressive drugs exacerbates the risk in this cohort³ and has led to the reporting of complications such as tuberculosis, bacterial pneumonia and septicaemia.⁴

Our case illustrates how a life-threatening and infective complication presented insidiously in an immunosuppressed patient. To our knowledge, this highly unusual course of events has not been reported previously.

The patient's illness began with a spontaneous rupture of the Achilles tendon. During the course of her illness, she ruptured two further tendons in each hand. Tendon rupture in rheumatoid patients is well recognised, although multiple ruptures are rare.^{5 6} Rheumatoid granulation tissue has previously been identified within ruptured tendons (and entheses) on histological analysis.⁷ Hypoxia, angiogenesis and corticosteroid use have been implicated in pathogenesis.^{5 8} In this case, sepsis in the tenosynovium and leflunomide therapy are also possible contributory factors. The mechanism for tendon rupture is unclear with the latter – it is postulated that it may be due to an avascular effect.

In association with this patient's aggressive staphylococcal infection, a striking CRP of almost 500 mg/l was noted on presentation. A proportion of this CRP level was probably related to rheumatoid inflammation, although a rise of this degree is suggestive of superimposed infection. However, the CRP level fell rapidly with the initiation of antimicrobial therapy.

Staphylococcus is a common pathogen in the general population, and oral carriage has been shown to be higher in the rheumatoid patient. It has been suggested that combination immunosuppression may increase carriage.⁹ The progress of the infection was notably atypical and invasive. Metastatic complications are known to occur in a substantial proportion of cases of staphylococcal septicaemia, and common foci include the joints and heart valves.¹⁰ Despite appropriate therapy, multiple joint abscesses developed in our patient, all requiring surgical intervention.

CT imaging revealed septic destruction of the manubrium and resultant mediastinitis. The size and depth of the chest wall abscess had been previously underestimated on ultrasound, due to the presence of inflammatory debris as well as its retrosternal positioning. Such mediastinal pathology is rare in the rheumatoid patient.

Similarly, acute mediastinitis is another highly unusual feature. Seen most often in cases of open-chest surgery and oesophageal perforation, it rarely occurs as a result of direct infection from adjacent tissues.¹¹ When the latter occurs, staphylococcus is frequently implicated and associated with significant rates of relapse and mortality.¹²

In this case, cross-sectional images provided the diagnosis of mediastinitis as well as the aetiology – displaying clear evidence of mediastinal invasion through a destroyed manubrium.

Prior to her acute illness, leflunomide was used with a view to combating severe and refractory rheumatoid disease. This immunomodulatory agent reduces activated lymphocyte and T cell proliferation as well as cytokine production. Its active metabolite (which has a long half-life) operates through mitochondrial enzyme and cell-cycle inhibition.^{13–15} Multiple trials have demonstrated safety and efficacy maintained over several years.^{16–18} Unsurprisingly for an immunosuppressive drug, however, infections are occasionally seen. In our case neither bone marrow suppression nor unusual pathogenic organisms were responsible. In the spectrum of infections seen, pneumonia is the commonest.¹⁴ Contradictory studies have been published commenting on postoperative infection rates.^{19 20} One long-term study reported an incidence of severe infection rate (requiring hospitalisation) as 3.3/100 patient years. This case-note audit included patients who varied in terms of disease status, co-morbidity and drug therapies. Therefore, a causative relationship could not be established.⁴

Most relevant to our patient's case are the reports of atypical and severe infections such as a paravertebral abscess (with vertebral erosions) as well as pyomyositis of the forearm in leflunomide treated patients. It was noted these extensive and striking lesions appeared in a relatively short period of time.²¹ In addition, leflunomide has been associated with abscess formation as well as tendon rupture – both relevant features here.

In summary, there are many factors likely to have contributed to this unusual course of events. Swelling of the joints (subsequently aspirated) may have initially gone unnoticed by the patient and been attributed to a flare up of her disease. It is possible that leflunomide and steroid therapy precipitated a staphylococcal septicaemia from this source. An abscess subsequently developed in the chest through haematogenous spread; metastases are a recognised phenomenon of staphylococcal infection.¹⁰

Finally, this abscess may have led to osteomyelitis of the manubrium through direct spread. Bony destruction which permitted this is rarely seen in the immunocompetent host and has been particularly noted in seropositive rheumatoid cases.²² Alternatively, the manubrium itself may have been the original source of infection. Here, underlying bone abnormality as well as trauma from the use of crutches may have been relevant factors. A bone scan was not performed at this stage, although, in retrospect, this may have been a useful examination to conduct in this context.

Irrespective of the sequence of events, diagnosis was complicated by a variety of factors. In terms of the patient's response, inflammatory markers and temperature fell despite underlying disease progression. Further difficulties were related to the nature of the diagnosis itself. Mediastinal infection is rare, and mediastinitis, when subacute, frequently presents in a subtle fashion.^{23 24} It is likely that this response was further dampened by immunosuppression. Finally, the imaging modality used precluded the visualisation of retrosternal pathology.

CONCLUSION

Despite the significant level of mortality associated with staphylococcal joint infection and mediastinitis,^{12 25} this patient made a remarkable recovery. Although the full clinical picture was unclear, the isolation of the infecting organism early on led to appropriate antibiotic therapy and regular microbiological input. Full recognition of the potentially devastating outcome of her illness was only seen through the employment of cross-sectional imaging. This led to specialist cardiothoracic intervention – crucial to her ultimate recovery.

This case highlights the need for vigilance with regards atypical and insidious presentations of serious infections in rheumatoid patients treated with leflunomide. Securing such diagnoses requires an open, enquiring mind and targeted investigation.

Learning points

- ▶ Elevation of CRP combined with fever or additional symptoms in a rheumatoid patient who is receiving steroids and immunomodulators warrants extensive procedure to exclude infection.
- ▶ Although CRP elevation may be related to inflammation in a rheumatoid patient, significantly elevated levels tend to imply superimposed infection.
- ▶ Infections may present insidiously and advance rapidly in immunosuppressed patients.
- ▶ In complicated cases, discussion with colleagues in radiology can help to target imaging appropriately.
- ▶ Close liaison with and co-ordinated input from specialities, including microbiology, radiology, orthopaedics, plastics and cardiothoracics, were invaluable in this patient's care and recovery.

Competing interests None.

Patient consent Obtained.

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