Staphylococcus aureus subcapsular splenic abscess and associated empyema in the setting of tocilizumab therapy: A case report

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Title

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Key Clinical Message

We report a case of *Staphylococcus aureus* subcapsular splenic abscess and associated empyema after recent commencement of tocilizumab, masquerading as musculoskeletal pain. This highlights the importance of considering unusual underlying infections in patients on tocilizumab.

Introduction

Tocilizumab is an anti-interleukin-6 (IL-6) receptor monoclonal antibody used in the management of rheumatoid arthritis.[1] It is effective at decreasing disease activity and improving function, and is used as monotherapy or in combination with other disease-modifying anti-rheumatic drugs.[1] However, tocilizumab increases the risk of serious infections,[2,3] which can present atypically for patients on tocilizumab – such as having mild clinical features despite disseminated infection,[4] or having disproportionately low or normal C-reactive protein (CRP).[5] We present a previously unreported case of*Staphylococcus aureus* subcapsular splenic abscess with associated empyema in the setting of recent commencement of tocilizumab therapy.

Case presentation

A 56-year-old woman presented to hospital with progressively worsening left upper quadrant and flank pain, which had persisted following a mechanical rotational injury to the thoracic spine sustained four weeks prior. This was initially diagnosed as musculoskeletal pain secondary to injury by her general practitioner, however her symptoms continued to worsen despite resting and avoiding further mechanical aggravation.

Her medical history was significant for seronegative rheumatoid arthritis, for which she took leflunomide 10 mg daily and methotrexate 20 mg weekly with folic acid supplementation for the last two years, and prednisolone at a stable dose 2.5 mg daily. She had also been commenced on subcutaneous tocilizumab 162 mg weekly, three months prior by her rheumatologist.

She also had a recurrent Bartholin cyst infection for the preceding six weeks, from which microbiological swab samples taken had cultured methicillin-sensitive *Staphylococcus aureus* (MSSA). This had been managed by her general practitioner with short courses of amoxicillin-clavulanic acid – including most recently a five-day course, completed two weeks prior to presentation. Her immunosuppressive therapy was withheld for the preceding two weeks but she continued low dose prednisolone.

She did not report any adverse reaction to amoxicillin-clavulanic acid and had also tolerated this previously for other indications. She did not have any known allergies. She did not start any new herbal or over the counter medications, or prescribed medications, except for tocilizumab.

She did not have any urinary symptoms, other infective symptoms, nor a history of renal stones or gallstones. She did not have any prior history of immunodeficiency, hyposplenism, diabetes mellitus, endocarditis or other recent systemic infection. She did not have any history of intravenous drug use, excessive alcohol use, prostheses or implants. She did not have any significant or severe infections in the preceding two years while taking methotrexate and leflunomide.

On examination, she was febrile but haemodynamically stable. She had left upper quadrant abdominal tenderness and guarding on palpation, and reduced breath sounds with dullness on percussion over the left lung base. She did not have any new rashes, arthralgia or active tenosynovitis. Blood investigations revealed elevated inflammatory markers with a CRP of 286.2 mg/L and neutrophilia of 10.17 x 10^9/L. Her renal function was normal with no electrolyte derangement. Her liver function tests were unremarkable.

Computerised Tomography (CT) of the abdomen revealed findings concerning for a subcapsular splenic abscess and a left-sided empyema (Figure 1). These findings were new compared to a CT performed four weeks prior at the time of the original injury.

Splenic abscess drainage was performed under ultrasound guidance, revealing frank pus with heavy growth of MSSA. Video assisted thoracoscopy (VATS) and washout of the left-sided empyema and pleural effusion was performed, with MSSA again isolated on two pleural biopsy specimens. Blood cultures were negative for any growth. A transthoracic echocardiogram was normal with no evidence of vegetations or valvular abnormalities. A nuclear medicine bone scan did not demonstrate any evidence of focal osteomyelitis.

Outcome and follow-up

The patient was diagnosed with a MSSA subcapsular splenic abscess and associated empyema, in the context of being immunosuppressed and recently commencing tocilizumab. Following the identification of MSSA, the patient was changed from empirical antibiotic treatment with intravenous amoxicillin-clavulanic acid to intravenous flucloxacillin monotherapy. There was subsequently a good biochemical and clinical response with normalisation of neutrophilia and a slow downtrend in the CRP to 27 mg/L, after three weeks of intravenous antibiotic therapy and source control with splenic abscess drainage and VATS washout. She was discharged home on oral flucloxacillin monotherapy to complete a four-week total course of antibiotic therapy and made a full recovery. Tocilizumab was ceased, and leflunomide and methotrexate were withheld on discharge in the context of infection, with ongoing follow-up planned with her rheumatologist.

Discussion

Tocilizumab has been associated with both atypical and delayed presentations of infections.[5] Atypical presentations of common conditions in patients on tocilizumab include case reports of pneumonia with absence of fever and disproportionately normal or mildly elevated biochemical markers.[5] Delayed presentations of severe infection have also been reported in patients on tocilizumab, with case reports of disseminated *Staphylococcus aureus*bacteraemia associated with epidural abscess, polyarticular septic arthritis, and empyema.[4] Other unusual presentations include re-activation of latent tuberculosis presenting as fulminant sepsis with splenic abscess two weeks after initiating tocilizumab.[6] An increased risk of fungal co-infections and reports of invasive fungal disease have also been observed in patients after a single dose of tocilizumab for the management of COVID-19.[7,8]

We present a case of *Staphylococcus aureus* subcapsular splenic abscess and associated left-sided empyema in the setting of tocilizumab. Using "tocilizumab" and "splenic abscess" search terms on PubMed and Google Scholar, there was a single case report of splenic abscess in context of reactivated tuberculosis.[6] There were no previously reported cases of non-mycobacterial splenic abscess associated with tocilizumab therapy, and hence this would be the first reported case to the best of our knowledge.

In this clinical case, we hypothesise the formation of splenic abscess was by haematogenous seeding from transient but uncaptured*Staphylococcus aureus* bacteraemia in the context of antibiotic therapy suppression, with the recurrent Bartholin cyst infection being the likely primary source of infection. The left sided empyema/pleural effusion with biopsy-proven pleural infection, was likely a continuation of the adjacent

splenic abscess *Staphylococcus* infection through the presence of otherwise clinically-insignificant congenital diaphragmatic defects,[9] given the similar radiological appearance (Figure 1). While the rotational injury of the spine which prompted the patient's presentation may have coincidentally caused concurrent musculoskeletal pain in her left upper quadrant and flank, it is likely to be a red herring in the setting of the splenic abscess being the more plausible cause for progressively worsening pain. The significant immunosuppressive regimen of leflunomide, methotrexate and tocilizumab likely contributed to the development of the atypical infection and delayed presentation, due to the patient having a markedly suppressed ability to mount an immune response and hence remaining relatively asymptomatic during the early stages of infection. However, we postulate that this atypical presentation was in particular due to the recent commencement of tocilizumab – given the patient had previously tolerated methotrexate and leflunomide for two years prior without developing significant infections.

This case emphasises the importance of considering infection as a differential diagnosis for common presentations such as suspected musculoskeletal pain in patients who are on tocilizumab. Additionally, given tocilizumab inhibits IL-6 mediated production of CRP,[5] a normal CRP may be unreliable for excluding infection. Conversely, elevation in CRP in the setting of active tocilizumab therapy may be a marker of severe disseminated infection – as exemplified by the present case. As the availability and use of tocilizumab increases, it is increasingly important for clinicians to have a high index of suspicion for delayed presentations of unusual infections in patients on tocilizumab therapy, including those who present with otherwise common presentations such as suspected musculoskeletal pain.

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Figure

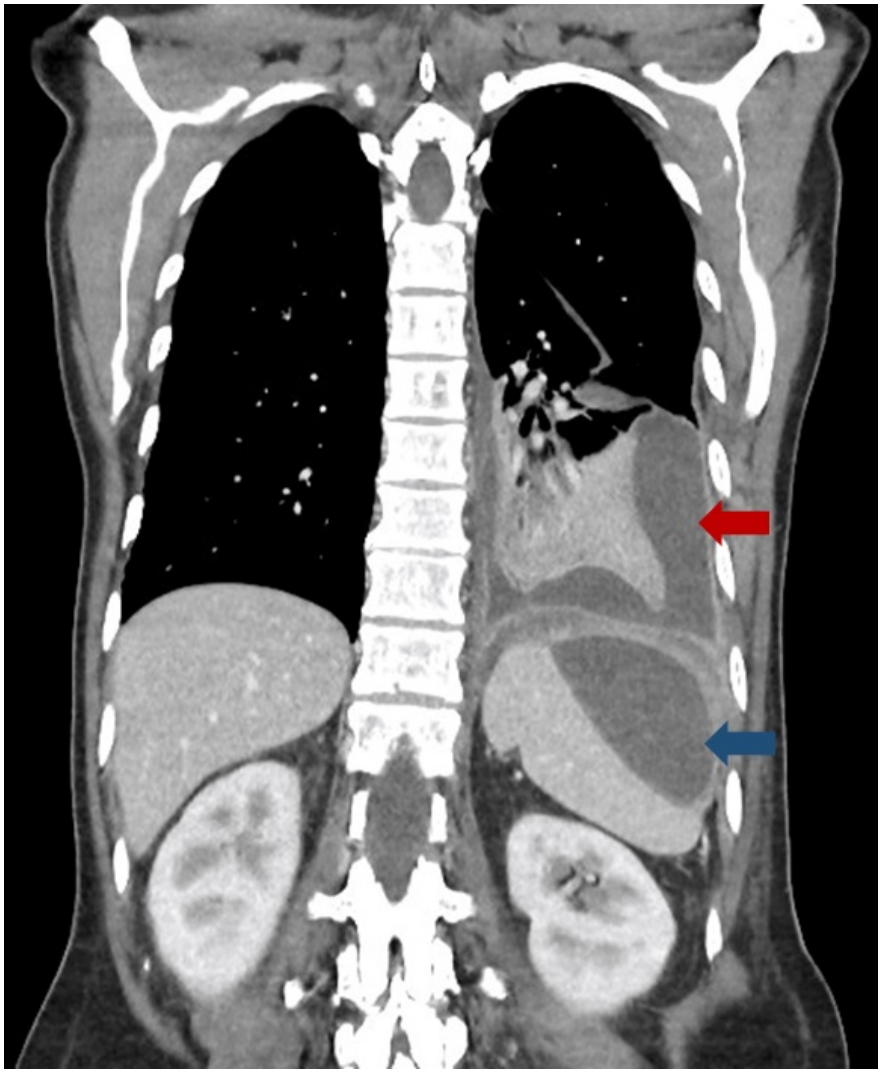

Figure 1: CT image of the chest/abdomen demonstrating a 51 mm x 40 mm x 49 mm hypodense lesion with peripheral enhancement consistent with a subcapsular splenic abscess (blue arrow) and left-sided moderate-volume loculated pleural effusion with peripheral enhancement in keeping with an associated empyema (red arrow).