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CASE REPORT

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

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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.

KEYWORDS

abscess, empyema, spleen, *Staphylococcus aureus*, tocilizumab

1 | 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 antirheumatic 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.

2 | CASE HISTORY/EXAMINATION

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 4 weeks prior. This was initially diagnosed as musculoskeletal pain at

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the time of injury; 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 2 years, and prednisolone at a stable dose 2.5 mg daily. She had also been commenced on subcutaneous tocilizumab 162 mg weekly 3 months prior by her rheumatologist for active tenosynovitis and significant arthralgia. She had a stable weight of 60 kg. She had significant improvement after commencing tocilizumab and did not have any arthralgia nor active tenosynovitis on presentation.

She also had a Bartholin cyst infection with increasing pain and swelling over the preceding 6 weeks. The timeline of events is presented in Figure 1. She saw her general practitioner (GP) for this, 2 weeks prior to her hospital admission, where the cyst was 1.5 × 1.5 cm with surrounding erythema and swelling. As the cyst was already spontaneously draining, incision and drainage was not performed. Microbiological swab samples taken cultured methicillin-sensitive *S. aureus* (MSSA). She was managed with a 5-day course of oral amoxicillin–clavulanic acid, and her immunosuppressive therapy including tocilizumab was withheld 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 2 years while taking methotrexate and leflunomide.

On examination, she was febrile but hemodynamically 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. There was no heat sensation or other abnormal sensation over the abdomen. She did not have any new rashes, arthralgia, or active tenosynovitis.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Blood investigations revealed elevated inflammatory markers with a CRP of 95 mg/L and neutrophilia of 12.6×10^9/L. Her renal function was normal with no electrolyte derangement. Her liver function tests were unremarkable. Computerized tomography (CT) of the abdomen revealed findings concerning for a subcapsular splenic abscess with subphrenic component and a left-sided empyema (Figure 2). These findings were new compared to a CT performed 4 weeks prior at the time of the original injury.

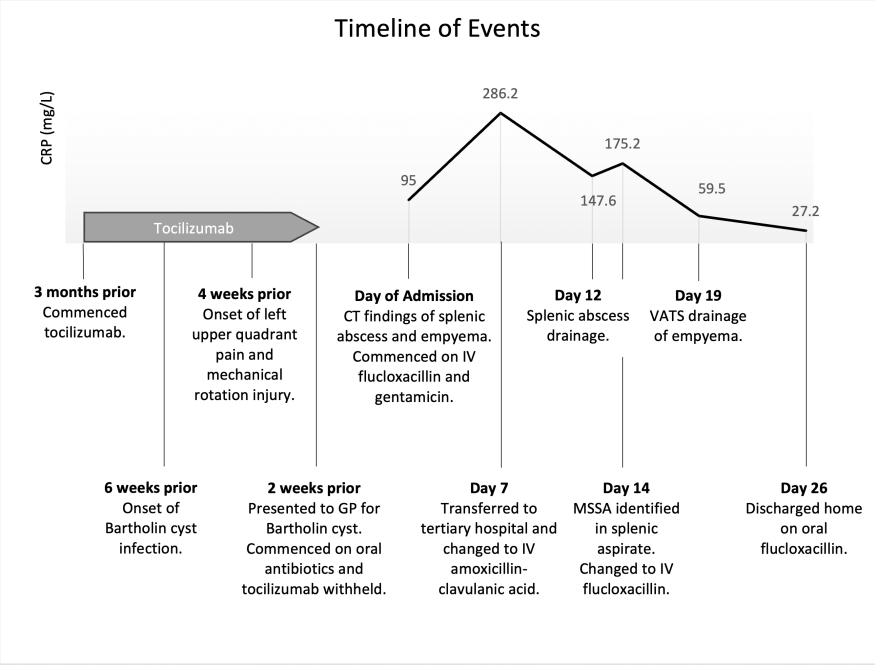

FIGURE 1 A timeline of the case study, with overlay showing the duration of tocilizumab administration (gray arrow) and schematic representation of C-reactive protein (CRP) in mg/L during key events (black line).

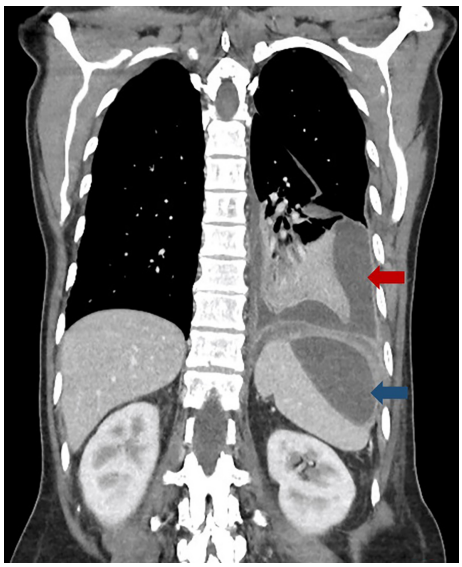

FIGURE 2 CT image of the chest/abdomen demonstrating a 51 × 40 × 49 mm hypodense lesion with peripheral enhancement consistent with a subcapsular splenic abscess (blue arrow) with subphrenic component and left-sided moderate-volume loculated pleural effusion with peripheral enhancement in keeping with an associated empyema (red arrow).

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.

4 | 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 normalization of neutrophilia and a slow downtrend in the CRP to 27 mg/L, after 3 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 4-week total course of antibiotic therapy and made a full recovery. Her arthritis disease activity remained well-controlled after discontinuation of tocilizumab for the duration of her admission until her discharge. Tocilizumab was ceased, and leflunomide and methotrexate were withheld on discharge in the context of infection, with ongoing follow-up planned with her rheumatologist.

5 | 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 *S. aureus* bacteremia associated with epidural abscess, polyarticular septic arthritis, and empyema.[4] Other unusual presentations include reactivation of latent tuberculosis presenting as fulminant sepsis with splenic abscess 2 weeks after initiating tocilizumab.[6] An increased risk of fungal coinfections 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]

The use of tocilizumab in patients with rheumatoid arthritis increases the risk of infection for a population already known to have immunological dysfunction from the chronic disease itself, with the incidence of infection in patients with rheumatoid arthritis approximately twofold compared to the general population.[9] The use of immunosuppressive medications in the management of rheumatoid arthritis further increases this risk of infection, such as with glucocorticoid use, with a dose-dependent increase in serious infection of up to fourfold.[9] The use of conventional DMARDs and concomitant biological DMARDs can also increase the risk of infection, for example, with tocilizumab compared to methotrexate alone (odds ratio of 1.3).[3]

We present a case of *S. 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 hypothesize that the formation of the splenic abscess was by hematogenous seeding from transient but uncaptured *S. aureus* bacteremia in the context of antibiotic therapy suppression, with the Bartholin cyst infection being the likely primary source.

Earlier assessment and management of the Bartholin cyst infection, including withholding immunosuppressive agents including tocilizumab, may have prevented the dissemination of infection. Soft tissue injury sustained from the rotational injury of the spine may have been a seeding site for infection and subsequent adjacent spread to the spleen. 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,[10] given the similar radiological appearance (Figure 2). While the rotational injury of the spine which prompted the patient's presentation may have 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 2 years prior without developing significant infections.

This case emphasizes 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 tocilizumab therapy may be a marker of disproportionately severe disseminated infection. Patients on tocilizumab should be informed and supported to seek early medical assessment in case of suspected infection. 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.

AUTHOR CONTRIBUTIONS

Audrey Lee: Writing – original draft; writing – review and editing. **Yi Tong Vincent Aw:** Conceptualization; formal analysis; writing – review and editing.

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The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

This research was carried out in accordance with the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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