CASE REPORT

Necrotising soft tissue infection without systemic toxicity in a patient with rheumatoid arthritis treated with tocilizumab

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SUMMARY

A Japanese woman aged 76 years with rheumatoid arthritis treated with prednisolone and tocilizumab presented with a 2-day history of redness and pain in her right thigh. She was hospitalised with a primary diagnosis of cellulitis and antimicrobial therapy was initiated. She had been stable until the fourth day of admission, when the swelling of her right thigh rapidly worsened and demonstrated purpura; she was subsequently unable to walk because of the pain. A diagnosis of necrotising soft tissue infection (NSTI) was made and extensive debridement was performed. Over the next 4 months, additional debridement was performed four times. Her condition improved significantly and she was able to walk later. Physicians should recognise that tocilizumab can mask systemic toxicities and inflammatory findings even in severe infections. To avoid delays in diagnosis and surgical intervention, clinicians should consider NSTIs when they encounter patients treated with tocilizumab, even if it mimics cellulitis.

BACKGROUND

Necrotising soft tissue infections (NSTIs) are life-threatening severe infectious diseases and clinically characterised by fulminant tissue destruction, systemic toxicities and a high mortality rate (70%–80%). Therefore, early and aggressive surgical intervention is essential. However, the use of antibiotic therapy without debridement is associated with a mortality rate close to 100%.¹ Clinical signs and symptoms include but are not limited to severe pain, which extends beyond the visible erythema, crepitus, bullous lesions and rapid progression of clinical manifestations. Tocilizumab is a humanised anti-interleukin (IL)-6 receptor antibody that has recently been approved for use in rheumatoid arthritis (RA). Tocilizumab can control the activity of RA by inhibiting the action of the inflammatory cytokine IL-6, but at the same time it also hinders the manifestation of the acute phase reaction of infectious diseases.² NSTIs related to tocilizumab may be difficult to distinguish from cellulitis in the early stage of its onset. Herein, we report a case of NSTI with masked inflammatory findings occurring in a patient with RA treated with tocilizumab and review five other cases.^{3–7}

CASE PRESENTATION

A Japanese woman aged 76 years with rheumatoid arthritis treated with prednisolone at 7.5 mg/

day, tocilizumab at 400 mg/month and iguratimod at 50 mg/day presented with a 2-day history of redness and pain in her right thigh. She had rheumatoid arthritis for the past 19 years and developed interstitial lung disease 10 years ago and methotrexate-induced lymphoproliferative disease 5 years ago. Three years before presentation, tocilizumab therapy was initiated and successfully suppressed the disease activity. The last tocilizumab dose was administered 26 days before the presentation.

She had stable vital signs; the temperature was 36.5°C, pulse 83 beats per minute, blood pressure 141/63 mm Hg, respiratory rate 18 breaths per minute and oxygen saturation 100% while she was breathing ambient air. Her quick Sequential Organ Failure Assessment score was 0. No crepitus, bullae or severe pain were noted.

INVESTIGATIONS

Laboratory studies showed a white blood cell count of 16 400 cells/ μ L, C reactive protein (CRP) level of 10.73 mg/dL, haemoglobin level of 12.6 g/dL, creatinine level of 0.95 mg/dL, sodium level of 141 mEq/L, glucose level of 206 mg/dL and glycated haemoglobin level of 6.5%. The serum creatine kinase level was not elevated (19 IU/L). Other findings were normal. The laboratory risk indicator for necrotising fasciitis score was 3.⁸

DIFFERENTIAL DIAGNOSIS

She was hospitalised with a provisional diagnosis of cellulitis and antimicrobial therapy with cefazolin was initiated. She had been afebrile and stable until the fourth day of her admission, when the swelling of her right thigh rapidly worsened and demonstrated purpura (figure 1); she was subsequently unable to walk because of the pain. A CT scan revealed multiple abscesses with gas formation in her right thigh. These abscesses spread within the pelvis along the iliopsoas muscle (figure 2). A T2-weighted magnetic resonance short T1 inversion recovery image showed a high-intensity area in the muscle (figure 3). A diagnosis of necrotising myositis and retroperitoneal abscesses was made.

TREATMENT

Extensive debridement was performed (figure 4). We changed the antibiotics to tazobactam/piperacillin, vancomycin and clindamycin and added intravenous immunoglobulins. After the operation, the pain was so

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Figure 1 Clinical findings on the fourth day of admission. The swelling of the patient's right thigh rapidly worsened and demonstrated purpura.

severe that the deep sedation and analgesia were needed, resulting in a shock state that required vasopressor therapy. However, the patient could be weaned off the vasopressor on the third postoperative day. Although she required ventilatory support after the operation, extubation performed on the tenth postoperative day was successful. The CRP level increased to its peak at 24.82 mg/dL on the fourth day of her admission, and normalised on the tenth day. Multiple organisms including extended-spectrum β -lactamase-producing *Escherichia coli*, *Bacteroides fragilis* group, *Streptococcus* sp and alpha-haemolytic *Streptococcus* were cultured from the pus; therefore, we changed the antibiotics to meropenem. Over the next 4 months, additional debridement was required four times. Subsequently, the defect of the anterior aspect of the right thigh was repaired using a tensor fascia lata muscle flap.

OUTCOME AND FOLLOW-UP

She regained enough strength for gait training and was transferred to a rehabilitation hospital on the 172th day.

Figure 2 The CT images of the abdomen (A) and the thighs (B) on the fourth day of admission. The CT image shows multiple abscesses with gas formation in the right thigh (B, arrow). These abscesses spread within the pelvis along the iliopsoas muscle (A, arrow).

DISCUSSION

The most important clinical finding from this case was that tocilizumab can mask systemic toxicities even in patients with NSTIs. The clinical onset of infections can be delayed until 3–4 weeks

Figure 3 The MRI findings (coronal (A) and axial (B) section) of the thighs on the fourth day of admission. A T2-weighted magnetic resonance short T1 inversion recovery image shows a high-intensity area in the muscle (arrow).

Figure 4 Intraoperative findings. Pus with a foul smell and green colliquative necrosis of the muscle was observed. The necrosis extended around the femoral artery (A) and vein (V) and nerve (N) and communicated with the retroperitoneal space.

after the last administration of tocilizumab.⁹ Moreover, tocilizumab can mask systemic toxicities by inhibiting inflammatory cytokine IL-6, which is a key driver of the acute-phase reaction and mediates the production of CRP in the liver. At the time of initial presentation, our patient demonstrated neither variations in the vital signs nor local findings suggestive of NSTIs, although CRP was positive; thus, she was diagnosed as having cellulitis.

A brief literature search of PubMed identified five other case reports of NSTIs in patients with RA treated with tocilizumab. In three cases, an elevation in CRP level was not observed.^{3–7} It is well known that the suppression of inflammatory findings may result in delays in diagnosis and surgical intervention. In a cohort study of 112 patients with RA starting tocilizumab therapy, the median time from the last infusion to clinical manifestations of infectious complications among 26 patients was 23.7 days. Despite the direct dependence of CRP induction on IL-6, severe infections led to a significant increase in CRP levels in six out of eight patients.⁹ With regard to the previous five cases, the time from the last infusion to clinical manifestation was available for only two cases. In a case wherein the last administration of tocilizumab was 2 weeks before onset, CRP was undetectable.³ On the other hand, in a case where the last dose was administered 24 days before onset, CRP was detected.⁵ It is important not to rely on CRP for the diagnosis of severe infectious diseases, especially in the early stages.

In the present case, the NSTIs appeared to be cellulitis. Other infectious diseases such as pneumonia, bacteraemia and septic arthritis, which do not show typical findings, have been reported in patients with RA.^{10–12} Tocilizumab prescribed for RA is associated with higher infection rates, although these rates are comparable with those observed with other biologics.¹³ Nonetheless,

Learning points

- Tocilizumab can mask systemic toxicities and inflammatory findings even in severe infections.
- The clinical onset of infections can be delayed until 3–4 weeks after the last administration of tocilizumab.
- Necrotising soft tissue infections should be considered when we encounter patients with rheumatoid arthritis treated with tocilizumab, even if it mimics cellulitis.

the most commonly reported infections are pneumonia and cellulitis.

Recognition of the fact that tocilizumab can mask systemic toxicities and delay the clinical onset of infections may facilitate quicker diagnosis and earlier surgical intervention. We should consider NSTIs in the differential diagnosis and work around that when we encounter patients with soft tissue infections treated with tocilizumab, especially early after the final administration, even if signs of severe inflammation are not observed. Imaging studies to judge need for surgical intervention are also important. Moreover, stable vital signs may delay recognition of severe infections. Conversely, suppression of the release of proinflammatory mediators in response to an infection by tocilizumab might have prevented the cytokine storm and improved the prognosis of patients with severe NSTIs. Even though the local finding was severe, such that it required debridement five times, the severity of organ failure was mild and only minimal vasopressor treatment and ventilatory support were necessary. After this patient was found to have NSTI, she was transferred to the intensive care unit and underwent multiple debridements; she recovered despite extensive necrosis. Recently, Honda *et al* discovered that IL-6 produced by marginal zone B cells around the spleen played a pivotal role in the exacerbation of endotoxic shock. They also showed that the anti-IL-6 receptor antibody markedly reduces mortality in sepsis-induced mice.¹⁴ Further studies are required to see if this applies to human sepsis.

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