

Case Report

Acute appendicitis in a rheumatoid arthritis patient treated with tocilizumab: report of a case

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A 55-year-old woman had been treated for rheumatoid arthritis with tocilizumab 1 month prior to the onset of mild abdominal pain. Computed tomography revealed swelling of the appendix and ascites around the appendix. She was diagnosed with acute appendicitis and underwent emergency surgery. Although her symptoms and laboratory data indicated mild infection, surgery was conducted because of the computed tomography findings and because we believed that the physical findings and laboratory data were not dependable due to the tocilizumab.

Upon surgery, a perforated inflamed appendix and abscess formation around the appendix were confirmed. Tocilizumab, which is relatively new, may conceal signs of infection or dull response to tests such as the Blumberg sign for peritonitis. It should be widely noted that the physical findings and laboratory data of patients with abdominal distress under tocilizumab treatment may be misleading.

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Introduction

Tocilizumab is a new biologic disease-modifying anti-rheumatic drug directed against the activity of interleukin-6 (IL-6), a key proinflammatory cytokine in the pathogenesis of rheumatoid arthritis (RA).¹ This drug has proved highly effective in RA patients, including those who had previously not responded to anti-tumor necrosis factor (TNF) agents. However, because this drug reduces inflammation and lessens symptoms during IL-6 blocking activity, it should be noted that the rare but severe side effect of gastrointestinal perforations can occur.²

We herein report a case of acute appendicitis that occurred

during treatment of a RA patient with tocilizumab.

Case report

A 55-year-old Japanese woman had a history of RA that had been diagnosed approximately 13 years prior to her appendicitis. She had been treated with steroids, methotrexate, and infliximab 5 months prior to the diagnosis of appendicitis, but had stopped the steroids. RA activity had then increased at 4 months prior to the appendicitis, and tocilizumab had been administered 1 month prior to the appendicitis. The patient had been experiencing abdominal distension and

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diarrhea over a 3-day period, and she had visited the hospital to obtain a second dose of tocilizumab. No significant inflammatory changes were noted in laboratory tests, but abdominal computed tomography (CT) revealed swelling of the appendix and the presence of ascites around the appendix (Fig. 1). The patient was then referred to our hospital with a diagnosis of acute appendicitis. At the time of admission, her blood pressure was 154/98 mmHg with a heart rate of 112 beats/min, a body temperature of 37.2°C, and an oxygen saturation (SpO₂) level of 99% on room air. Physical examination revealed mild tenderness in the right lower quadrant, without rebound tenderness. Laboratory tests revealed a white blood cell (WBC) count of 11,100 cells/m³, a hemoglobin level of 15.2 g/dl, a platelet level of 10.8 × 10⁴ cells/m³, an albumin level of 4.1 g/dl, a blood urea nitrogen (BUN) level of 11.8 mg/dl, a creatinine level of 0.61 mg/dl, and a C-reactive protein (CRP) level of 0.35 mg/dl. The patient's transaminase level was normal. Although the acute appendicitis had appeared mild in the physical findings and laboratory data, we decided to conduct emergency surgery because CT revealed swelling of the appendix and the presence of ascites around the appendix and our sense was that the physical findings and laboratory data were not dependable due to the effect of the tocilizumab.

The patient underwent operation under general anesthesia, and a 5-cm Lennander's pararectal incision was made. At the time of surgery, a perforated inflamed appendix and abscess formation around the appendix were confirmed (Fig. 2). Appendectomy was performed, the local area was irrigated with 3,000 ml of saline, and a drain was inserted into the pouch of Douglas. Pathological examination revealed the appendix with abscess formation and perforation (Fig. 3). There were no effects of tocilizumab such as inhibition of inflammatory cell infiltration. The patient had an uneventful postoperative recovery, but we followed up carefully, taking

the effects of the tocilizumab into consideration. On the first day after the operation, the patient's WBC count was 10,400 cells/m³, and her CRP level was 0.55 mg/dl, and she began to take meals. On the third day after surgery, her WBC count had decreased to 8,100 cells/m³, her CRP level was 1.69 mg/dl and her temperature was below 37.0°C. On the fourth postoperative day, the drain was removed. On the fifth day, her WBC count had decreased to 6,700 cells/m³ and her CRP level was 1.33 mg/dl; antibiotics were stopped. However, on the seventh day, the patient's body temperature began to rise, and her RA symptoms steadily worsened. She was transferred to a hospital specializing in RA on the fourteenth day after surgery. The previous administration of tocilizumab did not appear to have affected the healing process.

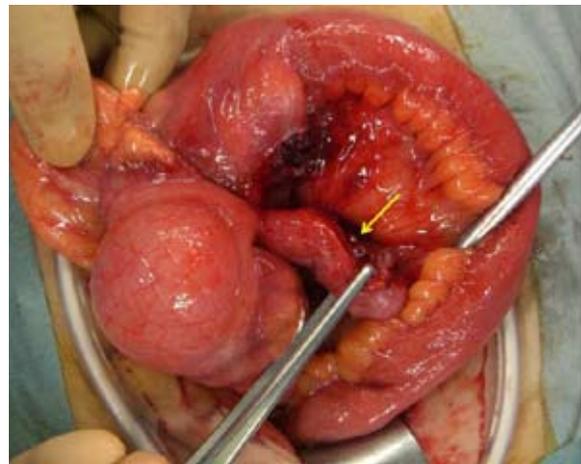


Figure 2. Surgical findings. A perforated inflamed appendix and abscess formation around the appendix were confirmed (arrow).

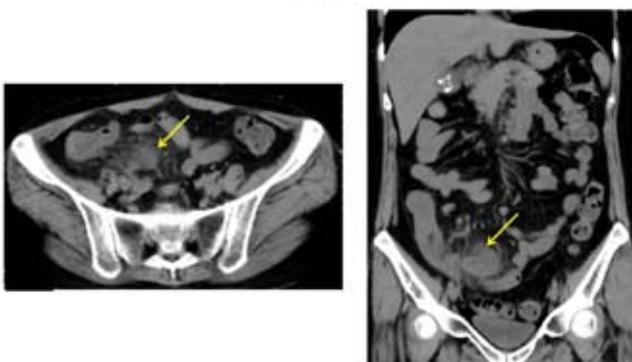


Figure 1. CT images. Abdominal CT revealed a swelling of the appendix and the presence of ascites around the appendix (arrow).

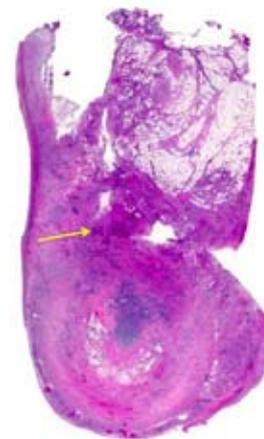


Figure 3. Pathological examination revealed the appendix with abscess formation and perforation (arrow). There were no effects of tocilizumab such as inhibition of inflammatory cell infiltration.

Discussion

The anti-inflammatory effects of tocilizumab may mask signs of infection and typical symptoms such as the Blumberg sign in acute appendicitis. Furthermore, serum CRP concentrations do not increase during tocilizumab therapy.^{3,4} Therefore, physicians must be aware that severe infections may be hidden in the conditions inferred from the clinical findings of a patient under tocilizumab treatment.

Clinical trials and the above-mentioned combined analysis showed a rate of gastrointestinal perforation following tocilizumab treatment of 0.26 per 100 patient years.⁵ According to a post-marketing study of tocilizumab for RA in Japan, 7 gastrointestinal perforations were reported in 6 patients.⁶ During Roche clinical trials abroad, 26 cases (0.65%) of gastrointestinal perforation were found among RA patients treated with tocilizumab at a rate of 1.9 per 1,000 patient years, of which most cases appeared to be complications of diverticulitis.⁷ There is consensus that tocilizumab should not be used in patients with a history of gastrointestinal perforation, intestinal ulcers or diverticulitis. According to Nakahara et al.⁸, anti-IL-6R mAb therapy reduces vascular endothelial growth factor (VEGF) in RA. Thus, this may be the mechanism by which tocilizumab causes gastrointestinal perforation, and we plan to continue research on this question.

Corticosteroids also mask many of the inflammatory signs of bowel perforation. Because the typical clinical sign of peritonitis is often absent, the interval between onset of symptoms and diagnosis of perforation is delayed.^{9,10}

Tocilizumab is a new drug for RA therapy, and is therefore relatively unfamiliar to most surgeons in comparison with corticosteroids. It should be widely noted that the administration of tocilizumab masks physical symptoms in acute abdomen patients and laboratory data may be misleading. Therefore, surgeons must take particular care in determining the most appropriate timing of surgical intervention.

Disclosure

Conflict of interest statement: Y. Maruya and other co-authors have no conflict of interest.

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