DOI：10.6314/JIMT.202504_36(2).07 內科學誌 2025：36：151-155

Tocilizumab-Associated Colon Perforation in Rheumatoid Arthritis: A Case Report Highlighting a Rare but Serious Adverse Event

Yeong-Jang Lin, Hung-An Chen, Chao-Yu Chen

Division of Allergy, Immunology, and Rheumatology,
Department of Internal Medicine, Chi Mei Medical Center

Abstract

Tocilizumab, a humanized monoclonal antibody targeting the interleukin-6 receptor, has demonstrated significant efficacy and tolerability in patients with rheumatoid arthritis (RA) who have had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs or tumor necrosis factor inhibitors. Despite its effectiveness in controlling inflammation, tocilizumab is associated with serious adverse events, including gastrointestinal perforation, a rare but potentially life-threatening complication. This report presents a case of colon perforation in a patient with RA receiving tocilizumab therapy.

Key Words: rheumatoid arthritis; colon perforation, tocilizumab

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that primarily affects the joints but can also lead to systemic complications. Gastrointestinal (GI) perforation, although rare, is a severe and potentially life-threatening complication in patients with RA. A retrospective analysis by Curtis et al. reported an incidence of GI perforation in RA patients of approximately 1.7 per 1,000 patient-years, with 83% of these perforations occurring in the lower GI tract[1]. Key risk factors included advanced age, a history of diverticulitis, and the use of glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs)[1].

Tocilizumab, a monoclonal antibody targeting the interleukin-6 (IL-6) receptor, is widely used in the management of various rheumatic diseases, including RA, juvenile idiopathic arthritis, adult-onset Still's disease, giant cell arteritis, and Takayasu arteritis, as well as other conditions such as Castleman disease and cytokine release syndrome[2]. While effective in controlling inflammation, many studies have consistently highlighted an elevated risk of GI perforation, a rare but potentially life-threatening complication, among RA patients treated with tocilizumab[3-5]. However, a review of the literature shows that tocilizumab-induced GI perforation in RA patients is rarely published in

Reprint requests and correspondence：Yeong-Jang Lin
Address：Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Chi Mei Medical Center, No.901, Zhonghua Rd. Yongkang Dist., Tainan City 710, Taiwan

the form of case reports. Here, we describe a case of colon perforation in a patient with RA receiving tocilizumab therapy, aiming to improve case recognition and treatment.

Case report

A 77-year-old female patient presented with a progressively enlarging left flank mass persisting for 1 to 2 months. She had a 6-year history of seropositive RA. Due to persistently high disease activity despite treatment with conventional synthetic disease-modifying antirheumatic drugs (DMARDs), she started receiving tocilizumab (162 mg subcutaneous injection every two weeks) three years prior to the current presentation. Her arthritis markedly improved following the initiation of tocilizumab, achieving a state of low disease activity.

On physical examination, a soft, tender mass measuring 7.5 x 8 cm was identified, without overlying skin erythema. The patient denied fever, chills, abdominal pain, or diarrhea. Laboratory tests revealed a white blood cell count of 13,900/mm^3 (83.5% neutrophils), hemoglobin of 10.5 g/dL, platelet count of 260,000/mm^3, erythrocyte sedimentation rate (ESR) of 36 mm/hr (reference range: 0-20), and C-reactive protein (CRP) level of 11.1 mg/L (reference range: < 5). Other routine blood chemistry results were within normal limits.

A computed tomography scan of the abdomen revealed the following: (1) multiple small outpouchings along the descending and sigmoid colon, consistent with colonic diverticulosis (Figure 1a); (2) lobulated abscesses with an air-fluid level, measuring up to 8.3 x 4.7 x 12 cm, involving the left abdominal wall, psoas muscle, and retroperitoneum adjacent to the descending colon (Figure 1b); and (3) a contrast-opacified fistula connecting the descending colon to the abdominal wall abscess (Figure 1b). These findings suggested prior diverticulitis of the descending colon with perforation and abscess formation, complicated by a fistula connecting the descending colon to the abdominal wall abscess. Echo-guided percutaneous drainage of the abdominal abscess was performed, and cultures of the pus grew Klebsiella pneumoniae and Escherichia coli.

The patient was treated with broad-spectrum antibiotics and subsequently underwent laparoscopic left hemicolectomy with retroperitoneal abscess drainage. Tocilizumab-associated diverticulitis and colon perforation were considered the likely etiology. The patient is now receiving abatacept and has maintained a low disease activity state.

Discussion

Tocilizumab was first identified as having an increased risk of GI perforation following a cumulative safety analysis of five core phase 3 clinical trials[3]. Specifically, 26 cases of GI perforation were

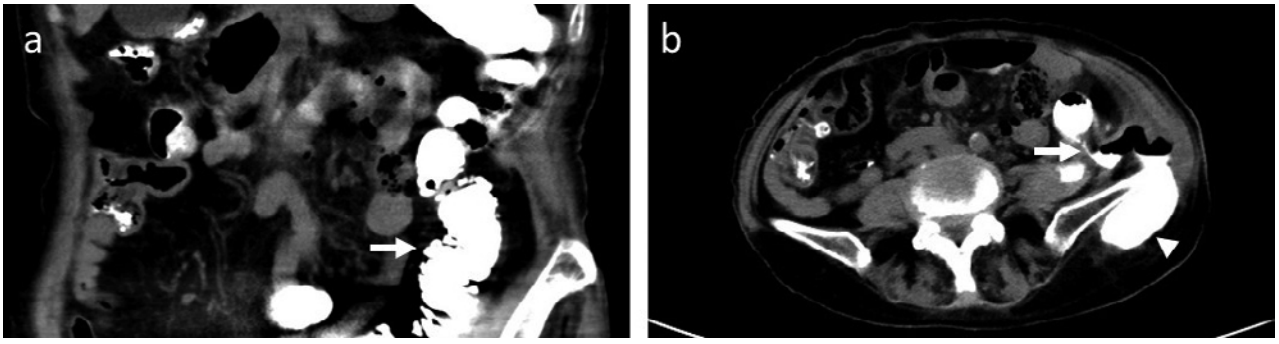

Figure 1. A computed tomography scan of the abdomen revealed (1) multiple small outpouchings along the descending and sigmoid colon, consistent with colonic diverticulosis (arrow in a); (2) lobulated abscesses with an air-fluid level involving the left abdominal wall (arrowhead in b), psoas muscle, and retroperitoneum adjacent to the descending colon; and (3) a contrast-opacified fistula (arrow in b) connecting the descending colon to the abdominal wall abscess.

reported in patients receiving tocilizumab (at a rate of 2.8 events per 1,000 patient-years), while no cases were observed in the control group[3]. The majority (69%) of these events occurred in the colon, and 16 of the 26 cases involved patients with underlying diverticulitis[3]. This highlights that pre-existing diverticular disease is a significant risk factor for GI perforation in patients receiving tocilizumab therapy.

Moreover, tocilizumab has been shown to significantly increase the risk of lower GI perforation compared to other RA treatments, including biological and targeted synthetic DMARDs[4-5]. A comparative analysis of data from the German biologics register, Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), revealed that tocilizumab significantly increased the risk of lower GI perforation compared to other therapies, such as conventional synthetic DMARDs, tumor necrosis factor inhibitors, abatacept, and rituximab[4]. Notably, patients on tocilizumab often did not exhibit typical symptoms of lower GI perforation[4]. Only 27% of patients reported acute abdominal pain, and just 9% had highly elevated CRP levels[4]. The 30-day mortality rate following perforation was 46% in tocilizumab-treated patients[4]. Although this rate was not statistically significantly higher than that observed with other therapies, it remains concerningly high[4]. These findings highlight the substantial risk of lower GI perforation in RA patients treated with tocilizumab and emphasize the need for prompt detection and intervention.

Another similar study using real-world data from Medicare and MarketScan assessed the risk of GI perforation in RA patients treated with tofacitinib, tocilizumab, or other biologic agents[5]. The incidence of upper GI perforation was comparable across all treatment groups[5]. In contrast, lower GI tract perforation risk was significantly elevated with tocilizumab treatment, and numerically elevated with tofacitinib treatment, versus treatment with tumor necrosis factor inhibitors[5]. Most perforations occurred in the lower GI tract, consistent with findings from other studies[3-4]. Key risk factors for GI perforation included advanced age, a history of diverticulitis, and the use of prednisone at doses exceeding 7.5 mg/day, indicating the need for careful patient selection and monitoring when prescribing tocilizumab[5].

Our case developed descending colon diverticulitis with perforation three years after initiating tocilizumab therapy. The patient presented with an enlarging left flank mass, which was a result of an abdominal wall abscess and served as the sole clinical manifestation of the colon perforation. The suppression of IL-6-driven inflammatory responses often leads to atypical presentations of colon perforation[4]. Common symptoms and laboratory findings, such as fever, severe abdominal pain, leukocytosis, and elevated CRP, are often diminished or absent, leading to delayed diagnosis and increased morbidity and mortality.

Early detection of infection in tocilizumab-treated patients is particularly challenging due to suppressed fever and CRP responses. In individuals receiving anti-IL-6 therapy, procalcitonin may serve as a more reliable biomarker for bacterial infection. Clinicians should maintain a high index of suspicion for atypical manifestations, such as fatigue, localized pain, or respiratory symptoms, even in the absence of fever. High-risk patients, including those on corticosteroid therapy or with significant comorbidities, require closer surveillance.

The association between tocilizumab and GI perforation is likely due to its inhibition of IL-6 signaling. IL-6 plays a vital role in maintaining intestinal homeostasis[6]. It is essential for mucosal repair, as it is produced early by intraepithelial lymphocytes in response to intestinal injury, promoting epithelial cell proliferation and wound healing[6]. By inhibiting IL-6 signaling, tocilizumab may impair these critical processes of intestinal epithelial prolif-

eration and repair following injury, thereby increasing the risk of bowel perforation.

The literature emphasizes the importance of screening and identifying high-risk patients before initiating tocilizumab therapy. Alternative treatments or closer monitoring may be necessary for patients with diverticulosis, advanced age, or concurrent corticosteroid use[5]. Moreover, minimizing long-term corticosteroid and NSAID use may help reduce the risk of GI complications. Diagnosing GI perforation in RA patients receiving tocilizumab can be particularly challenging due to the frequently atypical presentations. Patient education regarding the warning signs of GI perforation and regular monitoring are essential. Clinicians must remain vigilant regarding the increased risk of lower GI perforation associated with tocilizumab. In these patients, CRP levels may remain suppressed even in the presence of severe infection, making it vital to maintain a high level of suspicion. Early imaging studies should be considered for RA patients presenting with unexplained abdominal pain to facilitate timely diagnosis and intervention.

In conclusion, tocilizumab is associated with an increased risk of lower GI perforation in RA patients, particularly those with advanced age, pre-existing diverticular disease, and concurrent corticosteroid therapy. Recognizing the atypical presentation of GI perforation in RA patients treated with tocilizumab can improve early detection and management. Careful patient selection, vigilant monitoring, and timely intervention are crucial to optimizing the therapeutic benefits of tocilizumab while minimizing its potentially life-threatening risks.

References

1. Curtis JR, Lanas A, John A, Johnson DA, Schulman KL. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64(12):1819-28.
2. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol 2020;16(6):335-45.
3. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13(5):R141.
4. Strangfeld A, Richter A, Siegmund B, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. Ann Rheum Dis 2017;76(3):504-10.
5. Xie F, Yun H, Bernatsky S, Curtis JR. Brief Report: Risk of Gastrointestinal Perforation Among Rheumatoid Arthritis Patients Receiving Tofacitinib, Tocilizumab, or Other Biologic Treatments. Arthritis Rheumatol 2016;68(11):2612-7.
6. Kuhn KA, Manieri NA, Liu TC, Stappenbeck TS. IL-6 stimulates intestinal epithelial proliferation and repair after injury. PLoS One 2014;9(12):e114195.

Tocilizumab 相關的類風濕性關節炎結腸穿孔：病例報告強調罕見但嚴重的不良事件

林永章　陳宏安　陳昭宇

奇美醫學中心內科部風濕免疫科

摘要

Tocilizumab 是一種針對介白素 -6 受體的人源化單株抗體，已在對傳統疾病修飾抗風濕病藥物或腫瘤壞死因子拮抗劑反應不佳的類風濕性關節炎患者中展現出顯著的療效和安全性。儘管 Tocilizumab 可有效控制發炎，但它也與一些嚴重的不良事件相關，包括胃腸道穿孔，這是一種罕見但可能危及生命的併發症。本文報告了一例正在接受 Tocilizumab 治療的類風濕性關節炎患者發生結腸穿孔的病例。