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CASE REPORT

Tuberculosis Arthritis in the Wrist While Using Rituximab for Rheumatoid Arthritis Treatment

This article was published in the following Dove Press journal:
Open Access Rheumatology: Research and Reviews

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Introduction: Data from clinical trials indicate that there are no increased risk of tuberculosis (TB) infections in rheumatoid arthritis (RA) patients while using rituximab (RTX). Herein, we report a RA patient who developed TB arthritis while using RTX.

Case Report: A 49-year-old patient was treated with methotrexate and prednisolone along with RTX for two years. Later, she presented with increasing pain, swelling, redness and cutaneous fistulization in her left wrist for two months. The lesion on the wrist was debritted. Histopathologic evaluation revealed the presence of acid-fast bacilli. Polymerase chain reaction test and culture confirmed mycobacterium tuberculosis. RTX, methotrexate and prednisolone were withdrawn. The patient was treated with 12-month course of antituberculous treatment and responded well. The patient, who did not have pain or swelling in her other joints, was not given any treatment for RA after antituberculous treatment.

Conclusion: Clinicians should keep in mind that TB infections may be encountered while using RTX. Latent TB screening may be appropriate in patients using concomitant corticosteroid and living in TB endemic areas.

Keywords: rheumatoid arthritis, rituximab, tuberculosis, infection

Introduction

Biological disease-modifying antirheumatic drugs (DMARDs) have revolutionized the treatment of rheumatoid arthritis (RA). However, an increased risk of serious and opportunistic infections associated with biological DMARDs has long been well known. Especially, the link between tumour necrosis factor (TNF) inhibitors and latent tuberculosis (TB) reactivation has been a worldwide challenge for clinicians.[1] Rituximab (RTX), an anti-CD20 monoclonal antibody, is indicated in the treatment of RA, but the association of tuberculosis infections with the use of RTX is not well understood.[2] The low or absent risk of latent TB reactivation associated with RTX use has been widely accepted all over the World. Indeed, only sporadic cases of active TB infection, not exceeding the frequency of the disease in general population, were reported using RTX in patients with RA.[3] According to the Rituximab Consensus Expert Committee, the screening procedures for latent TB infection before therapy starting seem unnecessary.[2] European League Against Rheumatism recommended that RTX may be considered as a first-line biological agent in the presence of latent TB with contraindications to use of TB prophylaxis.[4] Recently European Society of Clinical Microbiology and Infectious Diseases Study Group evaluated the risk of infection entailed by the use of monoclonal antibodies targeting CD19, CD20 and CD52 and not recommended the latent TB screening

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DovePress
http://doi.org/10.2147/OARRR.S268852

before RTX therapy.[5] On the other hand, American College of Rheumatology recommended screening patients for latent TB infection before starting all biological agents including RTX.[6] Herein, we report a patient with RA who developed TB arthritis in the wrist using RTX.

Case Report

A 49-year-old female patient came to our clinic with increasing pain and swelling in her left wrist for two months. She was a housewife and had no known disease other than hypertension and RA. The patient was treated with a diagnosis of seronegative RA in another clinic, and she has been using methotrexate (MTX) 10 mg/week and prednisolone 5 mg/day along with RTX for two years (4 cures of RTX in total). The last infusion of RTX was administered approximately 5 months before the date she applied to our hospital. There were no signs of inflammation in her joints except the left wrist. In laboratory tests, hemogram, liver transaminases, urea, creatinine, uric acid levels and urine analysis were within normal limits. The erythrocyte sedimentation rate (ESR) was 46 mm/h and the C-reactive protein (CRP) level was 18 mg/L. Rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (ant-CCP) and antinuclear antibodies (ANA) were negative. Chest radiography and sacroiliac joint radiography were within normal limits. Thereupon, the dose of methotrexate was increased to 15 mg/week and the dose of prednisolone to 10 mg/day. At the control two months later, there was no decrease in the patient's complaints. Moreover, redness and cutaneous fistulization developed on the radial side of the left wrist (Figure 1). The patient complained of intermittent fever and loss of appetite. Her temperature was 37.0°C, blood pressure 135/80 mmHg, and heart rate 72/minutes. Chest and abdominal examinations were normal. There was no lymphadenopathy in head and neck examination. Laboratory evaluation showed an increase in ESR (62 mm/h) and CRP (53 mg/L). There was no infiltrative lesion or pleural effusion on chest radiography. The patient was hospitalized. Blood and urine cultures were found negative. The lesion on the left wrist was debritted. Histopathologic evaluation revealed the presence of acid-fast bacilli. Polymerase chain reaction test and culture confirmed mycobacterium tuberculosis. Quadruple anti-TB treatment (ethambutol, rifampicin, pyrazinamide and isoniazid) was started. Prednisolone was terminated by reducing 2.5 mg per week. MTX and RTX were withdrawn. She was

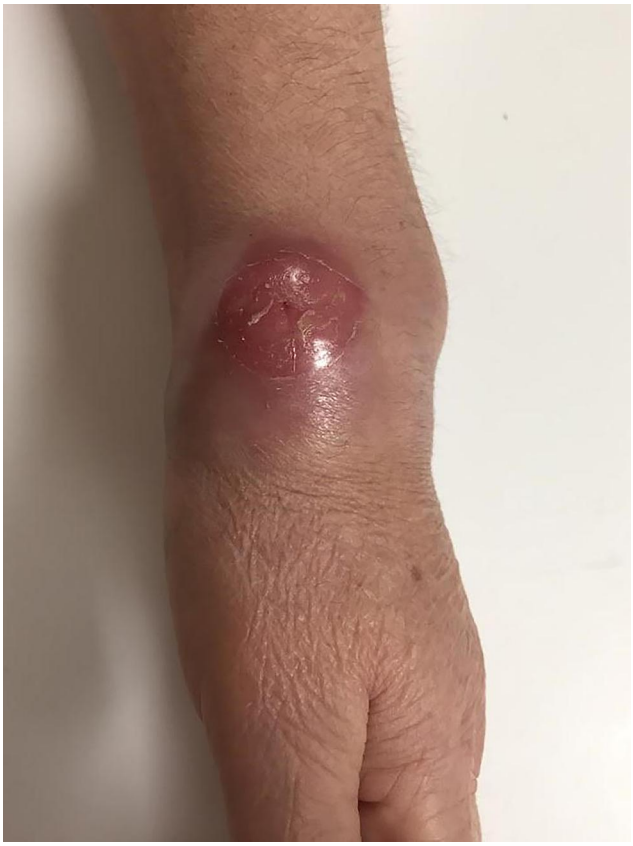

Figure 1 Before antituberculous treatment. Swelling, redness and cutaneous fistulization are shown on the left wrist.

treated with 12-months course of antituberculous treatment and responded well (Figure 2). After antituberculous treatment, the patient who did not suffer pain or swelling in her other joints was not given any medication for RA. The absence of joint complaints despite not receiving immunosuppressive therapy for over a year, negative serological tests for RF, anti-CCP and ANA, and the absence of typical erosions for RA in the joints suggest that the initial diagnosis of RA may not be correct. The patient may have had viral arthritis or reactive arthritis. Less likely, the patient may be in prolonged remission.

Discussion

Data from clinical trials and drug registries indicate that there is no increased risk of TB in RA patients using RTX; thus, latent TB screening before commencing RTX therapy is not recommended.[2,3,7–9] Data from 3194 RA patients recruited in 8 randomized clinical trials and 2 long-term open-label extension trials demonstrated that the overall rates of serious infections were similar between RTX and Placebo. Only two cases of pulmonary TB occurred in the

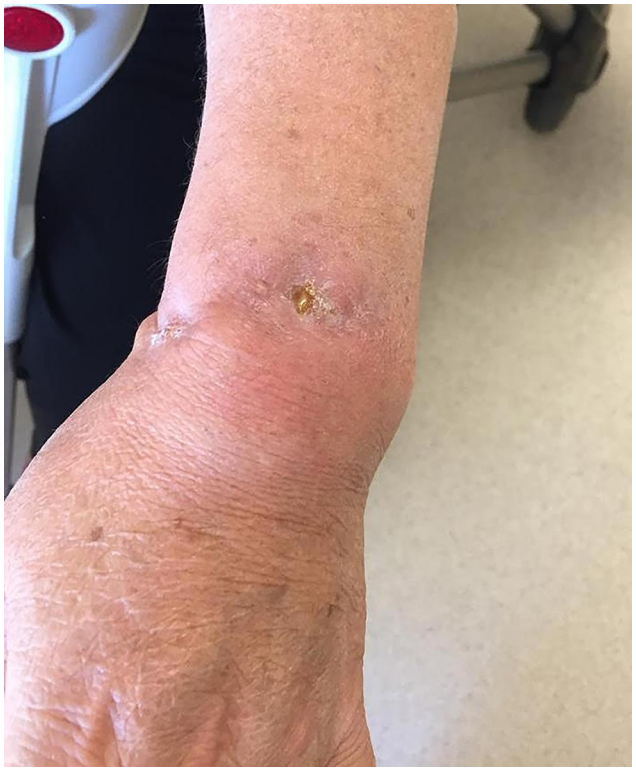

Figure 2 After 12 months course of antituberculous treatment. Swelling, redness and cutaneous fistulization on the left wrist recovered.

RTX group.[8] The incidence of TB was significantly lower among RTX users than TNF-inhibitor users in the cohort of The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Of 12,039 patients using TNF-inhibitors, 56 (0.46%) developed TB, while only 2 TB cases occurred in 5072 patients using RTX, resulting in a hazard ratio of 0.16 (95% CI 0.04¬-0.67).[1] Similarly, only one TB case was reported in the German registry consisting of 2484 RA patients using RTX.[9] Confirming the low risk, in a nationwide database from an endemic area for TB, of 763 RTX-exposed patients with RA (6179 patient-years), only two TB cases were recorded. Using conventional DMARDs-exposed group as reference, a Hazard Ratio of TB was of 0.08 with RTX use.[10] A retrospective study from another endemic area for TB assessed the risk of latent TB reactivation with RTX use and found no TB flare-ups following the therapy. However, the follow-up period of this study was less than one year.[11]

RTX seems to be a safe alternative for patients in whom TNF-inhibitors are contraindicated due to recent TB infection. Two RA patients with active TB were successfully treated with RTX without any TB reactivation, and the patients were followed up to 3 years.[12] Burr et al[13] presented a case of RA who was safely treated with RTX after developing disseminated TB infection following treatment with infliximab. Another patient with active RA who had a past medical history of pulmonary TB and aspergillosis was successfully treated with RTX monotherapy resulting in low disease activity. Neither TB nor aspergillosis was recurred.[14] Xanthouli et al[15] reported that nine RA patients with a history of TB were treated with RTX. The mean follow-up of these patients was 16.5 months. During this period, no relapse of TB was noted. However, all these patients received prophylactic isoniazid for nine months in accordance with the German guidelines for TB prophylaxis during treatment with biologic drugs.

On the other hand, the case reports and national registries indicate that TB infection is also possible using RTX.[8,16–18] Three cases of active TB were reported in a survey conducted by the Emerging Infections Network.[19] A 42-year-old woman with RA developed knee TB arthritis while receiving RTX. She was also using concomitant MTX and low-dose prednisolone.[16] A case of pleural TB under RTX therapy was reported in a patient with anti-synthetase syndrome. In this patient, RTX was concomitantly used with azathioprine and low-dose prednisolone.[17] Parikh et al[18] reported two cases of TB infection while using RTX. Firstly, a patient with SLE using mycophenolate sodium and prednisolone developed pulmonary TB four months after RTX administration. Secondly, in a patient using monthly cyclophosphamide infusion and prednisolone 20 mg/day with the diagnosis of dermatomyositis, miliary TB developed 10 days after RTX infusion. Since both, the patients reported were on more than one immunosuppressant, the probability of TB could be due to the added effect of immunosuppression and not due to RTX alone. Similarly, our patient was using MTX and prednisolone along with RTX. Therefore, the exact role of RTX is difficult to define in our patient. Besides antibody production, B lymphocytes play an important role in activating T lymphocytes by presenting antigens and secreting cytokines. Depletion of B lymphocytes with RTX not only suppresses humoral immunity, but also suppresses cellular immunity. Therefore, suppression of cellular immunity by RTX may pose a potential risk for TB.[20]

Conclusion

Currently, RTX is considered as the first-line biological agent for patients at high risk of TB reactivation for the management of rheumatological diseases. But, as presented here, increasing case reports warn physicians that

TB infections may be seen during RTX therapy, especially in endemic areas. Although this case would not support latent TB screening for all patients before starting RTX, it may be appropriate in patients living in TB endemic areas and using corticosteroid (≥5mg/day).

Consent Form

The patient has provided written informed consent for the case details and images to be published. Institutional approval is not required to publish the case details.

Disclosure

The authors report no conflicts of interest in this work.

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