Letter to the Editor

Cryptococcosis in a patient with rheumatoid arthritis following glucocorticoid and JAK inhibitor therapy: a case description on stabilization with tocilizumab

Meiju Zhou[#], Huilan Guan[#], Yan Huang, Fang Yuan

Department of Rheumatology and Immunology, Zhejiang Hospital, Hangzhou, China

[#]These authors contributed equally to this work.

Correspondence to: Fang Yuan, MD. Department of Rheumatology and Immunology, Zhejiang Hospital, Gudun Road No. 1229, Hangzhou 310030, China. Email: yuanfany@126.com.

Submitted Aug 29, 2024. Accepted for publication Mar 07, 2025. Published online Mar 28, 2025.
doi: 10.21037/qims-24-1825
View this article at: https://dx.doi.org/10.21037/qims-24-1825

Introduction

Rheumatoid arthritis (RA) is the most prevalent and chronic autoimmune inflammatory disease of the synovial tissues, causing joint discomfort, stiffness, swelling, and limited joint movement, ultimately resulting in structural damage, deformity, and disability (1). Disease-modifying antirheumatic drugs (DMARDs) and biological agents have significantly changed the prognosis of RA (2). Prompt use of antirheumatic drugs is critical for preventing disease progression. However, increased infection risk is associated with DMARD use in the course of RA therapy (3). *Cryptococcus neoformans* infection is a universal health concern, especially in immunosuppressed patients.

Specifically, Janus kinase (JAK) inhibitors relieve symptoms and improve disease progression in RA patients (4). However, the inhibition of the JAK-signal transducer and activator of transcription (STAT) pathway may lead to the dysfunction of cellular immunity, which results in decreased production of several proinflammatory cytokines (5). Consequently, various opportunistic infections related to the use of JAK inhibitors for management of disease have been reported previously, such as cutaneous cryptococcosis (6), cryptococcal pneumonia (7), and disseminated cryptococcosis (8). However, management is very difficult for RA patients when complicated with severe infection (9).

Herein, we reported a case of cryptococcosis with pulmonary involvement in a patient with RA treated with low-dose steroids, methotrexate (MTX), and full-dose tofacitinib (Xeljanz). The disease was stable upon follow-up with tocilizumab therapy. As demonstrated in this case, tocilizumab may be a viable treatment option for severe infections in patients with RA.

Case presentation

A 31-year-old woman was hospitalized for 2 weeks due to fever and cough. Approximately 6 months earlier, she had presented to a clinic with swollen and painful proximal interphalangeal joints, metacarpophalangeal joints, wrist joints, knee joints, and elbow joints, and was positive for rheumatoid factor and anti-cyclic citrullinated peptide antibody. RA was diagnosed, without pulmonary lesions (*Figure 1A*). The patient started receiving low-dose prednisone (10 mg/day) and MTX (10 mg/week) simultaneously, but discontinued MTX after 1 month because of a severe gastrointestinal reaction. Subsequently, a T-SPOT.TB (T-lymphocyte spot test for tuberculosis) test was performed, which returned negative results. So, prednisone was reduced to 5 mg/day, and MTX was replaced with tofacitinib (Xeljanz, 10 mg/day). One month later, the patient's symptoms were relieved, after which time she received tofacitinib monotherapy for nearly for 4 months.

Furthermore, laboratory tests revealed a white blood cell count of 15×10^9/L [normal value, $(3.5–9.5)\times10^9$/L], a neutrophil count of 12.5×10^9/L, a lymphocyte count of

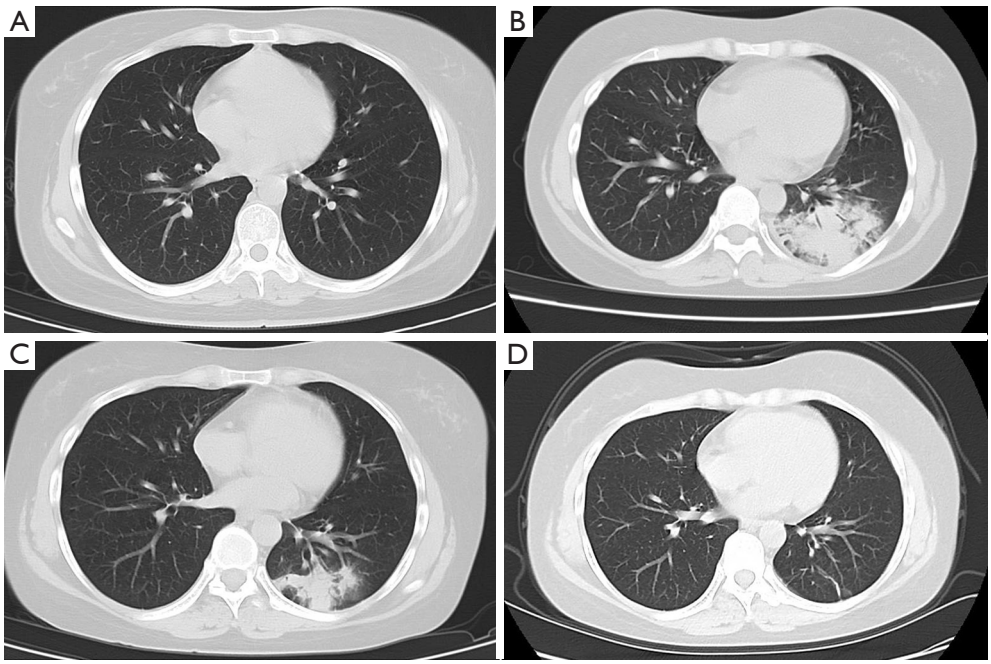

Figure 1 Representative pulmonary chest CT images. (A) Chest CT scan revealed no abnormal findings at the time of the initial diagnosis of RA. (B) Chest CT scan showed pulmonary consolidation lesions in the left lobe. (C) Chest CT showed significant improvement of the pulmonary lesions after fluconazole treatment for 2 weeks. (D) Chest CT scan showed the lesion evidently absorption after fluconazole and tocilizumab treatment for 1 year. CT, computed tomography; RA, rheumatoid arthritis.

1.8×10^9/L, C-reactive protein (CRP) 193.68 mg/L (normal value: <4 mg/L), and erythrocyte sedimentation rate (ESR) of 93 mm/h (normal value: 0–20 mm/h) at the visit. Additionally, anti-cyclic citrullinated peptide antibodies and rheumatoid factors were tested and came out to be positive. The result of serum cryptococcal antigen test was also strongly positive. A chest computed tomography (CT) scan showed infiltration of the left lower lobe (*Figure 1B*).

Bronchoscopy was performed, and *Cryptococcus neoformans* was found in the bronchoalveolar lavage fluid using metagenomic next-generation sequencing and India ink dyeing glass slice. The patient underwent lumbar puncture, and the cryptococcal antigen test, India ink staining, T-SPOT.TB, and smear cultures of the cerebrospinal fluid were negative.

Simultaneously, no other pathogen was detected. Therefore, the patient was diagnosed with cryptococcal pneumonia. Tofacitinib was discontinued and fluconazole was started at 400 mg once per day. The patient's respiratory symptoms improved, and there was no fever after 2 weeks. Chest CT showed significant improvement (*Figure 1C*). However, significant joint swelling and tenderness were observed (DAS 28-CRP was 4.59). After 1 month of fluconazole use, a dose of 400 mg per month of intravenous tocilizumab (80 mg/kg/month, the weight of the patient was around 46 kg) was prescribed. Around 2 weeks later, the joint symptoms were relieved, and the ESR and CRP level were significantly reduced; the DAS 28-CRP was 3.14.

After one year of tocilizumab treatment, a repeat pulmonary CT scan demonstrated nearly normal pulmonary imaging (*Figure 1D*). The serum cryptococcal antigen test remained positive, and the ESR and CRP level were normal. Therefore, fluconazole was discontinued, 400 mg per month of intravenous tocilizumab was continued. The disease remained stable throughout the 3-year follow-up.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this article and the accompanying image. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The present case describes a patient with RA who

developed pulmonary cryptococcosis because of DMARDs treatment, and received tocilizumab therapy. Cryptococcosis is an important, opportunistic, life-threatening fungal infection that is mainly caused by *C. neoformans* and *C. gattii* (10). In RA patients, pulmonary cryptococcosis can also develop as a complication of immunosuppressive therapy (11).

Glucocorticoids have broad immune-suppressing and anti-inflammatory effects that alter the distribution and impair the function of lymphocytes, monocytes, and neutrophils, increasing susceptibility to cryptococcal infection (12,13). Yang *et al.* (14) reported that among 28 pulmonary cryptococcosis patients with RA with a mean age of 70 years, 90% of patients were exposed to steroids and 49% to bioagents, and all patients had elevated white blood cell count or CRP.

In the present case, the patient received prednisone 10 mg/day + MTX for 1 month, and then prednisone 5 mg + tofacitinib for 1 month, and then tofacitinib monotherapy for nearly 4 months. However, cryptococcal pneumonia occurred after presumably 5 months of tofacitinib used (only 3.5 months tofacitinib monotherapy). As a JAK inhibitor, tofacitinib selectively inhibits JAK1, JAK3, and the JAK-STAT signaling pathway. Nonetheless, there is a safety issue regarding the risk of serious and opportunistic infections in patients using JAK inhibitors (15). Clinical instances of cryptococcal infection have been documented following the application of JAK inhibitors (16-18). Furthermore, JAK-STAT activated in human monocytes could be the active pathway in response to *Cryptococcus neoformans* infection (19). Our case indicated that patients with autoimmune diseases undergoing JAK inhibitor therapy should exercise caution due to the risk of cryptococcal infection (17,20).

It is very difficult to manage RA patients with severe infections. Abatacept has been documented as a treatment option for disseminated cryptococcosis-complicated RA (21). Another retrospective study reported a 0.22% prevalence of cryptococcal infection in RA patients (22) and found that exposure to tumor necrosis factor inhibitors significantly correlated with an increased risk of cryptococcosis (23). A meta-analysis of randomized controlled trials (RCTs) found no evidence of an increased risk of infection related to tocilizumab use (24). Data from Japan have confirmed the safety and effectiveness of tocilizumab in patients with RA in a real-world clinical setting and identified factors that contributed to the successful use of tocilizumab for RA (25). Evidence regarding the association of the usage of biologic agents, etanercept, tocilizumab, adalimumab, tofacitinib, and traditional DMARDs with the incidence and risk factors of cryptococcal infection is limited. In this case, tocilizumab, an interleukin (IL)-6 inhibitor, was chosen as a long-term therapy.

In conclusion, cryptococcosis is an important opportunistic infection associated with the use of low-dose glucocorticoids or JAK inhibitors in the treatment of RA. We are the first to report about tocilizumab therapy for RA complicated by pulmonary cryptococcosis. Tocilizumab therapy may be a choice for RA patients who are concomitantly complicated with cryptococcosis and receiving intensive antifungal therapy.

Acknowledgments

The authors thank the patient for her commitment to this research. The first author Meiju Zhou wants to thank Qizuan Chen in particular for the patience, care, and encouragement during the research.

Footnote

Funding: The study was financially supported by Zhejiang Hospital.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1825/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this article and the accompanying image. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Zhou M, Lu C, Yuan F. A Cross-Sectional Survey of Physicians' Knowledge and Awareness of Chronic Pain Associated with Rheumatoid Arthritis in Rheumatology Departments in Zhejiang Province, China. Int J Gen Med 2023;16:5281-8.
2. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
3. Kerschbaumer A, Sepriano A, Bergstra SA, Smolen JS, van der Heijde D, Caporali R, Edwards CJ, Verschueren P, de Souza S, Pope JE, Takeuchi T, Hyrich KL, Winthrop KL, Aletaha D, Stamm TA, Schoones JW, Landewé RBM. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2023;82:95-106.
4. Wisłowska M. Comparison of treatment of severe rheumatoid arthritis patients with biological agents and JAK-STAT inhibitors. An extension study. Reumatologia 2024;62:322-9.
5. Parampalli Yajnanarayana S, Stübig T, Cornez I, Alchalby H, Schönberg K, Rudolph J, Triviai I, Wolschke C, Heine A, Brossart P, Kröger N, Wolf D. JAK1/2 inhibition impairs T cell function in vitro and in patients with myeloproliferative neoplasms. Br J Haematol 2015;169:824-33.
6. Chen JC, Yuan CT, Lin CC. Cutaneous cryptococcosis in a patient with myelofibrosis receiving JAK-inhibitor. EJHaem 2022;3:252-3.
7. Shan X, Li Z, Dong L. A case of pneumonia caused by infection with Tropheryma whipplei complicated by cryptococcus during treatment with a Janus kinase inhibitor: a case report. BMC Pulm Med 2024;24:625.
8. Ogai A, Yagi K, Ito F, Domoto H, Shiomi T, Chin K. Fatal Disseminated Tuberculosis and Concurrent Disseminated Cryptococcosis in a Ruxolitinib-treated Patient with Primary Myelofibrosis: A Case Report and Literature Review. Intern Med 2022;61:1271-8.
9. Motokura Y, Ito A, Yokoe S, Iri O, Nishimura K, Kamiyama S, Ishida T. Pulmonary Cryptococcosis Diagnosed by a Transbronchial Lung Cryobiopsy in a Patient with Rheumatoid Arthritis. Intern Med 2023;62:583-7.
10. Yamamura D, Xu J. Update on Pulmonary Cryptococcosis. Mycopathologia 2021;186:717-28.
11. Yanagawa N, Sakai F, Takemura T, Ishikawa S, Takaki Y, Hishima T, Kamata N. Pulmonary cryptococcosis in rheumatoid arthritis (RA) patients: comparison of imaging characteristics among RA, acquired immunodeficiency syndrome, and immunocompetent patients. Eur J Radiol 2013;82:2035-42.
12. Ibrahim A, Ahmed M, Conway R, Carey JJ. Risk of Infection with Methotrexate Therapy in Inflammatory Diseases: A Systematic Review and Meta-Analysis. J Clin Med 2018;8:15.
13. Kim H, Cho SK, Lee J, Bae SC, Sung YK. Increased risk of opportunistic infection in early rheumatoid arthritis. Int J Rheum Dis 2019;22:1239-46.
14. Yang G, Chen J, Ye J, Yao Y, Pan Z. Possible environmental exposure-associated pulmonary cryptococcosis in a patient with rheumatoid arthritis: a case report and literature review. J Int Med Res 2020;48:300060520962302.
15. Clarke B, Yates M, Adas M, Bechman K, Galloway J. The safety of JAK-1 inhibitors. Rheumatology (Oxford) 2021;60:ii24-30.
16. Seminario-Vidal L, Cantrell W, Elewski BE. Pulmonary Cryptococcosis in the Setting of Tofacitinib Therapy for Psoriasis. J Drugs Dermatol 2015;14:901-2.
17. Li Z, Shan Y, Dong J, Mei H, Kong Q, Li Y. Disseminated cryptococcosis presenting with generalized cutaneous involvement in a rheumatoid arthritis patient receiving tofacitinib: A case report. J Dermatol 2024;51:e39-41.
18. Li J, Yu Y, Xie J, Jiang Y, Lu L. Cryptococcal pneumonia in a patient with rheumatoid arthritis treated with baricitinib. Rheumatology (Oxford) 2021;61:e6-7.
19. Chen S, Yan H, Zhang L, Kong W, Sun Y, Zhang W, Chen Y, Deng A. Cryptococcus Neoformans Infection and Immune Cell Regulation in Human Monocytes. Cell Physiol Biochem 2015;37:537-47.
20. Sánchez EG, Acosta D, Álvarez J, Sánchez G, García-Casallas J. Disseminated cryptococcosis by biological therapy: We must manage the risk. Biomedica 2022;42:218-23.
21. Higashiguchi M, Yamazaki F, Nishioka K, Kimura H, Matsumoto T. Abatacept for rheumatoid arthritis complicated by disseminated cryptococcosis: a case report. Mod Rheumatol Case Rep 2021;5:229-35.
22. Liao TL, Chen YM, Chen DY. Risk factors for cryptococcal infection among patients with rheumatoid

arthritis receiving different immunosuppressive medications. Clin Microbiol Infect 2016;22:815.e1-3.
23. Kozic H, Riggs K, Ringpfeil F, Lee JB. Disseminated Cryptococcus neoformans after treatment with infliximab for rheumatoid arthritis. J Am Acad Dermatol 2008;58:S95-6.
24. Lee YH, Bae SC. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. Int J Rheum Dis 2016;19:1103-11.
25. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Takei S, Tanaka Y, Sano Y, Yaguramaki H, Yamanaka H. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol 2014;41:15-23.

Cite this article as: Zhou M, Guan H, Huang Y, Yuan F. Cryptococcosis in a patient with rheumatoid arthritis following glucocorticoid and JAK inhibitor therapy: a case description on stabilization with tocilizumab. Quant Imaging Med Surg 2025;15(4):3738-3742. doi: 10.21037/qims-24-1825