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CASE REPORT

Rare Case Report of Primary Active Pulmonary Tuberculosis During Ixekizumab Treatment for Plaque Psoriasis

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Abstract: Biologic agents have become a mainstay in the treatment of psoriasis, particularly in moderate to severe, refractory, and special types of the disease. Among these, ixekizumab is a humanized IgG4 monoclonal antibody targeting interleukin-17A, approved for the treatment of moderate to severe plaque psoriasis. Its adverse effects include infections such as nasopharyngitis, upper respiratory tract infections, and injection site reactions. While the incidence of tuberculosis (TB) associated with IL-17A antagonists is extremely low, this paper reports a case of active pulmonary tuberculosis occurring after ten doses of ixekizumab treatment for chronic plaque psoriasis. This highlights the importance for clinicians to remain vigilant regarding tuberculosis infection in patients undergoing therapy with this class of medications, emphasizing the need for enhanced screening and monitoring for tuberculosis during treatment.

Keywords: interleukin-17A antagonists, ixekizumab, psoriasis, primary active pulmonary tuberculosis

Introduction

Plaque psoriasis, a common form of psoriasis, is a chronic inflammatory skin condition characterized by localized or widespread erythematous plaques or patches with scaling, affecting the entire body, scalp, extensor surfaces of limbs, and palms and soles. Ixekizumab is a humanized IgG4 monoclonal antibody targeting interleukin-17A, approved for the treatment of moderate to severe plaque psoriasis.[1] In a study conducted by Blauvelt et al, evaluating the efficacy of ixekizumab over 5 years, approximately half of the patients achieved complete clearance of psoriasis, with a favorable safety profile of the medication.

Interleukin (IL)-17A is a cytokine originally reported to induce neutrophil-mediated inflammatory and antimicrobial activity. It has been shown that IL-17A-producing TCR γδ T cells are involved in the immune response during the early stages of infection with Listeria monocytogenes and Mycobacterium bovis in mice, but IL-17A-deficient mice exhibit reduced survival and increased bacterial loads in the lungs after infection.[2,3] During mycobacterial infection, autophagy, a process regulated by cytokines, is essential for successfully generating a host response. Autophagy works synergistically with the human immune response against Mycobacterium tuberculosis, and one study found that IL17A expression in lymphocytes from tuberculosis patients correlated with disease severity. In monocytes from patients with severe tuberculosis, IL17A fails to enhance autophagy due to defects in the MAPK1/3 signaling pathway.[4]

IL-17 inhibitors have gained attention in recent years as emerging therapies for treating various autoimmune diseases (eg, psoriasis, ankylosing spondylitis).[5] Compared with other IL-17 inhibitors, Ixekizumab has a unique dual mechanism of action, inhibiting not only IL-17A but also IL-17F heterodimers.IL-17A and IL-17F are cytokines secreted by Th17 cells, and although they are structurally similar and have overlapping functions, their roles in inflammatory responses are subtly different.IL-17A is mainly involved in acute inflammatory responses, whereas IL-17F is more associated with chronic inflammation and tissue damage.[6] IL-17 is a cytokine produced by Th17 cells and is involved in inflammatory

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responses and immune regulation. IL-17 helps maintain intestinal barrier function and antimicrobial defense. However, IL-17 inhibitors disrupt this protective mechanism in the gut by blocking IL-17 signaling, leading to increased intestinal mucosa susceptibility and triggering inflammatory bowel disease (IBD) flare-ups.[7]

Research data suggest that the most common adverse reactions in psoriatic arthritis patients treated with ixekizumab include infections (such as nasopharyngitis and upper respiratory tract infections) and injection site reactions.[8] However, adverse reactions leading to primary active pulmonary tuberculosis as a result of Ixekizumab usage have yet to be documented. This article reports a case of active pulmonary tuberculosis occurring after the tenth dose of ixekizumab treatment for plaque psoriasis, highlighting the necessity for clinicians to closely monitor tuberculosis infection in patients undergoing such therapy and to strengthen tuberculosis screening and monitoring during treatment, thereby facilitating early detection and management of potential tuberculosis reactivation and mitigating the risk of tuberculosis during treatment.

Case Presentation

The patient, a Male, 59 years old, presented with recurrent episodes of plaque psoriasis and irregular treatment with ixekizumab injection (80mg). He developed a cough with scanty sputum and night sweats over the past two weeks. The chest CT scan revealed multifocal infective lesions in both lungs with cavitation, suggestive of secondary pulmonary tuberculosis. He was advised to seek treatment at an infectious disease hospital. The patient reported stable mental status and sleep pattern since onset, with a weight loss of 10 pounds over the past 3 months. He had an 8-year history of psoriasis and had received ixekizumab injections irregularly for the past 2 years, totaling 10 doses, with no other history of infectious diseases. Laboratory findings showed elevated C-reactive protein (61 mg/L) and positive interferon-gamma release assay for tuberculosis infection. The CT scan of the chest revealed a symmetrical thoracic cage, centrally located trachea, increased bronchovascular markings bilaterally, and patchy opacities with cavitation in the left upper lobe apicoposterior segment, lingular segment, basal segments of the lower lobe, and segments of the right upper lobe and middle lobe. There were also slightly enlarged mediastinal lymph nodes, calcifications in the walls of the aorta and coronary arteries, and bilateral pleural thickening, but no evidence of pleural effusion or soft tissue abnormalities in the chest wall (Figure 1). Dermatological examination reveals scattered dark red patches ranging from walnut to palm size on the lumbar and dorsal regions, with minimal white scales present on the surface (Figure 2). The treatment plan included ixekizumab injection (80mg) every two months, along with oral isoniazid, rifampicin, ethambutol, and pyrazinamide, nutritional supplementation, and regular monitoring and examinations at the infectious disease hospital. The patient was advised to take preventive measures such as covering the mouth and nose with tissue when coughing and avoiding close contact with others to reduce the spread of tuberculosis.

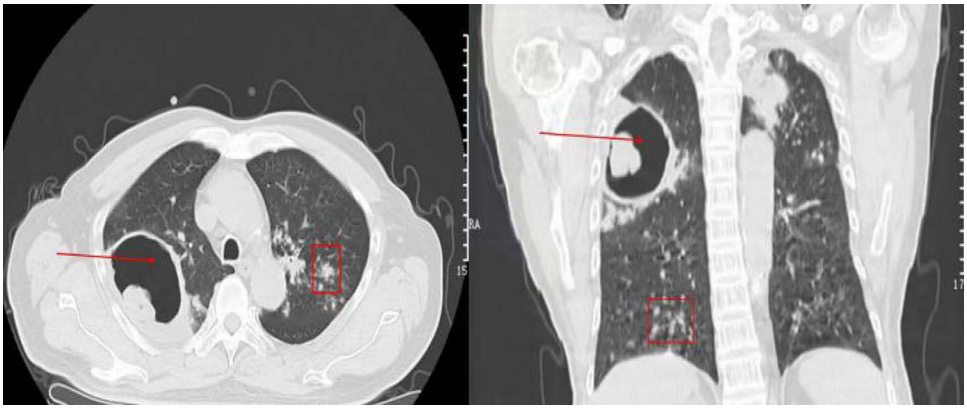

Figure 1 The chest CT scan revealed a symmetrical thorax with a centrally positioned trachea and increased bronchovascular bundles in both lungs. Speckled streaks and flaky densities were observed in multiple areas, including the apical posterior, lingual, dorsal lower lobe, and posterior basal segments of the left lung, as well as the apical, anterior, posterior, middle, dorsal, anterior, and medial basal segments of the right upper lobe of the right lung. These findings were accompanied by slightly blurred edges. Cavitation was noted in the apical posterior segment of the left lung and in the right lung, with larger cavitations particularly prominent in the right upper lung. (Red arrows indicate cavitation, while boxes highlight exudation.).

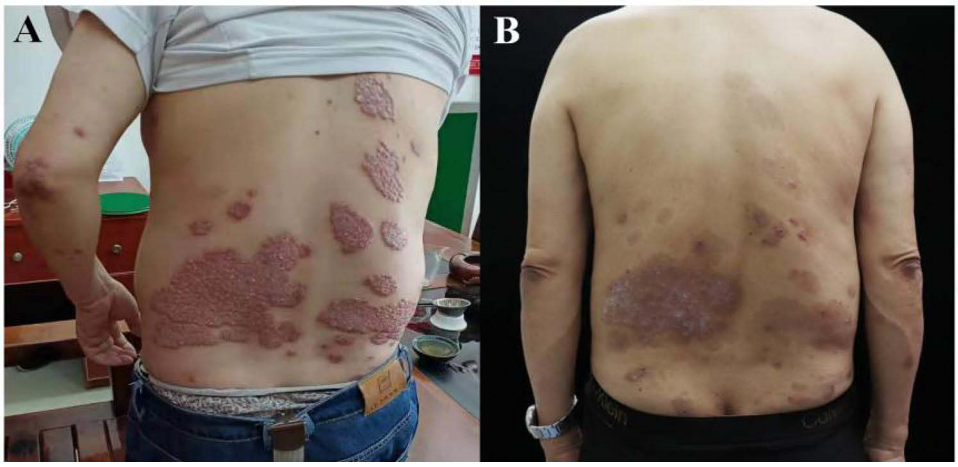

Figure 2 (**A**) Before beginning treatment with ixekizumab, the patient exhibited several nuclear palm-sized dark red spots on the lumbar back. These spots were partially fused into patches and covered with white scales. (**B**) After treatment with ixekizumab, scattered walnut to palm-sized dark erythematous plaques were observed on the lower back. These plaques displayed a few white scales on their surface.

Discussion

Psoriasis has an uncertain etiology, but it is currently understood to be driven by a network of immune-inflammatory cells, cytokines, and their interactions.[9] Interleukin (IL)-17, particularly IL-17A, plays a crucial role in the inflammatory response of psoriasis and has become a significant target for its treatment.[10] Clinically, psoriasis manifests in four main types: plaque, pustular, erythrodermic, and psoriatic arthritis.[1] Plaque psoriasis is the most common type and tends to recur. Traditional medications and topical treatments often fail to fully meet patients' needs, leading to a growing reliance on biologic agents, which offer greater efficacy and longer periods of remission. Currently, in China, two IL-17 inhibitors, secukinumab and ixekizumab, have been formally approved for the treatment of moderate to severe plaque psoriasis.[11]

Ixekizumab is a recombinant, high-affinity, humanized monoclonal IgG4 antibody that alleviates inflammation by selectively binding to the key factor IL-17A in the inflammatory pathway.[12] In Phase I and II trials, ixekizumab demonstrated significant efficacy in the treatment of psoriasis compared to placebo. Phase I studies showed that ixekizumab (150mg, every two weeks) achieved maximum disease control at 6 weeks. In Phase II studies, the dose was reduced to 75mg as additional benefits were minimal at higher doses. Safety data from phase I and II trials were notable, with no reports of serious adverse events in either the high-dose or low-dose treatment groups. The incidence of infections or other adverse reactions showed no dose-response relationship. Two cases of asymptomatic neutropenia were reported in the 75mg and 150mg treatment groups, which were also observed in later trials.[13] Adverse events reported with ixekizumab in studies include infections, as biologic therapy for psoriasis may increase the risk of infections such as bacterial, fungal, and viral infections. Allergic reactions, including rash, urticaria, and difficulty breathing. Injection site reactions such as pain, redness, and induration. Hematologic adverse reactions such as leukopenia and anemia. Immune system reactions such as exacerbation of allergic reactions and autoimmune diseases. Other adverse reactions include headache, fatigue, nausea, and abnormal liver function.[14–16]

IL-17A serves as a crucial immunomodulator, playing a significant role in the body's immune responses. One of its primary functions is to activate inflammatory responses and facilitate the migration and aggregation of immune cells, particularly neutrophils, to sites of inflammation to combat infections and injuries.[17] Mycobacterium tuberculosis is one of the pathogenic bacteria that causes tuberculosis, and the immune response against this bacterium involves the participation of various immune cells and factors. Among these, the activation and migration of neutrophils play a role in clearing Mycobacterium tuberculosis. These cells function to engulf and kill bacteria, preventing the spread of infection and playing a crucial role in the early stages of the immune response.[18] IL-17A antagonists reduce inflammatory responses and the migration and aggregation of immune cells, including neutrophils, by inhibiting the action of IL-17A.[19] While this mechanism is highly effective in treating autoimmune diseases, it may also lead to a diminished immune response against

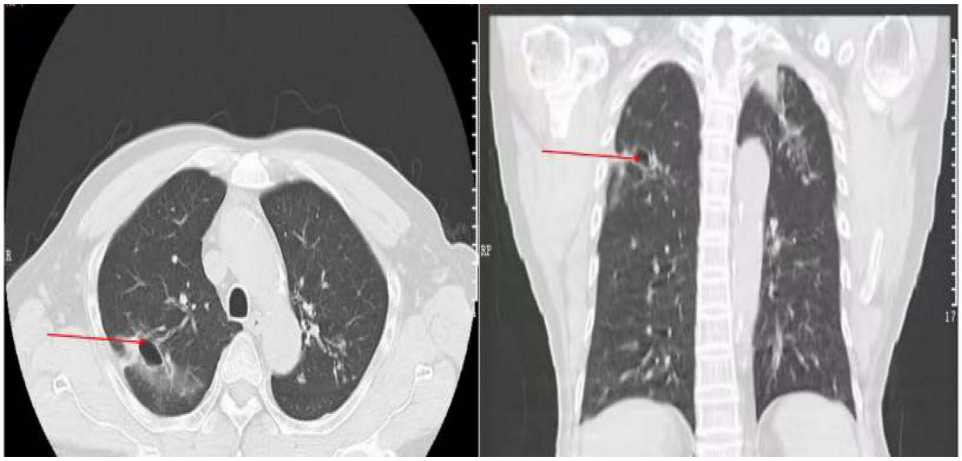

Figure 3 The chest CT scan depicted substantial improvement following the administration of treatment, showing largely resolved mottled streaks and flaky dense material in various regions. Specifically, these improvements were noted in the apical posterior, lingual, dorsal lower lobe, and posterior basal segments of the left lung, as well as in the apical, anterior, posterior, middle, dorsal, anterior, and medial basal segments of the right lung. Furthermore, shrinking cavities were observed in the apical posterior, lingual, dorsal lower lobe, and posterior basal segments of the left lung. Red arrows were used to denote cavities.

pathogens such as Mycobacterium tuberculosis. This is because these drugs inhibit signaling pathways that guide immune cells to sites of infection, thereby weakening the body's antibacterial immune response to some extent. However, the immune systems of most patients receiving IL-17A antagonists still retain some level of antibacterial capability.[20] This is likely due to the presence of other immune pathways and cell types in the immune system that participate in the immune response against pathogens such as Mycobacterium tuberculosis. Therefore, while IL-17A antagonists may increase the risk of tuberculosis infection in some individuals, for most patients, their immune systems are still capable of effectively responding to these pathogens, thereby reducing the risk of tuberculosis.

A retrospective observational multinational study conducted across 14 dermatology centers in Portugal, Spain, Italy, Greece, and Brazil observed patients with moderate to severe chronic plaque psoriasis and newly diagnosed LTBI who received IL-17 inhibitors treatment from January 2015 to March 2022. According to local guidelines, LTBI was diagnosed when the tuberculin skin test and/or interferon-gamma release assay were positive before starting IL-23 or IL-17 inhibitors. The results indicated that the risk of tuberculosis reactivation in patients with psoriasis and LTBI did not appear to increase with IL-17 or IL-23 inhibition.[21] The subsequent observation results in this case are similar. The patient received treatment for active pulmonary tuberculosis with isoniazid, rifampicin, pyrazinamide, and ethambutol at an infectious disease hospital. Simultaneously, the patient also received regular Ixekizumab injections to stabilize the psoriasis condition. After six months of treatment, there was an improvement in the pulmonary tuberculosis manifestation (Figure 3).

Conclusions

In summary, the efficacy of ixekizumab in treating psoriasis has been validated in clinical trials, particularly demonstrating significant advantages for patients with moderate to severe conditions. However, these drugs may weaken the body's immune response to pathogens such as Mycobacterium tuberculosis, increasing the risk of infection. Compared to TNF inhibitors, ixekizumab appears to pose a milder risk of infection, but the case of active pulmonary tuberculosis following ixekizumab treatment for psoriasis underscores the importance for clinicians to closely monitor the risk of tuberculosis infection when using ixekizumab for psoriasis treatment. Necessary screening and monitoring measures should be implemented to ensure patient safety and treatment efficacy.

Patient Consent Statement

The authors certify that they have obtained all appropriate patient consent forms for use of patient photographs and data obtained.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Ethics Statement

The publications of images were included in the patient's consent for publication of the case. The Hospital Ethics Committees of the Fifth People's Hospital of Hainan Province approved to publish the case details.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Yiu ZZN, Becher G, Kirby B, et al.; BADBIR Study Group. Drug survival associated with effectiveness and safety of treatment with guselkumab, ixekizumab, secukinumab, ustekinumab, and adalimumab in patients with psoriasis. *JAMA Dermatol*. 2022;158(10):1131–1141. doi:10.1001/jamadermatol.2022.2909
2. Umemura M, Okamoto-Yoshida Y, Yahagi A, et al. Involvement of IL-17A-producing TCR γδ T cells in late protective immunity against pulmonary *Mycobacterium tuberculosis* infection. *Immun Inflamm Dis*. 2016;4(4):401–412. doi:10.1002/iid3.121
3. Stewart EL, Counoupas C, Quan DH, et al. Lung IL-17A-Producing CD4+ T cells correlate with protection after intrapulmonary vaccination with differentially adjuvanted tuberculosis vaccines. *Vaccines*. 2024;12(2):128. doi:10.3390/vaccines12020128
4. Tateosian NL, Pellegrini JM, Amiano NO, et al. IL17A augments autophagy in Mycobacterium tuberculosis-infected monocytes from patients with active tuberculosis in association with the severity of the disease. *Autophagy*. 2017;13(7):1191–1204. doi:10.1080/15548627.2017.1320636
5. Berry SPD, Dossou C, Kashif A, et al. The role of IL-17 and anti-IL-17 agents in the immunopathogenesis and management of autoimmune and inflammatory diseases. *Int Immunopharmacol*. 2022;102:108402. doi:10.1016/j.intimp.2021.108402
6. de Morales JMGR, Puig L, Daudén E, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: an updated review of the evidence focusing in controversies. *Autoimmun Rev*. 2020;19(1):102429. doi:10.1016/j.autrev.2019.102429
7. Orzan OA, Țieranu CG, Olteanu AO, et al. An insight on the possible association between inflammatory bowel disease and biologic therapy with IL-17 inhibitors in psoriasis patients. *Pharmaceutics*. 2023;15(8):2171. doi:10.3390/pharmaceutics15082171
8. Gordon KB, Blauvelt A, Papp KA, et al.; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345–356. doi:10.1056/NEJMoa1512711
9. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet*. 2021;397(10275):754–766. doi:10.1016/S0140-6736(21)00184-7
10. Singh R, Koppu S, Perche PO, Feldman SR. The cytokine mediated molecular pathophysiology of psoriasis and its clinical implications. *Int J Mol Sci*. 2021;22(23):12793. doi:10.3390/ijms222312793
11. Fitzgerald T, Zhdanava M, Pilon D, et al. Long-term psoriasis control with guselkumab, adalimumab, secukinumab, or ixekizumab in the USA. *Dermatol Ther*. 2023;13(4):1053–1068. doi:10.1007/s13555-023-00910-6
12. Farahnik B, Beroukhim K, Zhu TH, et al. Ixekizumab for the treatment of psoriasis: a review of phase III trials. *Dermatol Ther*. 2016;6(1):25–37. doi:10.1007/s13555-016-0102-0
13. Miller J, Puravath AP, Orbai AM. Ixekizumab for psoriatic arthritis: safety, efficacy, and patient selection. *J Inflamm Res*. 2021;14:6975–6991. doi:10.2147/JIR.S229752

14. Deodhar A, Poddubnyy D, Rahman P, et al. Long-term safety and efficacy of ixekizumab in patients with axial spondyloarthritis: 3-year data from the COAST program. *J Rheumatol*. 2023;50(8):1020–1028. doi:10.3899/jrheum.221022
15. Ying L, Suyun J, Yanhua L, et al. Safety and efficacy of ixekizumab in Chinese adults with moderate-to-severe plaque psoriasis: a prospective, multicenter, observational study. *Adv Ther*. 2023;40(12):5464–5474. doi:10.1007/s12325-023-02672-1
16. Mills KHG. IL-17 and IL-17-producing cells in protection versus pathology. *Nat Rev Immunol*. 2023;23(1):38–54. doi:10.1038/s41577-022-00746-9
17. Glatt S, Baeten D, Baker T, et al. Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. *Ann Rheum Dis*. 2018;77(4):523–532. doi:10.1136/annrheumdis-2017-212127
18. Chen K, Kolls JK. Interluekin-17A (IL17A). *Gene*. 2017;614:8–14. doi:10.1016/j.gene.2017.01.016
19. McGonagle DG, McInnes IB, Kirkham BW, Sherlock J, Moots R. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies. *Ann Rheum Dis*. 2019;78(9):1167–1178. doi:10.1136/annrheumdis-2019-215356
20. Kim HW, Kim EH, Lee M, Jung I, Ahn SS. Risk of cancer, tuberculosis and serious infections in patients with ankylosing spondylitis, psoriatic arthritis and psoriasis treated with IL-17 and TNF-α inhibitors: a nationwide nested case-control analysis. *Clin Exp Rheumatol*. 2023;41(7):1491–1499. doi:10.55563/clinexprheumatol/qkiorp
21. Nogueira M, Warren RB, Torres T. Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis - time for a paradigm change. *J Eur Acad Dermatol Venereol*. 2021;35(4):824–834. doi:10.1111/jdv.16866