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EDITORIAL

Early screening to identify and diagnose primary nasal tuberculosis in patients with tumor necrosis factor inhibitors

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Abstract

In this editorial, we comment on the article by Liu *et al*. Based on our analysis of a case report, we consider that early screening and recognition of primary nasal tuberculosis are crucial for patients undergoing treatment with tumor necrosis factor inhibitor (TNFi). While TNFi therapy increases the risk of reactivating latent tuberculosis, primary nasal tuberculosis remains rare due to the protective mechanisms of the nasal mucosa. Risk factors for primary nasal tuberculosis include minimally invasive nasal surgery, diabetes, and human immunodefi-

ciency virus. Patients with early symptoms such as nasal congestion, rhinorrhea, altered olfaction, epistaxis, or ulceration, and unresponsive to conventional antibiotics and antihistamines should undergo early rhinoscopy, possibly followed by repeated tissue biopsies and acid-fast bacilli culture when necessary. When diagnosis is challenging, it is essential to consider local tuberculosis epidemiology and the efficacy of diagnostic anti-tuberculosis treatment. The preferred method for tuberculosis screening is the Interferon Gamma Release Assay, with a general recommendation for screening at 3 and 6 months after initial treatment and then every six months. However, the optimal frequency is not yet consensus-driven and may be increased in economically viable settings.

Key Words: Tumor necrosis factor inhibitor; Interferon-gamma release assay; Primary nasal tuberculosis; Rhinoscopy; Diabetes mellitus

Core Tip: Patients receiving tumor necrosis factor inhibitor therapy rarely develop primary nasal tuberculosis, with diabetes, human immunodeficiency virus, and minimally invasive nasal surgery being risk factors. Early nasal endoscopy and an appropriately increased frequency of interferon gamma release assay testing may aid in the early screening and identification of nasal tuberculosis.

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INTRODUCTION

Tumor necrosis factor inhibitors (TNFi) have promising efficacy in refractory inflammatory bowel disease, rheumatoid arthritis, psoriasis, and ankylosing spondylitis, but inevitably have some adverse effects. Before starting TNFi therapy, infectious diseases, such as coronavirus disease 2019 (COVID-19), human immunodeficiency virus (HIV), hepatitis, and tuberculosis, are generally screened. Patients with psoriasis or inflammatory bowel disease undergoing TNFi treatment are not at an increased risk of developing severe COVID-19[1], and overall, COVID-19 vaccination is considered safe[2]. Notably, tumour necrosis factor alpha is an important cytokine for macrophage activation and is essential for host control of *Mycobacterium tuberculosis* (Mtb). However, TNFi can cause latent tuberculosis (TB) reactivation with an approximate 2–8-fold risk[3], and the incidence of TB is 3–4-fold higher with adalimumab and infliximab than with etanercept[4]. Most cases are extrapulmonary tuberculosis; primary nasal TB is rare. This condition is related to the protective mechanisms of the nasal mucosa, including ciliary clearance, bactericidal activity of nasal secretions, mechanical filtration by nasal hairs, and intrinsic resistance to mycobacterial infections[5], leading to a delayed diagnosis or misdiagnosis. For patients with latent tuberculosis infection (LTBI) who require TNFi, prophylactic anti-TB treatment is administered first.

IDENTIFICATION AND DIAGNOSIS OF PRIMARY NASAL TB

Liu *et al*[6] reported the case of a 58-year-old man who presented with right-sided nasal congestion and bloody discharge for one month, with a medical history of psoriasis, three years of adalimumab therapy, and right-sided functional endoscopic sinus surgery. The patient was diagnosed with primary nasal TB due to seroconversion in the 3rd year of adalimumab treatment; thickening, inflammation, and crusting changes in the nasal mucosa seen on nasal endoscopy; chronic granulomatous changes seen on repeat biopsy of the lesion; and antacid bacilli detected by Ziehl-Neelsen staining. The lesion improved after anti-TB treatment was administered. This case reminds clinicians to be vigilant for the development of nasal TB when early nonspecific nasopharyngeal symptoms develop in patients using TNFi, and that regular screening can avoid delayed diagnosis. The current frequency of LTBI screening in patients with psoriasis treated with TNFi should be based on medical history, risk of exposure, tuberculin skin testing (TST), and interferon gamma release assay (IGRA) results[7], generally once every six months[8]. However, the study did not state the frequency of T-SPOT TB tests, which could potentially delay the diagnosis of TB.

Primary nasal TB is more prevalent in females[7], and it is considered rare due to the protective mechanism of the nasal mucosa. To date, only two cases of primary nasal TB in patients treated with TNFi have been reported. Patients with primary nasal TB present with symptoms such as nasal congestion, nasal discharge, altered sense of smell, epistaxis, and ulceration; primarily unilateral[9] and conventional antibiotic and antihistamine therapy is ineffective. Early refinement of endoscopy is recommended as it can reveal sessile masses, crusts, scarring, and adhesions at the nasal septum and turbinates. In later stages, ulceration, septal perforation, and involvement of the sinuses and orbits may occur. A pathological biopsy of the nasal mass is necessary to visualize granulomatous inflammation, some of which lacks caseous

Table 1 Key characteristics of primary nasal tuberculosis induced by tumor necrosis factor inhibitor

Symptoms	Risk factors	Epidemiology	Types of TNFi	Treatment	IGRA	Nasal biopsy	Tissue culture
Nasal congestion; Rhinorrhea; altered olfaction; Epistaxis; Ulcers, *etc.*	Diabetes; HIV; Minimally invasive nasal surgery	High tuberculosis prevalence areas	Adalimumab and infliximab increase TB risk 3-4 times more than etanercept	Ineffective conventional antibiotics and antihistamines; diagnostic anti-tuberculosis effective	Negative to positive	Granulomatous inflammation with or without caseous changes	Positive for Mtb

TNFi: Tumor necrosis factor inhibitor; HIV: Human immunodeficiency virus; IGRA: Interferon gamma release assay.

changes. A repeat biopsy may help detect antacid bacilli. The diagnosis of primary nasal TB requires a combination of clinical presentation, seroconversion, Ziehl-Neelsen staining, and pathological biopsy. Positive Mtb culture results are considered the gold standard for diagnosis. However, the negative rate is high (50%–75%)[10], and conducting multiple cultures repeatedly can help increase the positivity rate. Additionally, when diagnosis is difficult, considering the local epidemiology of TB and the effectiveness of diagnostic anti-TB treatments is crucial[11]. Furthermore, differentiating this disease from other conditions such as midline granulomas (*i.e.*, granulomatosis with polyangiitis, leprosy, sarcoidosis, subcutaneous phycomycosis, and granulomatous syphilis) or neoplastic disorders (natural killer T-cell lymphoma, carcinoma)[12] is critical.

Notably, TST often yields false-negative results in immunocompromised patients; therefore, IGRA is the preferred method for TB screening during TNFi treatment. In clinical practice, screenings 3 and 6 months after the initial dosing and every six months thereafter is generally recommended. However, there is still no consensus on these guidelines. The risk of TB induced by monoclonal antibodies is significantly higher than that induced by etanercept, and the frequency of monitoring should be increased when economically feasible. Minimally invasive nasal surgery and HIV are high-risk factors that can diminish local immunity in the nasal cavity. In addition, diabetes can worsen the natural progression of immune-mediated diseases treated with biological therapies, thereby increasing the risk of nasal TB. Consequently, an increase in screening frequency is required.

CONCLUSION

In summary, we believe that when patients receiving TNFi therapy exhibit nasopharyngeal symptoms, it is crucial to be vigilant for nasal TB. Early completion of rhinoscopy and an appropriately increased frequency of IGRA monitoring, in conjunction with some key characteristics (Table 1), may aid in the early detection and diagnosis of primary nasal TB. However, determining the optimal frequency of TB screening by considering the socioeconomic factors is also necessary.

FOOTNOTES

Author contributions: Shen DX, Li C, and Ying ZH conceptualized and designed the research; Shen DX and Wang YW prepared the manuscript and contributed equally to this article, ensuring a cohesive presentation of the research findings; Lin ZM and Jin D were responsible for the meticulous analysis and interpretation of the case, providing essential insights that underpinned the study's conclusions; Li C and Ying ZH, as co-corresponding authors, were at the helm of conceptualizing and designing the research ideas, setting the stage for the study with their innovative and well-defined framework; Li C conceptualized, designed, and supervised the whole process of the project. He searched the literature, revised and submitted the early version of the manuscript. Ying ZH was instrumental and responsible for revision, table plotting, comprehensive literature search, preparation, and submission of the current version of the manuscript. All authors have read and approved the final manuscript, with Shen DX and Wang YW recognized as co-first authors for their significant contributions to the manuscript preparation, and the collaborative efforts of the team were instrumental in bringing the research to fruition.

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