An unusual case of cutaneous tuberculosis and paradoxical TB in a patient with spondyloarthritis treated with adalimumab

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ABSTRACT

Cutaneous tuberculosis (TB) is an uncommon condition the diagnosis of which can be challenging. Biologic disease modifying anti-rheumatic drugs (bDMARDs) are associated with a higher risk of opportunistic infections including TB. We present a case of cutaneous TB in a 56-year-old male with psoriatic arthritis on Adalimumab. He developed skin lesions in his thumb and axilla, and *Mycobacterium tuberculosis* was isolated in cultures sent from a skin biopsy. Four months after commencement of tuberculosis treatment, he presented with a new onset of seizures. A MRI head showed two tuberculomas, with no further lesions identified in cross-sectional imaging. A tapering course of steroids was started alongside a 12-month course of anti-TB treatment for post-tuberculous treatment paradoxical reaction. In conclusion, although uncommon, cutaneous TB should be considered in patients on bDMARD treatment with atypical skin lesions.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis (Mtb)*. It remains a major public health concern, affecting millions worldwide and increasing incidence rates since 2021[1]. Although pulmonary TB is the most common presentation, TB is a great mimicker and can affect any organ leading to a wide variety of clinical manifestations. Cutaneous TB is uncommon and only accounts for 1 – 1.5% of extra-pulmonary tuberculosis[2].

Cutaneous TB can be exogenous (caused by direct inoculation into the skin) or endogenous (caused by haematogenous spread, extension into the skin from a nearby focus of infection, or self-inoculation). Skin manifestations are non-specific and variable, and can include nodules, papules, verrucous plaques and ulcers.[2,3] Clinical diagnosis can therefore be challenging, requiring a high index of suspicion. Skin biopsy for mycobacterial culture and histology is key. Histological findings can vary from classic granulomas to non-specific inflammation. Due to the characteristic slow-growth of Mtb, cultures can take several weeks to grow; polymerase chain reaction (PCR) amplification test can therefore be useful to identify its presence more rapidly.[4]

Targeted therapies such as adalimumab have revolutionised the treatment of inflammatory arthritis. Adalimumab is a monoclonal antibody that binds to and inhibits the action of TNFα. It is associated with an increased risk of serious and atypical infection, including reactivation of latent TB infection (LTBI).[5] Prior to treatment with TNFα inhibitors, patients undergo a chest-X-ray and interferon-gamma (IFN-γ) release assay (IGRA) to exclude LTBI. [6,7]

CASE PRESENTATION

A 56 year-old male was referred to rheumatology with a history of psoriasis and finger swelling. He reported cervical and thoracic pain with morning stiffness, nocturnal pain and good response to ibuprofen. Past history included psoriasis not responsive to methotrexate, currently treated with acitretin, and type 2 diabetes. His brother had psoriasis. He owned a catering business. He had never smoked and did not drink alcohol. He was born in Bangladesh and moved to the UK in 1990.

Examination revealed extensive skin psoriasis, synovitis of the right ring finger proximal interphalangeal joint, a flattened and stiff lumbar spine, and fused cervical spine. Investigations revealed normocytic anaemia with elevated CRP (78mg/L) and ESR (80mm/hr). Imaging confirmed fused sacroiliac joints and extensive syndesmophytes. Standard biologic screening tests were performed: chest x-ray was normal; IGRA (QuantiFERON) and HIV tests were negative. He was diagnosed with spondyloarthritis and started adalimumab in December 2019 with an excellent response.

In June 2022 he was referred to oral surgery with buccal mucosal ulceration of the right cheek. No lymphadenopathy was found on examination. Histological examination showed granulomatous inflammation, and a diagnosis of orofacial granulomatosis was suggested. Deeper levels highlighted a possible area of necrosis within a granuloma. No micro-organisms were seen on routine culture and **Ziehl-Neelsen stain was negative; TB PCR was not performed.** The symptoms resolved spontaneously.

In December 2022 he presented to dermatology with itching and cutaneous eruptions, including a 6 month history of skin changes in the right axilla which seemed to improve on temporarily withholding adalimumab, and recurred on restarting it. He described a nodule on the left thumb which developed slowly after knocking it on a wall one year earlier. Examination revealed eroded plaques in the right axilla, swelling of the right cheek and lower lip, ulceration of the right buccal mucosa and an eroded nodule on the left thumb (Fig 1). Histology from the thumb nodule demonstrated dermal granulomata with central necrosis. Acid fast bacilli were not seen but mycobacterial culture was positive for *Mtb*, confirmed on whole genome sequencing. CT chest demonstrated mild axillary lymphadenopathy but no lung lesions. **His skin lesions were largely resolved at his dermatology review in February 2023.** Adalimumab was stopped and he was treated from July 2023 with a two month course of rifampicin, isoniazid and pyrazinamide followed by a two month course of rifampicin and isoniazid.

In October 2023 the patient was admitted to hospital with headache, fever, vomiting and a seizure. **His skin lesions had resolved at the time of this admission**. MRI head showed an enhancing lesion in the left frontal lobe, and a second lesion in the left cerebellum, thought to be tuberculomas. There was no sign of disseminated TB on cross-sectional imaging. Cerebrospinal fluid showed no evidence of TB on culture or PCR. He was treated for a post-tuberculous treatment paradoxical reaction, with a reducing dose of

dexamethasone and continuation of anti-tuberculosis treatment for 12 months. He responded well with no further seizures.

His psoriasis and arthritis deteriorated **after stopping adalimumab**, and he started secukinumab (IL-17 inhibitor) in February 2024 with a good response.

DISCUSSION

Cutaneous tuberculosis is an uncommon condition that can present with a wide variety of skin manifestations. Delayed diagnosis is therefore common with subsequently a higher risk of disseminated disease. Cultures can take weeks to show a positive result. In this case, the skin manifestations were multiple and of slow progression with no associated systemic symptoms.

Prior to treatment with adalimumab, screening tests for LTBI were negative. The patient is originally from area of high tuberculosis incidence, increasing the likelihood of previous exposure. It is important to highlight that a negative IGRA test does not exclude active or latent TB. Some studies have described higher false negative IGRA results in extra-pulmonary TB (depending also in the anatomical site of infection)[8]. Similarly, cases of IGRA test conversion (from negative to positive) have been reported after treatment with biologic disease modifying anti-rheumatic drugs (bDMARDs); thus periodic re-screening has been suggested especially in rheumatology patients with risk factors. [7] Therefore, the patient's previous IGRA test could have been a false negative making it difficult to know whether this was a case of primary cutaneous tuberculosis or a reactivation.

The fluctuating skin lesions over time, with improvement when the anti-TNF agent was withheld, highlight the finely balanced host-pathogen interaction in TB[9]. The presentation in October 2023 was thought to be a post-tuberculous treatment paradoxical reaction rather than a microbiological relapse, **delayed TB dissemination or a possible subclinical CNS TB at the time of the initial diagnosis.** Differentiating between these conditions can be difficult. Paradoxical reactions are defined as clinical or radiological worsening of pre-existing tuberculous lesions, or the development of new lesions, in patients receiving anti-tuberculous treatment who initially improved on treatment[10]. Reactions are thought to be driven by an immune-driven inflammatory reaction to residual *M. tuberculosis* antigen in tissues, rather than representing treatment failure.

CONCLUSION

Cutaneous tuberculosis is an uncommon type of extra-pulmonary TB and its diagnosis can be challenging. Immunocompromised patients are more at risk, especially those treated with TNFα inhibitors. Unusual or slowly progressive skin or mucosal lesions in these patients should prompt consideration of cutaneous TB with a low threshold for skin biopsy and culture for Mtb.

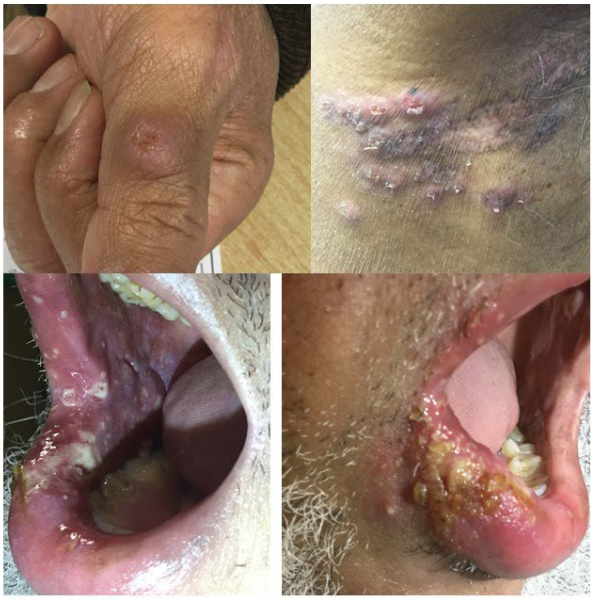

Figure 1 Lesions in thumb and axilla (top two pictures) and in oral mucosa (bottom two pictures)

REFERENCES:

1. Global tuberculosis report 2024. Geneva: *World Health Organization*; 2024. Licence: CC BY-NC-SA 3.0 IGO
2. **Van Zyl L, du Plessis J, Viljoen J.** Cutaneous tuberculosis overview and current treatment regimens. *Tuberculosis (Edinb).* 2015 Dec;95(6):629-638. doi: 10.1016/j.tube.2014.12.006.
3. **Hill MK, Sanders CV**. Cutaneous Tuberculosis. *Microbiol Spectr*. 2017 Jan;5(1). doi: 10.1128/microbiolspec.TNMI7-0010-2016.
4. **Nguyen KH, Alcantara CA, Glassman I, et al.** Cutaneous Manifestations of *Mycobacterium tuberculosis*: A Literature Review. *Pathogens*. 2023 Jul 8;12(7):920. DOI: 10.3390/pathogens12070920
5. **Dobler CC**.2016.Biologic Agents and Tuberculosis. *Microbiol Spectr.*, 2016, Dec 4(6). DOI: 10.1128/microbiolspec.TNMI7-0026-2016
6. **Handa R, Upadhyaya S, Kapoor S, et al.** Tuberculosis and biologics in rheumatology: A special situation. Int J Rheum Dis. 2017 Oct;20(10):1313-1325. DOI: 10.1111/1756-185X.13129
7. **Fragoulis GE, Nikiphorou E, Dey M, et al** 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases Annals of the Rheumatic Diseases 2023;82:742-753. DOI: 10.1136/ard-2022-223335
8. **Kim YJ, Kang JY, Kim SI, et al.** Predictors for false-negative QuantiFERON-TB Gold assay results in patients with extrapulmonary tuberculosis. BMC Infect Dis. 2018 Sep 10;18(1):457. DOI: 10.1186/s12879-018-3344-x
9. **Tezera LB, Mansour S, Elkington P**. Reconsidering the Optimal Immune Response to *Mycobacterium tuberculosis*. Am J Respir Crit Care Med. 2020 Feb 15;201(4):407-413. DOI: 10.1164/rccm.201908-1506PP

10. **Meintjes, Graeme et al.** Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. The Lancet Infectious Diseases, 2008, Volume 8, Issue 8, 516 – 523. DOI: 10.1016/S1473-3099(08)70184-1