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CASE REPORT

Lymph node tuberculosis-associated paradoxical immune reconstitution inflammatory syndrome in a non-HIV patient: Case report and review of literature

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Abstract

Tuberculosis (TB) is a global health threat, especially in HIV patients who may experience immune reconstitution inflammatory syndrome (IRIS) upon *Mycobacterium tuberculosis* infection. Diagnosing and defining IRIS in non-HIV patients remains challenging. A 63-year-old male with acute leukaemia underwent induction therapy with a regimen containing fludarabine. Febrile neutropenia led to further investigations, revealing non-cavitary pulmonary TB, prompting anti-tuberculosis therapy (ATT) alongside resumed leukaemia treatment with sorafenib. Persistent extra-pulmonary TB, specifically lymph node involvement, were observed and IRIS was suspected, evidenced by enlarged lymphadenopathies, scrofula, and skin lesions that developed during the 13-month course of ATT, with no recurrence after its cessation. This article explores a case of lymph node TB-associated paradoxical IRIS in a non-HIV leukaemia patient, revealing the intricate interplay between tuberculosis and haematological malignancies and emphasizing the lack of standardized diagnostic criteria and treatment consensus. Challenges in lymph node TB diagnosis and management highlight the need for tailored therapeutic approaches. The report explores the potential immunomodulatory effects of fludarabine and sorafenib, questioning their roles in TB-IRIS. This case illuminates TB-IRIS dynamics in non-HIV patients, urging further research and collaborative efforts to enhance understanding and outcomes. As medical complexities persist, personalized therapeutic approaches and advancements in TB-IRIS research are crucial.

KEYWORDS
fludarabine, IRIS, leukaemia, sorafenib, Tuberculosis

1 | INTRODUCTION

Tuberculosis (TB) is a globally significant transmissible disease, exerting a substantial toll on human well-being. It is a communicable illness caused by *Mycobacterium tuberculosis* and disseminated via aerosol droplets containing bacilli, primarily emitted during coughing episodes. It stands as a prominent contributor to worldwide morbidity and remains a principal agent of mortality on a global scale. In 2022, an estimated 10.6 million people contracted TB, resulting in approximately 1.3 million deaths [1].

Regions with a significant population of individuals living with HIV still face a considerable TB burden. Nonetheless, there are other causes of immunosuppression in which TB may be of detrimental importance and clinical significance. Specifically, individuals who have undergone haematopoietic stem cell transplant and those diagnosed with haematological malignancies face heightened susceptibility to contracting TB (and other nontuberculous mycobacterial infections), due to the impairment of the antituberculosis immune response, observed in the quality of the T-cell response and the interferon-gamma [IFN-γ] immune axis). The reported TB frequency in this population ranges from 0.7% to 2.7%, depending on the local incidence of TB [2].

Treatment for drug-susceptible TB in such individuals typically aligns with general therapeutic guidelines (2 months of treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of treatment with isoniazid and rifampicin. Extended treatment durations, typically ranging from 9 to 12 months, are necessary for may be particularly relevant for cases of disseminated TB or in highly immunocompromised patients. It is advised to consider reducing ongoing immunosuppressive therapy whenever possible while remaining vigilant for the risk of immune reconstitution inflammatory syndrome (IRIS) [2].

IRIS is a well-recognized phenomenon in people living with HIV. This syndrome is characterized by severe inflammatory features of TB occurring after rapid reconstitution of the immune system [3]. It is characterized by an exaggerated and dysregulated inflammatory response to *M. tuberculosis* and its antigen release after a hasty killing, paired with a shift from anti-inflammatory TH-2 to pro-inflammatory TH1 and TH17, leading to high levels of inflammatory cytokines [4]. A study group demonstrated significantly elevated concentrations of interleukin-10 (IL-10) and IL-22 in TB-associated IRIS patients compared with those in non-IRIS patients with TB [5].

TB-IRIS more commonly affects lymph nodes and lungs, presenting with marked clinical heterogeneity. In HIV-negative individuals, TB-IRIS predominantly presents with extrapulmonary TB and the median time of onset following the initiation of ATT demonstrates significant variability, although IRIS typically emerges within a 3-month timeframe [6].

According to standardized definitions by the International Network for the Study of HIV-associated IRIS, TB-IRIS manifests in two forms – paradoxical and unmasking, both occurring in the context of antiretroviral therapy (ART) initiation [7].

In paradoxical TB-IRIS, patients are diagnosed with active TB before starting ART and have shown positive responses to antituberculosis treatment (ATT). Within the first few weeks to 3 months after ART initiation, reinitiation, or alteration, IRIS is characterized by the emergence of recurring, new, or worsened TB symptoms. A connection has been established between paradoxical TB-IRIS and substantial increases in T cells specifically responsive to purified protein derivatives and heightened levels of pro-inflammatory cytokines [7]. Unmasking TB-IRIS refers to the onset or worsening of TB symptoms in HIV-infected individuals shortly after starting ART, revealing previously occult TB infections due to the improved immune response from ART.

Despite being a known complication in TB-HIV patients, there's a lack of precise definitions and diagnostic criteria for TB-IRIS in non-HIV patients.

Adapting both from the TB-IRIS diagnostic criteria in HIV patients, first developed in 2008 in low-income settings, and the suggested diagnostic criteria from Lanzafame et al. [3], Sueki et al. proposed the following definition for non-HIV IRIS [8]:

- Essential criteria (required) – i) HIV-negative; ii) the disorder is linked to recovery from an immunocompromised state; (iii) the inflammatory disorder is caused by a pre-existing antigen (including a drug) or pathogenic microorganism leading to immune recovery (unmasking), exacerbation of an existing disorder (paradoxical disorder), or both.
- Exclusion criteria: i) exacerbation of primary disease post-appropriate treatment; ii) relapse/exacerbation of primary disease due to withdrawal of effective treatment; iii) inflammatory disorder caused by a newly ingested antigen or pathogenic microorganism post-recovery from immunocompromised condition.
- Supportive findings: i) multiple inflammatory disorders may develop simultaneously or sequentially; ii) primary diseases include severe cutaneous adverse drug reactions such as drug-induced hypersensitivity syndrome; iii) autoimmune, collagen, and related diseases; malignant tumours; and pregnancy.

If a condition meets all inclusion and exclusion criteria, that condition is considered non-HIV IRIS [8].

We thereby present a case of lymph node TB-associated paradoxical IRIS in a non-HIV patient after recovering from an immune-suppressed state.

1.1 | Case report

Male patient, 63 years old. Past medical history includes obesity, chronic alcoholism, and right knee osteoarthritis.

He presented to the Emergency Department (ED) of a local hospital with a 1-month history of fatigue, dyspnoea on moderate exertion, associated cough, mild weight loss, and a single episode of haemoptysis. Physical examination revealed no significant findings. Complementary studies performed in the ED showed bicytopaenia (anaemia with haemoglobin 6.5 g/dL) and severe thrombocytopenia (42,000 platelets/μL); no leukopenia was described, but there were 22% blasts. Lactate dehydrogenase levels were measured at 393 U/L. A blood smear confirmed the presence of blast cells in the white cell series, slight anisocytosis in the red cell series, a few dacrocytes, some macrocytic erythrocytes, moderate anisochromia, and mild hypochromia. A chest computed tomography (CT) scan revealed small mediastinal lymph nodes, some partially calcified and thickening of interlobular septa in both lungs, more prominent at the lung bases, with scattered centrilobular micronodules, predominantly in the upper right lobe.

Initial suspicion included sarcoidosis and carcinomatous lymphangitis. After transfer to our hospital (a tertiary hospital), further

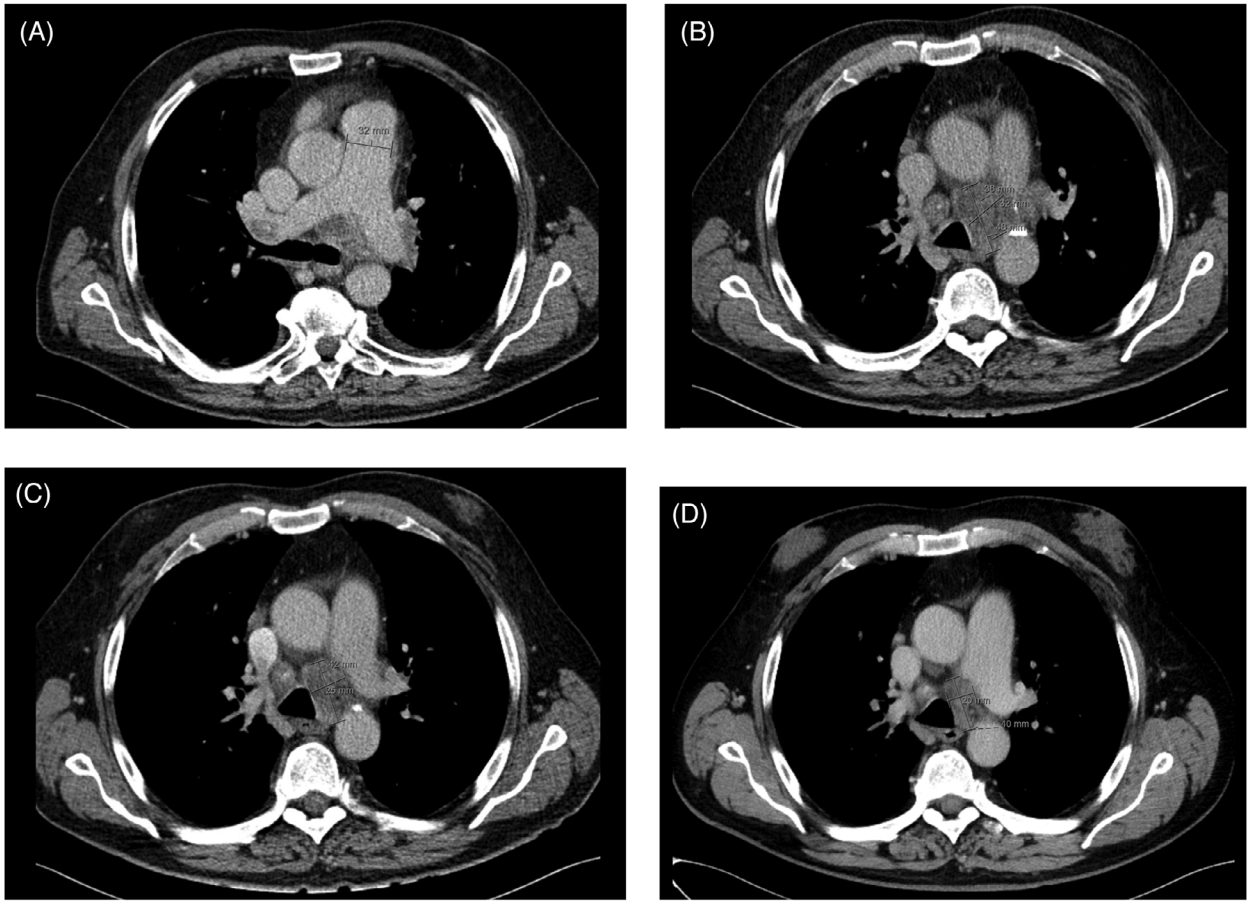

FIGURE 1 Evolution of hilar and mediastinal lymphadenopathies at (A) 2 months into anti-tuberculosis therapy (ATT); (B) 3 months into ATT; (C) 6 months into ATT; (D) 9 months into ATT.

investigations confirmed the diagnosis of acute leukaemia (AL) of mixed myeloid/B phenotype with FLT3-ITD mutation (high ratio). He commenced induction therapy with fludarabine, cytarabine and idarubicin, displaying good tolerance and clinical response evidenced by morphological and immunophenotypic remission in a follow-up bone marrow examination a month after chemotherapy initiation.

During his stay at the Haematology department, the patient experienced prolonged febrile neutropenia, undergoing several cycles of broad-spectrum antibiotic therapy without initial isolation of a microbiological agent. However, upon positive acid-fast bacilli results in respiratory samples, he was transferred to the Infectious Diseases department, suspected of having non-cavitary pulmonary TB, later confirmed by a positive *M. tuberculosis* identification in the same respiratory sample through nucleic acid amplification testing (NAAT). Despite having non-pathological features, a few hilar and mediastinal prominent ganglia were also documented. Following negative results in molecular resistance tests for first- and second-line anti-TB drugs, the patient commenced ATT with HRZE (isoniazid, rifampicin, pyrazinamide, and ethambutol) and was scheduled for outpatient follow-up. Regarding AL treatment, after a transient 3-month interruption during TB diagnosis and considering the leukaemia phenotype, treatment was resumed with sorafenib.

Three months into ATT, the patient still had a positive direct mycobacteriological examination in secretions, leading to an extension of the quadruple therapy phase to 8 months before transitioning to HR. Chest CT scans at 2 and 3 months into therapy revealed larger, necrotic-appearing bilateral hilar and mediastinal lymphadenopathies (Figure 1A,B), as well as newly developed axillary and right supraclavicular lymphadenopathies (Figure 2A,B). The patient firmly denied poor adherence to treatment. Due to suspected lymph node involvement in TB, a guided ultrasound-assisted lymph node biopsy was performed. A microbiological study of the biopsy revealed a positive NAAT for *M. tuberculosis*, while molecular resistance tests demonstrated maintained susceptibility to ongoing drugs.

At 6–7 months into treatment, the patient exhibited growing axillary and pectoral lymphadenopathies, now draining to the skin surface, indicative of scrofula (Figure 2C,D). A subsequent aspiration biopsy yielded another positive NAAT result. Necrotic lymphadenopathies emerged in the upper abdomen, particularly around the hepatic hilum and periaortic region around the ninth month of ATT (Figure 3). Additionally, at the 12th month of ATT, a new subcutaneous lesion appeared on the left thoracic wall. A repeated aspiration biopsy, now targeted at the thoracic lesion, yielded yet another positive NAAT for *M. tuberculosis*. All mycobacteriological examinations remained negative.

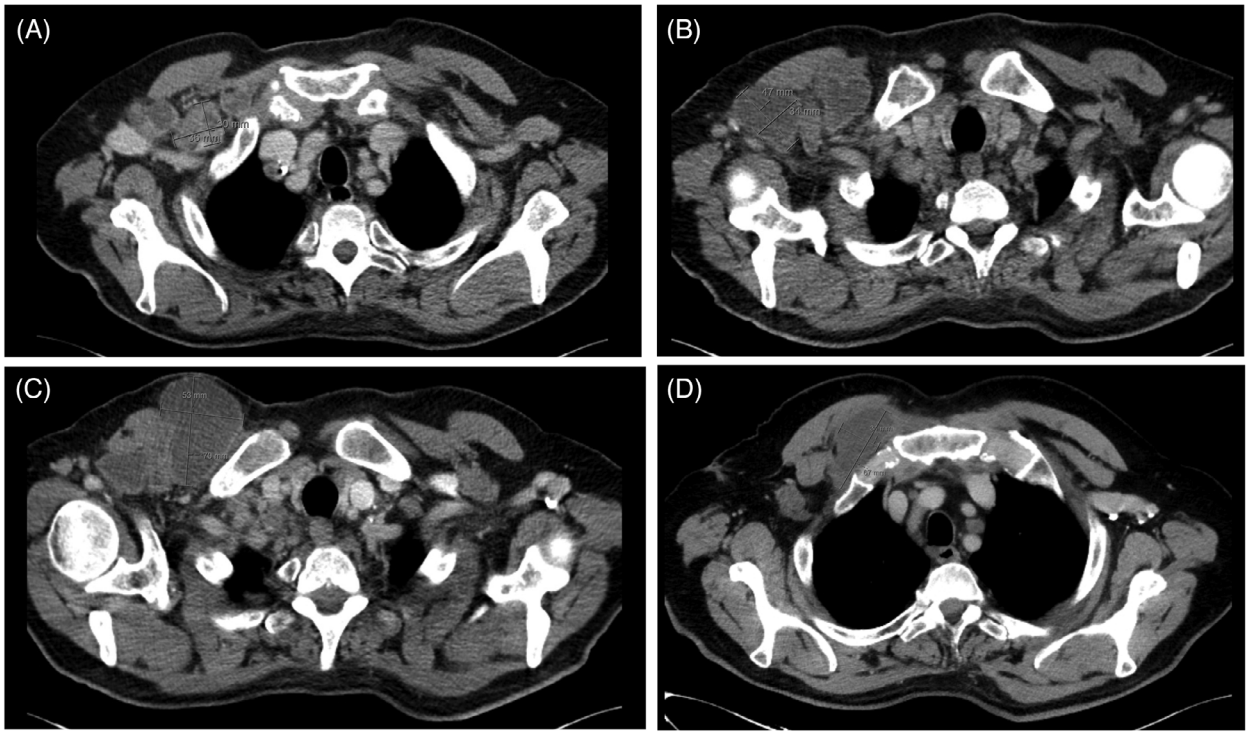

FIGURE 2 Evolution of axillary lymphadenopathies at (A) 2 months into anti-tuberculosis therapy (ATT); (B) 3 months into ATT; (C) 6 months into ATT; (D) 9 months into ATT.

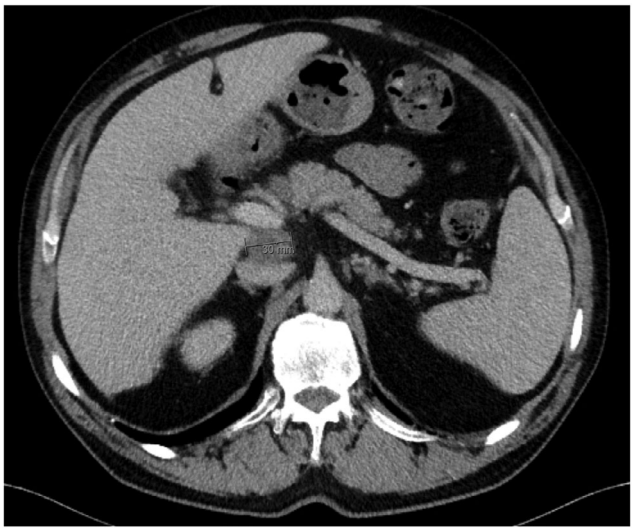

FIGURE 3 Necrotic adenopathy around the hepatic hilum.

This constellation of symptoms was interpreted as paradoxical IRIS. ATT was continued for 13 months, and no steroids were introduced. Following ATT cessation, no further episodes of active skin lesions or subsequent lymph growth were reported. Bone marrow examination showed no evidence of AL recurrence. Further CT evaluations revealed a reduction in the size of some supraclavicular adenomegaly and stability in others.

2 | DISCUSSION

To our knowledge, this is the first reported case of lymph node paradoxical TB-IRIS in a non-HIV patient with leukaemia.

TB-IRIS in HIV-uninfected patients is more frequent in extrapulmonary (especially in pleural and lymph node forms) than in pulmonary TB [3]. Lymph node TB is reported in percentages ranging from 16.7% in the USA to 30% in Morocco, predominantly affecting cervical areas (about 80%). It usually presents as painless, gradually increasing swelling of one or more lymph nodes over weeks to months. Commonly affected superficial lymph nodes include posterior and anterior cervical chains, suprascapular fossae, and others like submandibular, periauricular, inguinal, and axillary groups. It is often bilateral, and non-contiguous lymph nodes can be involved. Suprajacent skin initially presents as normal but undergoes progressive alterations leading to fistulisation. In our patient, enlarged lymphadenopathies first manifested at 2 months after starting ATT, which is within the usual timeframe for its manifestation [6]. Furthermore, he displayed axillary and right supraclavicular lymphadenopathies, along with involvement in the hilar, mediastinal, thoracic wall, and upper abdomen locations.

Diagnosis of lymph node TB can be definitively confirmed through aspiration of the lymphadenopathy upper pole for direct microbiological study and subsequent culture. Nevertheless, this diagnostic procedure yields positive results in merely 30% of cases. Polymerase chain reaction analysis of the node sample presents as the fastest and most sensible diagnostic technique [9]. Every so often, biopsy procedures for lymph node aspiration can create an iatrogenic tract with

recurrent drainage, which appeared to be the case for this patient. Closure of this fistulous tract proves to be a challenging endeavour.

Primary diseases in which non-HIV IRIS is secondary include severe cutaneous adverse drug reactions, such as drug-induced hypersensitivity syndrome, autoimmune and collagen diseases, pregnancy, and internal malignancies (cancers, lymphoma/leukaemia and sarcoma). In this population, TB-IRIS may be triggered by various factors, including rapid recovery from immune suppression (e.g. in neutropenic haematological malignancy patients after neutrophil recovery, solid organ and hematopoietic cell transplant recipients after immunosuppression withdrawal, cessation of tumour necrosis factor alpha-blocker therapy), postpartum state (typically 3–6 weeks after childbirth), initiation of dialysis, use of immune checkpoint antagonists for advanced malignancies, and commencement of TB medications, particularly in extensive TB cases [8].

On retrospective analysis of the presented case, the immunity recovery after the institution of proper leukaemia treatment may have been the main contributing factor to the extent of the presentation of this disease.

Consensus regarding the standard treatment for TB-IRIS has not yet been fully established. There are no available guidelines, thus the optimal treatment remains uncertain. Incremental benefits are observed when the treatment is tailored to the patient's extent of disease, immune reaction, and underlying illness [6]. The optimal duration of treatment is also unknown. Although most patients with TB-IRIS exhibit clinical improvement within 2 months following ATT, the timeframe for improvement varies widely. Pulmonary lesions and lymphadenopathy typically resolve after 3–18 months of ATT treatment [4]. Some individuals may benefit from a prolonged period of the intensive or continuous phase during ATT, as documented in certain cases [6].

In severe cases, systemic corticosteroids are usually recommended and a benefit in reduction of morbidity and hospitalization was demonstrated in a randomized controlled trial after the administration of prednisone for 4–6 weeks [6]. We did not administer any steroid treatment to the patient; despite its absence, the patient exhibited clinical improvement and resolution of the infection.

Management of lymph node TB itself also poses a therapeutic challenge. Generally, standard ATT regimens for treating pulmonary TB are expected to demonstrate efficacy in cases of lymph node TB as well. The main challenges related to its management mainly rely on the appearance of freshly involved nodes or enlargement of the existing nodes during treatment, the development of fluctuation, and the appearance of sinus tracts and relapses [10], most observable in our patient's evolution. Possible explanations for this suboptimal response of therapy in lymph node TB include unidentified drug resistance, poor drug penetration, unfavourable local milieu, and enhanced delayed hypersensitivity reaction in response to mycobacterial antigens released during treatment [10].

There is a potential secondary effect of chemotherapeutic agents contributing to the surge and/or exacerbation of the disease. Fludarabine, an antineoplastic agent efficacious in treating various lymphoproliferative malignancies, induces notable alterations in immunoregulatory T-cell counts due to its purine nucleoside analogue properties. Given its lymphocytotoxic nature, particularly affecting T-cells, specifically CD4 T-cells, some scholars have drawn comparisons between the cellular immunodeficiency induced by fludarabine and that observed in acquired immunodeficiency syndrome [11]. TB has been documented as a complication arising from the utilization of fludarabine-based chemotherapy in diverse lymphoproliferative disorders, including chronic lymphocytic leukaemia and non-Hodgkin lymphoma [2, 12].

Sorafenib, a multikinase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), and thyroid carcinoma, has been shown as a potent inhibitor of FLT3-ITD. Although sorafenib has not been approved by the FDA for AL treatment, there are reports of its off-label use in patients with AL [13]. In-vitro reports have suggested that sorafenib may have numerous immunomodulatory effects, specifically by altering the signal transduction during T-cell activation, reducing antigen-specific IFN-γ production, interfering with the function and maturity of dendritic cells by downregulation of major histocompatibility complex and co-stimulatory molecules, and also impairing natural killer cell activity [13]. There are, at least, two reported cases of onset of active TB in patients under sorafenib, one of them being treated for HCC and the other one for RCC [13, 14]. In both reports, it was hypothesized that the immunomodulatory effects of sorafenib could therefore increase the risk of progression of latent to active TB. Although our patient had been receiving ATT for 3 months after starting sorafenib, the possibility of sorafenib contributing to the exaggerated clinical presentation cannot be ruled out.

3 | CONCLUSION

Our case report illuminates the intricate dynamics of lymph node TB-associated paradoxical IRIS in a non-HIV patient with leukaemia. This rare scenario underscores the intricate interplay between TB-related complications and underlying haematological malignancies.

Challenges inherent arise in the definition and diagnosis of IRIS in non-HIV patients. The adaptation of criteria from HIV-associated IRIS serves as a valuable framework for precise identification, emphasizing the importance of a standardized approach.

Our patient's complex clinical course, marked by scrofula, lymphadenopathies in several non-contiguous ganglion chains, and skin lesions, highlights the nuanced immune responses that can unfold following immune recovery. The use of fludarabine and the introduction of sorafenib, an FDA-approved multikinase inhibitor, adds a novel dimension, prompting careful consideration of their potential immunomodulatory effects and association with TB progression.

The absence of a consensus on standard treatment for TB-IRIS in non-HIV patients underscores the ongoing challenges in managing these intricate cases. Tailoring treatment to individual patient factors, including disease extent, immune reaction, and underlying illnesses, remains pivotal.

Our report contributes to the expanding literature on TB-associated IRIS in non-HIV patients, emphasizing the urgency for further research, standardized diagnostic criteria, and personalized therapeutic approaches. As medical complexities persist, collaborative efforts in research and clinical practice are essential to advance our comprehension and enhance outcomes for patients confronting these complex health challenges.

4 | FINDINGS

This case report underscores the challenges in diagnosing and managing TB-IRIS in non-HIV haematological patients, particularly in extrapulmonary TB, discusses the lack of standardized criteria for diagnosis and treatment and raises questions about the immunomodulatory effects of certain leukaemia treatments, specifically fludarabine and sorafenib.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception, design, data collection, analysis and interpretation of the study. Both authors were actively involved in drafting and critically revising the manuscript for important intellectual content. All authors have given final approval for the version to be published and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

No funding or financial support was received for the conduct of this study or the preparation of this manuscript. The study was conducted solely based on the authors' academic and research interests.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available upon reasonable request. Requests for access to the data should be directed to André Guimarães at arguimaraes@med.up.pt. Please note that certain restrictions may apply to the availability of specific data, due to confidentiality or ethical considerations.

PATIENT CONSENT STATEMENT

The clinical case presented in this article has been published with the full, informed consent of the patient, ensuring confidentiality and ethical considerations are respected.

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