



Case Report

Fatal *Mycobacterium tilburgii* disseminated infection in a patient with cryptic interleukin-12R β 1 deficiency: A case report



Sophie Eon^{1,*}, Jean Baptiste Giot^{1,2}, Frederic Frippiat², Vanessa Mathys³, Jean Radermacher⁴, Constance Paquot¹, Raphael Schils²

¹ Department of Internal Medicine and Immunology, University Hospital Center of Liège, Liège, Belgium

² Department of Infectious and Tropical diseases, University Hospital Center of Liège, Liège, Belgium

³ National Reference Centre Mycobacterium, Bacterial Diseases Service, Sciensano, Brussels, Belgium

⁴ Department of Pathology, MontLégia Hospital, Liège, Belgium

ARTICLE INFO

Article history:

Received 13 November 2025

Revised 6 January 2026

Accepted 7 January 2026

Keywords:

Mycobacterium tilburgii

Mendelian susceptibility to mycobacterial disease

IL12R β 1 deficit

Fatal infection

ABSTRACT

We report the case of an immunocompromised patient with previously unrecognized Mendelian susceptibility to mycobacterial disease due to interleukin-12R β 1 deficit, who developed fatal disseminated *Mycobacterium tilburgii* infection. Mycobacterial invasion caused severe neurologic complications, including refractory status epilepticus, leading to death, despite therapies, including surgical interventions.

© 2026 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Mycobacterial disease (MSMD) is a rare group of inherited immunodeficiencies caused by genetic defects affecting interferon- γ (IFN- γ)-mediated immunity, especially predisposing to mycobacterial and non-typhoidal salmonellosis and, less commonly, severe infections caused by other intracellular bacteria, fungi, or parasites. Viral infections and certain malignancies have also been reported, although these may result from secondary immunodeficiency after infections rather than directly from the underlying MSMD-causing defect [1].

The clinical spectrum is highly heterogeneous and depends on the underlying genotype, with infection severity inversely correlated with residual IFN- γ activity; complete IL12RB1 deficiency is the most common form [2].

Infections caused by rare mycobacteria such as *Mycobacterium tilburgii* are uncommon and challenging to diagnose and manage. Severe disease should prompt consideration of an underlying primary immunodeficiency. Here, we describe the first fatal presentation of IL12R β 1 deficiency complicated by invasive *M. tilburgii* infection, representing only the second such case ever reported in association with this genetic defect.

Case report

A 45-year-old man with no significant medical history presented with abdominal pain in the left hypochondrium, night sweats, unintentional weight loss of 13 kg, and bilateral axillary lymphadenopathy.

Laboratory investigations revealed normocytic anemia (hemoglobin level of 7.3 g/dl), elevated C-reactive protein at 231 mg/l, thrombocytopenia at 71,000/mm³, and acute kidney injury (Acute Kidney Injury Network stage 1), with a creatinine level of 1.73 mg/dl. The QuantiFERON-TB Gold assay was negative. HIV serology was negative and no immunoglobulin deficiency was detected.

A positron emission tomography-computed tomography showed hepatosplenomegaly and widespread hypermetabolic lymphadenopathy.

A bone marrow biopsy identified an inflammatory profile with an excess of macrophages, without evidence of lymphomatous or neoplastic cells. Immunohistochemistry using anti-clusters of differentiations 68 antibodies revealed an inflammatory pattern rich in macrophages.

Two cervical lymph node biopsies demonstrated reactive lymphoid hyperplasia with numerous macrophages, without evidence of malignancy. Ziehl staining highlighted numerous bacilli in the cytoplasm of macrophages (Figure 1). Broad-range polymerase

* Corresponding author. S. Eon. Tel.: +32 492 68 31 48.
E-mail address: sophie.eon@student.uliege.be (S. Eon).

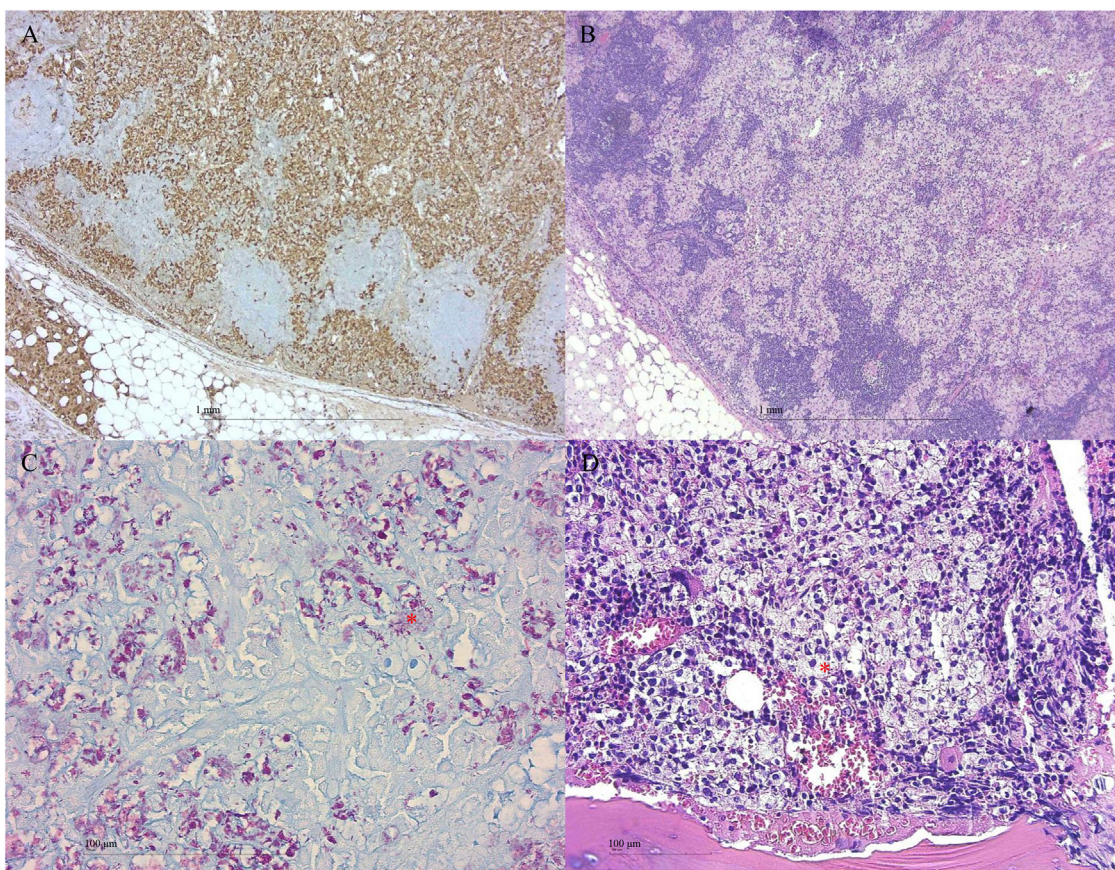


Figure 1. (a) Lymph node ($\times 4$) section with CD68 immunohistochemistry showing significant CD68 expression by histiocytes, evidenced by brown staining. (b) Lymph node ($\times 4$) section shows a reactive pattern with numerous macrophages. No evidence of a lymphomatous process. The lighter-stained trabeculae correspond to areas rich in macrophages, whereas the darker-stained areas mainly contain lymphocytes. (c) Lymph node ($\times 40$) section with Ziehl staining revealing numerous macrophages containing acid-fast bacilli. *Indicates a macrophage containing acid-fast bacilli. (d) Bone marrow ($\times 20$) section : macrophagic proliferation. *Macrophage. CD, clusters of differentiation.

chain reaction (PCR) for mycobacteria was positive on a lymph node biopsy, whereas PCR specific to *Mycobacterium tuberculosis* was negative. The species identification tests yielded no result, likely due to an insufficient quantity of extracted DNA.

Subsequently, within less than 3 months of symptom onset, the patient developed acute confusion. Brain computed tomography scan and magnetic resource imaging showed no acute abnormalities. cerebrospinal fluid analysis revealed normal glucose and protein levels, no nucleated cells, and negative cultures.

A total of 48 hours later, the patient's condition quickly deteriorated, with altered consciousness requiring intensive care unit admission and endotracheal intubation. Empirical treatment for meningitis was initiated (dexamethasone 10 mg every 6 hours, aciclovir 10 mg/kg every 8 hours, ceftriaxone 2 g every 12 hours, and amoxicillin 12 g/day). Empirical antimycobacterial therapy was also started (rifampicin 600 mg daily, azithromycin 500 mg on day 1 then 250 mg daily, ethambutol 1200 mg daily, and moxifloxacin 400 mg daily). Probably unrelated to treatment initiation, the patient subsequently developed seizures; brain magnetic resource imaging demonstrated rhombencephalitis with diffuse cortical involvement and early uncal herniation, accounting for the neurologic presentation. Decompressive craniectomy with external ventricular drain placement was performed.

Despite maximal supportive care, the patient succumbed to refractory status epilepticus, cerebral edema, and bilateral uncal herniation, leading to ischemia in the posterior cerebral artery territory.

Autopsy confirmed disseminated invasive mycobacterial infection involving the liver, spleen, and cervical lymph nodes. PCR

analyses of cerebrospinal fluid and brain biopsy specimens revealed the presence of atypical mycobacterial DNA. Sequencing of a 16S rRNA gene fragment identified low-level mycobacterial DNA compatible with *M. tuberculosis*, a finding subsequently confirmed by additional molecular analysis using *Hsp65* gene sequencing. No other species were identified.

The post-mortem immunodeficiency workup revealed MSMD and identified two mutations in the gene encoding the IL-12R β 1, consistent with a probable compound heterozygous state.

Discussion

MSMD is a rare primary immunodeficiency characterized by mycobacterial infections (especially *M. tuberculosis*).

Clinical manifestations of MSMD are non-specific and typically begin in childhood [2,3].

A total of 19 genes are currently recognized as responsible for MSMD, with 35 variants identified across these loci. In our case, the immunodeficiency workup identified two heterozygous variants in the gene encoding the IL-12R β 1. The first, c.94C>T (p.Gln32*), introduces a premature stop codon, leading to early truncation of the protein or complete absence of expression. The second, c.2T>C (p.Met1?), is of uncertain significance. We suspect this combination accounted for the absence of severe infections during childhood while still conferring susceptibility to invasive infections caused by atypical mycobacteria.

IL-12R β 1 is a component of the IL-12 and IL-23 receptors. After phagocytosis of mycobacteria, myeloid cells secrete IL-12 and IL-23, structurally related cytokines but having different functions.

IL-12 mainly drives T-helper (Th1) responses, activating T and natural killer cells, which subsequently produce IFN- γ -enhancing macrophage antimicrobial activity [2], whereas IL-23 primarily sustains Th17 responses. Mutations in IL-12R β 1 impairing both pathways, defective Th1- and Th17-mediated immunity, increases susceptibility to mycobacterial, Salmonella infections, and compromised mucosal defense [4].

M. tilburgii is a rare non-culturable mycobacterium identifiable only by molecular methods, most commonly, PCR amplification and sequencing of ITS1, *hsp65*, *rpoB*, or 16S rRNA genes directly from clinical specimens. The accuracy of identification depends largely on the quality and quantity of the DNA extracted [5].

Here, 16S rRNA sequencing on cerebrospinal fluid and brain biopsy revealed sequences with 99% similarity to *M. tilburgii* using NCBI BLAST analysis, confirmed by *hsp65* gene sequencing analysis.

To the best of our knowledge, only 17 cases of *M. tilburgii* infection have been reported to date [5–11], including two deaths: a 57-year-old previously healthy man who died from pneumonia and multi-organ failure with hyperammonemia [7] and a 26-year-old woman with no medical history, who died of sepsis after 18 months of treatment without identified immunodeficiency [6]. Most cases were identified by 16S rRNA gene sequencing from lymph node samples [5–11].

Previously, only one case of invasive *M. tilburgii* associated with IL12R β 1 deficiency—compound heterozygous mutations with a known frameshift in exon 14 (c.1623_1624delGCinsTT) and a novel missense in exon 4 (p.Ser117Tyr)—was reported in a healthy 33-year-old woman who presented with night sweats and lymphadenopathy [9].

Management of infections due to *M. tilburgii* represents a true challenge, as highlighted here.

Given its non-culturable nature, a phenotypic antibiogram is impossible to perform and susceptibility tests based on molecular methods do not currently exist. Furthermore, there is no recommendation relative to the antibiotic treatment for this species. In patients with MSMD, management focuses on prolonged antimicrobial therapy, hematopoietic stem cell transplantation for severe cases, and adjunctive IFN- γ therapy [12].

Conclusion

We report the first fatal case of *M. tilburgii* infection in a patient with a previously undiagnosed MSMD due to IL-12R β 1 deficiency. Identification and management were challenging, highlighting the urgent need for better understanding of this mycobacterium to guide therapy. This case also emphasizes the importance of considering MSMD in patients with unusual or severe non-tuberculous mycobacterial infections, including for adults previously considered to be healthy.

It is also hoped that improved knowledge about MSMD will lead to specific and targeted treatments of this kind of primary immunodeficiency.

Funding

The authors acknowledge the financial support of University of Liège for publication costs.

Ethical approval

Written informed consent could not be obtained from the patient because he is deceased. All patient information has been

anonymized to protect privacy. Ethical approval was not required for this case report according to institutional guidelines.

Declaration of generative AI and AI-assisted technologies in the preparation of this manuscript

During the preparation of this work, the authors used ChatGPT, a generative AI-based tool, solely for language refinement and editorial clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final version of the manuscript.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Sophie Eon: Conceptualization, Methodology, Resources, Investigation, Writing – original draft, Writing – review & editing. **Jean Baptiste Giot:** Supervision, Writing – review & editing. **Frederic Fripiat:** Supervision, Funding acquisition, Writing – review & editing. **Vanessa Mathys:** Resources, Investigation, Writing – review & editing. **Jean Radermacher:** Resources, Visualization, Writing – review & editing. **Constance Paquot:** Writing – review & editing. **Raphael Schils:** Supervision, Writing – review & editing.

References

- [1] Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN- γ immunity. *Semin Immunol* 2014;**26**:454–70. doi:10.1016/j.smim.2014.09.008.
- [2] Errami A, El Baghdadi J, Aïal F, Benhsaien I, Ouazhrou K, Abel L, et al. Mendelian susceptibility to mycobacterial disease: an overview. *Egypt J Med Hum Genet* 2023;**24**:1–9. doi:10.1186/s43042-022-00358-x.
- [3] Khavandegar A, Mahdavi SA, Zaki-Dizaji M, Khalili-Moghaddam F, Ansari S, Alijani S, et al. Genetic, immunologic, and clinical features of 830 patients with Mendelian susceptibility to mycobacterial diseases (MSMD): a systematic review. *J Allergy Clin Immunol* 2024;**153**:1432–44. doi:10.1016/j.jaci.2024.01.021.
- [4] Van de Vosse E, Haverkamp MH, Ramirez-Alejo N, Martinez-Gallo M, Blancas-Galicia L, et al. IL-12R β 1 deficiency: mutation update and description of the IL12RB1 variation database. *Hum Mutat* 2013;**34**:1329–39. doi:10.1002/humu.22380.
- [5] Yuan M, Dong G, Han N, Yan L, Tang H. Disseminated *Mycobacterium tilburgii* infection in a person with AIDS: a case report. *Heliyon* 2024;**10**:e35616. doi:10.1016/j.heliyon.2024.e35616.
- [6] Akpinar T, Bakkaloglu OK, Ince B, Tufan F, Kose M, Poda M, et al. Case report of fatal *Mycobacterium tilburgii* infection. *J Infect Chemother* 2015;**21**:538–40. doi:10.1016/j.jiac.2015.02.006.
- [7] ten Doesschate TM, Meinders AJ, Voorn GP, Kummer JA, Moeniralam H. Hyperammonemia as a manifestation of *Mycobacterium tilburgii* infection: a case report. *Infect Dis Clin Pract* 2018;**26**:e28–30. doi:10.1097/IPC.0000000000000586.
- [8] Van Gyse M, Thomeer M, Vankeerberghen A, De Beenhouwer H, Stessens L, Oris E, et al. Disseminated *Mycobacterium tilburgii* infection in a non-HIV-infected patient. *Clin Microbiol Newsl* 2007;**29**:62–4. doi:10.1016/j.clinmicnews.2007.04.002.
- [9] Schepers K, Schandené L, Bustamante J, Van Vooren JP, De Suremain M, Casanova JL, et al. IL-12R β 1 deficiency and disseminated *Mycobacterium tilburgii* disease. *J Clin Immunol* 2013;**33**:1285–8. doi:10.1007/s10875-013-9941-y.
- [10] Temmerman S, Vandekerckhove L, Sermijn E, Vogelaers D, Claeys G, Vaneechoutte M, et al. Disseminated infection with *Mycobacterium tilburgii* in a male immunocompromised patient. *J Clin Microbiol* 2014;**52**:1777–9. doi:10.1128/JCM.03148-13.
- [11] Heyckendorf J, Aries SP, Greinert U, Richter E, Schultz H, Lange C. Functional immune reconstitution by interleukin-2 adjunctive therapy for HIV/mycobacterial co-infection. *Emerg Infect Dis* 2015;**21**:1685–7. doi:10.3201/eid2109.150461.
- [12] Dalvi A, Bargir UA, Natraj G, Shah I, Madkaikar M. Diagnosis and management of infections in patients with Mendelian susceptibility to mycobacterial disease. *Pathogens* 2024;**13**:203. doi:10.3390/pathogens13030203.