

Connecting the dots; Anti-PL7 Antisynthetase Syndrome, Infliximab, and Granulomas – A Case Report

Iris A. Simons

Amsterdam UMC location University of Amsterdam

Lilian J. Meijboom

Amsterdam UMC location Vrije Universiteit Amsterdam

Jacobus A. Winkelman

Amsterdam UMC location Vrije Universiteit Amsterdam

Teodora Radonic

Amsterdam UMC location Vrije Universiteit Amsterdam

Esther J. Nossent

e.nossent@amsterdamumc.nl

Amsterdam UMC location Vrije Universiteit Amsterdam

Case Report

Keywords: Connective tissue disease (CTD)-associated interstitial lung disease (ILD), disseminated histoplasmosis, Histoplasma capsulatum, nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP), antisynthetase syndrome, surgical biopsy, case report

Posted Date: July 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10043601/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Pulmonary Medicine on September 23rd, 2026. See the published version at <https://doi.org/10.1186/s12890-026-04714-0>.

Abstract

Background

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*. Immunosuppressed patients are at risk of developing severe disseminated disease. We report a case of disseminated histoplasmosis resulting from reactivation of a latent infection more than four decades after initial exposure in a patient receiving long-term immunosuppressive therapy for connective tissue disease-associated interstitial lung disease (ILD), illustrating diagnostic challenges that can occur.

Case presentation

A 72-year-old man of Hindustani descent with ILD secondary to anti-PL7-positive antisynthetase syndrome had been receiving long-term therapy with mycophenolate mofetil. Following a provisional diagnosis of Crohn's disease, his treatment was switched to infliximab. Follow-up high-resolution computed tomography demonstrated the development of new centrilobular and perilymphatic micronodules. Extensive microbiological evaluation of bronchoalveolar lavage fluid yielded negative results. Treatment with corticosteroids for a presumed infliximab-induced sarcoid-like reaction was initiated; however, the radiological abnormalities progressed. Subsequent lung biopsy revealed necrotising granulomatous inflammation. After four weeks of incubation, fungal culture of lung tissue grew *Histoplasma capsulatum*, establishing the diagnosis of disseminated histoplasmosis with pulmonary and abdominal involvement.

Conclusions

In immunocompromised patients presenting with a new inflammatory granulomatous lung disease emerging during treatment, reactivation of histoplasmosis should be considered in the differential diagnosis, even when exposure occurred many years earlier.

Background

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*. Although the disease has traditionally been considered endemic in the Americas and parts of Africa, an increasing number of cases have been reported worldwide, reflecting both expanding recognition and a broader geographic distribution than previously appreciated [1]. Infection is acquired through inhalation of aerosolised fungal microconidia. *H. capsulatum* thrives in soil enriched with bird or bat droppings, and infectious spores may become airborne and disperse over considerable distances. Following inhalation, the spores transform into the yeast phase within the lungs, where infection is usually asymptomatic or causes only a mild, self-limiting influenza-like illness in immunocompetent individuals [2]. After primary infection, the organism may persist in a latent state within granulomas in the lungs and reticuloendothelial system for many years. Reactivation can occur when cell-mediated immunity becomes impaired, particularly in

individuals with HIV infection, solid-organ transplantation, or prolonged immunosuppressive therapy, potentially resulting in disseminated histoplasmosis [1, 2].

The clinical presentation of disseminated histoplasmosis is highly variable and often non-specific, ranging from constitutional symptoms such as fever, weight loss, fatigue, and night sweats to involvement of multiple organ systems, including the lungs, liver, spleen, gastrointestinal tract, and bone marrow. As these manifestations overlap considerably with those of other infectious, inflammatory, and malignant conditions, the diagnosis is frequently delayed or overlooked. In particular, histoplasmosis may closely mimic tuberculosis and other chronic pulmonary infections, contributing to diagnostic uncertainty and occasional misdiagnosis [3, 4]. This challenge is even greater in non-endemic regions, where clinical awareness of histoplasmosis is often limited and reactivation disease may not be readily considered in immunocompromised patients. Consequently, the diagnosis of disseminated histoplasmosis requires a high index of suspicion and should be supported by a combination of clinical, radiological, histopathological, microbiological, and laboratory findings.

Case Presentation

A 72-year-old man of Hindustani descent with fibrotic non-specific interstitial pneumonia and organising pneumonia (NSIP/OP) secondary to anti-PL7-positive antisynthetase syndrome presented with progressive dyspnoea after having remained clinically stable for six years while receiving mycophenolate mofetil monotherapy (Fig. 1C-D). Previous attempts to taper and discontinue mycophenolate mofetil had been unsuccessful. He had no recent travel history and had not visited Suriname, his childhood home, for over four decades.

Approximately one year before the onset of his respiratory symptoms, the patient developed malaise, abdominal discomfort, and unintentional weight loss. Colonoscopy and magnetic resonance enterography revealed ulcerative, erythematous, and oedematous lesions involving the colon and terminal ileum. Histopathological examination demonstrated granulomatous inflammation without evidence of malignancy, including Epstein–Barr virus–associated lymphoma. Extensive microbiological investigations, including polymerase chain reaction testing and cultures for *Mycobacterium tuberculosis*, were negative. Based on these findings, a provisional diagnosis of Crohn’s disease was established. Mycophenolate mofetil was subsequently discontinued, and treatment with infliximab was initiated. Follow-up colonoscopy demonstrated improvement of the colonic ulcerations, although persistent lesions remained within the small bowel.

Pulmonary function testing showed a decline in forced vital capacity (–10.2%) and diffusion capacity of the lungs for carbon monoxide (–14.5%). High-resolution computed tomography (HRCT) demonstrated a stable fibrotic NSIP/OP pattern in the lower lobes, with new diffuse centrilobular and perilymphatic micronodules predominantly in the upper lobes (Fig. 1F-E). The differential diagnosis included infection, such as tuberculosis, and a sarcoid-like reaction secondary to infliximab [5]. Laboratory tests revealed normal CRP and leucocyte counts. Extensive microbiological evaluation of the bronchoalveolar lavage

yielded negative results, including cultures for *Mycobacterium tuberculosis*, other mycobacterial species, and fungal pathogens. HIV serology was negative. A sarcoid-like reaction secondary to infliximab was considered likely, so infliximab was discontinued, and corticosteroid therapy was initiated; however, the radiological abnormalities progressed. Subsequent non-intubated thoracic surgical lung biopsies demonstrated fibrosing NSIP with superimposed necrotising granulomas (Fig. 2A). Periodic acid-Schiff with diastase and Ziehl–Neelsen stains were negative for micro-organisms, including spirochetes and *Pneumocystis*; however, fungal culture of the lung tissue grew *Histoplasma capsulatum* after four weeks of incubation. Urine *Histoplasma* antigen testing confirmed the diagnosis of reactivated disseminated histoplasmosis.

The patient was treated with liposomal amphotericin B followed by oral itraconazole, leading to clinical and radiological improvement of both pulmonary and abdominal manifestations. The diagnosis of Crohn's disease was subsequently rejected, and the previously observed small bowel ulcerations were attributed to disseminated histoplasmosis. Following 18 months of antifungal therapy, the patient experienced marked clinical improvement, with complete resolution of dyspnoea and a return to his previous level of physical activity. Follow-up imaging showed a substantial reduction in peribronchovascular and centrilobular nodules, particularly in the central lung parenchyma, with only minimal residual architectural distortion.

Discussion

This case illustrates the diagnostic challenges of reactivated histoplasmosis. Although the patient had not visited an endemic area for over forty years, all the findings were consistent with reactivation of latent histoplasmosis in the context of prolonged immunosuppression. *Histoplasma capsulatum* may persist in a latent state for decades, particularly in individuals with pre-existing lung disease or impaired immune surveillance [2]. Ashbee et al. noted cases of histoplasmosis in patients in Europe who had not travelled for many years, including some with reactivation fifty years after the initial infection [6]. In this patient, prolonged immunosuppressive therapy with mycophenolate mofetil, followed by tumour necrosis factor (TNF)- α inhibition with infliximab, likely disrupted immune control of a latent *Histoplasma capsulatum* infection, resulting in reactivation and subsequent dissemination. Notably, immunosuppressive agents, particularly TNF- α inhibitors, are well-established risk factors for the reactivation of histoplasmosis, reflecting the pivotal role of cell-mediated immunity and TNF- α signalling in controlling latent infection [7].

Disseminated histoplasmosis commonly involves the lungs and reticuloendothelial organs, including the liver, spleen, bone marrow, and lymph nodes. Gastrointestinal involvement is also frequent, particularly in disseminated disease, although overt gastrointestinal symptoms are relatively uncommon. Autopsy studies have demonstrated gastrointestinal lesions in up to 70% of patients with disseminated histoplasmosis, whereas only 3–12% develop clinically apparent gastrointestinal disease [8]. Gastrointestinal histoplasmosis may mimic a variety of other conditions, including Crohn's disease, intestinal tuberculosis, and malignancy, often leading to diagnostic delay [9]. In the present case, the

initial improvement in colonic ulcerations following immunosuppressive therapy may have obscured an underlying infectious process, while persistent small-bowel abnormalities and subsequent pulmonary manifestations ultimately raised suspicion of disseminated histoplasmosis. These observations underscore the importance of considering histoplasmosis in the differential diagnosis of granulomatous colitis, particularly in immunocompromised patients or those receiving prolonged immunosuppressive therapy.

The chest CT findings in our patient—diffuse centrilobular and perilymphatic micronodules throughout both lungs—were consistent with disseminated histoplasmosis and likely reflected haematogenous spread of infection. This pattern of innumerable micronodules is a well-recognised radiological manifestation of disseminated disease, although it is not specific to histoplasmosis [3]. Clinically and radiologically, disseminated histoplasmosis may closely resemble tuberculosis, non-tuberculous mycobacterial infection, or sarcoidosis. Such overlap can further complicate the diagnostic process in patients with underlying interstitial lung disease (ILD) or autoimmune disorders, in whom granulomatous inflammation has a broad differential diagnosis.

Given the non-specific clinical and radiological presentation, laboratory investigations play a pivotal role in establishing the diagnosis. In retrospect, earlier testing for *Histoplasma* antigen may have facilitated a timelier diagnosis and potentially reduced the need for invasive diagnostic procedures. Current diagnostic recommendations favour *Histoplasma* antigen enzyme immunoassay testing, typically performed on urine and, when indicated, serum samples [10]. According to the U.S. Centers for Disease Control and Prevention, urinary antigen testing demonstrates a sensitivity of approximately 79% and a specificity of 99% in adult [10]. Fungal culture of blood, bone marrow, bronchoalveolar lavage fluid, or tissue specimens can provide definitive microbiological confirmation; however, require growth may not be detected for several weeks and sensitivity is low [10, 11].

Treatment recommendations from the Infectious Diseases Society of America for moderately severe to severe disseminated histoplasmosis consist of induction therapy with liposomal amphotericin B for one to two weeks, followed by oral itraconazole for a minimum total treatment duration of 12 months [12]. Long-term suppressive itraconazole therapy may be considered in patients who require re-initiation of immunosuppressive treatment and are therefore at increased risk of relapse [2, 12]. Throughout treatment, monitoring of antifungal drug concentrations and serial *Histoplasma* antigen levels is recommended to assess treatment response and facilitate early detection of disease recurrence.

Conclusion

This case illustrates the diagnostic challenges that may arise in patients requiring prolonged immunosuppressive therapy for connective tissue disease-associated ILD when a new inflammatory granulomatous lung disease emerges during the course of treatment. In this case the emergence of a diffuse micronodular pattern on HRCT closely resembled an infliximab-induced sarcoid-like reaction, thereby complicating the diagnostic process. This underscores the importance of maintaining a broad

differential diagnosis, including reactivation of histoplasmosis, even in the absence of recent travel to endemic regions, and of re-evaluating alternative diagnoses considered earlier in the disease course. A definitive diagnosis of disseminated histoplasmosis relies on the integration of exposure history, radiological findings, microbiological investigations (including urinary antigen testing), and, in some cases, tissue biopsy. Early multidisciplinary assessment involving pulmonologists, radiologists, infectious disease specialists, gastroenterologists, and pathologists is essential to minimize diagnostic delays and ensure timely initiation of appropriate therapy.

Abbreviations

HRCT

High-Resolution Computed Tomography

ILD

Interstitial Lung Disease

NSIP

Nonspecific Interstitial Pneumonia

OP

Organising Pneumonia

TNF

Tumour Necrosis Factor

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the participant for inclusion in this case report. Ethical approval was not required for this study in accordance with local regulations.

Consent for publication

Written informed consent for publication of clinical details and images was obtained from the participant.

Availability of data and materials

The raw data in this study are available from the corresponding author, Drs. Nossent, upon reasonable request.

Competing interests

All authors have no competing interests.

Funding

No funding was received for this study.

Authors' contributions

IS contributed to the drafting of the manuscript. EN initiated the case report, supervised data interpretation, and contributed to manuscript writing. All authors critically reviewed and approved the definitive version of the manuscript.

Acknowledgements

Not applicable

References

1. Dao A, Kim HY, Halliday CL, Oladele R, Rickerts V, Govender MNP, Shin JH, Heim J, Ford NP, Nahrgang SA et al. Histoplasmosis: A systematic review to inform the World Health Organization of a fungal priority pathogens list. *Med Mycol* 2024, 62(6).
2. Galgiani JN, Kauffman CA. Coccidioidomycosis and Histoplasmosis in Immunocompetent Persons. *N Engl J Med*. 2024;390(6):536–47.
3. Arauz AB, Papineni P. Histoplasmosis. *Infect Dis Clin North Am*. 2021;35(2):471–91.
4. Surja SS, Valentina D, Thantry ADK, Subagya JC, Yuwono E, Darmadi D, Fauziah N, Adawiyah R, Wahyuningsih R. Misdiagnosis and Coinfection of Localized Pulmonary Histoplasmosis with Pulmonary Tuberculosis: A Systematic Review of Published Cases. *J Fungi*. 2026;12(3):190.
5. Cavalcante Neto PM, Soares MR, Castro MDC, Matias SLK, Resende ACL, Silva SAEHC, Cerezoli MT, Miranda GFM, Fukuda CY, Arida VEM, et al. Sarcoidosis-Like Reaction Secondary to Infliximab. *Am J Respir Crit Care Med*. 2022;205(Supplement1):A1421–1421.
6. Ashbee HR, Evans EG, Viviani MA, Dupont B, Chryssanthou E, Surmont I, Tomsikova A, Vachkov P, Enero B, Zala J, et al. Histoplasmosis in Europe: report on an epidemiological survey from the European Confederation of Medical Mycology Working Group. *Med Mycol*. 2008;46(1):57–65.
7. Vergidis P, Avery RK, Wheat LJ, Dotson JL, Assi MA, Antoun SA, Hamoud KA, Burdette SD, Freifeld AG, McKinsey DS, et al. Histoplasmosis complicating tumor necrosis factor- α blocker therapy: a retrospective analysis of 98 cases. *Clin Infect Dis*. 2015;61(3):409–17.
8. Kahi CJ, Wheat LJ, Allen SD, Sarosi GA. Gastrointestinal histoplasmosis. *Am J Gastroenterol*. 2005;100(1):220–31.
9. Mandavdhare HS, Shah J, Prasad KK, Agarwala R, Suri V, Kumari S, Dutta U, Sharma V. Gastrointestinal histoplasmosis: a case series from a non-endemic region in North India. *Intest Res*. 2019;17(1):149–52.
10. Smith DJ, Free RJ, Thompson GR III, Baddley JW, Pappas PG, Benedict K, Gold JAW, Group EMDASME, Tushla LA, Chiller T, et al. Clinical Testing Guidance for Coccidioidomycosis,

Histoplasmosis, and Blastomycosis in Patients With Community-Acquired Pneumonia for Primary and Urgent Care Providers. Clin Infect Dis. 2024;78(6):1559–63.

11. Guimarães AJ, Nosanchuk JD, Zancopé-Oliveira RM. DIAGNOSIS OF HISTOPLASMOSIS. Braz J Microbiol. 2006;37(1):1–13.
12. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, Kauffman CA. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807–25.

Figures

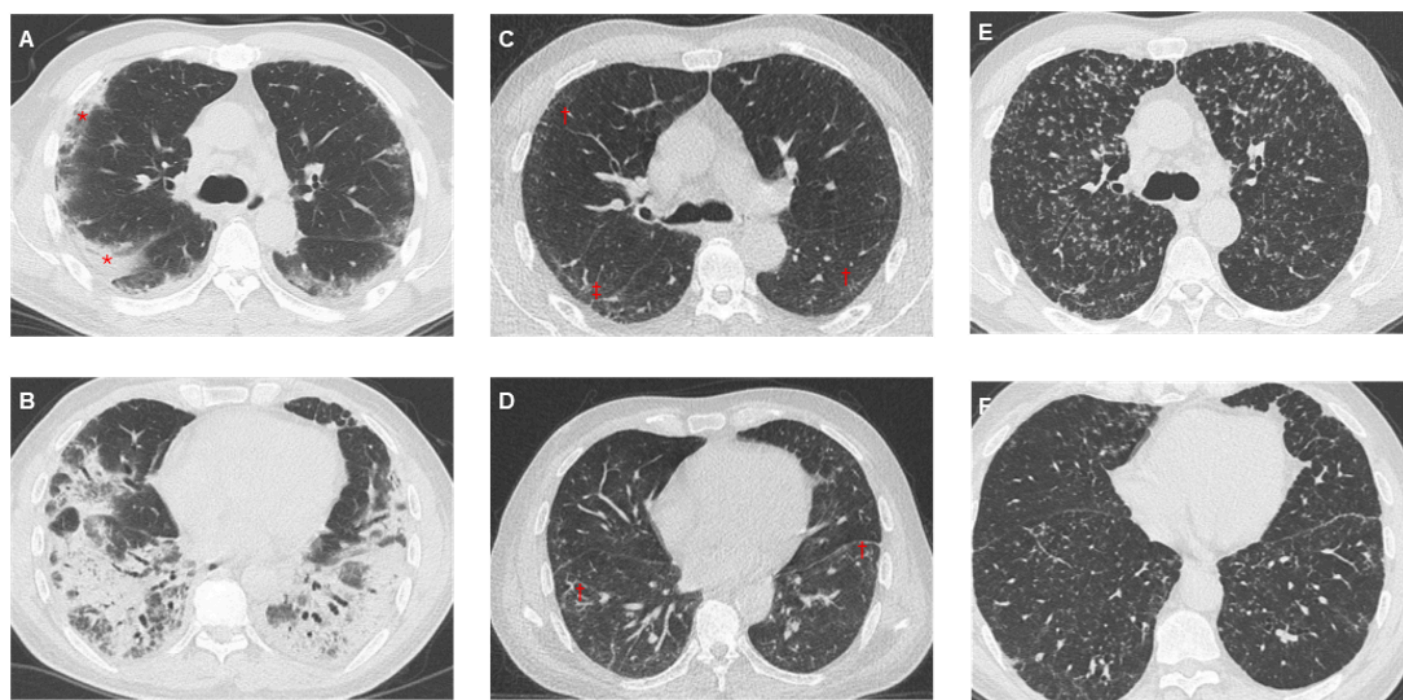


Figure 1

Serial high-resolution computed tomography (HRCT) images illustrating the evolution from connective tissue disease-associated interstitial lung disease to granulomatous lung disease caused by reactivation of latent histoplasmosis in a patient with anti-PL7-positive antisynthetase syndrome.

(A–B) Axial HRCT images of the upper (A) and lower (B) lung lobes at initial presentation demonstrating a nonspecific interstitial pneumonia/organising pneumonia (NSIP/OP) pattern, characterised by predominant subpleural consolidations with a partially perilobular pattern (*), surrounding ground-glass opacities, and subtle reticulation with lower-lobe predominance. **(C–D)** Follow-up axial HRCT images after initiation of immunosuppressive treatment show near-complete resolution of the consolidations with residual ground-glass opacities replacing the previous areas of consolidation (†), alongside persistent subtle subpleural reticulation and band-like opacities (⊕). **(E–F)** Axial HRCT images acquired at the time of clinical deterioration reveal the development of extensive bilateral centrilobular and

perilymphatic micronodules throughout both lungs, while the pre-existing subtle fibrotic interstitial reticulation remains unchanged and no new consolidations are present.

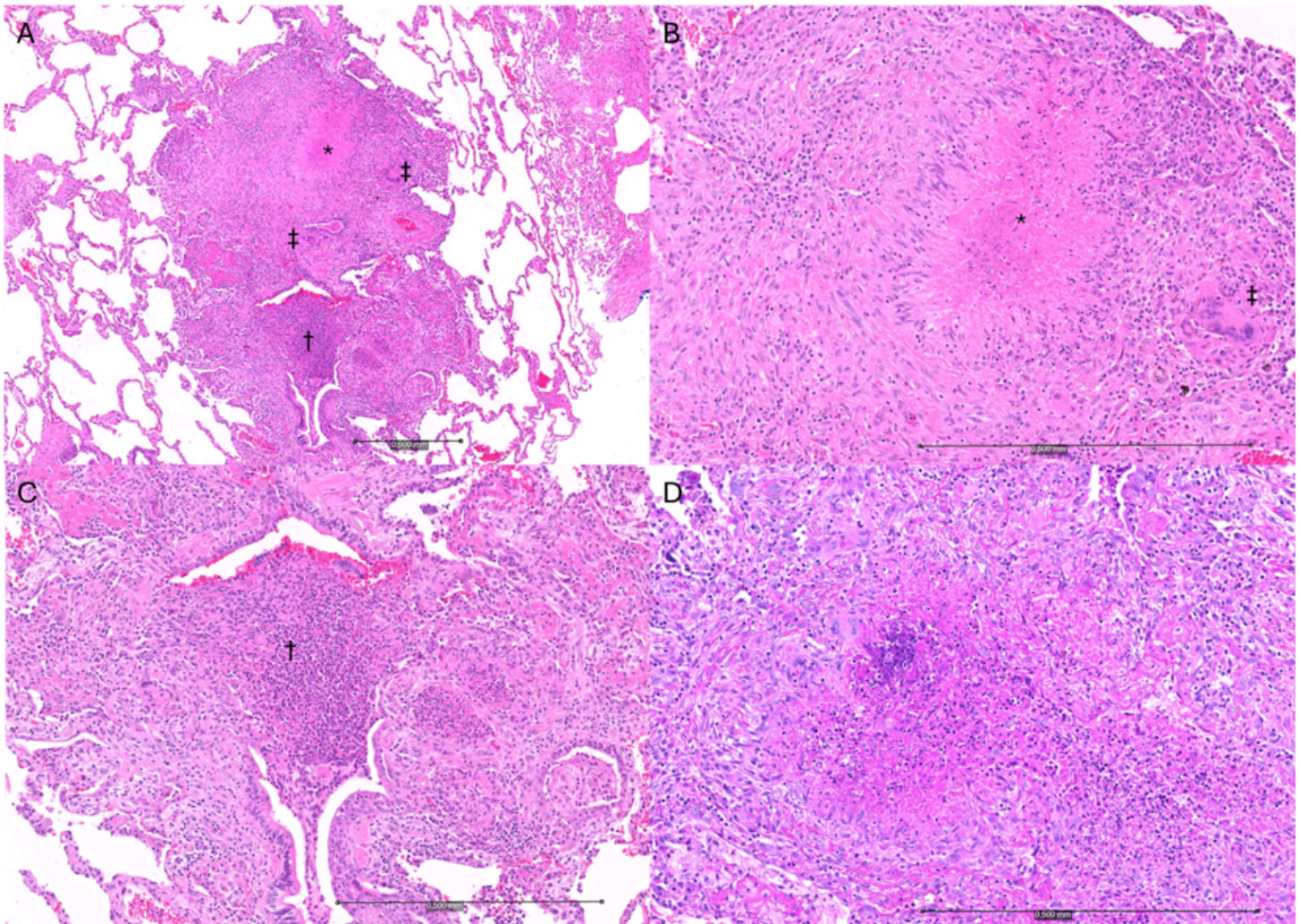


Figure 2

Histopathological findings of surgical lung biopsy demonstrating necrotising granulomatous inflammation due to reactivation of latent histoplasmosis on a background of fibrotic nonspecific interstitial pneumonia (NSIP) in a patient with anti-PL7-positive antisynthetase syndrome.

(A) Surgical lung biopsy from the right lower lobe showing a pattern of fibrotic nonspecific interstitial pneumonia (NSIP), accompanied by superimposed peri- and centrilobular granulomas (*) containing central necrosis and multinucleated giant cells (†), as well as a component of neutrophil-rich inflammation (‡). **(B)** Higher-magnification image (×16) of a necrotising granuloma, demonstrating prominent central necrosis (*). Necrotising granulomas are a well-recognised but non-specific histopathological finding and may be associated with infectious, autoimmune, or drug-induced processes. **(C)** Higher-magnification image (×16) showing focal neutrophilic inflammation, a finding suggestive of bronchiolitis. **(D)** Periodic acid–Schiff with diastase stain highlighting fungal organisms

consistent with *Histoplasma* species. Additional Ziehl–Neelsen, spirochete, and *Pneumocystis jirovecii* stains were negative (latter not shown).