Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Disseminated Histoplasmosis Due to Anti-IFN-γ Autoantibodies-Associated Immunodeficiency

Lan Huang[1–3], Dongyan Zheng[1–3], Tiantian Li[1–3], Xiuying Li[1–3], Jinliang Kong[4], Ke Wang[4], Shuangjie Wang[5], Cunwei Cao[1–3]

[1]Department of Dermatology and Venereology, the First Affiliated Hospital of Guangxi Medical University, Nanning, 530021, People's Republic of China; [2]Guangxi Scientific and Technological Innovation Cooperation Base of Mycosis Prevention and Control, Nanning, 530021, People's Republic of China; [3]Fangchenggang Wanqing Institute of Mycosis Prevention and Control, Fangchenggang, 538000, People's Republic of China; [4]Department of Respiratory and Critical Care, the First Affiliated Hospital of Guangxi Medical University, Nanning, 530021, People's Republic of China; [5]Department of Clinical Laboratory, Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, Nanning, 530021, People's Republic of China

Correspondence: Cunwei Cao, Department of Dermatology and Venereology, the First Affiliated Hospital of Guangxi Medical University, No. 6, Shuang Yong Road, Nanning, Guangxi, People's Republic of China, Email caocunwei@yeah.net

Background: Disseminated histoplasmosis caused by the temperature-dependent dimorphic fungus *Histoplasma capsulatum* is an invasive fungal disease rarely reported in southern China. Here, we report a case of disseminated histoplasmosis due to anti-IFN–γ autoantibodies (AIGA)- associated immunodeficiency.

Case Presentation: We present the case of a 57-year-old HIV-negative female patient with disseminated histoplasmosis in southern China. The patient showed progressively enlarging multiple clavicular, neck, and upper chest skin nodules and dyspnea, which led to the initial suspicion of pulmonary tuberculosis or lung cancer. Bacterial cultures results were negative. Histopathology of a skin tissue showed infectious granulomas. Disseminated histoplasmosis was diagnosed via next-generation sequencing (mNGS) and fungal culture. Furthermore, enzyme-linked immunosorbent assay results from a peripheral blood confirmed that the patient had a high-titer of AIGA.

Conclusion: This case prompts clinicians to consider histoplasmosis an important differential diagnosis in a region where talaromycosis is highly endemic. This case report emphasizes that clinicians should be vigilant for immunodeficiency and consider testing for AIGA in HIV-negative patients who are suspected of having complex opportunistic infections.

Keywords: *Histoplasma capsulatum*, anti-interferon-γ autoantibodies, metagenomic next-generation sequencing, a case report

Introduction

Histoplasmosis is an endemic mycosis caused by the dimorphic fungus *H. capsulatum*. It is prevalent in the Ohio and Mississippi River valleys and parts of North, Central, and South America.[1] Histoplasmosis is rarely reported in southern China, where infection caused by endemic fungus, such as *T. marneffei* is more common.[2] Aspiration of *H. capsulatum* spores in the feces of chickens, pigeons, and bats usually results in asymptomatic lung infection in immunocompetent hosts. Disseminated infection occurs primarily in immunocompromised hosts (acquired immunodeficiency syndrome, immunosuppressive use, organ transplantation).[3] Symptoms of disseminated disease include constitutional symptoms, hepatosplenomegaly, systemic lymphadenopathy, lung and liver involvement, bone marrow and adrenal gland involvement, and the presence of the disease. Severe cases even damage the central nervous system.[4–6] Here, we present a case of an indigenous disseminated histoplasmosis in a patient with anti-IFN–γ autoantibodies (AIGA) -associated immunodeficiency.

Case Presentation

A 57-year-old female patient presented to our hospital with progressively enlarging multiple clavicular and neck skin nodules, dyspnea, and low backbone pain, which had been ongoing for four months. She had been suspected of having an

Received: 22 December 2024
Accepted: 13 March 2025
Published: 25 March 2025

infection at a local hospital but her symptoms did not resolve following antibiotic treatment. The patient, a farmer from a rural village, confirmed no clear exposure to bird or bat droppings, and had never travelled outside Guangxi.

Physical examination revealed several erythematous tenderness nodules on the skin of the left neck and upper chest, ranging from egg-sized to fist-sized. Some nodules were ulcerated, with visible secretions and oozing (Figure 1A). An enlarged lymph node, approximately 2 centimeters in size, was palpable in the left axilla, with well-defined borders and no tenderness. A computed tomography (CT) scan of the chest identified an irregular soft tissue mass (diameter is about 107.53 mm) on the left anterior upper chest wall (Figure 1B), and multiple enlarged lymph nodes in the left axilla (Figure 1C). Emission computed tomography (ECT) also revealed small patches of abnormally dense shadows of the contrast agent in the facial skull, parietal bone, left middle and lower humerus, right scapula, and fourth lumbar vertebrae, suggesting multiple sites of bone destruction throughout the body (Figure 1D). Laboratory tests indicated anemia (hemoglobin concentration 109.20 g/L), leukocytosis (white blood cell count, 11.17×10^9/L) with neutrophilia (absolute neutrophil count, 8.8×10^9/L) and negative human immunodeficiency virus (HIV) antibodies. No other underlying diseases were detected. A smear of pus collected from skin lesions showed fungal yeast with a slightly pointed end at one pole, a bluntly rounded end at the other, and thin necks at the budding sites. (Figure 2A). A skin biopsy was collected for metagenomic next-generation sequencing (mNGS), fungal culture, and pathological examination. It was observed that mNGS conducted within 48 hours confirmed the presence of *H. capsulatum*. Pathological examination of the skin tissue confirmed the presence of infectious granulomas, and fungal cultures revealed the growth of dimorphic fungus, with white, densely fluffy hyphae growing on Brain-heart infusion (BHI) agar medium at 28°C,

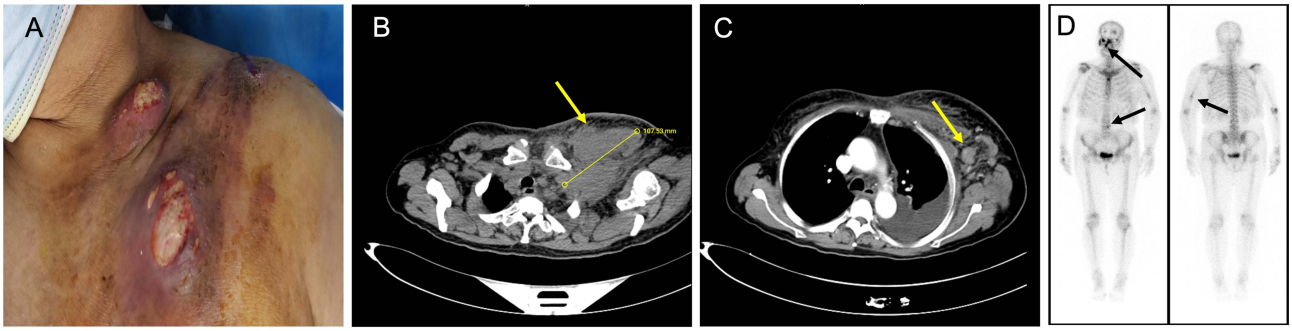

Figure 1 Clinical manifestations, imaging findings. (**A**) Several erythematous swellings, ranging from egg-sized to fist-sized, were seen on the skin of the left neck and upper chest. Some swellings were ulcerated, with visible secretions and oozing. (**B**) CT scan of the chest revealed an irregular soft-tissue mass (diameter is about 107.53 mm) in the left anterior upper chest wall (yellow arrow). (**C**) Multiple enlarged lymph nodes in the left axilla (yellow arrow). (**D**) ECT showed small patches of abnormally dense shadows (black arrows).

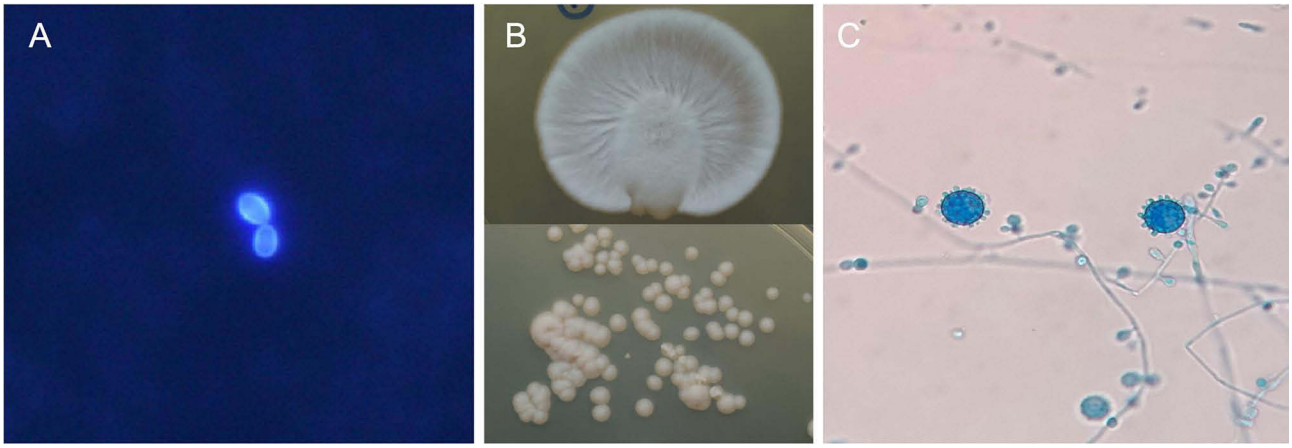

Figure 2 Pathogen examination of specimen. (**A**) Smears revealed yeast cells (fungal fluorescence stain × 400). (**B**) Hyphae grew on BHI agar medium at 28°C, yeast colonies grew on BHI at 37°C after 30 days. (**C**) Cogwheel-shaped conidia were visible under the microscope (cotton blue preparation × 400).

smooth, moist yeast colonies grew on BHI at 37°C after 30 days. (Figure 2B). Large, rounded, thickly walled, spiny, cogwheel-shaped conidia were visible under the microscope (Figure 2C).

Finally, based on these tests, the patient was diagnosed with disseminated histoplasmosis (skin, lymph nodes, and bone were involved). Subsequently, the patient was treated with amphotericin B (20 mg/ daily) for 14 days, resulting in a partial response. Maintenance therapy with itraconazole (200 mg/ twice daily) has continued until now. Due to concerns about her immune status, a peripheral blood test for AIGA was performed, yielding a positive result at a titer of 1:2500. The patient is currently undergoing follow-up.

Discussion

Histoplasmosis is a sporadic condition in China, mainly prevalent in the Yangtze River flows[7] but it is rare in the Guangxi region. In the present case, the patient had never traveled outside Guangxi or in endemic areas of histoplasmosis and had no history of contact with bats or caves. It was an indigenous infection. Therefore, the warm and humid geographical environment of Guangxi may also be suitable for the growth of *H. capsulatum*. The clinical manifestations of *H. capsulatum* infection are nonspecific and variable. At the same time, it is very similar to the symptoms of *T. marneffei* infection, which is prevalent in southern China, and it is easy to be misdiagnosed.[8] It is worth mentioning that this case presented with skin lesions as the initial symptom, which is rare in HIV-negative patients.

Fungal culture is the gold standard for diagnosing histoplasmosis, and traditional fungal pathogen cultures usually take 4–6 weeks or longer.[9] Even if fungi are successfully isolated, identification is difficult for physicians in nonendemic areas because the cultured organisms may be fungi that are not commonly in clinical laboratories. Histopathologists can also detect tiny granuloma yeasts with low sensitivity,[10] making an accurate diagnosis challenging. However, mNGS detected *H. capsulatum* in this patient's skin tissue samples quickly (within 48 hours). Treatment with amphotericin B followed by itraconazole relieved the patient's symptoms, as confirmed by *H. capsulatum* culture 30 days later. In conclusion, mNGS technology can be an important supplement to diagnostic methods, improving the diagnostic efficiency of rare pathogens such as *H. capsulatum*.

Initially, we suspected that this patient had a malignancy or autoimmune disease, and she was negative for tumor markers, antinuclear antibody profiles, and pathological reports. So we suspected that she had a rare infection, and fortunately, mNGS of the skin tissue gave us the correct answer quickly. However, the patient did not have known common immunodeficiency, which conferred a predisposition to rare fungi. Because of the doubts about her immune status, our team suspected that she might have AIGA- associated immunodeficiency, which is highly prevalent in the Guangxi region. We tested her blood samples, and the results showed that the patient had a high titer of AIGA.[11]

Anti-IFN-γ autoantibodies syndrome is an emerging adult-onset immunodeficiency syndrome first described in 2004 and characterized by high levels of anti-IFN-γ autoantibodies.[12,13] Previous studies have suggested that high titers of AIGA in patients' serum can inhibit IFN-γ-induced STAT-1 phosphorylation and IL-12 production of CD4+ T cells, leading to severe dysfunction of T helper one cell responses.[14,15] The production of such antibodies is closely associated with genetic variants carrying human leukocyte antigen (HLA) class II alleles: HLA-DRB1*16:02/DQB1*05: 02 and HLA-DRB1*15:02/DQB1*05:01.[16,17] These patients are susceptible to infection with intracellular pathogens, such as *T. marneffei* and nontuberculous mycobacteria.[11,18] However, cases of AIGA-associated *H. capsulatum* infection are still rarely reported.

Disseminated histoplasmosis is progressive and fatal if left untreated.[19] For moderate to severe cases, guidelines recommend treatment with amphotericin B for 1 to 2 weeks, followed by itraconazole for at least 1 year.[1,20] However, for immunocompromised patients who fail to reduce immunosuppression, lifelong maintenance therapy may be required. The presence of AIGA may create an environment that promotes opportunistic infections and affect the efficacy of antifungal treatments.[21] Such patients require long-term follow-up and management. This case has limitations. The patient is still in the follow-up, and we cannot determine whether the patient's clinical prognosis is related to the antibody titer level for the time being, which needs our close attention in future follow-up.

Conclusion

Disseminated histoplasmosis and disseminated talaromycosis marneffei may both occur in opportunistic infections. Both have nonspecific clinical symptoms such as fever, weight loss, lymphadenopathy, and mucocutaneous lesions, but the skin lesions of histoplasmosis are mostly papules and ulcers. In contrast, disseminated talaromycosis marneffei presents with a typical necrotizing papule with a central depression. In addition, *H. capsulatum* infection can be rapidly diagnosed by highly sensitive urinary antigens.[22] In the absence of specific disseminated clinical symptoms and fungal culture, skin lesions can be an early symptom, and mNGS of skin biopsy helps diagnose disseminated histoplasmosis. Clinicians should be vigilant for immunodeficiency and consider testing for AIGA in HIV-negative patients who are suspected of having complex opportunistic infections.

Ethical Statement and Informed Consent

The study was approved by the Ethics Committee at the First Affiliated Hospital of Guangxi Medical University. The patient's written informed consent was obtained for publications of all the images and case details. No institutional approval was required to publish the case details.

Acknowledgments

We would like to thank Dr. Liyan Xi, Professor of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, for her reading of the manuscript and for providing valuable suggestions. We thank the patient and her family members for granting permission to publish this information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Key Research and Development Program of China (2022YFC2504800), the National Natural Science Foundation of China (82173433), and the Natural Science Foundation of Guangxi Province of China (AB24010134).

Disclosure

All authors agree with the submission and declare that they have no conflict of interest.

References

1. Wheat LJ, Freifeld AG, Kleiman MB, et al. 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):807–825. doi:10.1086/521259
2. Cao C, Xi L, Chaturvedi V. Talaromycosis (Penicilliosis) due to talaromyces (Penicillium) marneffei: insights into the clinical trends of a major fungal disease 60 years after the discovery of the pathogen. *Mycopathologia*. 2019;184(6):709–720. doi:10.1007/s11046-019-00410-2
3. Borges AS, Ferreira MS, Silvestre MT, Nishioka Sde A, Rocha A. [Histoplasmosis in immunodepressed patients: study of 18 cases seen in Uberlandia, MG]. Histoplasmose em pacientes imunodeprimidos: estudo de 18 casos observados em Uberlandia, MG. *Rev Soc Bras Med Trop*. 1997;30(2):119–124.. doi:10.1590/s0037-86821997000200006
4. Smith JA, Riddell J, Kauffman CA. Cutaneous manifestations of endemic mycoses. *Curr Infect Dis Rep*. 2013;15(5):440–449. doi:10.1007/s11908-013-0352-2
5. Rodríguez-Cerdeira C, Arenas R, Moreno-Coutiño G, Vásquez E, Fernández R, Chang P. Systemic fungal infections in patients with human immunodeficiency virus. *Actas Dermosifiliogr*. 2014;105(1):5–17. doi:10.1016/j.ad.2012.06.017
6. Martin-Iguacel R, Kurtzhals J, Jouvion G, Nielsen SD, Llibre JM. Progressive disseminated histoplasmosis in the HIV population in Europe in the HAART era. Case report and literature review. *Infection*. 2014;42(4):611–620. doi:10.1007/s15010-014-0611-7
7. Pan B, Chen M, Pan W, Liao W. Histoplasmosis: a new endemic fungal infection in China? Review and analysis of cases. *Mycoses*. 2013;56(3):212–221. doi:10.1111/myc.12029
8. Cao C, Bulmer G, Li J, et al. Indigenous case of disseminated histoplasmosis from the Penicillium marneffei endemic area of China. *Mycopathologia*. 2010;170(1):47–50. doi:10.1007/s11046-010-9295-4

9. World Health Organization. *Guidelines for Diagnosing and Managing Disseminated Histoplasmosis Among People Living With HIV*. WHO Guidelines Approved by the Guidelines Review Committee; 2020.
10. Almeida MA, Almeida-Silva F, Guimaraes AJ, Almeida-Paes R, Zancope-Oliveira RM. The occurrence of histoplasmosis in Brazil: a systematic review. *Int J Infect Dis*. 2019;86:147–156. doi:10.1016/j.ijid.2019.07.009
11. Guo J, Ning XQ, Ding JY, et al. Anti-IFN-gamma autoantibodies underlie disseminated Talaromyces marneffei infections. *J Exp Med*. 2020;217 (12). doi:10.1084/jem.20190502
12. Doffinger R, Helbert MR, Barcenas-Morales G, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. *Clin Infect Dis*. 2004;38(1):e10–4. doi:10.1086/380453
13. Hoflich C, Sabat R, Rosseau S, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with Mycobacterium chelonae and Burkholderia cocovenenans. *Blood*. 2004;103(2):673–675. doi:10.1182/blood-2003-04-1065
14. Chen YC, Weng SW, Ding JY, et al. Clinicopathological manifestations and immune phenotypes in adult-onset immunodeficiency with anti-interferon-gamma autoantibodies. *J Clin Immunol*. 2022;42(3):672–683. doi:10.1007/s10875-022-01210-y
15. Shih H-P, Ding J-Y, Yeh C-F, Chi C-Y, Ku C-L. Anti-interferon-gamma autoantibody-associated immunodeficiency. *Curr Opin Immunol*. 2021;72:206–214. doi:10.1016/j.coi.2021.05.007
16. Chi CY, Chu CC, Liu JP, et al. Anti-IFN-gamma autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1*16:02 and HLA-DQB1*05:02 and the reactivation of latent varicella-zoster virus infection. *Blood*. 2013;121(8):1357–1366. doi:10.1182/blood-2012-08-452482
17. Ku CL, Lin CH, Chang SW, et al. Anti-IFN-gamma autoantibodies are strongly associated with HLA-DR*15:02/16:02 and HLA-DQ*05:01/05:02 across Southeast Asia. *J Allergy Clin Immunol*. 2016;137(3):945–8e8. doi:10.1016/j.jaci.2015.09.018
18. Qiu Y, Fang G, Ye F, et al. Pathogen spectrum and immunotherapy in patients with anti-IFN-gamma autoantibodies: a multicenter retrospective study and systematic review. *Front Immunol*. 2022;13:1051673. doi:10.3389/fimmu.2022.1051673
19. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. *Infect Dis Clin North Am*. 2016;30(1):207–227. doi:10.1016/j.idc.2015.10.009
20. Carlos WG, Rose AS, Wheat LJ, et al. Blastomycosis in Indiana: digging up more cases. *Chest*. 2010;138(6):1377–1382. doi:10.1378/chest.10-0627
21. Chen ZM, Li ZT, Li SQ, et al. Clinical findings of Talaromyces marneffei infection among patients with anti-interferon-gamma immunodeficiency: a prospective cohort study. *BMC Infect Dis*. 2021;21(1):587. doi:10.1186/s12879-021-06255-9
22. Martinez-Gamboa A, Niembro-Ortega MD, Torres-Gonzalez P, et al. Diagnostic accuracy of antigen detection in urine and molecular assays testing in different clinical samples for the diagnosis of progressive disseminated histoplasmosis in patients living with HIV/AIDS: a prospective multicenter study in Mexico. *PLoS Negl Trop Dis*. 2021;15(3):e0009215. doi:10.1371/journal.pntd.0009215