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Brain abscess caused by *Mycobacterium avium complex* in an adolescent with an inborn error of immunity

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ABSTRACT

Mycobacterium avium complex (MAC) infections of the central nervous system are rare and represent a diagnostic challenge, especially in immunocompromised patients. Comprehensive management requires early diagnosis, prolonged antimicrobial treatment, and, in some cases, neurosurgical interventions.

We present the case of a 16-year-old patient with an inborn error of immunity caused by a variant in the *NFKB1A* gene, who consulted for paresis of the left upper limb. A diagnosis of brain abscess was made using central nervous system (CNS) imaging, and the etiological agent was confirmed by neurosurgical biopsy culture after an unfavorable clinical course with initial empirical treatment. The patient was treated with rifampicin, ethambutol, levofloxacin, linezolid, clarithromycin, and high-dose dexamethasone, achieving significant clinical and radiological improvement after prolonged treatment.

Keywords: *brain abscess;* Mycobacterium avium complex*; non-tuberculous mycobacteria; primary immunodeficiency diseases; case reports.*

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INTRODUCTION

Non-tuberculous mycobacteria (NTM) are widely distributed in the environment.[1] Most of them are not pathogenic to humans.[2] More than 150 species have been identified to date, with significant differences in their clinical relevance.[1] *Mycobacterium avium* complex (MAC) is the most frequently isolated NTM in humans since the onset of the HIV-AIDS epidemic.[1,3,4] It is an ubiquitous microorganism, present in water, sewage systems, animals, and food.[2,5] The portal of entry in humans is the respiratory or digestive mucosa.[5,6] However, screening tests on respiratory secretions and fecal matter are not useful to predict the disease.[1,7]

In immunocompetent children, lymphadenitis is the most common form of clinical presentation,[1,2,6] whereas in patients with chronic lung disease, it can lead to pneumonia. In immunocompromised individuals, the infection can spread and affect the spleen, mesenteric lymph nodes, and intestine.[1,3,4,6] Although NTM infections of the central nervous system (CNS) are rare,[3,4,8] they can occur in the context of disseminated disease, neurosurgery, or trauma,[3] and are more common in patients with HIV and CD4 lymphocyte counts below 50/mm^3.[3] These infections have a high mortality rate, ranging from 35% to 70%, mainly in immunocompromised hosts.[4,8]

Inborn errors of immunity (IEIs) are a group of genetic disorders that predispose individuals to increased susceptibility to infections, autoimmunity, autoinflammation, allergy, bone marrow failure, and/or malignancy. Although some IEIs may be rare individually, IEIs as a group are not rare and represent a significant health concern. They play a relevant role in susceptibility to NTM infections. For example, gain-of-function variants in the *NFKB1A* gene, which encodes the alpha inhibitor of NFkB (IkBα), are associated with combined immunodeficiency and ectodermal dysplasia.[9] These alterations affect both innate and adaptive immune signaling, including B and T lymphocytes, predisposing individuals to severe and recurrent infections by opportunistic pathogens such as MAC, as well as inflammatory manifestations.[10,11]

CLINICAL CASE

A 16-year-old patient with IID due to a gain-of-function variant in the *NFKB1A* gene (diagnosed at the age of 3). Since birth, he has had multiple severe infectious: disseminated bacillus Calmette-Guérin infection disease at 2 years of age (BCG vaccine administered at birth) and pneumonia due to untyped NTM at 9 years of age. At 4 years of age, he underwent hematopoietic progenitor cell transplantation, with graft failure. He receives replacement gamma globulin every 21 days and triweekly chemoprophylaxis with azithromycin and trimethoprim-sulfamethoxazole.

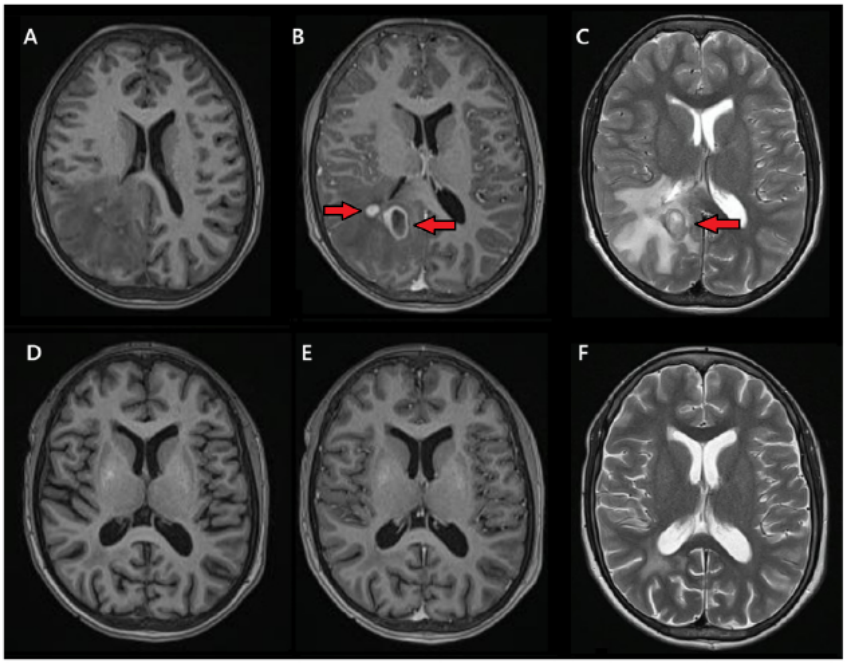
He consulted for the sudden onset of left upper limb paresis, which resolved spontaneously within 1 to 2 hours. Upon admission, he was evaluated as being in good general condition, chronically ill and thin, hemodynamically stable, lucid (Glasgow 15/15), afebrile, with no cranial nerve involvement or motor signs. A complete laboratory workup was performed, revealing the following results: white blood cells, 10 300/mm^3 (51% neutrophils, 39% lymphocytes, 9% monocytes); hemoglobin, 12.7 g/dL; platelets, 328 000/mm^3; blood glucose, 98 mg/dL; and C-reactive protein, 11.8 mg/L. Renal function, liver function tests, serum electrolytes, and coagulation tests were normal.

A contrast-enhanced magnetic resonance imaging (MRI) scan of the central nervous system revealed a multilobulated, heterogeneous space-occupying lesion with perilesional edema and annular enhancement in the right parieto-occipital region. It was interpreted as a brain abscess (*Figures 1A-C*).

The initial diagnostic considerations included bacterial, fungal, or mycobacterial abscesses, as well as cerebral toxoplasmosis. Since there were no significant mass effect, hydrocephalus, or signs of intracranial hypertension, a lumbar puncture was performed to obtain samples for culture and analysis. The cytochemical analysis revealed mild pleocytosis (11 cells/mm^3, with a predominance of mononuclear cells), hypoglycorrhachia (37 mg/dL, corresponding to a blood glucose level of 98 mg/dL), and hyperproteinorrachia (88 mg/dL). Cerebrospinal fluid samples were submitted for culture of bacteria, fungi, and mycobacteria, as well as molecular testing for toxoplasmosis, mycobacteria, fungi, JC virus, and cryptococcal antigen. All cultures and molecular studies were negative.

Given the severity of the condition, empirical antimicrobial therapy was initiated to cover all suspected etiologies. Treatment was indicated with intravenous ceftriaxone 100 mg/kg/day, vancomycin 60 mg/kg/day, metronidazole 30 mg/kg/day, trimethoprim-sulfamethoxazole 20 mg/kg/day, and amphotericin B 5 mg/kg/day. At the same time, oral treatment was started with

Figure 1. Magnetic resonance imaging of the central nervous system with contrast



Axial slices weighed in T1 without contrast (A, D), T1 with contrast (B, E), and T2 (C, F).
A-C: Upon admission.
In the depth of the right parietal lobe, a cluster of cavities of varying diameters is observed, the largest of which is approximately 1.8 cm. The lesions show annular enhancement and are surrounded by vasogenic edema. The findings are interpreted as abscesses (red arrows).
D-F: After 4 months of appropriate treatment.
No cavitated lesions are observed; slight hypointensity persists on T1 (hyperintensity on T2), which is interpreted as a residual lesion.

isoniazid 300 mg/day, rifampicin 450 mg/day, ethambutol 800 mg/day, and levofloxacin 500 mg/day. The patient developed multiple drug-related toxicities (gastrointestinal intolerance, thrombocytopenia, coagulopathy, hypokalemia), requiring treatment to be interrupted and modified on several occasions. After one month of hospitalization, a CNS MRI was repeated, showing no regression of the lesions.

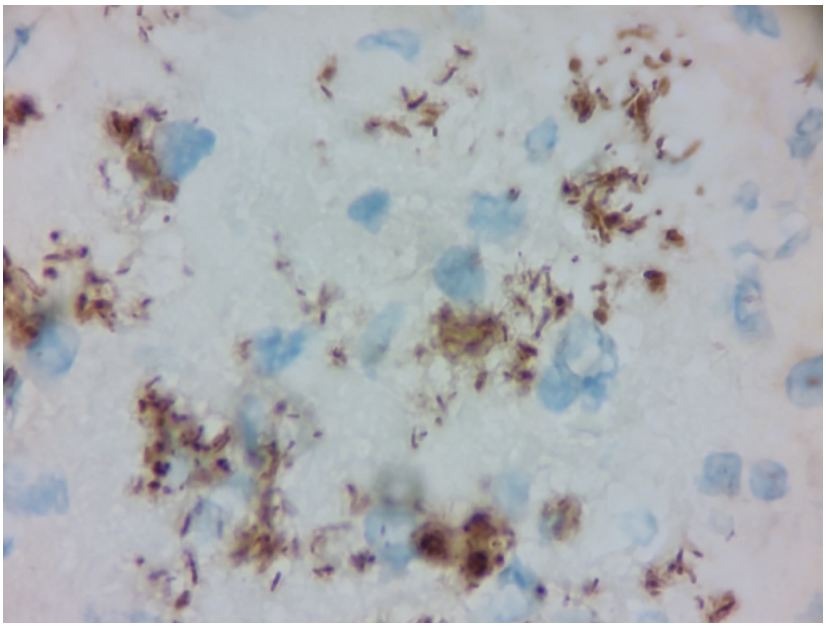
Given the need to establish a definitive diagnosis in a patient with immunodeficiency, a neuronavigation-guided surgical biopsy was performed. Samples were submitted for culture and molecular testing. The fresh examination revealed the presence of acid-fast bacilli (AFB) with positive Ziehl-Neelsen staining, and the pathological anatomy reported: "Subacute inflammatory process with the presence of AFB" (*Figure 2*). The diagnosis of mycobacterial abscess was assumed, and the antimicrobial regimen was adjusted to cover typical and atypical mycobacteria with rifampicin 450 mg/day, levofloxacin 500 mg/day, linezolid 10 mg/kg/day, and clarithromycin 500 mg/day intravenously, combined with isoniazid 300 mg/day and ethambutol 800 mg/day orally. High-dose dexamethasone (0.6 mg/kg/day intravenously) was also indicated.

The patient progressed favorably; after one month of appropriate treatment, a new MRI of the CNS was performed, confirming a marked reduction in the size of the lesion and the surrounding edema. Finally, *Mycobacterium avium complex*, which was sensitive to clarithromycin, was recovered in the mycobacterial culture. The study of the remaining microorganisms yielded negative results. All medication was switched to oral administration, and corticosteroid therapy was gradually reduced with good clinical evolution. In the follow-up images taken at 4 months, the lesions continued to regress (*Figures 1D-F*).

DISCUSSION

A brain abscess is a purulent collection in the

Figure 2. Pathology and immunohistochemistry technique



Positivity for mycobacteria by the immunohistochemistry technique (anti-mycobacterial antibodies) in brain biopsy material. The brownish coloration is due to staining with diaminobenzidine.

brain parenchyma of various infectious etiologies. MRI is the study of choice for detecting and characterizing the lesion; culture of the material is the gold standard for microbiological diagnosis.[3] Direct examination, molecular tests, culture for common germs, anaerobes, mycobacteria, fungi, and pathological anatomy should be performed on the sample obtained.[3] Broad-spectrum empirical treatment should be started early and adjusted according to the rescue.

In all NTM infections, treatment with multiple drugs is essential to eradicate the bacilli in their different stages and prevent the development of resistance.[1,5] There are significant discrepancies between *in vitro* susceptibility and clinical response to treatment *in vivo*, which is partly explained by the synergism of first-line tuberculostatics.[5] MAC is usually resistant to rifampicin and ethambutol alone, but sensitive to combinations and other groups of antibiotics, mainly macrolides.[1,3] Clarithromycin is the only drug recommended for susceptibility testing and is considered the primary treatment agent in combination with other drugs.[1-3] Treatment is prolonged and may require adjuvant surgical intervention.[1] Studies have not yet identified a specific treatment for MAC infections in the CNS.[2,3]

Adverse effects and gastrointestinal intolerance to medication are common. In addition, pediatric formulations are not available for most drugs, which hinders adherence and worsens the prognosis.[2] Despite the severity of these infections, early diagnosis can lead to a cure.[3]

The guidelines of the Argentine Society of Infectious Diseases, the American Thoracic Society, and the American Society for Infectious Diseases recommend initiating treatment with at least two drugs for disseminated MAC disease, which should be administered for a minimum of 12 months.[3,7] Once the infection has been resolved, lifelong treatment or chemoprophylaxis with clarithromycin or azithromycin is recommended to prevent recurrence.[1,2,7]

This case highlights the importance of suspecting MAC infections in immunocompromised patients with brain lesions. These infections pose a diagnostic challenge due to the rarity of the entity, the multiple differential diagnoses, and the varied clinical presentations.[3] We emphasize the essential role of microbiological and anatomopathological studies in guiding the correct treatment, as well as multidisciplinary management to ensure good adherence and follow-up of the patient throughout prolonged treatment. ■

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