Pulmonary Geotrichosis in Chronic Granulomatous Disease

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Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI) that specifically affects phagocytic function by altering NADPH oxidase activity. Mutations can arise in different genes of the NADPH oxidase complex [1,2]. The CYBB gene is responsible for the most frequent genetic forms of CGD [1]. The ability to generate reactive oxygen species (ROS) is impaired in affected cells, thus preventing them from killing intracellular bacteria and fungi, and granulomatous inflammation is excessive [1]. The main fungal pathogens are Aspergillus and Candida species [3]. Next-generation sequencing has facilitated genetic examinations of IEI disorders during recent years, enabling suitable molecular diagnosis in patients with CGD [4]. We describe 2 unrelated CGD patients with pulmonary infections due to Geotrichum species, an emerging and opportunistic pathogen.

The first patient was a 9-year-old boy from a rural area who received the BCG vaccine as a newborn. At age 5 years, he developed a cervical abscess and received intravenous antibiotics. He was admitted to hospital with cough, fever, and dyspnea, with progressive respiratory failure, which required mechanical ventilation and admission to the ICU. Broad-spectrum antibiotics (ceftriaxone/levofloxacin) were initiated. Chest x-ray and CT images showed diffuse interstitial thickening in the lung parenchyma, multiple enlarged intrathoracic lymph nodes, pneumomediastinum, and subcutaneous emphysema, which suggested a fungal etiology; therefore, liposomal amphotericin B (L-AmB) was added empirically (Figure, A). Parenchymal micronodular calcifications, cavitated lesions in the left lobe, and calcified lymph nodes in the right axillary region suggested a previous infectious event (Figure, B). Pseudohyphae and arthroconidia were detected in cultures of bronchoalveolar lavage (BAL) samples (Figure 1S-2S), and Geotrichum capitatum was identified with MALDI-TOF mass spectrometry. Oral itraconazole was added to the initial treatment. An IEI was suspected, and abnormal findings in the dihydrorhodamine assay revealed absent ROS production. A mutation was found in the CYBB gene using next-generation sequencing (p.P383L/y), thus confirming the diagnosis of CGD. A subsequent BAL culture was negative for fungi. L-AmB was suspended after 6 weeks owing to a good clinical response, and itraconazole was administered as prophylaxis.

The second case involved a 19-year-old man from an urban area who had previously been diagnosed with CGD secondary to a mutation in the CYBB gene (p.H115Q/y) at age 14 years [1]. He had a history of multiple episodes of pneumonia, one of which was diagnosed as tuberculosis. Adherence to prophylactic antimicrobial treatment was poor. The patient arrived at the emergency room with myalgia, malaise, and dyspnea. The physical examination revealed fever, tachycardia, and tachypnea, and oxygen saturation was low (SpO2, 70%). The chest CT scan revealed parenchymal micronodular nodules suggestive of pneumonia, and sericopenem and vancomycin were initiated. In the first 24 hours, the patient required mechanical ventilation due to refractory hypoxemia; BAL fluid was collected during bronchoscopy. Empirical amphotericin B (AmB) was initiated in the absence of an improvement in pneumonia (Figure 3S). On day 28, Geotrichum species grew in culture of the BAL sample taken at admission. AmB was replaced with voriconazole, and the patient responded favorably (Figure 4S).

G capitatum (also known as Magnusiomyces capitatus) is known to cause disseminated opportunistic infections, especially in neutropenic patients with hematologic malignancies [5]. Other predisposing factors associated with
pulmonary infections include tuberculosis and a background of chronic obstructive pulmonary disease [5-7]. Erman et al [8] reported an adolescent with CARD 9 deficiency (an IEI) who presented with G capitatum cholangitis. Geotrichum species have not been previously reported in CGD patients. It is not uncommon for recurrent pneumonia to produce chronic pulmonary sequelae in CGD patients [1]. Interestingly, the second patient had a history of multiple episodes of pneumonia, including tuberculosis, whereas in the first patient, pulmonary geotrichosis was his first diagnosed lung infection, although CT images suggested sequelae from a past infection. Chronic pulmonary changes in both patients could be a facilitating factor for the development of pulmonary geotrichosis in association with CGD. Other known risk factors for geotrichosis are the presence of a central venous catheter and the use of broad-spectrum antibiotics, corticosteroids, and immunosuppressants [7,9]. G capitatum can be isolated in nature and in the environment [6,10]. In the first case we report, the first patient helped his father in crop farming.

The occurrence of geotrichosis should raise the suspicion of an underlying IEI [5]. In both cases we report, the patients were young, and geotrichosis in this age group should raise the suspicion of IEI. Geotrichum species infections can range in severity, affecting various organs, although the lung parenchyma is the most common site [5-7]. Pulmonary geotrichosis presents with a severe clinical course accompanied by a lack of improvement with antibiotic therapy [7]. The usual manifestations of these infections are cough with expectoration, chest pain, pulmonary infiltrates or consolidations, and spontaneous pneumothorax [5,7]; both patients in the present report developed pulmonary infiltrates or consolidations, thus making it difficult to differentiate from other more common bacterial or fungal infections. Of note, the first patient developed subcutaneous emphysema and pneumomediastinum. In both cases, the clinical condition progressed to respiratory failure, requiring intubation and mechanical ventilation, as frequently reported in cases of pulmonary geotrichosis [7]. Diagnosis of a Geotrichum species infection relies solely on the identification of the organisms in sterile fluids or tissues [5]. In the second case, a fungus grew in the BAL culture, and Geotrichum species was identified by direct microscopy. There are no differences between Geotrichum clavata and G capitatum in the macroscopic and microscopic analyses [7]. Distinguishing between these 2 organisms is essential for clinical reasons, as G clavata and G capitatum may have different antifungal susceptibility profiles [7]. In the first case, a newer approach was used to identify the microorganism, namely, MALDI-TOF mass spectrometry, which is an excellent diagnostic tool that reliably identifies most of the tested arthroconidial yeast strains to the species level [5]. Currently, there are no established guidelines concerning the most appropriate antifungal agent for the treatment of geotrichosis infections [5,7]. Based on in vitro data and given the limited clinical data available, the ESCMID and ECMM joint clinical guidelines suggest the use of any amphotericin B formulation with or without flucytosine [11]. Some authors have suggested combining voriconazole or itraconazole and amphotericin B [11]. G capitatum can colonize the human mucosa and the skin and may be present in some foods, such as dairy products [6,10]; therefore, adherence to prophylactic treatment is essential in CGD patients. We report the first 2 cases of CGD presenting with geotrichosis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


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Recurrence of Salmonella Infections and Nephritis Complicating IgA Vasculitis in a Patient with IL-12Rβ1 Deficiency

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Key words: Interleukin-12 receptor β1 deficiency (IL-12Rβ1). Salmonella species. Leukocytoclastic vasculitis. Recurrent infections. Nephritis secondary to IgA vasculitis.

Palabras clave: Deficiencia de la cadena beta receptor IL-12. Salmonella spp. Vasculitis leucocitoclástica. Infecciones recurrentes. Nefritis por IgA.

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of inborn errors of immunity (IEI) due to 32 defects in the interleukin (IL) 12/IL-23/ISG15/interferon-gamma (IFN-γ) axis. It predisposes to infections by intracellular bacteria of Mycobacterium species, Salmonella species, and other species [1]. IL-12Rβ1 deficiency is the most common genetic etiology of MSMD, with a frequency of 60% [1]. It is characterized by the total loss of IL-12Rβ1 function, which leads to elimination of the cellular response to IL-12 and IL-23 [1]. Some cases can be complicated by sepsis caused by Salmonella species associated with leukocytoclastic vasculitis [1-5]. We present the case of a Mexican patient with IL-12Rβ1 deficiency and nephritis secondary to IgA vasculitis associated with Salmonella infection. Informed consent was obtained from the patient’s family.

A 10-year-old girl from a nonendogamous community with no history of consanguinity presented with disseminated bacille Calmette-Guérin infection at 8 months of age. At 2 years of age, she presented the first septic event due to Salmonella group D associated with arthritis and palpable purpura of the lower extremities. Skin biopsy of the lesions confirmed leukocytoclastic vasculitis. At age 3 years, she developed generalized lymphadenopathy; the axillary lymph node biopsy revealed necrotizing granulomatous lymphadenitis and a positive PCR result for Mycobacterium species.

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