Pulmonary Geotrichosis in Chronic Granulomatous Disease

Palacios-Reyes D[1], Yamazaki-Nakashimada MA[2], Castaño-Jaramillo L[2], Roman-Montes CM[3,4], González-Lara MF[3,4], Scheffler-Mendoza S[2], Costta-Michuy Á[5], Bustamante J[6,7,8,9], Blancas-Galicia L[10]

[1]*Mycology Department, National Institute of Pediatrics, Mexico City, Mexico*
[2]*Immunology Department, National Institute of Pediatrics, Mexico City, Mexico*
[3]*Clinical Microbiology Laboratory, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[4]*Infectious Diseases Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[5]*Infectious Diseases Department, National Institute of Pediatrics, Mexico City, Mexico*
[6]*St. Giles Laboratory of Human Genetics of Infectious Disease, Rockefeller Branch, Rockefeller University, New York, USA*
[7]*Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM UMR 1163, Paris, France*
[8]*Imagine Institute, University of Paris, Paris, France*
[9]*Study Center for Immunodeficiencies, Necker Hospital for Sick Children, AP-HP, Paris, France*
[10]*Immunodeficiencies Research Unit, National Institute of Pediatrics, Mexico City, Mexico*

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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 (SpO_2, 70%). The chest CT scan revealed parenchymal nodules suggestive of pneumonia, and meropenem 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

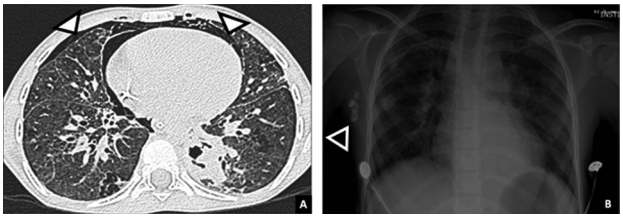

Figure. A, Chest CT scan (patient 1) showing bronchiectasis, parenchymal infiltrates, pneumomediastinum (arrowhead), and subcutaneous emphysema (arrowhead). B, Chest x-ray (patient 1) with hilar and parenchymal interstitial infiltrates and multiple calcifications in the right axillary region (arrowhead).

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.

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L Blancas-Galicia
1 Iman Street
National Institute of Pediatrics
Immunodeficiencies Research Unit, 9th Floor
Mexico City, Mexico, 04530
E-mail: blancas.lizbeth@gmail.com

