

Pulmonary Geotrichosis in Chronic Granulomatous Disease

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0749

Keywords: NADPH oxidase complex. Chronic granulomatous diseases. Fungus, *Geotrichum*.

Palabras clave: Enzima NADPH oxidasa. Enfermedad granulomatosa crónica. Hongo, *Geotrichum*.

Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI), that specifically affects phagocytic function in terms of the 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 the CGD [1]. The affected cells have an impaired ability to generate reactive oxygen species (ROS), thus failing to kill intracellular bacteria and fungi, and excessive granulomatous inflammation [1]. Fungal pathogens include, notably, the *Aspergillus* spp. and *Candida* spp. [3]. Next generation sequencing has facilitated genetic examinations of IEI disorders during the recent years, thus allowing a suitable molecular diagnosis in the CGD patients [4]. We describe two unrelated CGD patients with pulmonary infections due to *Geotrichum* spp., an emerging and opportunistic pathogen.

The first case (C-1) is a 9-year-old male from a rural area that received the BCG vaccine as a new-born, and at 5-years-of age, he suffered a cervical abscess and received intravenous antibiotics. His admission to the hospital was necessary due to a history of cough, fever, and dyspnea with progressive respiratory failure, which required mechanical ventilation and admission to the ICU. The administration of broad-spectrum antibiotics (ceftriaxone/levofloxacin) was initiated. Chest X-ray and CT scan images showed diffuse interstitial thickening in the lung parenchyma, multiple intrathoracic lymph node enlargements,

pneumomediastinum, and subcutaneous emphysema, which suggested a fungal etiology; therefore, liposomal amphotericin B (L-AmB) was added empirically (Figure 1A). Parenchymal micronodular calcifications, cavitated lesions in the left lobe, and calcified lymph nodes in the right axillary region suggested a previous infectious event (Figure 1B). 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 an abnormal dihydrorhodamine assay from the patient evidenced complete ROS production. A mutation was found in the *CYBB* through next-generation sequencing (p.P383L/y), confirming CGD diagnosis. A subsequent BAL-culture was negative for fungi. L-AmB was suspended after six weeks due to a good clinical response, and itraconazole was changed to a prophylactic dose.

The second case (C-2) is a 19-year-old male urban resident who was previously diagnosed with CGD secondary to a mutation in the *CYBB* (p.H115Q/y) at 14 years old [1]. He had a history of multiple pneumonia, one of which was diagnosed as tuberculosis. The patient had poor adherence to prophylactic antimicrobial treatment. He arrived at the emergency room with myalgia, malaise, and dyspnea. The physical examination revealed fever, tachycardia, and tachypnoea, and the oxygen saturation was low (SpO₂ 70%). Parenchymal nodules suggestive of pneumonia were visualized through thorax CT scan, and the administration of meropenem and vancomycin was initiated. In the first 24 hours, the patient required mechanical ventilation due to refractory hypoxemia; during the bronchoscopy sample-BAL culture was collected. In the absence of pneumonia improvement (Figure 3S), empirical amphotericin B (AmB) was

initiated. On the 28th day, *Geotrichum* spp. grew from the admission BAL culture; AmB was replaced with voriconazole with a favorable response (Figure 4S).

Geotrichum 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.* reported an adolescent with CARD 9 deficiency (an IEI) who presented with *G. capitatum* cholangitis [8]. *Geotrichum* spp. have not been previously reported in CGD patients. It is not uncommon that recurrent pneumonia produces chronic pulmonary sequelae in CGD patients [1]. Interestingly, the second patient had a history of multiple episodes of pneumonia, including tuberculosis; on the other hand, in the first patient, pulmonary geotrichosis was his first diagnosed lung infection, although CT scan images suggested earlier sequelae from a past infection. Chronic pulmonary changes in both reported patients could be a facilitating factor for the development of pulmonary geotrichosis in association with CGD. Other known geotrichosis risk factors are the presence of a central venous catheter and the use of broad-spectrum antibiotics, corticosteroids, and immunosuppressors [7, 9]. *G. capitatum* can be isolated in nature and the environment [6, 10]; notably, the first patient helped his father in the crop farming.

The occurrence of geotrichosis should raise the suspicion of an underlying IEI [5]. Both of our patients were young, and geotrichosis in this age group should raise the suspicion of an IEI. *Geotrichum* spp. infections can range in severity, affecting various organs; nevertheless, the lung parenchyma is the most common infection site [5-7]. Typically, pulmonary geotrichosis

presents a severe clinical course accompanied by a lack of improvement with antibiotic therapy [7]. Usual manifestations of these infections are cough with expectoration, chest pain, pulmonary infiltrates or consolidations, and spontaneous pneumothorax [5, 7]; both patients developed pulmonary infiltrates or consolidations, making it difficult to differentiate from other more common bacterial or fungal infections. Of note, the first patient developed subcutaneous emphysema and pneumomediastinum. Both patients had clinical progression to respiratory failure, requiring intubation and mechanical ventilation, which is reported frequently reported in cases of pulmonary geotrichosis [7]. Diagnosis of a *Geotrichum* spp. 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* spp. was identified by direct microscopy. There are no differences between *G. clavata* and *G. capitatum* in the macroscopic and microscopic analyses [7]. Distinguishing between these two organisms is essential for clinical reasons, as *G. clavata* and *G. capitatum* can have different antifungal susceptibility profiles [7]. In the first case, a newer approach was used for microorganism identification, the MALDI-TOF Mass Spectrometry, which is an excellent diagnostic tool that can provide reliable identification to the species level of most of the tested arthroconidial yeasts strains [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 the limited clinical data available; the ESCMID and the ECMM joint guidelines suggest the use of any amphotericin B formulation with or without flucytosine [11]. Some authors have suggested the use of voriconazole or itraconazole and amphotericin B combination therapy [11]. *G. capitatum* can colonize the human mucosa and the skin and can be present in some foods, such as dairy products. [6, 10]; therefore, prophylactic treatment compliance is essential in CGD patients. We described two

patients with CGD presenting with geotrichosis, the association has not been described previously.

Acknowledgements

We thank to Dr. Irma Virginia Díaz Jiménez, Q.F.B. Yanet E. Tovar Calderon, Q.F.B. Mónica Mirabal García and B. Marlene Luengas Bautista.

Competing of Interests

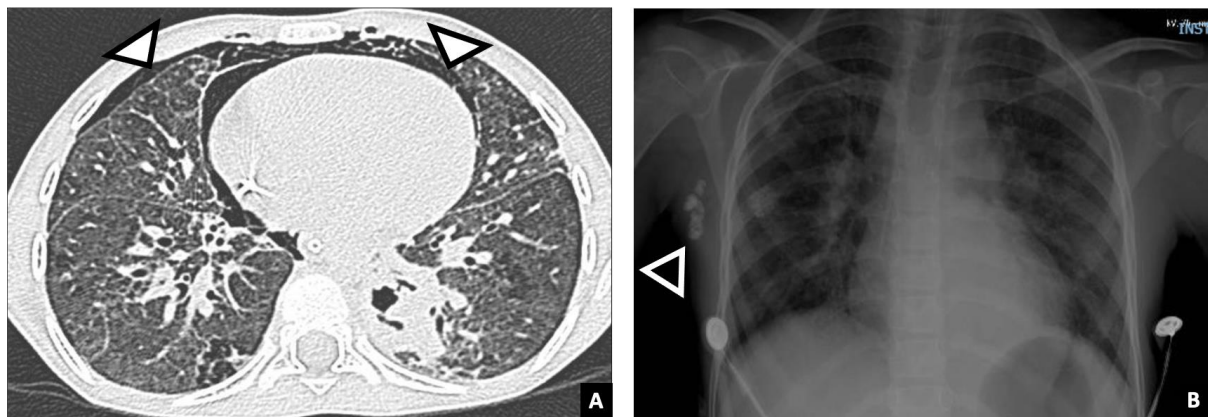
The authors declare that they have no conflict of interest.

Funding

This work was supported by “Fundación Mexicana para Niñas y Niños con Inmunodeficiencias A.C.”

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Figure 1

A. Thorax CT scan (case-1) with bronchiectasis, parenchyma infiltrates, pneumomediastinum (arrowhead), and subcutaneous emphysema (arrowhead). **B.** Chest X-ray (case-1) with hilar and parenchyma interstitial infiltrates, multiple calcifications in axillar right region (arrowhead).