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***Phellinus tropicalis* Abscesses in a Patient with Chronic Granulomatous Disease**

Manish Ramesh,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Elena Resnick,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Yiqun Hui,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Paul J. Maglione,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Harshna Mehta,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Jacob Kattan,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Nicole M. Bouvier,

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA

Vincent LaBombardi, Tanya R. Victor,

New York State Department of Health, Mycology Laboratory, Wadsworth Center, Albany, NY 12208, USA

Sudha Chaturvedi, and

New York State Department of Health, Mycology Laboratory, Wadsworth Center, Albany, NY 12208, USA

Charlotte Cunningham-Rundles

Departments of Medicine and Pediatrics, The Immunology Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1089, New York, NY 10029, USA,
Charlotte.cunningham-rundles@mssm.edu

Abstract

Chronic Granulomatous Disease (CGD), caused by genetic defects in components of the phagocyte NADPH oxidase pathway, leads to recurrent life-threatening bacterial and invasive fungal infections. While a number of unique pathogens have been associated with this disease, the causative organisms may be difficult to identify. Here, we present a 24 year old male with known X-linked CGD who concurrently developed a cervical abscess and an abscess in the subcutaneous tissues of the right hip, both of which were surgically drained. Cultures failed to identify any organisms. He was treated empirically with ertapenem but the hip abscess recurred at the original site and in contiguous dependent areas in the posterior thigh and knee. A filamentous organism was observed microscopically, initially considered a contaminant, but on culture yielded a mold growth, identified as *Phellinus tropicalis* (synonym: *Inonotus tropicalis*) based on phenotypic and molecular methods. This is the third case report of human infection with *P. tropicalis*, all in subjects with CGD. The patient was treated with voriconazole with resolution of his symptoms.

Keywords

Chronic granulomatous disease; *Phellinus tropicalis*; abscess; voriconazole

Introduction

Chronic granulomatous disease (CGD), caused by mutations in one of the protein subunits of NADPH oxidase, leads to defects in neutrophil function, and presents with recurrent bacterial and fungal infections. Pneumonia, suppurative adenitis and soft tissue abscesses are the most common infectious presentations [1]. The most common pathogens include *Aspergillus sp.*, *Staphylococcus*, *Burkholderia sp.*, *Serratia* and *Nocardia* [1, 2]. Invasive fungal infections have been the most significant cause of mortality in these patients though this has improved with the standard institution of itraconazole prophylaxis [3-5]. While it has been often difficult to identify organisms in each case [6], several novel and emerging pathogens have been reported, and are considered pathognomonic for CGD [2]. Examples include bacteria such as *Burkholderia sp* [1, 7]. and *Granulibacter bethesdensis* [8, 9], and fungi such as *Paecilomyces* [10, 11], *Aspergillus nidulans* [12, 13] and *Neosartorya udagawae* [13] In this report we describe infection in a patient with CGD caused by a novel opportunistic fungal pathogen; *Phellinus tropicalis* (synonym: *Inonotus tropicalis*).

Case

Here we present a 24 year old Hispanic man who was diagnosed with X-linked CGD at age three when he had a *S. aureus* liver abscess. He was placed on standard sulfamethoxazole-trimethoprim and later, itraconazole prophylaxis, but was often non-compliant. While being evaluated for bone marrow transplant, he was found to have asymptomatic pulmonary aspergillosis at age 16 and was treated for this infection. Based on

non-compliance, transplant was not performed but he remained well for the following 7 years on intermittent sulfamethoxazole-trimethoprim and itraconazole. At this time, he developed pain and swelling of the left side of his neck with odynophagia and dysphagia to solids. A contrast CT scan showed retropharyngeal edema without any discrete abscess or lymphadenopathy (Fig. 1a, b). Blood cultures drawn on admission grew pan-susceptible *Streptococcus constellatus*. He was treated with amoxicillin-clavulanate, which led to resolution of his dysphagia and odynophagia but he developed increased firmness and had continued cervical pain and swelling over the following month. A contrast CT of his neck was performed. A lobulated abscess had formed in the region of his previous edema with potential airway compromise (Fig. 1c, d). At the same time, he had a new large painful, swelling of his right hip region. MRI of his hip showed a large abscess within the subcutaneous tissues of the lateral soft tissues of the hip, and smaller abscesses in the proximal hamstring musculature with associated myositis (Fig. 1e, f). There was no evidence of osteomyelitis. The neck and the hip abscesses were drained and intravenous antibiotic therapy with vancomycin and piperacillin-tazobactam was initiated. A repeat ultrasound showed extension of the infection into the hamstrings towards the knee not amenable to drainage. He was switched to ertapenem 1 g daily for ease of home infusion and discharged.

Cultures remained negative

He returned a week later with worsening pain in the hamstring muscles. A CT scan showed multiple oval shaped abscesses in the posterior muscles of the right thigh (Fig. 1g, h). A CT guided aspiration was performed. Cultures remained negative during this hospitalization and ertapenem and prophylactic itraconazole were continued. Sustained improvement was noted and after 5 weeks of therapy, ertapenem was stopped. Three weeks after stopping therapy he presented with progressive pain, swelling in his right popliteal area and restriction of movement. An ultrasound showed a complex fluid collection extending along the posterior aspect of the right thigh from the proximal thigh to just below the knee. Cultures of the aspirate from his hip abscess, from his previous admission, that were previously negative, were noted to be growing a yet to be identified mold. The lesion was drained and the new cultures also grew a yellow-brown filamentous mold exhibiting branched septate hyphae that could not be identified by its phenotypic characteristics alone as this fungus did not sporulate on any of the media tested (Fig. 2a, b). Cultures grew mold in 20 days in Sabouraud dextrose agar (SDA) containing antibiotics. The isolate was submitted to Mycology Laboratory, New York State Department of Health for further characterization. Although, this fungus grew slowly on rich medium like SDA but comparative analysis indicated that it grew relatively faster at body temperature of 37 °C than at 30 °C or at 25 °C. Since this fungus did not sporulate on any of the media tested, the identification of the isolate was established by molecular methods. In brief, DNA from the isolate was extracted using MasterPure DNA/RNA extraction kit (Epicenter, Madison, WI, USA) with slight modification as described previously [14] followed by amplification of the internal transcribed spacer (ITS) regions (ITS1, 5.8S, and ITS2) using primer set V1827 5'-GGAAGTAAAGTCGTAACAAGG-3' and V50 5'-TCCTCCGCTTATTGATATGC-3' and nuclear large-subunit rRNA gene using primer set V1799 5'-GGTCCGTGTTTCAAGACGG-3' and V1798 5'-GCATATCAATAAGC GGAGGAAAAG-3'. The

PCR amplicons were sequenced, assembled, and edited using Sequencher Software 4.5 (Gene Codes Corp., Ann Arbor, MI, USA) and BLAST searched against two databases; GenBank (www.ncbi.nlm.nih.gov/) and Centraalbureau voor Schimmelcultures (www.cbs.knaw.nl/yeast/BioloMICSSequences.aspx). The nucleotide sequences for ITS and large-subunit rRNA gene were deposited in the GenBank with accession numbers KF695121 and KF695122, respectively. Voriconazole (200 mg twice daily) was started empirically while speciation was being performed. He was continued on voriconazole with clinical resolution of symptoms.

A retrospect analysis of in-vitro antifungal susceptibility testing of *P. tropicalis* using E-test method indicated that this isolate was susceptible to amphotericin B (0.25 µg/ml) and several of the azole drugs including voriconazole (0.032 µg/ml) posaconazole (0.12 µg/ml), itraconazole (0.03 µg/ml) and fluconazole (4 µg/ml). This isolate was resistant to caspofungin (>32 mg/ml), which is not surprising considering that this isolate is a Basidiomycete.

Discussion

This case highlights the complexity of managing infections in CGD. Organisms that cause opportunistic infections are often uncommon and difficult to culture. The blood culture isolate *Streptococcus constellatus* was never isolated from any of the abscesses and may have been a contaminant. After several unsuccessful attempts we were able to culture *P.s tropicalis* (synonym: *Inonotus tropicalis*), a wood decaying fungus of the family Basidiomycetes. The presence of an unusual mold in culture can lead to the suspicion of contamination of the culture. However, here the fungus was isolated in cultures taken at separate times a month apart confirming its presence in the abscess. Its role in the pathogenesis is further affirmed by its ability to grow at 37 ° C and the dramatic clinical response seen after the appropriate therapy, voriconazole, was instituted. Cultures from the neck abscess did not grow any organisms and though it was at an anatomically distinct site it bears a temporal relationship to the hip lesion. This points to one of the challenges in the diagnosis of infections in CGD where multiple abscesses can occur and cultures are not always indicative of causative organism.

There are only two other reports of this organism causing human infection. Both documented osteomyelitis in patients of CGD [15-17]. With these three reports all in patients with CGD we propose that infection with this organism be considered pathognomonic of CGD. This infection has an insidious course with the development of extensive tissue involvement [15-17]. While one patient responded to voriconazole and was disease free for at least 1 year, the other patient had not cleared the infection despite 7 years of multi-drug anti-fungal therapy [15]. Previous reports have suggested that this infection developed while on prophylaxis with itraconazole [15, 16]. Though antifungal susceptibilities were not available at the time of instituting therapy, voriconazole was effective in controlling this infection. Subsequent analysis has confirmed in vitro susceptibility. Posaconazole has been studied in patients with pulmonary invasive fungal infections who have failed prior therapy and has been proposed as an alternative agent for prophylaxis and could be considered as an alternative therapy [3, 5].

References

1. Winkelstein J, Marino M, Johnston R, Boyle J, Curnutte J, Gallin J, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine*. 2000; 79(3):155–69. [PubMed: 10844935]
2. Holland S. Chronic granulomatous disease. *Clin Rev Allergy Immunol*. 2010; 38(1):3–10. [PubMed: 19504359]
3. Segal B, Barnhart L, Anderson V, Walsh T, Malech H, Holland S. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2005; 40(11):1684–8.
4. Blumental S, Mouy R, Mahlaoui N, Bournoux ME, Debre M, Beate J, et al. Invasive mold infections in chronic granulomatous disease: a 25- year retrospective survey. *Clin Infect Dis*. 2011; 53(12):e159–69. [PubMed: 22080130]
5. Falcone EL, Holland SM. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. *Curr Opin Infect Dis*. 2012
6. Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. *Clin Immunol (Orlando, Fla)*. 2008; 126(2):155–64.
7. Ross J, Holland S, Gill V, DeCarlo E, Gallin J. Severe *Burkholderia (Pseudomonas) gladioli* infection in chronic granulomatous disease: report of two successfully treated cases. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 1995; 21(5):1291–3.
8. Greenberg D, Ding L, Zelazny A, Stock F, Wong A, Anderson V, et al. A novel bacterium associated with lymphadenitis in a patient with chronic granulomatous disease. *PLoS Pathog*. 2006; 2(4)
9. David EG, Adam RS, Adrian MZ, Michael EF, Kol AZ, Frida S, et al. Recurrent *Granulibacter thebesensis* infections and chronic granulomatous disease. *Emerg Infect Dis*. 2010; 16
10. Williamson P, Kwon-Chung K, Gallin J. Successful treatment of *Paecilomyces varioti* infection in a patient with chronic granulomatous disease and a review of *Paecilomyces* species infections. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 1992; 14(5):1023–6.
11. Edwards K. Multifocal osteomyelitis caused by *Paecilomyces varioti* in a patient with chronic granulomatous disease. *Infection*. 1995
12. Segal B, DeCarlo E, Kwon-Chung K, Malech H, Gallin J, Holland S. *Aspergillus nidulans* infection in chronic granulomatous disease. *Medicine*. 1998; 77(5):345–54. [PubMed: 9772923]
13. Dotis J, Panagopoulou P, Filioti J, Winn R, Tóptsis C, Panteliadis C, et al. Femoral osteomyelitis due to *Aspergillus nidulans* in a patient with chronic granulomatous disease. *Infection*. 2003; 31(2):121–4. [PubMed: 12682820]
14. Sidamonidze K, Peck MK, Rerez M, Baumgardner D, Smith G, Chaturvedi V, et al. Real-time PCR assay for identification of *Blastomyces dermatitidis* in culture and in tissue. *J Clin Microbiol*. 2012; 50:1783–6. [PubMed: 22403418]
15. Nguyen DK, Davis CM, Chinen J, Vallejo JG, Noroski LM. Basidiomycetous *Inonotus (Phellinus) tropicalis* osteomyelitis in pediatric and adult X-linked chronic granulomatous disease. *J Allergy Clin Immunol*. 2009; 123(2, Supplement):S13.
16. Davis C, Noroski L, Dishop M, Sutton D, Braverman R, Paul M, et al. Basidiomycetous fungal *Inonotus tropicalis* sacral osteomyelitis in X-linked chronic granulomatous disease. *Pediatr Infect Dis J*. 2007; 26(7):655–6. [PubMed: 17596815]
17. Sutton D, Thompson E, Rinaldi M, Iwen P, Nakasone K, Jung H, et al. Identification and first report of *Inonotus (Phellinus) tropicalis* as an etiologic agent in a patient with chronic granulomatous disease. *J Clin Microbiol*. 2005; 43(2):982–7. [PubMed: 15695724]

Fig. 1.

a, b CT neck with contrast showing retropharyngeal fluid and edema (*black arrow*) within the oropharynx and hypopharynx without discrete abscess, bilateral cervical lymphadenopathy and mediastinal lymphadenopathy. **c, d** CT neck with contrast showing resolution of inflammatory changes, a lobulated abscess (27 mm in greatest diameter) in the region of the previously noted edema (*black arrow*). There was swelling of the left aryepiglottic fold and airway compromise (*white arrow*). Lymphadenopathy was unchanged. **e, f** MRI of hip with contrast of hip. STIR (short t1 inversion recovery) axial (**e**) and coronal (**f**) images show a STIR signal bright lesion within the lateral soft tissues of the right hip which demonstrates peripheral irregular enhancement (*black arrows*), likely representing an abscess (7.1 cm×12.9 cm×8.8 cm). Additional smaller lesions were seen (*black arrows*). **g** CT with contrast of bilateral lower extremities (**g**) coronal and (**h**) axial images showing multiple (at least 4) oval low-attenuation lesions with surrounding rim enhancement in the right posterior thigh muscles, consistent with posterior muscle group abscesses (*black arrows*). The largest collection was 5.2 cm× 10.5 cm×1.9 cm in size

Fig. 2.

a Photomicrograph of lactophenol blue stained hyphae showing a smooth-walled hyaline mold of *Phellinus tropicalis*. **b** *Phellinus tropicalis* growth on Sabouraud dextrose agar: the growth of *P. tropicalis* at 14-days post incubation at different temperatures. The morphology on obverse (i, iii, v) and on reverse (ii, iv, vi) is shown. Maximal pigment production is seen at 30 ° C. Themorphology is typical of a basidiomycete