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First case of invasive *Rasamsonia argillacea* in a child with chronic granulomatous disease in Qatar

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ABSTRACT

Invasive fungal infections (IFI) are a major cause of mortality and morbidity in patients with chronic granulomatous disease (CGD). We report and comment on a case of IFI caused by *Rasamsonia argillacea* in a 16-year-old female with CGD. Additionally, we briefly review and discuss the most challenging aspects of the identification and treatment of this species.

1. Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by a defect in the phagocytic function of the innate immune system due to mutations in genes encoding the five subunits of the nicotinamide adenine dinucleotide phosphatase (NADPH) oxidase enzyme complex [1]. Patients with CGD are prone to recurrent life-threatening infections. The most common pathogens are *Staphylococcus aureus*, *Aspergillus* species, *Candida* species, *Nocardia* species, *Burkholderia* species, *Serratia* species, and *Salmonella* species [1]. Invasive fungal infections (IFI) are a major cause of mortality and morbidity in patients with CGD [1].

Rasamsonia argillacea is a filamentous fungus belonging to the *Trichocomaceae* family [2]. It was previously known as *Geosmithia argillacea* until 2011, when Houbraken et al. described the morphological and molecular characteristics of the new genus [2]. *R. argillacea* infections are mostly observed in immunocompromised patients and those with chronic lung conditions associated with bronchiectasis, particularly CGD and cystic fibrosis (CF) [3]. In fact, it has been suggested that the colonization of the lower respiratory tract of CF patients by *Rasamsonia* spp might be associated with a progressive deterioration of lung function [4]. Herein, we describe the first case of invasive fungal infection (IFI) caused by *R. argillacea* in a CGD patient in the Arabian Peninsula.

2. Case presentation

A sixteen-year-old girl with autosomal recessive CGD due to NCF-1 mutation presented with a 7-day history of a painful and progressive swelling of the right upper chest associated with fever for the last 24 hours. Her disease is complicated with bronchiectasis and oxygen-dependent respiratory failure. She has a history of recurrent bacterial and fungal lower respiratory tract infections, particularly with methicillin-susceptible *S. aureus*, *A. terreus* and *A. fumigatus*. She has poor adherence to the itraconazole and co-trimoxazole prophylaxis.

Upon arrival at the Emergency Department (day 1), she was ill-appearing and had tachycardia, hypotension, and moderate respiratory distress. Her physical exam was remarkable for a swelling over the right chest wall, between the 4th and 5th rib, with a size of about 10 × 10 cm, warm, red, and tender with fluctuation. The initial laboratory tests showed normal white cell count and differential, and C-reactive protein moderately elevated at 65 mg/L. A blood culture collected on admission (day 1) had no growth after 5 days of incubation. Chest computed tomography and magnetic resonance imaging performed after admission (day 2) (Fig. 1a–g) revealed a large chest wall collection extending to the superior and posterior mediastinum with a destructive lesion of the posterior right fifth rib. There was also a left paravertebral thick-walled collection; associated with collapsed T9 vertebrae with focal abnormal signal changes. In addition, there were extensive bronchiectasis with consolidation of the bilateral lower lobes. Wound, tissue,

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and fluid specimens obtained after surgical incision (day 1) grew a powdery mold on sheep blood, chocolate, and Sabouraud agar plates after 4 days of incubation at 37 °C (Fig. 2b) (day 5). Microscopic examination of the colonies showed roughened conidiophores and long phialides with tapering tip producing characteristic cylindrical conidia in chains (Fig. 2a). The fungal isolate was identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker, Bremen, Germany) as *Rasamsonia argillacea.* Identification was confirmed by DNA sequencing of the internal transcribed spacer (ITS). Minimum inhibitory concentrations (MIC) against amphotericin B, itraconazole, fluconazole, posaconazole, and voriconazole, caspofungin were measured by broth microdilution, and were 2.0 μg/mL, 0.5 μg/mL, >64 μg/mL, 0.5 μg/mL, >16.0 μg/mL, ≤0.015 μg/mL respectively.

In addition, bronchoscopy performed on day 6 showed purulent, viscous secretions in the right upper lobe, with whitish outgrowing tissue from the epithelium suggestive of fungal infection. A bronchoalveolar lavage (BAL) sample grew *A. terreus.* Itraconazole, posaconazole, voriconazole, and caspofungin MIC measured by broth microdilution were 0.125 μg/mL, 0.06 μg/mL, 0.06 μg/mL, 0.06 μg/mL respectively.

Initially, the patient required a high-flow nasal cannula for a few days. Subsequently, oxygen support was gradually reduced to her baseline of 1 L per minute during the daytime together with BiPAP at night. Surgical intervention was limited to one incision and drainage of the chest wall abscess on day 1, given the severe extent of lung disease, which made deep and further debridement difficult.

Our patient was initially treated with empirical triple antifungal therapy, including liposomal amphotericin B (4.3 mg/kg IV every 24 hours), voriconazole (Loading dose: 9 mg/kg/dose IV every 12 hours for 2 doses, followed by maintenance dose of 8 mg/kg/dose IV every 12 hours. The dose was adjusted to reach therapeutic level of 2–5.5 mg/L, and caspofungin (70 mg IV on day 1, then 50 mg IV every 24 hours), which was subsequently changed after 5 weeks to itraconazole (5 mg/kg/dose IV every 12 hours) and caspofungin (70 mg IV on day 1, then 50 mg IV every 24 hours) based on susceptibility testing results. After four months of treatment (2 months in the hospital and 2 months as an outpatient), follow-up imaging showed near complete resolution of the collection and resolving associated rib osteomyelitis (Fig. 3a and b). The patient remained clinically stable and was able to return to her baseline activities. Our plan is to complete treatment for at least 6 months then to be followed by lifelong itraconazole (5 mg/kg/dose IV every 12 hours) prophylaxis.

3. Discussion

Rasamsonia spp. are currently considered emerging pathogens in CGD patients. The main route of infection is believed to be through the inhalation of conidia, as it is mainly isolated from respiratory samples, and the lung is the main tissue affected [3,4]. Twelve (52.2 %) of the 23 cases described by Stemler et al. [3] were associated with CGD, and 90 % of infections affected the lung. Disseminated disease or involvement of adjacent organs was observed in 30.4 % and 17.4 %, respectively. Additionally, co-infection with other fungal species, such as in our case, was reported in 26 % of cases.

There are three distinguishable macroscopic and microscopic characteristics that can be used to identify *Rasamsonia* spp. It is able to grow at higher temperatures (37 °C or higher), it has rough-walled conidiophores, and the colonies are pale brown in color [1,4,5]. However, the identification of *Rasamsonia* spp. using phenotypic features may be challenging due to its morphological similarities to other genera, such as *Penicillium* and *Paecilomyces* [1,4,5]. Therefore, genotypic methods such as DNA sequencing may be required [4]. In our case, MALDI-TOF was an accurate method for identification up to the species level.

There are no clinically established antifungal breakpoints for *Rasamsonia* spp. Several reviews reported high MIC to voriconazole [3,4,6,7], in contrast to echinocandins, which showed the lowest, especially to micafungin [7]. In one study, *Rasamsonia* isolates tested against

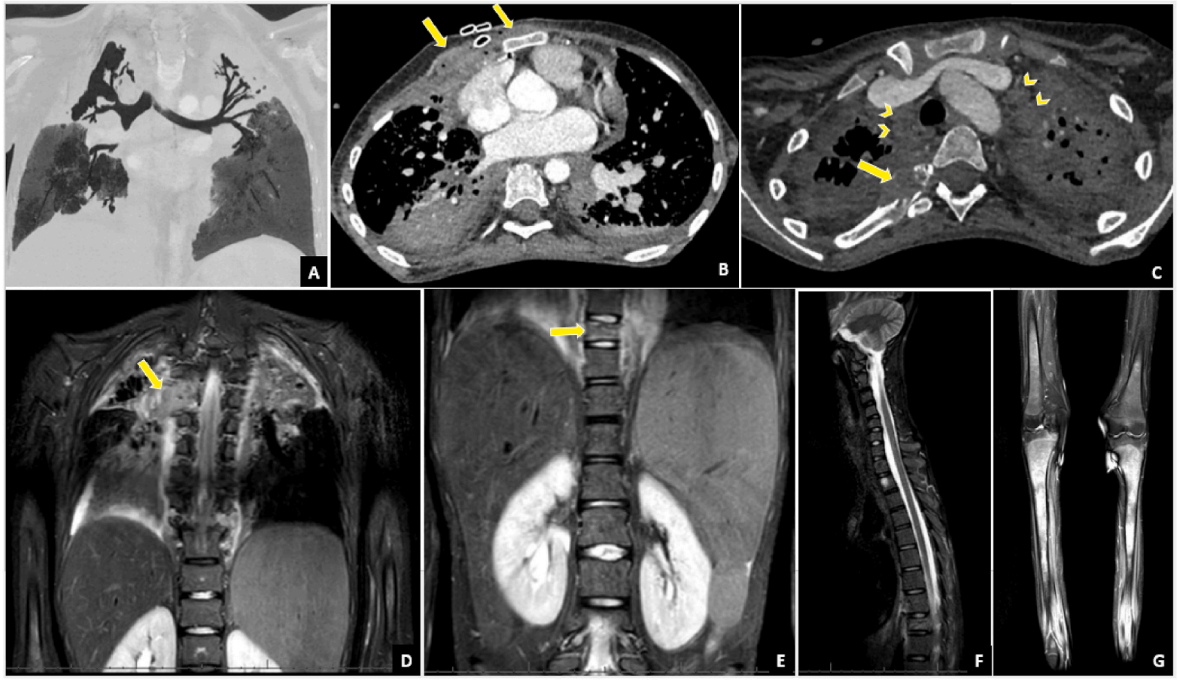
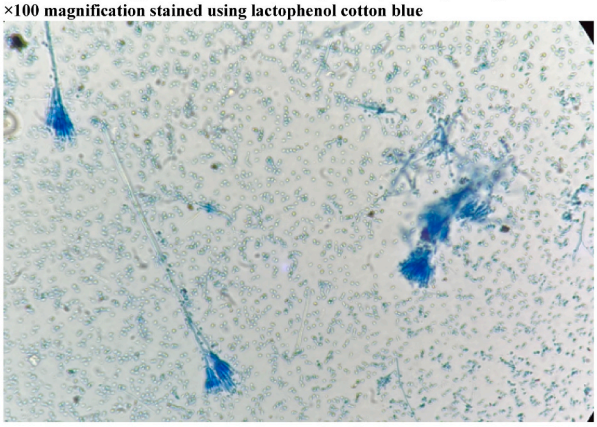


Fig. 1. Radiological images performed on day 2
Chest CT (A–C) and whole body MRI (D–G). Chest CT confirmed extensive bronchiectatic changes in the upper lobes (Coronal MinIP image, A) and bilateral atelectatic/consolidative changes (axial contrast-enhanced image, B) with small pleural effusions. Additionally, there is a pre-sternal and right para-sternal chest wall collection (B, arrows), a right posterior mediastinal collection with destructive bony changes (C, arrow), and mediastinal lymphadenopathy (C, arrowheads). Whole body MRI provided better delineation of the chest wall collection (D, arrow) and also revealed lower thoracic vertebral plana (E, arrow) along with multifocal marrow signal changes in the axial and appendicular skeleton (F, G).

A) Microscopic appearance *Rasamsonia argillacea* , conidiophores, phialides and conidia, ×100 magnification stained using lactophenol cotton blue



B) Macroscopic reverse appearance of *Rasamsonia argillacea*, Sabouraud glucose agar, 5-day-old wound culture

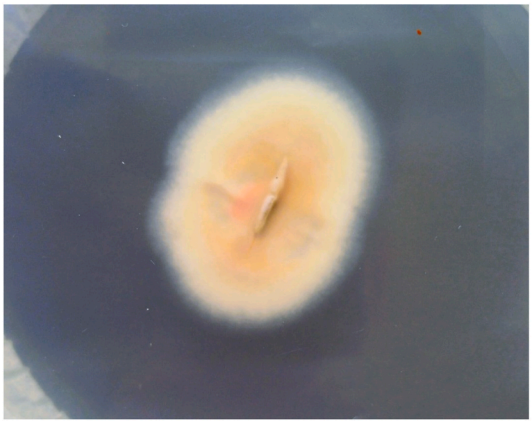


Fig. 2. Laboratory images
A) Microscopic appearance *Rasamsonia argillacea*, conidiophores, phialides and conidia, × 100 magnification stained using lactophenol cotton blue
B) Macroscopic reverse appearance of *Rasamsonia argillacea*, Sabouraud glucose agar, 5-day-old wound culture.

voriconazole showed high MIC values against all clinical isolates [6]. Therefore, it has been suggested that *Rasamsonia* spp. might be intrinsically resistant to voriconazole, which is significant since voriconazole is a first-line agent in the treatment of IFI caused by molds in immunocompromised individuals including patients with CGD. Other antifungals such as itraconazole, posaconazole and amphotericin B showed variable MIC [3,4,6,7].

In our case, the combination echinocandin-itraconazole therapy was based on limited evidence from case reports supporting the use of combination therapy for *Rasamsonia* infection [7–9]. It is also recommended to complement antifungal therapy with surgical resection or drainage of the lesions [7,8]. The treatment plan was challenging given that our patient had co-infection with *A. terreus* which necessitated treating her with combined antifungals as mentioned above. Although the clinical effectiveness of voriconazole against *Rasamsonia* spp., is uncertain, this agent was added to treat concomitant *A. terreus* infection. Our plan also included continuing with itraconazole as a secondary prophylaxis for aspergillosis indefinitely [10].

4. Conclusion

To our knowledge, this is the first case of *R. argillacea* IFI in CGD reported in the Arabian Peninsula. *Rasamsonia* spp. should be considered in patients with CGD in whom fungal infection is suspected. Phenotypic identification is challenging because its morphological characteristics are similar to other fungal species that are more frequently observed in clinical practice. Further studies, including randomized controlled trials are needed to establish *in vitro* activity and breakpoints for antifungals, as well as the optimal treatment for *Rasamsonia* infections.

Availability of data and materials

No datasets were generated or analyzed during this study.

CRediT authorship contribution statement

Nada Shurab: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Anju Sharma:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Eman Al Maslamani:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Andrés Pérez-López:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Osamah Al Walid:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Mohammed Suleiman:** Writing – original draft, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

This work did not need ethical approval.

Consent for publication

The patient provided written informed consent for the publication of this case report, which is available upon request.

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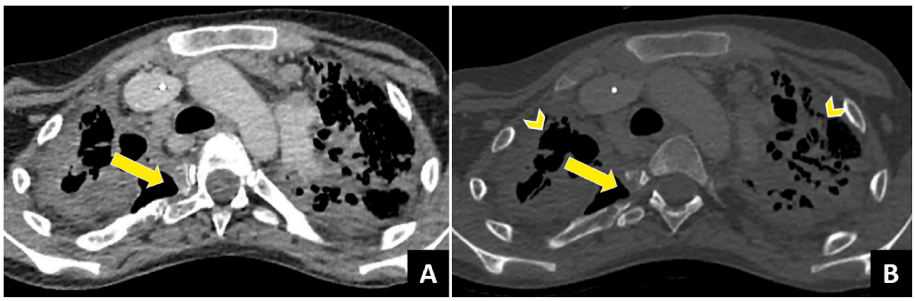

Fig. 3. Follow up radiological images
Follow-up chest CT revealed resolution of the paraspinal collection (A) and the osteomyelitis with established focal bone remodeling (B) and persistent bronchiectasis (arrowheads).

Declaration of competing interest

All authors have no relevant financial or non-financial interests to disclose.

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References

[1] A.A. Justiz-Vaillant, A.F.-A. Williams-Persad, R. Arozarena-Fundora, D. Gopaul, S. Soodeen, O. Asin-Milan, R. Thompson, C. Unakal, P.E. Akpaka, Chronic granulomatous disease (CGD): commonly associated pathogens, diagnosis and treatment, Microorganisms 11 (9) (2023) 2233, https://doi.org/10.3390/microorganisms11092233.

[2] J. Houbraken, H. Spierenburg, J.C. Frisvad, Rasamsonia, a new genus comprising thermotolerant and thermophilic Talaromyces and Geosmithia species, Antonie Leeuwenhoek 101 (2) (2012) 403–421, https://doi.org/10.1007/s10482-011-9647-1.

[3] J. Stemler, J. Salmanton-García, D. Seidel, et al., Risk factors and mortality in invasive Rasamsonia spp. infection: analysis of cases in the FungiScope® registry and from the literature, Mycoses 63 (3) (2020) 265–274, https://doi.org/10.1111/myc.13039.

[4] J. Houbraken, S. Giraud, M. Meijer, et al., Taxonomy and antifungal susceptibility of clinically important Rasamsonia species, J. Clin. Microbiol. 51 (1) (2013) 22–30, https://doi.org/10.1128/JCM.02147-12.

[5] J.B. Doyon, D.A. Sutton, P. Theodore, et al., *Rasamsonia argillacea* pulmonary and aortic graft infection in an immune-competent patient, J. Clin. Microbiol. 51 (2) (2013) 719–722, https://doi.org/10.1128/JCM.02884-12.

[6] A.M. Borman, M. Fraser, M.D. Palmer, et al., MIC distributions and evaluation of fungicidal activity for amphotericin B, itraconazole, voriconazole, posaconazole and caspofungin and 20 species of pathogenic filamentous fungi determined using the CLSI broth microdilution method, J Fungi (Basel) 3 (2) (2017) 27, https://doi.org/10.3390/jof3020027. Published 2017 May 31.

[7] H. Eshaghi, L. Moradi, P. Adimi, M. Gharagozlou, M. Movahedi, N. Parvaneh, Invasive Rasamsonia argillacea infection in chronic granulomatous disease: report of a new case and literature review, J. Mycol. Med. 31 (1) (2021) 101106, https://doi.org/10.1016/j.mycmed.2020.101106.

[8] A. Babiker, N. Gupta, C.F.C. Gibas, N.P. Wiederhold, C. Sanders, J. Mele, H. Fan, A. Iovleva, G. Haidar, C. Fernandes, Rasamsonia sp: an emerging infection amongst chronic granulomatous disease patients. A case of disseminated infection by a putatively novel Rasamsonia argillacea species complex involving the heart, Med Mycol Case Rep 24 (2019 Apr 16) 54–57, https://doi.org/10.1016/j.mmcr.2019.04.002. PMID: 31032179; PMCID: PMC6479014.

[9] Hoenigl, Martin et al. Global guideline for the diagnosis and management of rare mould infections: an initiative of the European confederation of medical mycology in cooperation with the international society for human and animal mycology and the American society for microbiology. Lancet Infect. Dis., Volume 21, Issue 8, e246 - e257.

[10] T.F. Patterson, GR 3rd Thompson, D.W. Denning, J.A. Fishman, S. Hadley, R. Herbrecht, D.P. Kontoyiannis, K.A. Marr, V.A. Morrison, M.H. Nguyen, B. H. Segal, W.J. Steinbach, D.A. Stevens, T.J. Walsh, J.R. Wingard, J.A. Young, J. E. Bennett, Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America, Clin. Infect. Dis. 63 (4) (2016 Aug 15) e1–e60, https://doi.org/10.1093/cid/ciw326. Epub 2016 Jun 29. PMID: 27365388; PMCID: PMC4967602.