



Case report

A case of primary disseminated rhinosporidiosis and dapsone-induced autoimmune hemolytic anemia: A therapeutic misadventure



Ritwik Ghosh^a, Subhargha Mondal^b, Dipayan Roy^{c,d}, Adrija Ray^e, Arpan Mandal^a, Julián Benito-León^{f,g,h,*}

^a Department of General Medicine, Burdwan Medical College & Hospital, Burdwan, West Bengal, India

^b Department of Pathology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India

^c Department of Biochemistry, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

^d Indian Institute of Technology (IIT), Madras, Tamil Nadu, India

^e R G Kar Medical College and Hospital, Kolkata, West Bengal, India

^f Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain

^g Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

^h Department of Medicine, Complutense University, Madrid, Spain

ARTICLE INFO

Article history:

Received 17 February 2021

Accepted 14 March 2021

Keywords:

Rhinosporidiosis

Rhinosporidium seeberi

Disseminated dermatopulmonary

rhinosporidiosis

ABSTRACT

Rhinosporidiosis, a chronic inflammatory disease, which is caused by the aquatic microorganism *Rhinosporidium seeberi*, is endemic in India and in many other regions of the tropics. It primarily infects mucocutaneous surfaces of nose, nasopharynx, and conjunctiva through transepithelial invasion. However, over the centuries, atypical involvement of other body parts, especially viscera, bone, subcutaneous layers, genitals, the tracheobronchial tree, and even the skull has been, though rarely, reported. This chronic granulomatous infection is notorious for its propensity for recurrence following autoinoculation and poor response to most of the anti-microbials except dapsone. Surgical excision followed by cauterization remains the treatment of choice when an operation is feasible. We herein report a case of an immunocompetent person with primary disseminated dermatopulmonary rhinosporidiosis, which created significant diagnostic dilemma at the beginning, got complicated due to dapsone-induced direct anti-globulin test-positive autoimmune hemolytic anemia, and finally responded to prolonged multidrug therapy with liposomal amphotericin B, ketoconazole and cycloserine. This report establishes the importance of tissue diagnosis in rhinosporidiosis and even, in resource-poor set-ups, a simple histopathological diagnosis can promote an early and affordable accurate diagnosis, and subsequently, a proper therapeutic intervention.

© 2021 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Rhinosporidiosis is a communicable chronic granulomatous infectious disease prevalent in the tropics for centuries, caused by a hydrophilic microorganism *Rhinosporidium seeberi*, a human pathogen belonging to an emerging protostistan Mesomycetozoa clade [1–3]. This entity has been classically featured with reddish, friable, slowly progressive, polypoid, mass-like mucocutaneous lesions that bleed easily on touch, which are predominantly seen in the nasal cavity, nasopharynx, and conjunctiva, and in rare

occasions, may involve skin, external genitals and viscera [1]. The mode of transmission is thought to be through direct exposure to spores to breached epithelium from natural aquatic bodies, especially stagnant waters, e.g. pond likely because of low content of chloride [1,4].

Exuberant lesions of cutaneous rhinosporidiosis, also titled dermosporidiosis, in the absence of associated nasal lesions, may masquerade as soft-tissue neoplasms [5] and are extremely rare even in endemic regions. Dissemination has been strikingly uncommon, but it has been reported in immunocompetent individuals [6]. Lung involvement is also exceedingly rare [7,8].

We herein report a case of an immunocompetent person with primary disseminated dermatopulmonary rhinosporidiosis, which created significant diagnostic dilemma at the beginning, got complicated due to dapsone-induced direct anti-globulin test

* Corresponding author at: Avda. de la Constitución 73, portal 3, 7º Izquierda, E-28821, Coslada, Madrid, Spain.

E-mail address: jbenitol67@gmail.com (J. Benito-León).

(DAT)-positive autoimmune hemolytic anemia, and finally responded to prolonged multidrug therapy with liposomal amphotericin B, ketoconazole and cycloserine.

Case report

A 55-year-old barber from rural district of Bardhaman, India, presented to the outpatient department with slow growing generalized multiple subcutaneous lumps for the last 4 months. The lesions were distributed over his trunk and extremities. These were slowly increasing in size and became painful. He was euglycemic, normotensive, and euthyroid. His past medical, surgical and family histories were unremarkable. On examination, many tender swellings of varying sizes were present over anterior upper chest, waist, hips, both arms, forearms, thighs, and legs (Fig. 1). These lesions were sessile/pedunculated-polypoid in appearance and subcutaneous in distribution. There was no regional lymphadenopathy. Mucous membranes and zones of mucocutaneous transition were nowhere involved. Systemic examinations were unremarkable. Complete hemogram, blood glucose, liver, thyroid and renal functions were within normal limits. Serologies for hepatitis B, C and HIV were negative and so was VDRL. Though he had no respiratory symptoms, a routine chest X-ray was done, revealing multiple well-defined opacities in left hemi-thorax (Fig. 2a). Based on the morphologies of the lesions, differential diagnoses that were kept were lipomas, liposarcomas or other soft tissue neoplasms, hamartomas, leiomyoma/leiomyosarcoma, infective granulomas, sarcoidosis, coccidioidomycosis, plexiform neurofibromatosis, and Schwann cell tumor. Tissues from skin lesions and lung lesions (CT-guided) confirmed the diagnosis of dermatopulmonary rhinosporidiosis (Figs. 3–5). Due to its disseminated nature, medical therapy over surgical excision was chosen and he was put on dapsone (100 mg/day) after ruling out the possibility of glucose-6-phosphate dehydrogenase (G6PD) deficiency by quantitative assay. He was kept under close follow up.

During his second follow up after 2 months of discharge, he presented with breathlessness on even mild exertion, lassitude,

weakness, anorexia, palpitations, and many other non-specific symptoms as well as persistence of cutaneous lesions. On examination and after relevant laboratory investigations, he was diagnosed to have an acute acquired hemolytic anemia (hemoglobin 6.8 g/dL, mean corpuscular volume 106, corrected reticulocyte count of 12%, lactate dehydrogenase 1400 U/L, low haptoglobin, and indirect hyperbilirubinemia with normal folate, cobalamin, and iron stores). Peripheral blood smear examination by two expert hematopathologists revealed the presence of spherocytes. A DAT was found to be positive, suggestive of immune-mediated hemolysis. G6PD level was rechecked and was normal. Further testing revealed it to be a warm antibody type (IgG) hemolytic anemia; however, anti-nuclear antibodies panel and other tests for relevant infections were negative. Since dapsone is known to cause hemolytic anemia, it was withdrawn. He was transfused with three units of best-matched packed red cells. After 10 days of withdrawal of dapsone, the laboratory markers of hemolysis started showing improvement and there was also a discernible clinical improvement.

However, specific treatment for dermatopulmonary rhinosporidiosis was getting delayed, complicated and difficult. An expert panel decided on starting a multi-drug therapy with cycloserine (250 mg thrice daily), ketoconazole (400 mg twice daily) and intravenous liposomal amphotericin B infusion (3 mg/kg IV once a day on days 1–5, 14, and 21). He was closely monitored for appearance of any adverse reactions. After five months of continuous therapy and vigilant monitoring with this multi-drug regimen, he responded well. Some of the lesions disappeared and most others decreased reasonably in size (Fig. 2b).

Discussion

Rhinosporidium seeberi is an aquatic protoctistan, which is known to cause infection in animals and humans, primarily affecting the nasal mucosa and ocular conjunctiva, giving rise to pink, friable polyps [1–3]. The disease can also manifest as cutaneous and disseminated forms [1–3]. Our patient had generalized, subcutaneous lumps without any mucocutaneous

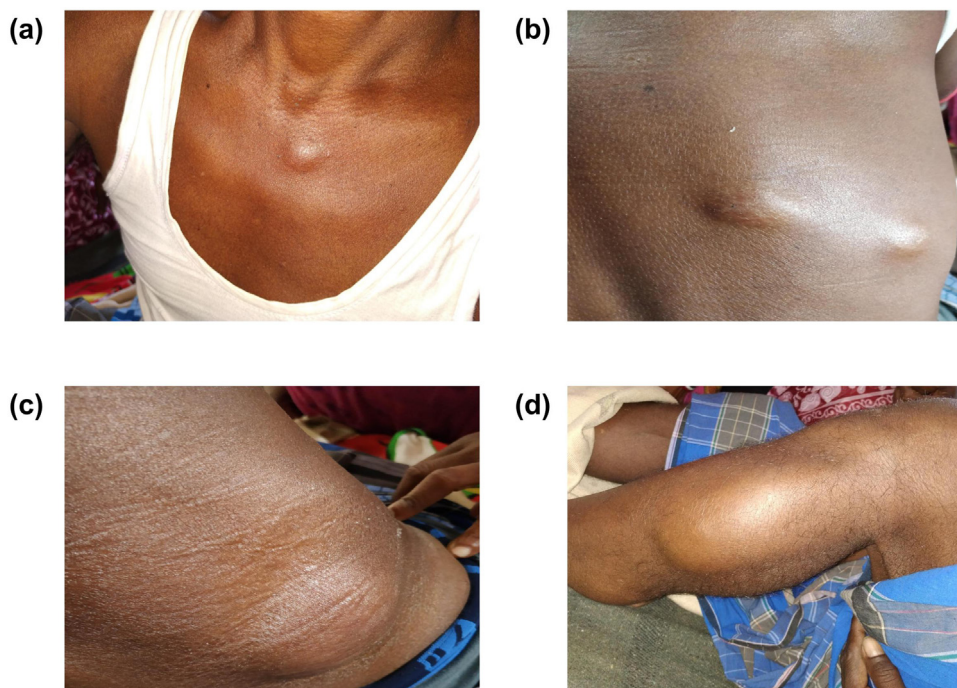


Fig. 1. Swellings of varying sizes over (a) upper chest, (b) back, (c) waist, and (d) leg.

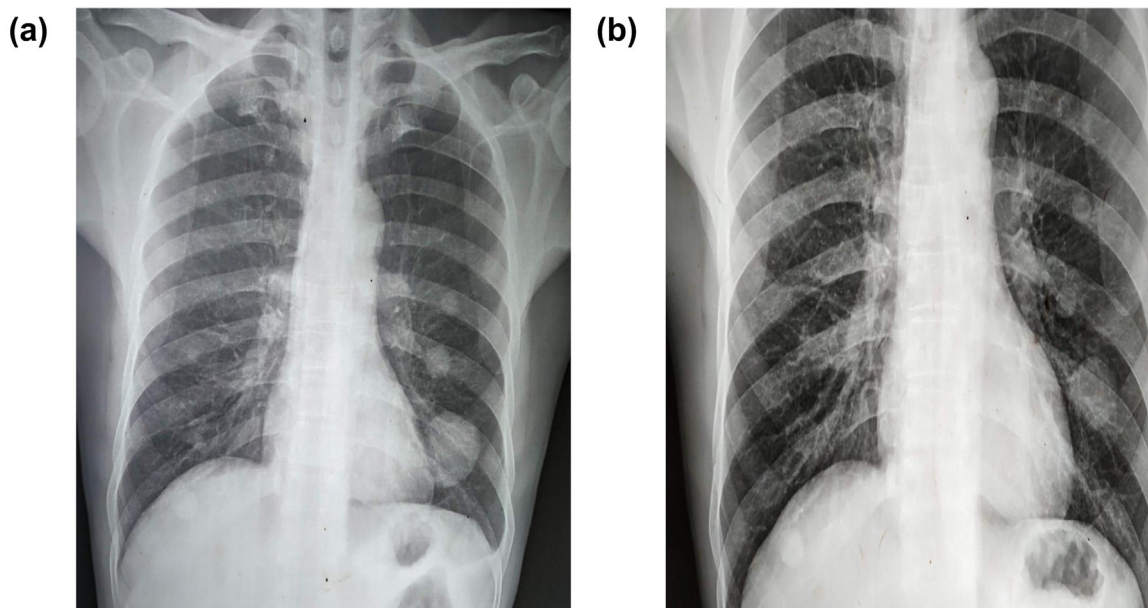


Fig. 2. Chest X-ray (a) pre-therapy, and (b) post-therapy, showing a decrease in size of the lung lesions.

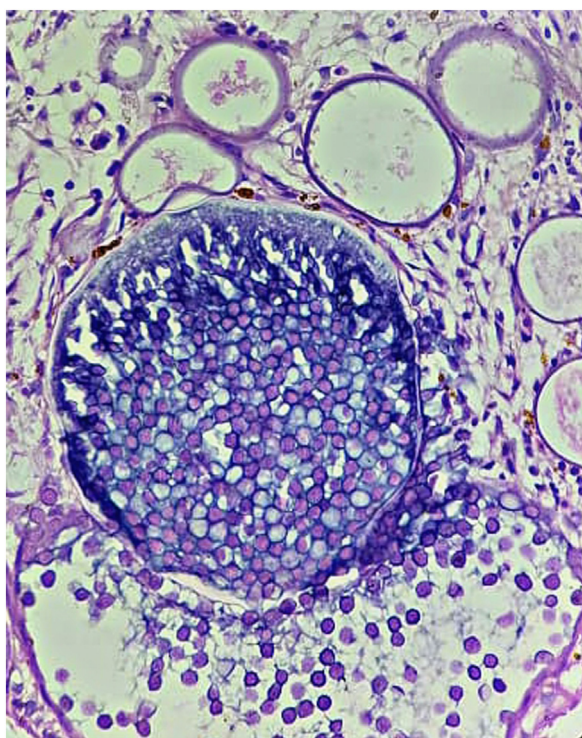


Fig. 3. Microscopic appearance (H & E 10X) showing sporangia containing numerous endospores.

involvement. Primary cutaneous rhinosporidiosis is strikingly rare even in endemic regions [1,4–8]. It means there is no history of primary nasal/ocular rhinosporidiosis and when this happens, it is easy to ignore the skin lesions or even misdiagnose them. Furthermore, rhinosporidiosis has historically been associated with lower socioeconomic status [9,10] and bathing in rivers and ponds [11]. After transepithelial transmissions in rhinosporidiosis, local and systemic spread are thought to occur by following means: direct inoculation of the pathogen through traumatized mucocutaneous barriers, autoinoculation with local spread, and distant

hematogenous/lymphatic spread [1,4–6]. Among these, direct inoculation and hematogenous/lymphatic spread are responsible respectively for primary dermosporidiosis and disseminated rhinosporidiosis [1,4–6]. Though in our case there was no history of taking bath/swimming in ponds during any period of his life, perhaps transdermal infection penetrated through abraded skin as a part of professional exposure, as he never used gloves during work.

Dermato-visceral (pulmonary) rhinosporidiosis is rare, especially in immunocompetent patients [7,8], but also in immunocompromised patients [12,13]. Though the mainstay of treatment remains complete surgical excision, it poses a threat for recurrence in many cases [1,13]. Dapsone is a trusted drug in disseminated cases and, when it is well tolerated, it not only treats the current infection, but also reduces chances of recurrence [14]. It probably inhibits maturation of sporangiospores and upregulates fibrosis in the stroma [14,15]. Dapsone has been reported to cause hemolytic anemia, especially in patients with underlying G6PD deficiency [16]. Its metabolites are also potent oxidants and can promote hemolysis [16]. However, in this case there was a DAT-positive hemolytic anemia that clearly started after a month of onset of dapsone and improved after its stoppage. Dapsone-induced autoimmune hemolytic anemia (DAT positive) probably has not been reported previously but the fact that drugs can be associated is well established [17]. However, the possibility of *Rhinosporidium seeberi* infection-induced hemolytic anemia should be taken into account, as rarely, an infection can give rise to immune hemolytic anemias [18].

Due to unavoidable reasons, dapsone had to be stopped. In addition, surgery could not be done as the disease was disseminated; hence, we put him on a multi-drug therapy [19]. Each of the drugs of this regime has some tested anti-sporicidal activities against *Rhinosporidium seeberi* infection [13,19]. With the onset of this multi-drug therapy, the friable vascular lesions disappeared fast and visceral and subcutaneous large mass-like lesions started disappearing and getting smaller in size. At the follow up, only a few of the subcutaneous lesions remained, which became smaller along with partial resolution of lung lesions.

In closing, the current case of rhinosporidiosis is of interest for its peculiar anatomical involvement, historical enigma (no contact with stagnant pond water), diagnostic dilemma, adverse reaction

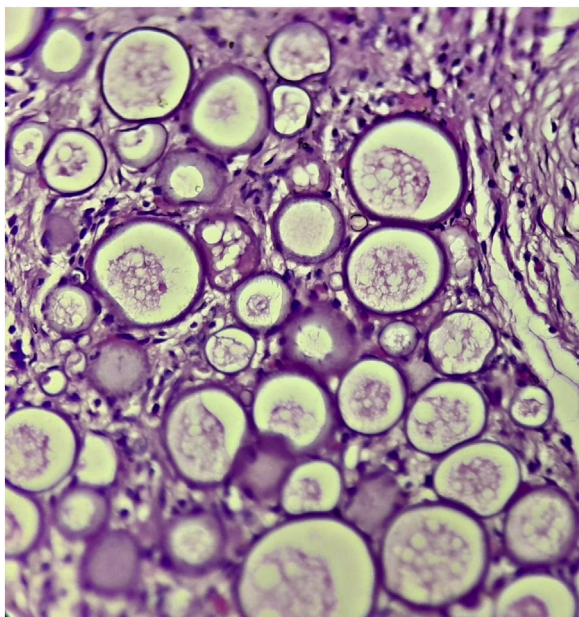


Fig. 4. High power view (H & E 40X) showing thick-walled sporangia containing spores.

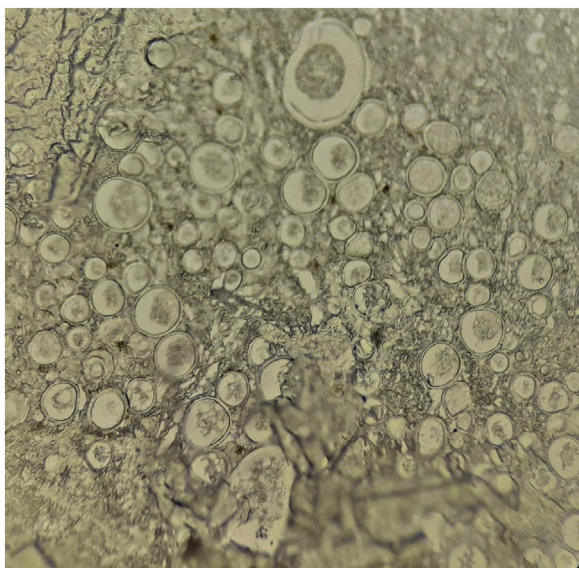


Fig. 5. KOH mount under 40X showing sporangium containing spores.

to therapeutics, and the response to a novel multi-drug regimen. We also highlight the importance of tissue diagnosis in rhinosporidiosis and even, in resource-poor set-ups, a simple histopathological diagnosis can promote an early and affordable accurate diagnosis, and subsequently, a proper therapeutic intervention.

Author contribution

All authors contributed equally to the creation of this manuscript; each fulfilled criteria as established by the ICMJE.

Funding

This work is not funded.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgement

None.

References

- [1] Töz S. *Rhinosporidium seeberi*: is it a Fungi or parasite? *Turkiye Parazitol Derg* 2020;44(December (4))258–60, doi:<http://dx.doi.org/10.4274/tpd.galenos.2020.7221> PMID: 33269573.
- [2] Herr RA, Ajello L, Taylor JW, Arseculeratne SN, Mendoza L. Phylogenetic analysis of *Rhinosporidium seeberi*'s 18S small-subunit ribosomal DNA groups this pathogen among members of the protostistan Mesomycetozoa clade. *J Clin Microbiol* 1999;37(September(9))2750–4, doi:<http://dx.doi.org/10.1128/JCM.37.9.2750-2754.1999> PMID: 10449446; PMCID: PMC85368.
- [3] Fredricks DN, Jolley JA, Lepp PW, Kosek JC, Relman DA. *Rhinosporidium seeberi*: a human pathogen from a novel group of aquatic protistan parasites. *Emerg Infect Dis*. 2000;6(May-June(3))273–82, doi:<http://dx.doi.org/10.3201/eid0603.000307> PMID: 10827117; PMCID: PMC2640875.
- [4] Prakash M, Johnny JC. Rhinosporidiosis and the pond. *J Pharm Bioallied Sci* 2015;7(April(Suppl 1))S59–62, doi:<http://dx.doi.org/10.4103/0975-7406.155804> PMID: 26015750; PMCID: PMC4439710.
- [5] Jain K, Sarfaraj SM, Sengupta M, Datta C, Chatterjee U. An unexpected host in a soft-tissue lesion of thigh. *Indian J Med Microbiol* 2020;38(July-December(3 & 4))478–80, doi:http://dx.doi.org/10.4103/ijmm.IJMM_20_236 PMID: 33154269.
- [6] Pradhan S, Sirka CS, Baisakh MR. Polymorphic presentation of disseminated cutaneous rhinosporidiosis in an immunocompetent individual. *Indian J Dermatol Venereol Leprol* 2018;84(September-October(5))614–7, doi:http://dx.doi.org/10.4103/ijdv.IJDVL_52_18 PMID: 30073987.
- [7] Rajakannu M, Sri Vengadesh G, Pai D, Jagdish S. Disseminated rhinosporidiosis - an unusual presentation with pulmonary involvement. *Int J Dermatol* 2006;45(March(3))297–8, doi:<http://dx.doi.org/10.1111/j.1365-4632.2006.02658.x> PMID: 16533233.
- [8] Sarkar NK, Mia MMR, Hasan MR. Tracheobronchial rhinosporidiosis: an uncommon life-threatening benign cause of airway obstruction. *Respirol Case Rep* 2020;8(August (7))e00653, doi:<http://dx.doi.org/10.1002/rcr2.653> PMID: 32874589; PMCID: PMC7450225.
- [9] Arseculeratne SN, Sumathipala S, Eriyagama NB. Patterns of rhinosporidiosis in Sri Lanka: comparison with international data. *Southeast Asian J Trop Med Public Health* 2010;41(1):175–91.
- [10] Jain MR, Sahal R. Rhinosporidiosis of lacrimal sac. *Ind J Opth* 1974;22:29–31.
- [11] Karthikeyan P, Vijayasundaram S, Pulimootil DT. A retrospective epidemiological study of rhinosporidiosis in a rural tertiary care centre in Pondicherry. *J Clin Diagn Res* 2016;10(5), doi:<http://dx.doi.org/10.7860/JCDR/2016/17465.7788> MC04-MC8.
- [12] Padmavathy L, Rao IL, Selvam SS, Sahoo CG. Disseminated cutaneous rhinosporidiosis in a HIV sero-positive patient. *Indian J Dermatol Venereol Leprol* 2001;67(November-December(6)) 332-3. PMID: 17664794.
- [13] George L, Dincy P, Chopra M, Agarwala M, Maheswaran S, Deodhar D, et al. Novel multidrug therapy for disseminated rhinosporidiosis, refractory to dapsone – case report. *Trop Doct* 2013;43(July(3))110–2, doi:<http://dx.doi.org/10.1177/0049475513493414> PMID: 23796478.
- [14] Kaushal S, Mathur SR, Mallick SR, Ramam M. Disseminated cutaneous, laryngeal, nasopharyngeal, and recurrent obstructive nasal rhinosporidiosis in an immunocompetent adult: a case report and review of literature. *Int J Dermatol* 2011;50(March(3))340–2, doi:<http://dx.doi.org/10.1111/j.1365-4632.2010.04509.x> PMID: 21342167.
- [15] Job A, Venkateswaran S, Mathan M, Krishnaswami H, Raman R. Medical therapy of rhinosporidiosis with dapsone. *J Laryngol Otol* 1993;107(September (9))809–12, doi:<http://dx.doi.org/10.1017/s002221510012448x> PMID: 8228595.
- [16] Lee Sm, Geetha D. Dapsone induced hemolysis in a patient with ANCA associated glomerulonephritis and normal G6PD level and implications for clinical practice: case report and review of the literature. *Springerplus* 2015;23(January (4))29, doi:<http://dx.doi.org/10.1186/s40064-015-0816-y> PMID: 25628986; PMCID: PMC4305048.

- [17] Sheikh-Taha M, Frenn P. Autoimmune hemolytic anemia induced by levofloxacin. *Case Rep Infect Dis* 2014;2014:201015, doi:<http://dx.doi.org/10.1155/2014/201015> Epub 2014 Jun 12. PMID: 25024854; PMCID: PMC4082951.
- [18] Capes A, Bailly S, Hantson P, Gerard L, Laterre PF. COVID-19 infection associated with autoimmune hemolytic anemia. *Ann Hematol* 2020;99(July(7)):1679–80, doi:<http://dx.doi.org/10.1007/s00277-020-04137-9> Epub 2020 Jun 16. PMID: 32542444; PMCID: PMC7295688.
- [19] Arseculeratne SN. Chemotherapy of rhinosporidiosis: a review. *J Infect Dis Antimicrob Agents* 2009;26(1):21–7.