

Acute paracoccidioidomycosis with duodenal and cutaneous involvement and obstructive jaundice



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ABSTRACT

Paracoccidioidomycosis (PCM) is the most widespread endemic mycosis in Latin America. If PCM is not diagnosed and treated early and adequately, the endemic fungal infection could result in serious sequelae. We report a case of PCM with duodenal and cutaneous involvement simulating cholangitis that was initially misdiagnosed as a lymphoproliferative disease. Clinicians should consider acute paracoccidioidomycosis in the differential diagnosis of jaundice and/or signs/symptoms of cholangitis developing in young patients from paracoccidioidomycosis endemic regions.

1. Introduction

The genus *Paracoccidioides* spp. contains a species complex, comprising at least 2 species, *Paracoccidioides brasiliensis* and *P. lutzii*, which are the etiological agents of paracoccidioidomycosis (PCM). This complex has a geographically restricted habitat [1], and is thermally dimorphic, as it switches from the non-pathogenic mycelial form at ambient environmental temperatures to the pathogenic multiple-budding yeast form when exposed to temperatures similar to those of the mammalian host [2–4]. Infection of the host is thought to occur via the inhalation of infective airborne propagules like conidia or, possibly, mycelial fragments from the environment. Inhaled propagules then differentiate in the lungs into the pathogenic yeast form, after which the fungus disseminates to other organs of the host [5].

PCM is a neglected health-threatening human systemic mycosis endemic to Latin America where up to ten million people are thought to be infected [2,6]. Disease can progress slowly, with roughly five new cases of disease per million infected individuals per year, with a male to female ratio of 13 to 1. About 80% of PCM cases occur in Brazil, followed by Colombia and Venezuela [2,6–8].

The genus *Paracoccidioides* encompasses two distinct species, *P.*

brasiliensis and *P. lutzii*. *P. lutzii* is a single monophyletic and recombining population reported to date in central, southwest, and north Brazil and Ecuador [3,4]. *P. brasiliensis* is monophyletic and comprised of distinct lineages classified as S1, PS2, PS3, and PS4. The S1 lineage is associated with the majority of PCM cases and is widely distributed in South America. PS2 has been identified to date only in Brazil and Venezuela, whereas PS3 is mainly found in regions of endemicity in Colombia. Recently, a novel lineage, PS4, was described from a region of Venezuela [4]. Isolates from each of these phylogenetic lineages of *Paracoccidioides* can infect humans; however they may vary in virulence and culture adaptation and can elicit different immune responses by the host. One feature that is correlated with different rates of infection is variation in the number of infective conidia [4,5].

The successful invasion of host tissues by the fungus is a complex event, usually involving various regulatory mechanisms of cellular homeostasis and the expression of different virulence factors during infection that allows the fungi to spread to different organs in the host [4,5]. This parasite shows tropism towards the monocyte-macrophage system in acute-subacute forms of the infection, and paracoccidioidomycosis may occur in mucosa-associated lymphoid tissues (MALT) in the gastrointestinal tract (Peyer's patches) [7]. Human NK

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cells have been divided into CD56 and CD56 subsets possessing either lytic or IFN- γ secretory function. A subset of tonsillar NK cells was shown to express the receptor Nkp44, which is not present on blood NK cells unless they are activated in vitro with IL-2 or IL-15. Nkp44 NK cells are present in tonsils and in Peyer's patches of the ileum and the appendix [3,8]. NK-22 cells are also found in mouse MALT and appear in the small intestine lamina propria during bacterial infection suggesting that NK-22 cells provide an innate source of IL-22 that may help constrain inflammation and protect mucosal sites [3,8]. Intra and extra peritoneal lymph nodes may facilitate spread of infection to the psoas muscles in juvenile paracoccidioidomycosis [7].

We report on a rare case of PCM with duodenal and cutaneous involvement simulating cholangitis that was initially misdiagnosed as a lymphoproliferative disease. The aim of this case report is to strengthen awareness for acute paracoccidioidomycosis in the differential diagnosis of jaundice and/or signs/symptoms of cholangitis developing in young patients from paracoccidioidomycosis endemic areas.

2. Case

A 19-year-old male patient, born and raised in the urban area of São Sebastião do Paraíso, Minas Gerais, Brazil, with no history of traveling to the countryside complained of low back pain for 10 days, that evolved to severe epigastric pain in two days later. Upper gastrointestinal endoscopy (UGE) was performed and showed two duodenal ulcers, measuring approximately 1.5 cm each, located in the anterior wall and bulb in the transition to the second portion of the duodenum, with regular edges, and covered by fibrin (Fig. 1); Culture for *Helicobacter pylori* was performed and it yielded negative results; an ulcer biopsy was not performed at that time. Omeprazole 40 mg/day *per oris* was prescribed, with no improvement of the symptoms. Six days later he developed jaundice, choluria, nausea, abdominal pain, fever, diarrhea and generalized lymphadenopathy.

The patient was referred to São Francisco Hospital, Ribeirão Preto, São Paulo (day 0), with the presumptive diagnosis of cholangitis. On physical examination, the patient presented with a low-grade fever (38 °C), jaundice, distended abdomen painful on palpation, and hepatosplenomegaly. There was cervical, subclavian and inguinal lymphadenopathy. Multiple acneiform lesions on the face and brownish maculopapular lesions with low flaking on the face and abdomen were observed (Fig. 2). Laboratory tests from day 0 revealed anemia, leukocytosis (white blood cell count at $18.6 \times 10^3/\mu\text{L}$ with a left shift), increased liver enzymes (aspartate aminotransferase = 156 U/L, alanine aminotransferase = 99 U/L, phosphatase alkaline = 81 U/L,

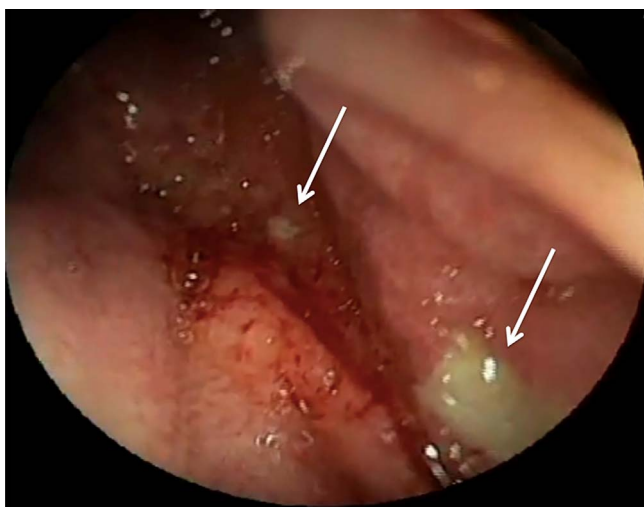


Fig. 1. Two duodenal ulcers with regular edges, covered by fibrin, involving the anterior wall and bulb in the transition to the second portion of the duodenum.

gamma-glutamyl transferase = 92 U/L), total bilirubin 6.28 mg/dl (direct = 4.98 mg/dl and indirect = 1.3 mg/dl), and increased inflammatory activity test (C-reactive protein = 168 mg/dl). Serological tests for hepatitis A, B and C, syphilis, HIV, mononucleosis, toxoplasmosis, cytomegalovirus and brucellosis were negative.

Computed tomography (CT) of the abdomen on day +2 showed hepatosplenomegaly, retroperitoneal and periportal coalescent lymphadenopathy, intra-abdominal free fluid; intrahepatic and extrahepatic biliary ductal dilatation was not observed. These data were confirmed by abdominal magnetic resonance imaging (MRI), and diagnostic hypothesis of lymphoproliferative disease was suggested (Fig. 3). On chest radiography, prominent pulmonary hilum and slight reduction in the transparency of the right hemithorax base with apparent elevation of the diaphragm were observed. Chest CT showed centrilobular micronodules scattered in the lungs, predominantly in the middle lobes and right, mediastinal lymphadenopathy and right pleural effusion (Fig. 4).

Biopsies of cervical and inguinal lymph nodes, and two abdominal papules were performed (day +4). Microscopic examination of cervical and inguinal lymph nodes and skin biopsies demonstrated multiple, narrow base, budding yeast cells the “steering wheels” of *Paracoccidioides spp* on Grocott's methenamine silver (GMS) staining (Figs. 5 and 6).

The diagnosis of acute/subacute paracoccidioidomycosis, juvenile type, was established. Treatment with intravenous amphotericin B (0.75 mg/kg/day) was started and a cumulative dose of 1.3 g was reached on day +40 with relevant clinical improvement. He was discharged (day +50) with instructions to return for follow-up in the outpatient clinic and amphotericin B was replaced for itraconazole 200 mg/day. Complete blood count, liver enzymes and inflammatory activity tests have remained in normal levels. UGE and abdominal CT performed in the sixth month of follow up were normal. The patient has been treated with itraconazole 200 mg/day for one year and remains asymptomatic.

3. Discussion

PCM is an endemic infection in Latin America, of special importance due to severity and clinical impact of some of its clinical forms [7,9]. In this report, we describe the diagnostic challenge of a severe and atypical acute systemic disease caused by *Paracoccidioides spp.* identified through biopsies of cervical and inguinal lymph nodes, and two abdominal papules. Paracoccidioidomycosis is predominantly a rural infection but the patient came from an urban area, and denied visiting or previously having lived in rural areas.

Paracoccidioides species complex causes a localized infection that may progress to systemic granulomatous disease with tegumentary and visceral disease [2,7]. Agents of systemic mycoses, such as *P. brasiliensis* and *P. lutzii*, express factors that facilitate their survival in severe conditions inside the host cells and tissues, and as such, benefit the disease's development (fungal dimorphism, alpha glucan in the yeast cell wall, etc).

PCM is considered a neglected infectious disease, despite being the first cause of death among all systemic mycoses in immunocompetent patients and eighth among chronic or recurrent infectious and parasitic diseases in Brazil [2,7]. The acute/subacute paracoccidioidomycosis (juvenile type) clinical presentation is responsible for 3–5% of cases of the disease, predominantly in children and adolescents. Eventually it may affect individuals up to 35 years old [2,9]. This clinical form is characterized by fast onset and progress of the mycosis. Patients usually seek medical attention between 4 and 12 weeks of illness [7,9]. In decreasing order of frequency, the presence of enlarged lymph nodes, digestive symptoms, hepatosplenomegaly, osteo-articular involvement and skin lesions are the main forms of presentation of this systemic mycosis [7,9–11]. Skin lesions include papules, papules and crusts, acneiform lesions with papules and pustules. The face is the most

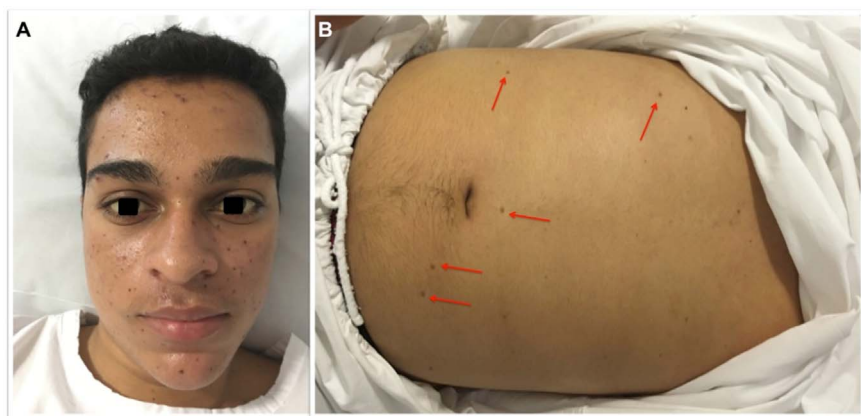


Fig. 2. (a) Scleral jaundice and multiple acneiform lesions on the face; (b) hepatosplenomegaly and brownish maculopapular lesions with low flaking on the abdomen (red arrows).

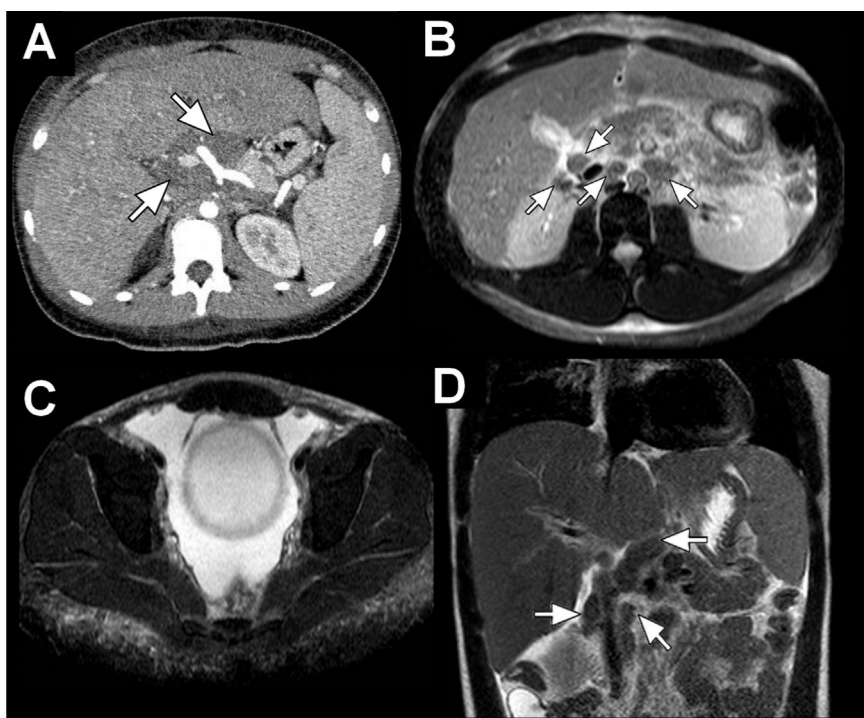


Fig. 3. (A) Abdomen axial CT after intravenous administration of contrast, arterial phase, featuring hepatosplenomegaly and periportal coalescent lymphadenopathy (arrows); (B-D): Abdominal MRI, T2-weighted sequences with fat saturation in the axial planes (B, C) and T2 in the coronal plane (D), showing lymphadenopathy already described (arrows) and intra-abdominal free fluid inside pelvis (C).

frequently affected site. Scattered lesions all over the body suggest severe disease. Nodular, verrucous lesions with or without ulceration may occur as well as elevated plaques. Bowel involvement (duodenal ulcers) observed in this case also occurred in 15% of subjects in a cohort of 20 children with paracoccidioidomycosis [7]. The increase in lymph nodes near the hepatic hilum can lead to obstructive jaundice [12–14]. Liver involvement in PCM is frequently seen in chronic multifocal (disseminated) forms. The extrinsic compression of common bile duct by lymph nodes is followed by jaundice. Other causes of jaundice are intraluminal granulomatous lesions in the common bile duct, hepatitis caused by *Paracoccidioides* spp. complex or pancreatic PCM [13,14]. A variety of diseases are included under the umbrella term cholangitis, including hepatobiliary diseases with an autoimmune pathogenesis and disease processes associated with intraductal stones and infectious etiologies [15]. Although PCM rarely involves intrahepatic bile ducts, in endemic areas it should be considered in the differential of obstructive jaundice.

In contrast to other fungal infections such as cryptococcosis, histoplasmosis and disseminated candidiasis, PCM is not usually associated with immunosuppressive diseases [2,7]. However, acute and sub acute profile of paracoccidioidomycosis is described in HIV co-infected

patients [6]. The gold standard for PCM diagnosis is the detection of fungal elements suggestive of *Paracoccidioides* spp in fresh examination of sputum samples or other clinical specimens (lymph node aspirate) and/or biopsy specimens as well as mycologic culture with fungal isolation. Serological diagnosis (anti-*Paracoccidioides* spp specific antibodies) has limited value because of cross-reactivity with other fungi. It may have value in assessing prognosis. Serologic tests are useful for therapeutic follow up. Criteria for cure and discharge include clinical, serological and radiologic evaluation [2,8].

Endoscopic evaluation in this case showed two lesions in the intestinal mucosa presumably duodenal PCM. Therapeutic response to amphotericin B, demonstrated by follow up endoscopy showing involution of ulcers, further supports this diagnosis. The PCM is the main systemic mycosis in South America, with heterogeneous distribution and must be included in the differential diagnosis of patients with lymphadenopathy associated with systemic symptoms. Highlights of this case report are acute onset with epigastric pain followed by rapid health deterioration, the initial clinical picture suggesting cholangitis, with associated ascites, pleural and pericardial effusions, and cutaneous papular lesions of juvenile paracoccidioidomycosis. The authors emphasize that clinicians should consider acute paracoccidioidomycosis in

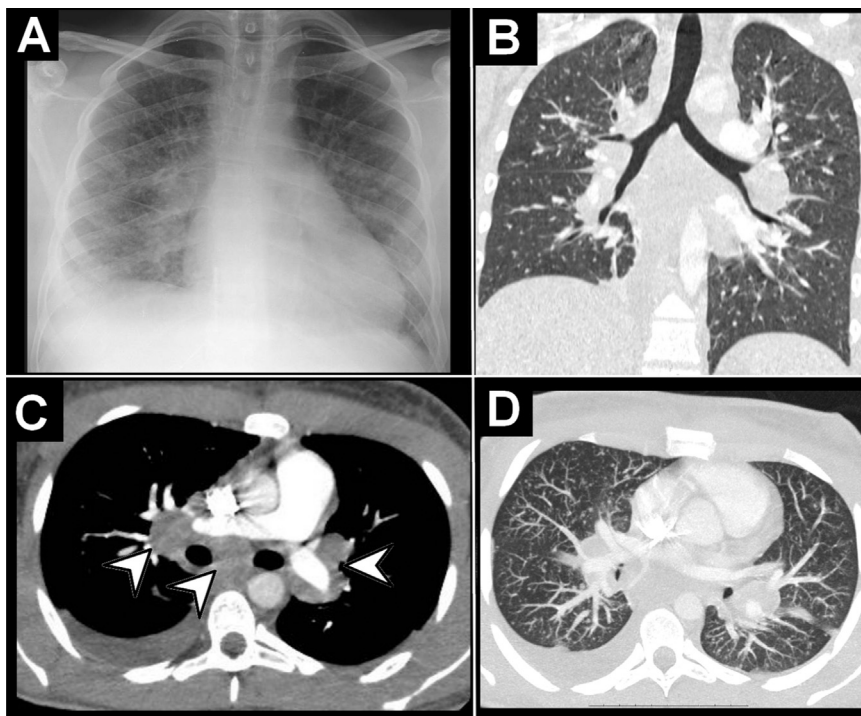


Fig. 4. (A) Chest radiography showing prominent pulmonary hilum and slight reduction in the transparency of the right hemithorax base with apparent elevation of the diaphragm; (B-D). CT scan images after administration of intravenous contrast - reconstruction in the coronal plane in pulmonary window (B), axial section with mediastinal window (C) and maximum intensity projection in the axial plane with pulmonary window (D) - demonstrating the centrilobular micronodules scattered in the lungs (B, D), pulmonary hilum and infracarinal lymphadenopathy (arrowheads) and a little right-sided pleural effusion (C).

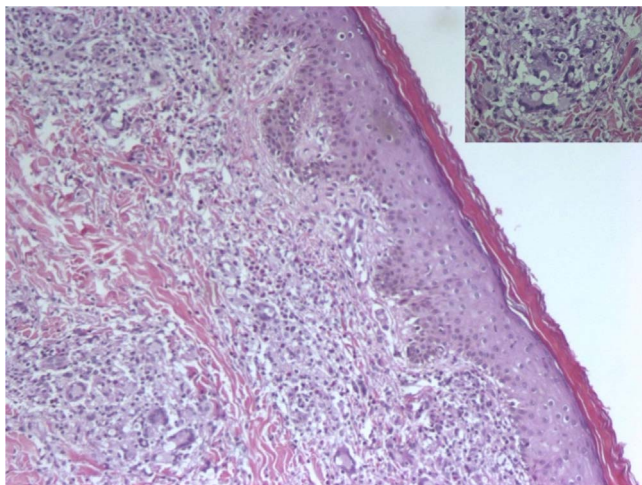


Fig. 5. Granulomatous reaction with *Paracoccidioides* spp yeast cells inside multinucleated giant cell (insert) (hematoxylin and eosin staining, 100×).

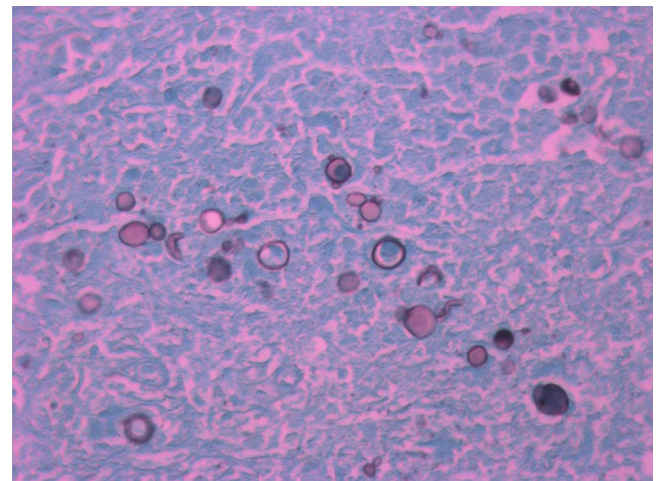


Fig. 6. Multiple, narrow base, budding yeast cells the “steering wheels” of *Paracoccidioides* spp (Grocott's methenamine silver staining, 400×).

the differential diagnosis of jaundice and/or signs/symptoms of cholangitis developing in young patients from paracoccidioidomycosis endemic regions.

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Conflict of interest

The authors have no conflicts of interest to declare and confirm that each one has made substantial contributions to the information or materials submitted for publication.

References

- [1] E. Bagagli, R.C. Theodoro, S.M. Bosco, J.G. McEwen, *Paracoccidioides brasiliensis*: phylogenetic and ecological aspects, *Mycopathologia* 165 (4–5) (2008) 197–207.
- [2] M.A. Shikanai-Yasuda, Q. Telles Filho Fde, R.P. Mendes, A.L. Colombo, M.L. Moretti, Guidelines in paracoccidioidomycosis, *Rev. Soc. Bras. Med Trop.* 39 (3) (2006) 297–310.
- [3] J.F. Muñoz, J.E. Gallo, E. Misas, M. Priest, A. Imamovic, S. Young, et al., Genome update of the dimorphic human pathogenic fungi causing paracoccidioidomycosis, *PLoS Negl. Trop. Dis.* 8 (12) (2014) e3348.
- [4] J.F. Muñoz, R.A. Farrer, C.A. Desjardins, J.E. Gallo, S. Sykes, S. Sakthikumar, et al., Genome Diversity, Recombination, and Virulence across the Major Lineages of *Paracoccidioides*, *mSphere* 1 (5) (2016) (pii: e00213–16).
- [5] H.C. de Oliveira, P.A. Assato, C.M. Marcos, L. Scorzoni, E. de Paula, A.C. Silva, F. Da Silva Jde, et al., *Paracoccidioides*-host Interaction: an Overview on Recent Advances in the Paracoccidioidomycosis, *Front Microbiol* 6 (2015) 1319.
- [6] R. Martinez, Epidemiology of paracoccidioidomycosis, *Rev. Inst. Med Trop. Sao Paulo* 57 (Suppl 19) (2015) 11–20.
- [7] S.A. Marques, Paracoccidioidomycosis: epidemiological, clinical, diagnostic and treatment up-dating, *Bras. Dermatol.* 88 (5) (2013) 700–711.
- [8] M. Cella, A. Fuchs, W. Vermi, F. Facchetti, K. Otero, J.K. Lennerz, et al., A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity,

- Nature 457 (7230) (2009) 722–725.
- [9] F. Bellissimo-Rodrigues, A.A. Machado, R. Martinez, Paracoccidioidomycosis epidemiological features of a 1,000-cases series from a hyperendemic area on the southeast of Brazil, *Am. J. Trop. Med Hyg.* 85 (3) (2011) 546–550.
- [10] R.M. Queiroz, M.P. Gomes, M.V. Valentin, Pulmonary paracoccidioidomycosis showing reversed halo sign with nodular/coarse contour, *Radiol. Bras.* 49 (1) (2016) 59–60.
- [11] L.G. Abud, R.M. Queiroz, T.G. Abud, Concomitant pulmonary and central nervous system paracoccidioidomycosis with cerebellar abscess, *Rev. Soc. Bras. Med Trop.* 48 (6) (2015) 789.
- [12] F.F. Oliveira, S.T. Machado, J.S. Rozas, E.C. Oliveira, A.H.C. Zaccariotto, V. Segatelli, Duodenal paracoccidioidomycosis, *Rev. Fac. Cienc. Med Sorocaba* 11 (3) (2009) 32–34.
- [13] T.B. Lima, M.A. Domingues, C.A. Caramori, G.F. Silva, C.V. de Oliveira, S. Yamashiro Fda, et al., Pancreatic paracoccidioidomycosis simulating malignant neoplasia: case report, *World J. Gastroenterol.* 19 (34) (2013) 5750–5753.
- [14] E. Cazzo, J.A. Ferrer, E.A. Chaim, Obstructive jaundice secondary to paracoccidioidomycosis, *Trop. Gastroenterol.* 36 (1) (2015) 46–47.
- [15] S.P. Lee, J.R. Roberts, R. Kuver, (F1000Res), *Chang. faces cholangitis* (2016) 5 (pii: F1000 Faculty Rev-1409).