Paracoccidioidomycosis: Case Report and Review


A previously well 59-year-old man presented with paracoccidioidomycosis, more than 15 years after leaving South America. He failed to respond to conventional therapies, first with oral itraconazole and then with amphotericin B plus sulfadiazine, and eventually died of recurrent arterial emboli possibly due to paracoccidioidomycotic aortitis. This patient's presentation demonstrates the difficulties that may be encountered in diagnosing and managing this disease. Paracoccidioidomycosis should be suspected in patients with an appropriate travel history who experience weight loss and have pulmonary, mucosal, and cutaneous lesions. This article comprehensively reviews the literature, with emphasis on epidemiology, clinical presentation, diagnosis, and therapy with imidazole antifungal medications.

Paracoccidioidomycosis is a multisystem infection that affects predominantly adult males from rural areas of South America [1-3]. It often presents with the triad of pulmonary, oral mucosal, and skin lesions [1, 2]. The current treatment of choice is a 6- to 12-month course of an imidazole such as ketoconazole or itraconazole [4-12]. We recently treated a patient with paracoccidioidomycosis who failed to respond to therapy, first with itraconazole and then with amphotericin B plus sulfadiazine, and eventually died of recurrent arterial emboli, a complication rarely described in the literature.

Case Report

A 59-year-old man from Calgary, Alberta, Canada, presented in April 1995 because of a 3-month history of anorexia, generalized muscle weakness, and a 20-kg weight loss (resulting in a weight that was 75% of the ideal body weight for his height). He also complained of painful oral ulcers and progressive shortness of breath on exertion, associated with a nonproductive cough. He denied any history of fever or night sweats.

His medical history was significant for alcohol abuse, a 60-pack-year smoking habit, and a bleeding gastric ulcer that required surgical intervention in 1975. He was not receiving medications at the time of admission. He denied prior tuberculosis infection as well as any recent or remote international travel. He worked as a local truck driver and had last been out of the province on a holiday to California in 1988. On questioning later during the hospitalization, he admitted to having worked in Brazil between 1958 and 1964 and in Argentina between 1979 and 1981.

Examination revealed that the man was cachectic but in no acute distress and had a temperature of 38.3°C. Inspection revealed the following: an ulcerative lesion on the tip of his nose; an erythematous papular rash on the scrotum, buttocks, and left leg; tender, raised hyperkeratotic papules on the soles of both feet; and an infiltrative lesion on the posterolateral aspect of his tongue (figure 1). The respiratory examination revealed fine inspiratory crackles bilaterally throughout the lower lung zones. Apart from a sodium level of 123 mmol/L, the complete blood cell count and serum electrolyte panel values were normal at the time of admission.

Microscopy of the urine revealed pyuria. Blood and urine cultures were negative. Roentgenography of the chest showed a fine reticular pattern throughout both lower lobes (figure 1). CT of the chest confirmed an interstitial pattern in both lower lobes as well as numerous small cavitating peripheral nodules. A 3-cm prostate nodule was evident on CT of the pelvis. HIV serology was negative.

A cytological examination of bronchial washings on day 2 after admission was negative for Pneumocystis carinii, fungi, acid-fast bacilli, and malignant endobronchial cells. Fungal cultures initially yielded only scant amounts of Candida albicans. Urine cultures were repeatedly negative for bacteria, including mycobacterial organisms. Chest roentgenographic findings continued to show progression of disease during the hospitalization, and bronchoscopy was repeated to obtain transbronchial bite biopsy specimens. The biopsy specimens contained predominantly noncaseating granulomas; intracellular and extracellular fungal elements evident on histologic sections were not pathognomonic of a specific mycotic infection (figure 2A-2C). The biopsy specimens were not cultured for fungi.

On day 16 a thoracoscopic lung biopsy was performed and tissue was sent for culture. After 6 days of incubation at 35°C, blood agar cultures yielded scant yeast, which was provisionally identified as Paracoccidioides brasilensis (figure 2D). Identification was subsequently confirmed by the National Ref-
Figure 1. A roentgenogram of the chest (A) of a 59-year-old man who was later found to have paracoccidioidomycosis was obtained on day 6 after admission and revealed a diffuse interstitial pattern throughout both lower lobes. An infiltrative lesion on the posterolateral margin of the tongue (B) and tender, raised hyperkeratotic papules on the plantar aspect of the feet (C) were noted at the time of admission.

Lesions on the nose and feet were also biopsied. These revealed granulomatous dermatitis with the presence of several yeast cells, and cultures yielded *P. brasiliensis* after 16 and 30 days, respectively. Because of persistent hyponatremia, hyperkalemia, and hypotension, a 1-hour intravenous-adrenocorticotropic-stimulation test of adrenal function was performed; an increment of 83–490 nmol/L was achieved, suggesting impaired but not absent adrenal gland function. Therapy with oral itraconazole at a dosage of 100 mg/d for 6 months was commenced, and the patient returned home on day 29.

He was readmitted 6 weeks later because of features of progressive systemic paracoccidioidomycosis, including further deterioration in his respiratory and nutritional status, despite the therapy with itraconazole. A weight loss of 8 kg was documented on readmission. He also complained of excruciating right-foot pain, consistent with worsening and now-necrotic skin lesions on the soles of his feet. Roentgenography of the chest revealed progressive pulmonary infiltrates. However, pyuria was now absent. Combination therapy with intravenous amphotericin B (1 mg/[kg·d]) and oral sulfadiazine (1 g q.i.d.) was initiated. A nasogastric feeding tube was inserted for enteral dietary supplementation.

By day 10 his condition was improving systemically and he had gained 3.5 kg. On day 11 his right leg was cold, pulseless, and painful, and transfemoral angiography demonstrated complete occlusion of the right common iliac artery. Urokinase infusion failed to improve circulation to the leg. There was no clinical or electrocardiographic evidence of atrial fibrillation or recent myocardial infarction. On day 17, despite an intravenous heparin infusion, an acute abdomen developed; laparotomy revealed an ischemic bowel.

Two meters of bowel (from mid-jejunum to transverse colon) was resected. Pathology confirmed the ischemic changes. The small bowel was sectioned, and specific examinations for granulomas and fungal elements were negative. No emboli or thrombi of mesenteric arteries were identified.

Postoperatively, hypoxic respiratory failure developed, and the clinical picture was suggestive of adult respiratory distress syndrome. He died on day 22, 2 days after laparotomy. Consent for autopsy was not given.
Figure 2. Histologic examination of open-lung biopsy specimens from the patient in figure 1 revealed multiple granulomata (A), mostly noncaseating, of no specific distribution (left upper and lower corners and right side of image) (stain, hematoxylin and eosin [H/E]; original magnification, ×40); (B) isolated pulmonary granulomata with caseous necrosis (H/E, ×100); and (C) numerous yeast cells, seen on Grocott-Gomori methenamine–silver nitrate staining (×100). Pilot’s-wheel budding (D) is typical of the yeast cell of P. brasiliensis (stain, calcofluor white; ×1,000).

Discussion

Infection with P. brasiliensis is virtually exclusive to South America: most reported cases occur in Brazil, Venezuela, Argentina, and Colombia, and the remainder occur in Latin America [1–3]. The organism is believed to lie dormant in soil, infecting humans via the respiratory route [13]. Primary infection is established in the lungs and can be contained there, with the possibility of reactivation up to 40 years later, or can disseminate early [13–15]. Person-to-person infection does not occur [2].

There are two forms of paracoccidioidomycosis. The less common is the subacute variety, which accounts for 5% of cases, affects mostly young adults, has a rapidly progressive course, and is associated with a high mortality rate [2]. The chronic progressive adult form accounts for the majority of cases and affects predominantly males between the ages of 30 and 60 years [2, 16]. Adult disease can be disseminated at onset (as it is in 75% of all patients) or can be restricted to the lungs [17]. Disseminated infection classically causes fever, weight loss, and anorexia as well as a triad of pulmonary, mucosal, and cutaneous lesions [1, 2]. Table 1 summarizes organ involvement in patients with disseminated paracoccidioidomycosis [16, 18, 19].

Lung involvement usually presents nonspecifically with cough, progressive dyspnea, and diffuse inspiratory crackles on examination. Chest radiography often reveals nodules and/or cavities superimposed on a diffuse interstitial or fibrotic pattern, typically involving the mid and lower lung zones [15].

Mucosal lesions are usually painful and appear infiltrated or ulcerative. They can be located on the lips, the tongue, and (less commonly) in the nasopharynx or larynx; lesions on the latter cause a degree of dysphonia [10, 18]. Skin lesions can be extremely polymorphic but often appear as warty, hyperkeratotic plaques or ulcerative, crusted lesions. They are commonly found near the mouth, anus, or genitalia [1, 18, 19].
biopsies of lung, lymph node, or skin). It can be difficult to distinguish infection due to this organism from other fungal infections, such as those caused by \textit{Coccidioides immitis}, \textit{Histoplasma capsulatum}, \textit{Aspergillus fumigatus}, and \textit{Cryptococcus neoformans}.

Histologic examination of tissue specimens is crucial for diagnosis, as the distinction between paracoccidioidomycosis and other fungal infections can be challenging. The patient's history, clinical presentation, and laboratory findings contribute to the differential diagnosis.

\textbf{Table 1. Organ involvement in cases of disseminated paracoccidioidomycosis reported in the literature.}

<table>
<thead>
<tr>
<th>Organ(s) involved</th>
<th>No. of cases with indicated involvement, per study</th>
</tr>
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<tbody>
<tr>
<td>Lungs, Mouth (nasopharynx, oropharynx, and/or larynx)</td>
<td>12/185/23/172/24/219 (71)</td>
</tr>
<tr>
<td>Skin</td>
<td>13/6/19/38/11</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>9/8/16/33 (10)</td>
</tr>
<tr>
<td>Spleen and/or liver</td>
<td>NR/2/15/17 (6)</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>1/0/0/1 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1/3/2/6 (2)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are percentages of total number of cases.

Adenopathy, occasionally complicated by draining sinuses, may involve cervical, axillary, or mediastinal lymph nodes [20, 21]. Adrenal involvement can range from subtle adrenal dysfunction to overt insufficiency. Involvement of the vascular system, CNS, spleen, liver, and male genitourinary tract have been reported less commonly [1].

The differential diagnosis of paracoccidioidomycosis is broad and includes other wasting diseases such as tuberculosis (which coexists in 10%-25% of cases [15, 22]), histoplasmosis, and disseminated malignancy [1, 2].

A common sequela of treated paracoccidioidomycosis is fibrotic scarring in the affected organs, particularly the lungs [10, 23]. Lung fibrosis may be severe, resulting in cor pulmonale. Adrenal involvement can be permanent, in the form of chronic adrenal insufficiency. There are case reports documenting recovery of adrenal gland function after successful long-term treatment [24, 25].

\textit{P. brasiliensis} is a dimorphic fungus that can exist either as an oval yeast cell with a distinguishing pilot's-wheel appearance (figure 2, D), when grown at 37°C, or as a mold, when grown at 19°C-28°C [1, 2]. In suspected cases of infection, laboratory diagnosis can occasionally be made by KOH examination of sputum or pus [1]. However, in cases that rarely encounter paracoccidioidomycosis, definitive diagnosis usually involves cultures of tissue specimens (excluding biopsies of lung, lymph node, or skin).

Typical histologic findings include granulomas and intracellular fungal elements (figure 2, A–C) [1, 2]. Unless the characteristic budding forms of \textit{P. brasiliensis} are seen on histology, it can be difficult to distinguish infection due to this organism from other fungal infections, such as those caused by \textit{Blastomyces dermatitidis}, \textit{Histoplasma capsulatum}, and \textit{Cryptococcus neoformans}. Fungal cultures then become essential to the diagnosis [1, 2]. Immunohistochemistry of mucocutaneous biopsy specimens has been recently described [26] and may become a useful diagnostic technique.

Serological tests have been described but are not routinely available in North American centers. The double-immunodiffusion test for circulating antibodies has a sensitivity and specificity of 91% and 100%, respectively [1, 2, 27]. Counterimmunoelectrophoresis is also a very sensitive (95%) and specific (100%) test [2, 27]. The CF test is of low specificity but is quantitative and can be used to follow response to therapy [2, 27].

Treatment of paracoccidioidomycosis is difficult but can be successful when the appropriate antifungal medications are used in conjunction with aggressive dietary supplementation. Current medications include the sulfonamides and amphotericin B (often in combination), as well as the oral imidazoles, ketoconazole, itraconazole, and fluconazole.

Sulfonamides were first used in 1940 and prior to the introduction of amphotericin B were the mainstay of therapy [28]. Sulfadiazine, at a dosage of 4–6 g/d in divided doses, has been shown to be 70% effective in inducing remission [2]. It is a relatively inexpensive and nontoxic antifungal agent that has fallen out of favor because of the requirement for prolonged treatment (often for >5 years) and the high relapse rate (which approaches 25%) following its withdrawal [1, 2].

Amphotericin B was first used in the late 1950s and is still prescribed for severe disseminated disease [19, 29]. A cumulative dose of 1.2–3.0 grams administered intravenously is combined with sulfonamides, as amphotericin alone is not usually curative [19]. Combination therapy for severe disseminated disease produces remission of symptoms in 50%-70% of cases, but as many as 20%-30% of those treated successfully will relapse [2].

Table 2 summarizes the literature on the prescribed use of imidazole antifungal medications for paracoccidioidomycosis. A total of 14 articles from 1978 to 1992 were reviewed [3–12, 16, 30–32]. Four were excluded: three [30–32] provided insufficient data for comparisons and one [3] was in reference to a patient group from a larger study already included in table 2. The remaining 10 publications listed in table 2 are descriptive reports of uncontrolled studies that present data consistent with level V evidence [33].

The oral imidazoles have become popular over the past 16 years, following the first prescribed use of ketoconazole in 1978. Ketoconazole, at a dosage of 200–400 mg/d for 6–12 months, can achieve clinical cures within 1 year for 84%-90% of patients [2, 4, 5, 10]. Relapse is not uncommon, however, and has been documented in 7%-11% of patients 3 years after full-course therapy [2, 34]. Possible side effects of high-dose ketoconazole administration include hepatic, gonadal, and adrenal dysfunction [2, 4, 35].

Itraconazole is now considered the drug of choice for paracoccidioidomycosis because it can be used for a shorter course (3–6 months), with fewer side effects and a lower relapse rate.
Table 2. Imidazole therapies used in cases of paracoccidioidomycosis described in the literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Number of patients with indicated organ involvement</th>
<th>Duration of disease: median (range)</th>
<th>No. (%) of patients previously treated*</th>
<th>Medical treatment (duration)</th>
<th>Outcome at the end of treatment period, for no. (%) of patients</th>
<th>Lost to follow-up</th>
<th>Who relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>[4]</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
<td>20 (41)</td>
<td>Ket, 200–400 mg/d (1–6 mo)</td>
<td>42 (84) 7 (14) 1 (2) 0</td>
<td>1 NR</td>
<td></td>
</tr>
<tr>
<td>[5]</td>
<td>46</td>
<td>31, L; 27, M; 14, S; 16, L, N</td>
<td>NR</td>
<td>NR</td>
<td>Ket, 200 mg/d (6–12 mo)</td>
<td>5 (9) 32 (70); major improvement for 30</td>
<td>4 3 (of 30 followed for 12–24 mo)</td>
<td></td>
</tr>
<tr>
<td>[6]</td>
<td>30</td>
<td>11, L; 22, M; 3, S; 9, L, N</td>
<td>7 mo (1–48 mo)</td>
<td>9 (30)</td>
<td>Ket, 400 mg/d (3–7 mo)</td>
<td>25 (83) 3 (10) 0 0</td>
<td>2 0 (of 20 followed for 3–12 mo)</td>
<td></td>
</tr>
<tr>
<td>[7]</td>
<td>16</td>
<td>8, L; 5, M; 3, S; 9, L, N</td>
<td>7 mo (2–72 mo)</td>
<td>10 (63)</td>
<td>Ket, 200–600 mg/d (2–19 mo)</td>
<td>11 (69) 5 (31) 0 0</td>
<td>0 0 (of 10 followed for 2–12 mo)</td>
<td></td>
</tr>
<tr>
<td>[8]</td>
<td>33</td>
<td>27, L; 24, M; 8, S; 15, L, N</td>
<td>NR</td>
<td>NR</td>
<td>Ket, 400 mg/d (1–3 mo); then 200 mg/d (2–18 mo)</td>
<td>29 (88) 1 (3) 2 (6) 0</td>
<td>1 NR</td>
<td></td>
</tr>
<tr>
<td>[9]</td>
<td>12</td>
<td>10, L; 5, S; 3, LN</td>
<td>5 mo (3 mo to 10 y)</td>
<td>6 (50)</td>
<td>Ket, 400 mg/d (1 mo); then 200 mg/d (17 mo)</td>
<td>0 10 (83) 2 (17) 0</td>
<td>0 3 (of 10 followed for 5 mo)</td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>13</td>
<td>12, L; 8, M; 4, S; 8, L, N</td>
<td>5 mo (2–36 mo)</td>
<td>3 (23)</td>
<td>Ket, 200 mg/d (3–12 mo)</td>
<td>0 10, free of mycosis; 2, residual disease activity (92)</td>
<td>0 0 (of 5 followed for 4–10 mo)</td>
<td></td>
</tr>
<tr>
<td>[11]</td>
<td>25</td>
<td>16, L; 19, M; 10, S; 13, L, N</td>
<td>NR</td>
<td>NR</td>
<td>Itc, 50 mg/d (6 mo)</td>
<td>19 (76) 6 (24) 0 0</td>
<td>0 2 (then cured by further treatment with Itc for 6 mo)</td>
<td></td>
</tr>
<tr>
<td>[12]</td>
<td>47</td>
<td>27, L; 26, M; 13, S; 20, L, N</td>
<td>NR</td>
<td>3 (6)</td>
<td>Itc, 100 mg/d (mean, 6 mo; range, 3–24 mo)</td>
<td>1 (2) 42, marked improvement; 0 0 0</td>
<td>0 0 (of 15 followed for 12 mo)</td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>28</td>
<td>12, L; 23, M; 13, L, N</td>
<td>NR</td>
<td>NR</td>
<td>Flu, 200–400 mg/d (median, 5 mo; range, 2–17 mo)</td>
<td>27; deemed responders (96)</td>
<td>1 (4) 0</td>
<td>1 (of 12 followed for 6–12 mo)</td>
</tr>
</tbody>
</table>

NOTE. A = adrenal gland dysfunction; Flu = fluconazole; Itc = itraconazole; Ket = ketoconazole; L = lung; LN = lymphadenopathy; M = oral mucosa; NR = not reported; S = skin; TB = tuberculosis.
* The actual therapeutic agents previously given were not stated in some publications.

(3%-8%) [2, 9, 10, 36]. High-dose itraconazole can also suppress adrenal gland function [37]. Major improvement or cure can be achieved in 85%-100% of cases in which it is used [11, 12]. Fluconazole is the latest imidazole to be investigated for use as monotherapy for paracoccidioidomycosis, and experience with this drug is still very limited. One study of 29 patients employed dosages of 200–400 mg/d and demonstrated clinical improvement or cure in 93% of patients treated for a median of 5 months [16].

Understanding the natural history of the disease in patients whose initial therapy failed is still difficult, as the majority of reports do not include information on duration of disease or previous treatment strategies (table 2).

Conclusion

In the case we presented, diagnosis was delayed because the patient did not initially provide an accurate travel history. Moreover, the interval required to culture the organism from urine, bronchial washings, and skin biopsy specimens was lengthy and could not realistically contribute to a timely diagnosis. Had the disease been suspected clinically, fungal culture of the initial transbronchial lung biopsy specimen or histologic examination of the skin might have led to an earlier diagnosis.

This patient's clinical presentation had many classic features, including the triad of pulmonary, oral mucosal, and skin lesions, as well as systemic symptoms, including a 20-kg weight loss and anorexia. His genitourinary tract also was involved, and he had pyuria and a large prostate nodule. Nodular prostatic involvement has been reported previously in one case [38] but was not confirmed in this case. The disseminated nature of this patient's disease at presentation might imply an immunocompromised state, which was not confirmed. In particular, the HIV serology was negative.
Although it was believed that our patient received optimal treatment, his condition deteriorated after 1 month of therapy with itraconazole. In retrospect, his remote gastric surgery may have involved vagotomy that produced chronic achlorhydria, thereby diminishing absorption of itraconazole [2]. Blood levels of itraconazole were not determined, so this was not confirmed. He appeared to initially respond to combination therapy with amphotericin B and sulfadiazine, but eventually he died of complications related to recurrent arterial emboli.

There are two reports in the literature regarding arterial emboli associated with paracoccidioidomycosis [39, 40]. One describes four necropsy cases of paracoccidioidomycotic aortitis with confirmed mycotic emboli in a pattern similar to that in this patient, involving the lower limb, intestinal, and splenic circulation [39]. The second report describes 2 patients, 1 with mesenteric artery thrombosis and 1 with gangrene of the legs, both believed to be related to paracoccidioidomycotic arteritis, as diagnosed before death on the basis of surgical histology [40].

Unfortunately, we were unable to confirm this arterial process histologically. However, the absence of other causes of arterial emboli suggests that this particular complication of *P. brasiliensis* infection also occurred in our patient.

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References


