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Incubation Period and Early Natural History Events of the Acute Form of Paracoccidioidomycosis: Lessons from Patients with a Single *Paracoccidioides spp*. Exposure

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Abstract Several aspects of the natural history of paracoccidioidomycosis are still poorly understood. Different from the most prevalent, chronic form of the disease, the acute form represents a continuum from the initial respiratory infection to the full-blown disease, thus providing an opportunity to elucidate the pathogenesis of the early phase of this mycosis. We describe, for the first time, two patients with a single time point exposure to *Paracoccidioides* spp., for whom we were able to determine the time lapsed between exposure to the fungus *Paracoccidioides* spp. and the onset of signs and symptoms. In case 1, the pulmonary infection was unapparent, and the first manifestations of the acute/subacute form of the disease presented 4 months after *Paracoccidioides* spp. exposure. In case 2, self-limited, non-specific respiratory and systemic symptoms presented 45 days after infection. Thus, our patients confirm that, within a few weeks of infection, *Paracoccidioides* spp. affects the pulmonary lymphatic system and initially causes no or mild-to-moderate self-limited symptoms, eventually causing abnormalities on a chest X-ray, all of which spontaneously subside. These cases provide some insight into the natural history of this mycosis, the extent of the host exposure to the fungus, and the determination of its incubation period.

Keywords Paracoccidioidomycosis · Pathogenesis · Pulmonary involvement · Natural history

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Introduction

More than a hundred years after Adolfo Lutz's description of the first two patients with paracoccidioidomycosis (PCM), we still do not know many aspects of the natural history of the mycosis [1, 2]. The disease comprises two well-defined clinical presentations that include an acute/subacute form (AF), characterized by the development of signs and symptoms some time after the exposure to *Paracoccidioides* spp. and a chronic form (CF) that develops many years or decades after the exposure from

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reactivated quiescent foci [3]. In contrast, the natural habitat of *Paracoccidioides* spp. remains elusive because the isolation of the fungus, even from soils of highly endemic areas, is very rare [4]. As an alternative, demographic studies of AF cases in children and young adults, which behave as epidemiologic sentinels due to their restricted migratory profiles, have helped to define the endemic areas and provided clues to the understanding of the ecological niche of the fungus [5–7]. However, as most patients with the AF live in endemic areas [8], it is not possible to ascertain whether they have been infected for a few weeks or for many months before the AF develops. This limitation helps to explain why the incubation period and the early events of disease pathogenesis remain poorly understood.

For the first time, we describe two AF PCM patients for whom we were able to determine precisely the time lapsed between the exposure to the fungus to the onset of signs and symptoms. In addition, these patients provide insights into the early phase of the disease, contributing to a better understanding of its natural history.

Case Reports

Case 1

In January 28, 2007, a healthy 16-year-old boy went on a one-day ecological trek along the Paraíba do Sul River, São Paulo State. There, he walked on trails and took part in aquatic activities. Remnants of subtropical forests and farms bordered the river. He had always lived in downtown São Paulo city and did not have any other potential episodes of exposure to *Paracoccidioides* spp. In the previous 3 years, he had travelled to the USA and small tourist cities in the mountains near São Paulo city (Serra da Mantiqueira, $\geq$1300 m of altitude). After 41 days, he presented with an acute flu-like syndrome for which he received a wide-spectrum antibiotic. At the time of symptom onset, laboratory tests showed hemoglobin levels of 12.6 g/dl, leukocyte levels of 11.900 cells/mm^3 and eosinophilia (21 %, 2499/mm^3). A chest X-ray reported normal pulmonary parenchyma and a left perihilar node, compatible with lymph node enlargement (Fig. 1a). Both findings remained without further investigation. In September, he started a standard treatment for acneiform eruptions on the face that appeared 3 months prior (Fig. 1b). In December, these lesions worsened and spread to the upper trunk. He also experienced fever, weight loss (from 70 to 64 kg), asthenia, and painful cervical and pre-auricular lymph node enlargements. In January 2008, a biopsy of a dorsal cutaneous lesion provided the diagnosis of PCM (Fig. 1c). A new chest X-ray showed normal pulmonary parenchyma and regression of the left perihilar node (Fig. 1d). Laboratory tests showed persistent eosinophilia (25 %). His serum anti-*P. brasiliensis* antibody titer was 1:16. Physical examination disclosed generalized lymph node enlargement (cervical, supra-clavicular, pre-auricular, axilar) and tender hepatosplenomegaly. Abdominal ultrasonography showed hepatosplenomegaly and disseminated lymph node enlargements. Treatment for the severe acute form of PCM with itraconazole (300 mg/day) was initiated, and improvement was observed after 1 week. However, the patient was hospitalized due to relapse of all symptoms 3 weeks later, requiring a 2-week treatment with an amphotericin lipid complex (5 mg/kg/day). He was discharged and continued his treatment with sulfadiazine (6 g/day). The patient was cured of PCM.

Case 2

A 42-year-old previously healthy women travelled at the end of May 2011 to a farm in a rural area of São José dos Campos, also near the Paraiba do Sul River Valley. The patient had always lived in São Paulo city and has no other previous travel to rural environments. She had previously travelled to non-endemic sites and short trips to the Foz de Iguaçu waterfalls (Paraná State) and Pindamonhangaba city (São Paulo State), 13 and 5 years previously, respectively, where she neither visited nearby rural areas nor went on trails or treks. In July, 45 days after the suspected exposure period, she presented with a fever, nonproductive cough, and night sweats. Fifteen days later, she experienced diffuse abdominal pain, erythematous patches on the face, trunk, and upper limbs and palpable bilateral cervical and axillar lymph nodes. The persistent cough was initially investigated with a chest X-ray (Fig. 2), which showed a mild left lung basal infiltrate, and with a thoracic CT one week later that showed left lung basal thin fibrotic stretches with residual aspect and

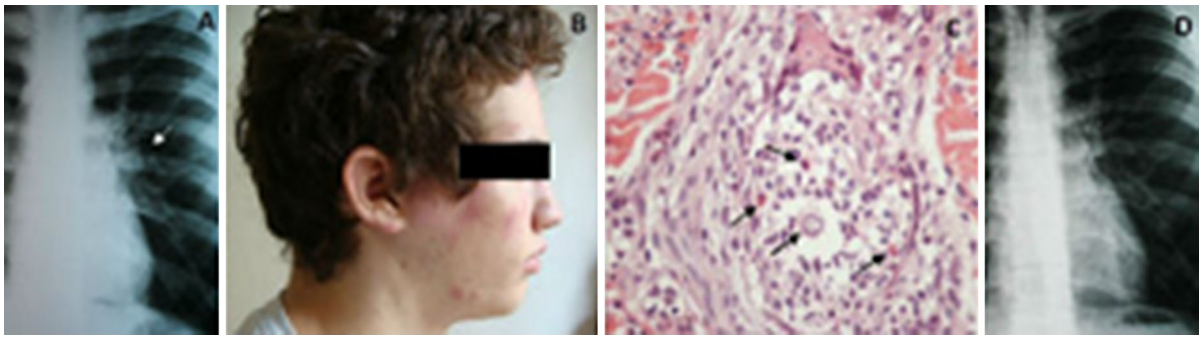

Fig. 1 Case 1. **a** Chest X-ray showing normal pulmonary parenchyma and left perihilar lymph node enlargement; **b** papular erythematous lesions on the face; **c** biopsy of the dorsal cutaneous lesion showing pilot's wheels and a loose granuloma formation with the presence of eosinophils and giant cells with yeast cells inside; and **d** normal chest X-ray

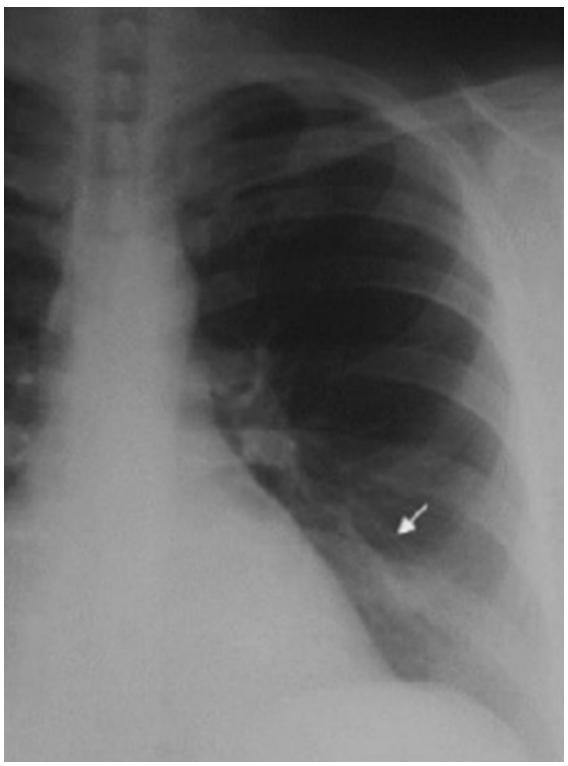

Fig. 2 Case 2. Chest X-ray showing mild left lung basal infiltrate

para-sternal and axillar lymph node enlargements. Laboratory work at that time showed hemoglobin levels of 10.4 g/dl, 11.100 leukocytes/mm^3 and eosinophilia (18.0 %, 1.998/mm^3). After 2 months, the cough subsided without specific treatment, but the other signs and symptoms progressed. With the suspicion of lymphoma, an abdominal CT revealed mesenteric and retroperitoneal lymphatic involvement. In November, a cervical lymph node biopsy diagnosed PCM. Additional abdominal and thoracic CTs showed the previously noted enlarged lymph nodes but normal pulmonary parenchyma. Laboratory results revealed persistent eosinophilia (970/mm^3) and anemia (Hb of 8.1 g/dl). Her serum anti-*P. brasiliensis* antibody titer was 1:256. The patient was treated with amphotericin B (1 mg/kg/day) followed by itraconazole (400 mg/day) and was cured of PCM.

Discussion

We describe two cases of AF PCM in patients with a single time point of exposure to *Paracoccidioides* spp. One case presented symptoms related to the initial pulmonary infection at 45 days post-exposure, while the initial pulmonary infection the other case went unnoticed. In both patients, there were laboratory data indicating an ongoing but subclinical infectious process such as marked eosinophilia and radiologic evidence of deep lymphatic involvement.

Different from the chronic form of the disease, the AF represents a continuum from the apparently silent initial respiratory infection to the full-blown disease [2]. However, this form of the disease generally develops in individuals living in endemic areas, and thus, being repeatedly exposed to the fungus, it has been difficult to determine when the initial infection with *Paracoccidioides* spp. has occurred [9]. This missing information has hindered the understanding of the first steps of the natural history of this disease, the

determination of its period of incubation, and the investigation of possible sources of infection.

The present AF cases indicate that PCM can occur in individuals who have not been repeatedly exposed to soil or vegetable matter from an endemic area [10, 11]. Both patients travelled only once to endemic areas and had no other epidemiological antecedent that could explain the infection. Indeed, as the patients had no evident risk factors for PCM, the diagnosis was delayed for several months. Based on non-autochthonous cases reported in the literature, the shortest time that a patient remained in an endemic area before he/she migrated to a non-endemic country where he/she developed the disease was 5 months [12]. However, we consider that the successful establishment of the infection (i.e., one that progresses toward the AF PCM or results in the formation of quiescent foci) in endemic areas is mainly related to the immunogenetic background of the patients combined with the amount of inhaled *Paracocccidioides* spp. conidia and the virulence of the isolate rather than to the length of time spent in the endemic area [2, 13].

Because the AF patients are already diagnosed with the full-blown disease, there are detailed descriptions of the multiple clinical presentations that arise from the lymphohematogenous dissemination of the fungus but little information regarding the events that preceded these manifestations [14]. It has been postulated that, in most cases, the initial pulmonary foci in the early phase of the PCM infection regress [2, 15, 16]. Occasionally, the host immune response apparently fails, and the primary pulmonary infection progresses either silently or with non-specific signs and symptoms. Our patients exemplify the latter two outcomes. In case 1, the perihilar lymph node enlargement and eosinophilia, which were accidentally found during a consultation for a flu-like syndrome 41 days after the exposure, already signaled an ongoing subclinical pulmonary *Paracoccidioides* spp. infection, which progressed to emerge approximately 4 months post-exposure as cutaneous lesions, typical of the AF PCM. In case 2, 45 days after the infection, the patient developed non-specific respiratory and systemic symptoms, concomitant with a mild left pulmonary interstitial infiltrate, which subsided spontaneously, and peripheral blood eosinophilia. Thus, in her case, the initial pulmonary infection resulted in noticeable self-limited symptoms that were followed approximately 2 weeks later (and 2 months after exposure) by skin lesions and superficial lymph node enlargements reflecting the hematogenous and lymphatic spread of the fungus.

Occasionally AF PCM patients, on admission, have been described to present symptoms of a non-specific respiratory involvement associated with or not associated with diverse pulmonary radiologic findings [17–19]. A few authors interpreted these symptoms as manifestations of a putative primary focus of the disease, which they called primary pulmonary lymph node complex or primary pulmonary lesion [15, 20–22]. The mild-to-moderate manifestations of the primary pulmonary focus are probably more frequently reported because, in the majority of the cases, medical assistance is sought only several months after their appearance [14] or is detected by chance, as in case 1.

Of note, case 2 developed a severe AF PCM at childbearing age (42 years old). Demographic characteristics such as occupation, age, and gender have been associated with either the acute or the chronic form of the disease [23]. The AF disease typically affects pre-puberty subjects of both genders and predominantly men after puberty, because of the protection conferred by estrogens that block the fungus conidia to yeast transformation within the host. However, as illustrated by case 2, this is not always the rule. Recent data showed that, despite the fact that post-pubertal women are less likely to develop PCM, they are more prone to develop the AF PCM, an issue requiring further investigation [23, 24].

In conclusion, the early events of the AF PCM are subject to host, parasite, and environmental factors and, therefore, are variable among patients, as demonstrated by the two patients here. Our patients demonstrate that *Paracoccidioides* spp. can affect the pulmonary lymphatic system a few weeks after infection and initially causes no or mild-to-moderate self-limited symptoms, eventually causing abnormalities on a chest X-ray, all of which spontaneously subside while the fungus spreads by the lymphohematogenous route to cause the AF of the disease.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Informed consent The patients provided written consent for the publication of this case report and accompanying photographs.

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