Paradoxical Reaction to Treatment in 2 Patients with Severe Acute Paracoccidioidomycosis: A Previously Unreported Complication and Its Management with Corticosteroids

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Paradoxical reactions have never been described in patients with paracoccidioidomycosis or other deep endemic mycoses out of the context of human immunodeficiency virus infection. We describe 2 patients with an acute form of paracoccidioidomycosis who presented with a worsening of their clinical manifestations while on appropriate antifungal treatment. These manifestations were severe and required adjunct corticosteroid therapy.

A paradoxical reaction is defined as a clinical deterioration during appropriate anti-infectious treatment. It has long been described in patients with tuberculosis and leprosy [1, 2]. Interest in this type of reaction was renewed by the observation that 15%–25% of patients with human immunodeficiency virus (HIV) infection who are on highly active antiretroviral therapy (HAART) develop an immune reconstitution inflammatory syndrome (IRIS) [3]. Two forms of IRIS have been described. One occurs when the subclinical infection that is present before HAART initiation is unmasked by the immune recovery induced by HAART. Another form is the IRIS induced by HAART.

In a patient who has recently had an opportunistic infection that has been treated. In the first form of IRIS, viable pathogens are easily found in samples obtained from infected sites, whereas in the second form of IRIS, pathogens are rare or not found [3]. Although IRIS has been described with virtually any opportunistic infection in HIV-infected patients, including the deep endemic mycoses histoplasmosis and coccidioidomycosis [4], it has not been described in paracoccidioidomycosis and blastomycosis. Interestingly, however, to our knowledge, paradoxical reactions have not yet been reported in the context of any of the deep endemic mycoses in the nonimmunosuppressed patient. We thus report here 2 patients with the disseminated juvenile form of paracoccidioidomycosis who presented with a worsening of their clinical manifestations while on appropriate antifungal treatment. These manifestations were severe and required adjunct corticosteroid therapy.

Patient 1. A 14-year-old boy from a rural area close to the city of São Paulo, Brazil, presented in February 2006 with fever, weight loss, abdominal pain, diarrhea, and cervical lymphadenopathy. Abdominal imaging exams showed coalescent enlarged lymph nodes and an intestinal semiocclusion due to compression by these lymph nodes. A cervical lymph node biopsy revealed the presence of Paracoccidioides brasiliensis (Figure 1). He was prescribed amphotericin B (AmB); after 30 days, the fever and the abdominal symptoms had subsided, and his general condition improved. He was then treated with cotrimoxazol (8 mg/kg, 3 times a day) for ~1 year, but compliance was poor and no further improvement was noticed. In May 2007, fever and weight loss reappeared along with new cervical lymph node enlargements; secretion draining from a lymph node was rich in P. brasiliensis yeast cells. Itraconazol (200 mg once a day) was then prescribed to facilitate compliance. However, after 1 month, new draining lymph nodes appeared, and his general condition deteriorated. He was hospitalized in July 2007 and then received itraconazol 300 mg/day under supervision, but again no improvement was seen. Purulent material from a draining lymph node revealed deformed P. brasiliensis yeast cells, an aspect suggestive of the antifungal activity. Repeated investigation for mycobacteria by direct examination and culture of the draining fluid resulted in negative results. Itraconazol was then changed to sulfadiazine (4 g/day) with slight improvement; however, a subcutaneous node biopsy still showed a granulomatous reaction with numerous P. brasiliensis yeast cells. Search for mycobacteria on direct examination and culture in several specimens of the draining material resulted in negative results. However, the patient developed a cutaneous
Figure 1. Hematoxylin-eosin stain of cervical lymph node biopsy showing (A) a granulomatous reaction with numerous Paracoccidioides brasiliensis yeast cells (arrows), with the yeast cells being better visualized on Grocott methenamine silver (GMS) stain (B); note the multiple budding yeast cells (arrows; original magnification, ×400). (C) Biopsy of a skin lesion over a draining cervical lymph node showing a granulomatous inflammation but no P. brasiliensis yeast cells (original magnification, ×400). GMS staining also did not show P. brasiliensis yeast cells (not shown).

rash accompanied by eosinophilia and fever attributed to sulfadiazine hypersensitivity. These manifestations disappeared with antihistamine treatment. Sulfadiazine was replaced with itraconazol 300 mg/day. In August, the patient relapsed again; he had lost 10% of his body weight in 18 days, and fever and the draining lymphadenopathy reemerged. A biopsy of a skin lesion over a draining cervical lymph node showed granulomatous inflammation but no P. brasiliensis yeast cells (Figure 1). Draining purulent materials were negative for fungi on direct examination. In addition, cultures for fungi and mycobacteria from these materials were all negative. He was initially prescribed AmB, which was replaced with liposomal AmB (4 mg/kg per day) due to renal toxicity. As there was no clinical improvement after 50 days of liposomal AmB, prednisone (1 mg/kg per day) was prescribed as adjunct therapy. Three weeks later, the fever disappeared, lymphadenopathy decreased, the draining lymph nodes healed, and the patient gained weight; an abdominal computed tomography scan showed a 20% reduction in lymph nodes size. The patient was discharged in December 2007 and received sulfadiazine after desensitization to sulfadiazine compounds was successfully performed. He was kept on this prednisone dose for 11 weeks, which was then tapered off and stopped after 5 weeks. Since then, he has been without complications and resumed all his normal activities.

**Patient 2.** A 12-year-old boy from Campinas, São Paulo State, Brazil, presented in May 2001 with manifestations of the juvenile form of paracoccidioidomycosis similar to patient 1. Diagnosis was made through a superficial lymph node biopsy. His clinical course was also similar to patient 1. Up to 2006, he had been treated with cotrimoxazol (8 mg/kg per day), alternating periods of improvement with periods of worsening clinical manifestation due to lack of compliance to treatment. Hospitalizations were required during the relapses, all of which were characterized by the presence of P. brasiliensis in the peripheral lymph node draining fluids. In April 2007, he was hospitalized because of new clinical deterioration, fever, and abdominal and peripheral lymphadenopathy after abandoning treatment. Purulent secretions draining from peripheral lymph nodes were rich in P. brasiliensis. P. brasiliensis grew in cultures of these secretions. However, at this time, a 21-day course of parenteral cotrimoxazol was ineffective and was replaced with itraconazole. Two weeks of itraconazole was also without benefit. The patient was put on AmB, 1 mg/kg per day. In spite of receiving 1 g of the drug, in spite of a sharp decrease in the number of fungi in the lymph node secretions, and in spite of negative culture results for fungi of these materials, the draining lymphadenopathy, high-grade fever, and clinical deterioration persisted. Cultures for mycobacteria were also all negative. Prednisone (1 mg/kg per day) was then given. After 6 days, the fever subsided, the lymph nodes began to decrease in size and number and stopped draining, and the patient put on weight. He received 500 mg of AmB and prednisone for >3 weeks, which was then tapered off (with dose reductions of 25% made every 10 days). He was discharged in November 2007 receiving itraconazole 200 mg. Since then, his follow-up period had been uneventful, and in December 2009 itraconazole was suspended. HIV tests were routinely repeated during the entire follow-up period, and all of them were negative for this patients and the previous patient.

**Discussion.** The pathogenesis and predisposing factors of paradoxical responses to anti-infectious treatments are incompletely understood. Remarkably, although paradoxical responses are frequently well documented in mycobacterial infections such as leprosy and tuberculosis, they have not been reported in patients harboring endemic deep mycoses, despite the fact that both mycobacterial infections and endemic mycoses are chronic granulomatous diseases with similar immunopathogeneses. More insights into the predisposing factors come from the IRIS that occurs in HIV-infected patients on HAART, in whom an immune reconstitution is clearly wit-
nessed. However, an increase in the CD4+ T cell count is not always required for the development of IRIS [5, 6]. Thus, the factors of immune reconstitution required to trigger IRIS are not yet known. It is generally accepted that these paradoxical reactions are the result of a hypersensitivity or exaggerated response to persistent microbial antigens, which become manifest when disease-related immunosuppressive mechanisms are blunted [3].

Similar to the other deep endemic mycoses that affect previously healthy individuals, the antigen-specific immune defect that arises during active paracoccidioidomycosis is partially restored after several months of antifungal treatment [7]. Thus, it is possible that this partial immune restoration may lead to an exacerbated inflammatory response and clinical deterioration in some patients. In fact, patients with paracoccidioidomycosis who presented with worsening signs and symptoms during treatment have already been described. Terra et al [8] reported a series of cases of acute paracoccidioidomycosis in children who required prolonged hospitalization because of “relapsing” clinical manifestations and total doses of AmB of >3 g to achieve consistent improvement and to enable oral antifungal treatment. Carvalho et al [9] reported a patient who developed vena cavae compression syndrome due to pericaval lymph node enlargements after 3–4 months of treatment for a relapse of the juvenile form of paracoccidioidomycosis. Similar cases have been observed in our services [10] (G.B., unpublished observations). In all cases, clinical deterioration was due to new lymph node enlargements (sometimes draining lymph nodes) and insurgence of a systemic inflammatory syndrome (eg, fever and weight loss). These episodes can now be potentially considered as paradoxical-like reactions. Furthermore, in all these cases, the disease was disseminated and severe, a condition that is associated with more pronounced failure of the cellular immune response [7]. This raises the possibility that, similar to the HIV-associated IRIS, the more immunosuppressed the patient, the higher the risk for a paradoxical response. Of note, our 2 patients presented with a long-lasting disease, with periods of improvement intercalated with relapses due to their low compliance. During relapses, P. brasiliensis was always found in the patients’ samples. But later on, the clinical deterioration became refractory to further antifungal therapy alone, and the patients’ samples did not yield P. brasiliensis on culture. Therefore, it is possible that the persistent antigen exposure may have contributed to the development of an exacerbated inflammatory response by the patients. On the other hand, paradoxical reactions may occur in less severely ill patients but pass unnoticed because they are less prominent or are missed during follow-up.

Treatment of IRIS in HIV-infected patients or treatment of paradoxical reactions in HIV-uninfected patients is an unresolved issue. Although, more recently, IRIS has been extensively investigated, no sufficient evidence base has yet been reached to produce guidelines for its treatment [11]. In a study of lymph node tuberculosis, duration of the paradoxical reaction did not differ between patients who received steroid treatment and those who did not [12]. Therefore, the potential benefits of using corticosteroid therapy should be weighed against the potential risks. Clearly, in our patients, the severity of inflammatory response was not controlled by the prolonged antifungal treatment, but our patients promptly responded to 1 mg/kg of prednisone.

In conclusion, we argue that paradoxical response to treatment may occur in patients with paracoccidioidomycosis. This may also hold true for patients with other deep endemic mycoses, because these mycoses all share common immunopathogenic mechanisms. Appropriate recognition and characterization of these paradoxical reactions would help improve treatment of such deep mycoses and would also increase our understanding of host-parasite interactions.

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References