Successful Treatment of a Critically Ill Patient with Disseminated Coccidioidomycosis, Using Adjunctive Interferon-γ

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Conventional antifungal therapy was not successful for a critically ill patient who had been hospitalized for 137 days in the intensive care unit with disseminated Coccidioides immitis infection and respiratory failure. The addition of interferon-γ to the therapeutic regimen resulted in improvement and discharge from the hospital. Adjunctive interferon-γ used in the successful treatment of severe coccidioidomycosis has not been reported previously.

Coccidioidomycosis is caused by Coccidioides immitis, a fungus that is endemic in the southwestern United States. The majority of persons infected with this fungus recover without significant sequelae. However, ~5% of patients develop severe and life-threatening disease [1]. Cell-mediated immunity is believed to play an important role in C. immitis infections, and impairment of the cell-mediated immune system is associated with more-severe disease [1–3]. Clinicians experienced with coccidioidomycosis know that patients with impaired immunity can die of disseminated infection, despite administration of available antifungal therapy. Theoretically, if the immune response in patients with severe disease could be enhanced, the effectiveness of antifungals might be improved. It is known that the immune-modulating agent IFN-γ can protect susceptible mice to challenge with C. immitis [4]. We are not aware of IFN-γ being used therapeutically for humans with C. immitis infection. We describe a patient with severe coccidioidomycosis whose condition improved after the addition of IFN-γ to her therapeutic regimen.

Case report. A 57-year-old black woman had progressive anterior chest pain that evolved over 3 months before admission to the hospital. She had no obvious fevers but had night sweats and weight loss. Initially, her chest pain was believed to have been due to costochondritis, and she was given increasing doses of prednisone to control the pain. Chest radiography was performed in the outpatient setting, and the findings were reported to be normal, and no serological tests for coccidioidomycosis were done. The patient eventually developed left-side head pain, which prompted clinicians to perform a bone scan, which revealed focal areas of uptake in the skull and sternum. This information became known at approximately the time that the patient was admitted to the hospital because of anterior chest pain and shortness of breath. Her admission chest radiograph showed bilateral infiltrates. She underwent intubation and received ventilatory support shortly after hospital admission. Bronchoscopy specimens obtained at admission yielded C. immitis on culture. A chest CT confirmed the presence of bilateral infiltrates and demonstrated an anterior sternal mass that had caused partial destruction of the sternum. This mass was surgically debrided, and cultures of specimens yielded C. immitis.

The patient was hospitalized in the intensive care unit (ICU) for 137 days. She was initially treated with amphotericin B (Fungizone; Bristol-Myers Squibb) but developed fever and hypotension with receipt of the initial dose. Because of the latter event, therapy was switched to amphotericin B lipid complex (Abelcet; Liposome). For most of the patient’s hospital course, she required vasopressor support and could not be weaned from ventilatory support. The patient was receiving a variety of antifungals during her hospitalization, which did not result in significant improvement. The antifungals used during her hospital course are summarized in figure 1.

Despite receiving antifungal therapy for 10 weeks in her initial treatment course, the patient could not be weaned from ventilatory support, and her prognosis was judged to be poor. On the basis of that opinion, the patient started receiving empirical treatment with IFN-γ-1b (Actimmune; InterMune Pharmaceuticals) at a dosage of 50 μg/m² subcutaneously 3 times per week for 9 weeks (figure 1).

At the time that the patient started IFN-γ therapy, she was receiving liposome amphotericin B (AmBisome; Fijisawa; 5 mg/kg iv). After approximately 1 month of IFN-γ therapy, she improved, and therapy was switched from liposome ampho-
The complement fixation antibody titers to *C. immitis* over the course of the patient’s hospitalization are shown in figure 2. The complement fixation titer increased from 1:16 shortly after admission to 1:1024 by the ninth week of hospitalization. IFN-γ therapy was started by approximately the tenth week of hospitalization. After IFN-γ therapy was started, titers decreased from 1:1024 to 1:16.

**Discussion.** The main question in this patient’s recovery is whether the administration of IFN-γ had anything to do with her improvement. The observation that this patient’s improvement was related to the administration of IFN-γ is supported by 3 factors. First, the prognosis was believed to be very poor by physicians who were experienced in treating coccidioidomycosis. This was based on her lack of improvement, despite the administration of available antifungals before IFN-γ therapy was started. Second, there is a known relationship between increasing duration of stay in the ICU with a variety medical conditions and a worsening prognosis [5]. Third, in severe coccidioidomycosis, there is an inverse relationship between high complement fixation antibody titers and a poor cell-mediated immune response [3]. At the time the IFN-γ was started, this patient’s complement fixation titer to *C. immitis* was elevated significantly, at 1:1024, which is consistent with a severe infection and poor cell-mediated immune response. A decrease in the complement fixation titer was associated with the administration of IFN-γ and the patient’s clinical improvement.

The main indication for IFN-γ therapy is treatment of chronic granulomatous disease [6]. Patients with this inherited disease have a defect in WBC function that improves with IFN-γ therapy; however, the precise mechanisms are not known. IFN-γ is a lymphokine capable of enhancing the immune response in fungal infections, presumably by activating macrophages and improving WBC phagocytic properties [7]. IFN-γ has been shown to increase the fungicidal capabilities of tissue macrophages, enabling them to kill *C. immitis* in vitro [8, 9].

On the basis of studies of patients with chronic paracoccidioidomycosis, it was postulated that the chronicity of this infection was associated with defective cytokine production—
in particular, the production of IFN-γ [10]. IFN-γ combined with antifungal chemotherapy has been shown to be synergistic for other human fungal infections, such as cryptococcosis and histoplasmosis [11, 12]. IFN-γ in combination with liposomal amphotericin B, inhaled amphotericin B, and granulocyte-macrophage colony-stimulating factor was used successfully to treat a patient with prolonged respiratory failure due to pulmonary aspergillosis [13]. There are no studies on the clinical use of IFN-γ for treatment of C. immitis infection in humans; such studies might help to define its effect on WBC function in this disease. However, there are experimental animal studies that have shown that mice can be protected from coccidioidomycosis by the use of IFN-γ, implying that this lymphokine may be important in the immune response to C. immitis [4].

Our patient was critically ill with disseminated C. immitis infection, and we believe that the addition of IFN-γ to therapy was the turning point in her clinical improvement. There was no dramatic improvement in her respiratory symptoms but, rather, a slow, progressive improvement, which may reflect a gradual impact on the immune response. If the use of IFN-γ did result in improvement in this patient’s immune response to C. immitis, could this reflect a correction of an immune defect similar to that seen in chronic granulomatous disease? There is a well-documented increased susceptibility of “dark-skinned” races to C. immitis infection, without identification of a specific defect in the immune system [1]. Perhaps there is a unique, genetically determined defect of variable penetrance in the cell-mediated immune system of certain populations that allows for more-severe infections due to this organism.

We report only a single case of coccidioidomycosis treated with IFN-γ, but the observations could have significant implications, if confirmed. Clinicians who treat serious C. immitis infections have had patients whose disease is only controlled and not cured by current therapies. The inability to cure this disease is believed to be related to a poorly defined impairment of the cell-mediated immune response. Enhancement of the immune response may be a novel therapeutic approach to use for patients with severe coccidioidomycosis, particularly those who do not respond to conventional antifungal therapy. Indirectly stimulating endogenous IFN-γ in C. immitis infections may be another potential therapeutic approach. Recent studies involving animals receiving IL-12 in experimental coccidio-

References