Treatment of Refractory Disseminated *Mycobacterium abscessus* Infection With Interferon Gamma Therapy

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

**REPORT OF A CASE**

A 60-year-old woman was admitted to the hospital with disseminated *Mycobacterium abscessus* infection. Her disease had been refractory to conventional antibiotic therapy and she continued to develop painful suppurring abscesses on her trunk and extremities. Her infection followed treatment for essential thrombocytosis, which was diagnosed in September 1993. For this, she initially was treated unsuccessfully with hydroxyurea (Hydrea) and plateletpheresis. She was then treated with phosphorus P 32 and busulfan, which was complicated by the development of a protracted pancytopenia with a white blood cell count at the lowest point of 0.0009 × 10^9/L. A bone marrow biopsy specimen showed mild myelodysplasia, and she was treated with filgrastim (Neupogen) and epoetin alfa (Epogen) over a several-month period, with eventual recovery of her blood cell counts to normal by May 1996. In December 1995, while still neutropenic, she was admitted to a second hospital for persistent fevers, which were initially attributed to suspected salpingitis. She underwent a total abdominal hysterectomy and a bilateral salpingoophorectomy. Her fever persisted and she was readmitted to her initial hospital, where examination showed new lesions on her skin and a biopsy specimen was obtained from which *M abscessus* was cultured. She was initially treated with amikacin sulfate, ceftriaxone sodium, and clarithromycin. Guided by subsequent in vitro antibiotic susceptibility testing, her regimen was adjusted to isoniazid (INH), rifampin, kanamycin sulfate, clarithromycin, and cefoxitin sodium, which she received for approximately 3 months. Despite antibiotics, her fevers persisted and she was again admitted to the hospital. She was found to have retroperitoneal lymphadenopathy on computed tomographic scan and, in April 1996, underwent a laparotomy with sampling of a celiac lymph node. Histopathologic results showed lymph node tissue with necrotizing granulomas and occasional acid-fast organisms. As she continued to develop new cutaneous abscesses, despite continued intravenous antibiotics, her diagnosis was questioned and a second skin biopsy was performed by the medical team in May 1996.

Histopathologic results again showed the presence of necrotizing suppurative granulomas with inflammation. Because of concern for potential toxic reactions from her prolonged course of aminoglycosides together with her lack of response to the antibiotic therapy, intravenous antibiotics were discontinued and she was receiving only oral clarithromycin when she was referred to the dermatology unit for evaluation in July 1996.

On initial presentation to our service, the patient had numerous large, fluctuant dusky-red to violaceous, tender nodules distributed over her trunk and extremities (Figure 1). Some lesions had a purulent, yellowish exudate. Deep incisional biopsy of one of the nodules was performed, which again showed suppurative and granu-
lomatous inflammation with evidence of acid-fast organisms on Fite stain.

**THERAPEUTIC CHALLENGE**

Treatment of disseminated *M abscessus* infection refractory to antibiotic therapy.

**SOLUTION**

Adjunctive therapy with interferon gamma was initiated. Regimens of kanamycin, cefoxitin, and clarithromycin were readministered together with interferon gamma, 50 µg/m2 subcutaneously, 3 times weekly. She tolerated this regimen well, with only mild flulike symptoms following each interferon injection. After her first month of treatment, she reported feeling better than she had ever felt during the past 1-year period. She was able to return to her household chores, which she had not been able to perform for approximately 1 year. Moreover, she experienced a dramatic improvement in her cutaneous lesions, with a significant reduction in pain and discharge. After her initial rapid response, improvement was slowly sustained with continued evidence of resolution of her cutaneous abscesses. However, auditory monitoring showed evidence of aminoglycoside-related otic toxicity and her antibiotic regimen was adjusted to include only imipenem and clarithromycin.

Because of her history of myeloproliferative disease, her blood cell count was closely monitored and remained stable with some fluctuation around her initial white blood cell count of 0.020 × 10⁹/L at the commencement of interferon therapy. She was additionally monitored closely by her oncologist without evidence of hematologic malignancy throughout the duration of interferon treatment.

A repeat skin biopsy performed during the fifth month of interferon treatment showed marked up-regulation of major histocompatibility complex class II expression on the surface of lesional histiocytes (Figure 2) compared with pretreatment levels (not shown). A portion of the specimen shown in Figure 2 was also submitted for mycobacterial culture and failed to show growth. Following her seventh month of treatment, she experienced near complete resolution of all cutaneous abscesses (Figure 3), which numbered greater than 20 at the outset of interferon therapy.

**COMMENT**

Susceptibility to infection by nontuberculous mycobacteria is usually observed under conditions of immunosuppression, as a complication of surgery, or in the setting of chronic disease. Recently, families have been identified with a marked predisposition to the development of severe mycobacterial infections associated with a genetic defect in the receptor for interferon gamma. These individuals fail to up-regulate immunomodulatory pathways downstream from interferon gamma stimulation, such as tumor necrosis factor α production, which are important in mediating resistance to intracellular infections. Other patients, however, appear to be susceptible to intracellular pathogens through alternate mechanisms, evidenced by their ability to respond to exogenous interferon gamma therapy with recovery from infection. In these patients, the primary defect is upstream from interferon gamma and is often associated with a down-regulation of helper T-cell type 1 responses. In our patient, T-cell subset analysis was not performed. However, her clinical response to interferon treatment together with up-regulation of major histocompatibility
complex class II expression supports an intact response to interferon gamma stimulation.

Recognizing the immunologic defect accounting for susceptibility to mycobacterial infection is important. Patients with defective production of interferon gamma will be candidates for therapeutic introduction of this cytokine. Support for the therapeutic role of interferon gamma in this setting is mounting. Successful treatments of patients with a variety of intracellular infections, including leishmaniasis, leprosy, and fungal pathogens, have been reported. More recently, a small number of patients with mycobacterial infections, including the nontuberculous variety, have responded to treatment with interferon gamma. Prior to initiation of interferon gamma therapy, these patients failed to improve with conventional antibiotic therapy, similar to the case presented here.

Conventional treatment of disseminated nontuberculous mycobacterial infection involves the use of combination antibiotics selected by in vitro susceptibility testing. Despite the selection of agents with potent in vitro activity, patients often show minimal improvement, despite prolonged treatment courses. The reason for the lack of responsiveness is unclear but likely involves the intracellular component of infection providing a barrier to antibiotic penetration. Moreover, the importance of host factors, such as immunomodulatory mechanisms (eg, interferon gamma), cannot be overlooked as an important contribution to the resolution of infection. This is supported in our patient by her continued improvement, despite the need to discontinue aminoglycoside treatment. Her remaining antibiotic regimen consisted only of clarithromycin, which had previously been ineffective alone, and imipenem, which was of only intermediate activity in the in vitro susceptibility testing.

The dramatic response of this case of refractory disseminated \textit{M} \textit{abscessus} infection to adjunctive treatment with interferon gamma supports the usefulness of this cytokine in the treatment of nontuberculous mycobacterial infections.

**REFERENCES**


**Submissions**

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.” Material for this section should be submitted to George J. Hruza, MD, Cutaneous Surgery Center, Suite 16411, 1 Barnes Hospital Plaza, St Louis, MO 63110. Reprints are not available.