A Case of Disseminated *Mycobacterium marinum* Infection in an Immunocompetent Patient

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An unusual case of *Mycobacterium marinum* cutaneous infection is described. As a result of marked delay in the diagnosis, extensive local inflammation and destructive osteomyelitis occurred together with cutaneous dissemination in an immunocompetent host. Pathologic fractures in the infected bone necessitated amputation of the involved digit. The most striking feature of this case was the development of multiple widespread cutaneous lesions for several months following amputation of the infected digit and initiation of appropriate antimicrobial therapy. These new cutaneous lesions may reflect local immune and inflammatory reactions to previously disseminated microorganisms.

Mycobacterium marinum is an atypical mycobacterium, historically classified as belonging to the Runyon Group I, the photochromogens. It has been well documented as a cutaneous pathogen (1–6), with rare dermal dissemination (7–9). Infection is generally associated with activities associated with water, primarily swimming, fishing, boating and tending aquariums (7). The infection is acquired after minor superficial trauma and usually remains localized, but on rare occasions may disseminate cutaneously. Dissemination is most often seen in immunocompromised hosts (9), isolated cases being reported in immunocompetent individuals (8). The reason for the tendency of *Mycobacterium marinum* to remain localized to the skin is believed to be the organism's optimal temperature requirement which is approximately 31 °C. In cases of cutaneous dissemination the mode of spread is unknown. Histologically the lesions change depending on the duration of infection (10–11); the Ziehl-Neelsen stain is positive in 11–100 % of cases (3) and the culture is positive in approximately 70–80 % of the specimens (3, 11). The most common site of infection is the dominant (usually the right) hand. Once the organism has been identified, therapy should be initiated with the recommended first line antimicrobial agents, i.e. rifampin and ethambutol for severe infections, or minocycline or trimethoprim-sulfamethoxazole for mild to moderate infections (12, 13). Quinolones, such as ciprofloxacin, also show good in vitro activity against *Mycobacterium marinum* (14). We report a case of disseminated cutaneous infection with this organism in an immunocompetent patient.

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Case Report. A 62-year-old female was referred from a community hospital for the evaluation of a chronic finger infection. The patient had been in good health until 12 April 1988, when she acquired a superficial puncture wound on her left middle finger with a rose thorn while gardening. Twenty-four hours later the area became red, swollen and painful. She was seen by a physician and placed on cefadroxil for two weeks, which resulted in local improvement. After discontinuing the antibiotic, her symptoms reappeared, and she was again placed sequentially on several oral antibiotics, this time without resolution. In September 1988, she underwent incision and drainage of the wound and was given saturated solution of potassium iodide without relief. She subsequently underwent four to five more local drainage procedures and was placed on oral ciprofloxacin 500 mg twice a day without any improvement. She was admitted to an area hospital on 7 November 1988. An x-ray taken on admission revealed soft tissue swelling and bony changes consistent with osteomyelitis. She once more underwent incision and drainage of the wound. An acid-fast stain of the purulent material revealed branching acid-fast microorganisms, and she was placed on isoniazid, rifampin and trimethoprim-sulfamethoxazole. She remained on this regimen until her transfer to our facility on 22 November 1988. At this time, she complained of low grade fever, night sweats and a 10 lb weight loss over the past month. Questioning revealed a history of Raynauds disease. She reported her regular activities included gardening and tending a tropical fish aquarium daily, and she was right-handed.

Physical examination was unremarkable, except of the left hand (Figure 1), which revealed erythema, and edema extending from the distal interphalangeal joint of the left middle finger into the metacarpal joint, with two areas of ulceration, one on the dorsal aspect and one on the ulnar

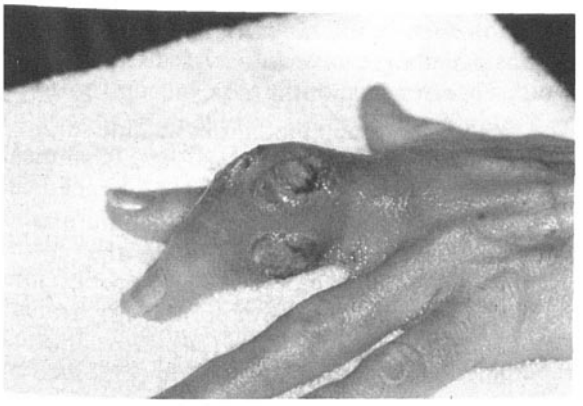

Figure 1: Left middle finger of patient approximately five months after initial infection.

aspect of the proximal interphalangeal joint, with tenderness and warmth around the metacarpophalangeal and proximal interphalangeal joints. An x-ray revealed advanced destructive changes around the proximal interphalangeal joint with pathologic fractures of the proximal and middle phalanx of her left middle finger. Her peripheral leukocyte count was 5,900/mm^3 with a normal differential count. The hemoglobin level was 12.0 g/dl, and the erythrocyte sedimentation rate was 80 mm/h. The patient again underwent extensive incision and drainage of the finger wound. The material drained was serosanguinous fluid, which on microscopy was seen to contain sheets of acid-fast organisms. Post-operatively, she was placed on intravenous penicillin, trimethoprim-sulfamethoxazole and amikacin. One week after surgery, the culture from 8 November 1988 was reported to be growing *Mycobacterium marinum.* She was sent home on rifampin and ethambutol with plans to be admitted at a future date for amputation. One week after discharge, her symptoms in the infected finger increased and she was readmitted for amputation. At this time she also had multiple 0.5–1 cm non-tender nodules on her forearm distributed in a random fashion. Because of the aggressive nature of the infection and the possibility of dissemination, immunologic studies were undertaken to exclude an immune defect. In vitro peripheral blood lymphocyte stimulation tests with phytohemagglutinin, concanavalin A, candida and tuberculoprotein were normal, as were polymorphonuclear chemotaxis, phagocytic and immunoglobulin studies. Amputation of the left middle finger was performed on 21 December 1988, and the patient was placed on intravenous trimethoprim-sulfamethoxazole together with oral rifampin and ethambutol. Stains and cultures for fungi, bacteria and mycobacteria were all negative. Histopathological examination revealed the presence of chronic inflammation with Langerhans cells and tubercle-like granulomata replacing the soft tissue. The patient was discharged home on rifampin, ethambutol and ciprofloxacin, however after seven days, she noticed an increase in the size of the previous nodules and the appearance of new lesions on her back, chest, arms and legs (Figure 2). The amputation site at this time was healed without evidence of inflammation. A skin biopsy of a nodule was performed on 7 January 1989, revealing a granulomatous reaction with epithelioid cells, giant cells, lymphocytes and plasma cells. No caseation or necrosis was present, and periodic acid-Schiff and acid fast-stains were negative. Immunohistochemical and electron microscopy revealed granulation tissue with predominant Leu M5 (+), Leu 3 (+) histiocytes and abundant helper T-cells in the periphery of the central granulation tissue. At this point, the results of susceptibility tests of *Mycobacterium marinum* were obtained, revealing resistance to isoniazid and streptomycin, but susceptibility to rifampin and ethambutol, the only antibiotics tested. She was continued on these two agents for another three weeks for a total period of 60 days. Over the next three months only occasional new lesions appeared, and thereafter follow-up over 12 months demonstrated no additional new lesions and a well healed incision site. Cultures obtained on two occasions from the biopsy sites while on therapy were negative.

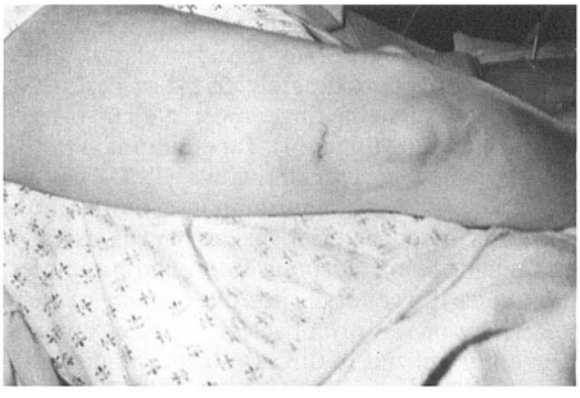

Figure 2: Posterior aspect of patient's right arm with two of the lesions which were non-tender, 0.5 x 0.5 cm in size, and varying from nodular to pustular in character.

Discussion. *Mycobacterium marinum* was first identified in 1926 by Aronson (15), who isolated the organism from a fish at a Philadelphia aquarium. Linell and Norden (16) diagnosed the first case of human infection with *Mycobacterium marinum.* At that time *Mycobacterium marinum* was called *Mycobacterium balnei* because of its association with swimming pools. This organism is a nontuberculous mycobacteria (atypical mycobacteria), and belongs to the photochromogen group, together with *Mycobacterium kansasii* and *Mycobacterium simiae.* This photochromogenic group is characterized by the production generally of a yellow pigment upon exposure to light for at least one hour. Infections with *Mycobacterium marinum* tend to produce chronic indolent, localized skin infections, which are usually self-limiting and rarely complicated by dissemination. Dissemination is usually found in an immunocompromised individual, but several cases have been reported in immunocompetent hosts (8, 9, 17, 18). The possible modes of dissemination are unknown, but lymphatic or hematogenous spread has been suggested. Some authors have suggested that *Mycobacterium marinum* resists higher core body temperatures in the circulation but recovers its growth capacity once deposited in the cooler skin (7). Cutaneous disease caused by *Mycobacterium marinum* has been characterized in the past by considerable delay in the diagnosis and ultimately in the therapy. Diagnosis requires a high index of suspicion and knowledge of *Mycobacterium marinum* epidemiology and clinical manifestations. These mycobacterial infections are often confused with sporotrichosis, and specific studies are usually not performed until empirical therapeutic measures have failed. Clinically, there are two main types of lesions, either multiple lesions spread in a sporotrichoid pattern found in 40 % of cases, or, the most frequent presentation, a single nodular lesion, generally found in the distal extremities in approximately 55 % of cases. According to Hurst, the finger most often involved is the right middle finger (4). Tuberculin skin testing with purified protein derivative (PPD) has not been helpful in distinguishing infection with the different mycobacterial species, but is useful in the diagnosis of *Mycobacterium marinum* infection, since it is generally positive because of cross-reactivity of the mycobacterial species antigens currently utilized in the skin test. The disease is usually indolent and occasionally self-limited, but if untreated will progress and produce severe disability (19, 20). Histologically, the initial lesions have non-specific inflammatory infiltrates; as the lesions age they evolve into typical tuberculoid structures after six months (11).

The various treatment modalities include surgical excision and electro-desiccation (21, 22), surgical debridement with chemotherapy (5), or medical treatment with either rifampin, ethambutol and trimethoprim-sulfamethoxazole, or the tetracyclines, including minocycline and doxycycline (23, 24). However, there are reports of treatment failures with the tetracyclines (24). Most authors recommend rifampin 600 mg/day in combination with ethambutol 15–25 mg/kg/day or trimethoprim 160 mg plus sulfamethoxazole 800 mg orally twice a day. Although Wolinsky (25) recommended a six week course of therapy, Darta et al. (12), suggested that therapy be continued for six to twelve weeks, particularly if there has been a delay in diagnosis. This includes at least four weeks of therapy after the patient becomes asymptomatic.

The case presented here is unusual for a variety of reasons. Progression of the local cutaneous and subcutaneous infection due to *Mycobacterium marinum* with development of osteomyelitis and destruction of the phalanges rarely occurs. This report reaffirms how the failure to elicit a complete history with respect to daily activities and hobbies, for example tending aquariums, led to a considerable delay in diagnosis and ultimate management. Establishing the diagnosis requires not only cognizance of *Mycobacterium marinum,* but also awareness that the pathologist and the microbiology laboratory need to be informed if the organism is suspected, because of its special growth requirements. Only a high index of suspicion, along with early diagnosis and early therapy will prevent the infection from progressing and resulting in extensive morbidity. Secondly, the widespread cutaneous dissemination in an immunocompetent host has only rarely been described, and most importantly, cutaneous and subcutaneous lesions continued to appear for several months following amputation and appropriate antimicrobial therapy. The appearance of new skin lesions for several months after initiation of therapy caused considerable consternation among the treating physicians. The initial fear was that of continuing dissemination of *Mycobacterium marinum,* possibly due to a resistant organism. Multiple skin biopsies, however, failed to demonstrate the organism histologically

and on transmission electron microscopy. This concern was finally eliminated when after delay, the cultures of the biopsy specimens were reported to be negative and the susceptibility pattern of the original isolates became available. It is likely, considering the delay in diagnosis and treatment, that cutaneous dissemination took place before therapy was started and the cutaneous lesions represent a local cell mediated immune response directed at non-viable organisms or mycobacterial antigen remnants. The absence of skin lesions early in the course of therapy may have reflected acquired cutaneous anergy to *Mycobacterium marinum,* which returned to normal after surgery and antibacterial therapy (26). The possibility of a drug reaction unrelated to antigen presence, but analogous to those seen with *Mycobacterium lepra* during the treatment phase, should also be considered.

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