Mycobacteria kansassi Disseminated Disease

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Mycobacterium kansasii is a slow-growing photochromatogenic mycobacterium that may affect immune-competent as well as immune-suppressed patients. It is the most pathogenic non-tuberculous mycobacterium affecting the lung. Late in the course of AIDS (acquired immunodeficiency syndrome) it may also present as disseminated disease [1]. The clinical course is usually chronic, and the time to diagnosis is long, requiring a diligent search for the pathogen.

We describe a patient with untreated human immunodeficiency virus infection and AIDS who presented with disseminated disease, including osteomyelitis of the skull due to *M. kansasii*. Similar cases are reviewed and recommendations for treatment are summarized.

PATIENT DESCRIPTION

A 30 year old HIV-infected woman complaining of a progressive headache of 2 weeks duration was admitted to our hospital. Five years previously she was diagnosed with AIDS, the first manifestation of which was Candida esophagitis. CD4 count at that presentation was 34 cells/ml, and her viral load was 340,000 copies/ml. She was treated with nelfinavir, lamivudine, zidovudine, fluconazole, azithromycin and sulphamethoxazole. During the next 5 years the patient showed poor compliance with the prescribed treatment and developed multiple complications, including bilateral cytomegalovirus chorioretinitis, recurrent candidial esophagitis and pancytopenia. Eighteen months before the current admission a bone marrow biopsy demonstrated hypocellular bone marrow and a single non-caseating granuloma. Acid-fast stain was negative. During the year preceding her current admission the patient discontinued all her medications and 2 weeks before admission she began experiencing a progressively painful headache.

On admission she complained of a headache localized to the left parietal area, which she described as squeezing and relentless. She also reported bilateral blurry vision. Physical examination revealed a severely malnourished and cachetic patient, with a body mass index (the weight in kilograms divided by their height in meters squared) of 14 kg/m^2. Vital signs and temperature were within the normal range. Examination of the scalp showed mild tenderness to palpation in the left parietal area, with no signs of trauma, nuchal rigidity or other signs of meningismus. Lung and neurological examinations were normal. Fundoscopic examination revealed findings consistent with bilateral cytomegalovirus retinitis. A complete blood count showed pancytopenia, with 1490/µl white blood cells, of which 83% were neutrophils and 8% band forms. Biochemical analysis revealed hypokalemia, hypoalbuminemia and a C-reactive protein level of 42 mg/L (normal range 0–5 mg/L). Her CD4 count was 7 cells/ml and her viral load 500,000 copies/ml. A chest X-ray film was normal. Treatment with intravenous gancyclovir was initiated. A day after admission she developed a fever of 38.3º C.

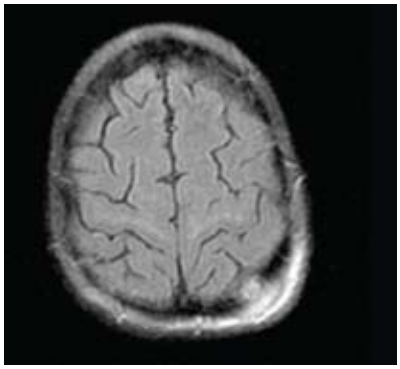
A computed tomography scan of the brain demonstrated a lytic lesion in the patient's left parietal bone, with minimal epidural swelling. The lesion showed enhancement after administration of intravenous contrast material. A lumbar puncture revealed a mildly elevated protein level (77 mg/dl, normal 15–45 mg/dl), normal glucose levels (45 mg/dl), and no cells in the cerebrospinal fluid. Acid-fast stain and a cryptococcal assay of the CSF were negative. Serology was negative for CMV, varicella zoster virus, JC virus, BK virus, herpes simplex virus and Epstein-Barr virus. Aerobic and anaerobic cultures were sterile. Results of mycobacterial cultures were pending. Methylene-diphosphnate-technetium whole body scan demonstrated multiple hot spots in the skull. Magnetic resonance imaging scan of the brain showed a destructive lesion in the left parietal bone, suggestive of osteomyelitis with outward extension to the surrounding soft tissue [Figure]. Two smaller, discrete lesions were seen in the left frontal bone.

Fine needle aspiration of the left parietal lesion was performed. A Ziel-Neelsen stain was positive. To confirm the nature of the pathogen, a 439 bp fragment encompassing the *hsp65* gene was amplified by polymerase chain reaction and subsequently digested with BstEII and HaeIII endonucleases, generating a restriction pattern typical of *Mycobacterium kansasii* [5]. Therapy was initiated with rifampicin, isoniazid

HIV = human immunodeficiency virus

CSF = cerebrospinal fluid
CMV = cytomegalovirus

T2-weighted image of the skull shows a destructive lesion in the left parietal bone with contrast enhancement following gadolinium injection.



and ethambutol. The molecular identification was later confirmed by standard methods in culture. The *Mycobacterium kansasii* isolate was susceptible to ethambutol, rifampin, clarithromycin, ofloxacin, ethionamide, and cycloserine; partly susceptible to ciprofloxacin; and resistant to capreomycin. Despite appropriate anti-mycobacterial treatment, 6 weeks after diagnosis of disseminated *M. kansassi* the patient was readmitted to our hospital in terminal condition. A week later she expired, most probably due to her advanced wasting and electrolyte abnormalities. Permission for a postmortem was not granted.

COMMENT

Mycobacterium kansasii is a slow-growing, atypical mycobacterium. It was first isolated 50 years ago and was initially termed the "yellow bacilli" due to its photochromatogenic properties. Under light microscopy, it is relatively long, thick, and cross-barred. It has been isolated from specimens obtained from water supplies in endemic areas. The primary route of infection is unknown but may be through inhalation or the digestive tract [1].

The most common clinical manifestation of *M. kansasii* in immune-competent and immune-compromised patients is a chronic pulmonary infection. In immune-competent patients there is usually, though not always, an underlying lung disease such as chronic obstructive pulmonary disease, pneumoconiosis, or carcinoma of the lung. In a review of pulmonary *M. kansasii* infection in Israel, the most common underlying lung disease was COPD (36% of patients) [2]. The clinical manifestations of pulmonary *M. kansasii* infection closely resemble those of *M. tuberculosis*, including a productive, sometimes blood-tinged, cough, fever, night sweats, and weight loss.

Disseminated *M. kansasii* most commonly occurs in immune-compromised patients, especially HIV patients, usually late in the course of AIDS. The CD4 count at diagnosis is usually < 50 cells/ml. Disseminated or extrapulmonary disease is considered an AIDS-defining illness. Among the non-tuberculosis mycobacteria causing disseminated disease in AIDS patients in the Unites States, *M. kansasii* is second only to *Mycobacterium avium* complex. Extrapulmonary sites of infection include the gastrointestinal tract, lymph nodes, bone marrow, facial sinuses, skin, synovia, pericard, meninges and central nerve system. The clinical manifestations of disseminated disease include fever and hepatosplenomegaly, in addition to site-specific symptoms and signs. Osteomyelitis is an extremely rare extrapulmonary manifestation of *M. kansasii*. A medline search (1966–2008) that we performed revealed only 13 reports of patients with *M. kansasii* osteomyelitis. Almost all the reported cases involved HIV-positive patients with advanced AIDS. Notably, the single most common location of osteomyelitis was the skull (five patients) [3,4]. Other locations included the vertebra, tibia, femur, ulna, and scaphoid. Multiple skeletal sites were common, as were associated cutaneous lesions.

A review of *M. kansasii* isolates in Israel showed consistent sensitivity to rifampin, ethambutol, clarithromycin and ofloxacin, and resistance to ciprofloxacin and capreomycin [2]. The recommended treatment of *M. kansasii* infection involves administration of isoniazid, rifampin and ethambutol for 18–24 months. Pulmonary infection appears to respond well to this regimen, but little is known about treatment of disseminated infection such as osteomyelitis. In all the cases we reviewed, rifampin and isoniazid were considered as primary therapy, and another antibiotic such as streptomycin, clarithromycin, amikacin or pyrazinamide was added to this regimen. Although initially considered universally fatal, there are now at least three reports of a full recovery following long-term treatment of *M. kansasii* osteomyelitis.

In conclusion, *M. kansassi* disseminated disease is an uncommon manifestation of a not uncommon pathogen in immune-suppressed patients. Special blood cultures and the use of polymerase chain reaction should be considered in the appropriate setting. Treatment should include rifampin and ethambutol for at least 18 months.

COPD = chronic obstructive pulmonary disease

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