

OSTEOMYELITIS CAUSED BY *MYCOBACTERIUM AVIUM*

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Osteomyelitis due to *M. avium* is extremely rare and frequently fatal. The successful cure of an 11-year-old patient with multiple mycobacterial lesions in the pelvis and right humerus is reported. Although the mycobacteria were *in vitro* resistant to most antituberculous drugs a five-drug regimen was given over a total of 2½ years. The accumulated streptomycin dose was 160 g but no adverse effects were noted. Streptomycin therapy was judged of major importance for the favourable outcome.

Key words: *Mycobacterium avium*; osteomyelitis; streptomycin; treatment

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The observed incidence of infection in children with the opportunistic *Mycobacterium avium* has recently increased in Sweden (Wickman 1978). Local lymph-node involvement has been the rule in these cases, and systemic dissemination is rarely seen. The outcome in disseminated skeletal *M. avium* infection is said to be unfavourable (Lincoln & Gilbert 1972, Wolinski 1979).

A case is now presented of disseminated skeletal *M. avium* infection which was successfully treated with antibiotics including streptomycin in a high total dose.

CASE REPORT

The patient was a boy, born in Iceland in 1966 but resident in Sweden since the age of 2 years. BCG vaccination into the left thigh at age 7 years was followed by transient lymphadenitis in the left groin. Other routine vaccinations had been performed without adverse reactions and he had no history of serious infection.

Three years after the BCG vaccination, swelling of neck glands and anaemia gradually developed, and some months later the boy began to lose weight. A painful swelling appeared over the left iliac crest and he was admitted to hospital for investigation.

On admission in June 1977, the boy was underweight

for his age (33 kg). He had haemoglobin 9.8 g/dl, ESR 50 mm and leukocytes $13.0 \times 10^9/l$. A skin test with 2 TU PPD-tuberculin RT 23 was positive (12×17 mm). X-ray examination revealed multiple osteolytic lesions of the pelvis (Figure 1A) and one lesion in the right humerus. The lungs were free of infiltrates. A biopsy specimen of pelvic bone showed a granulating process with giant cells but no epithelioid-cell granulomas. Acid-fast bacteria were found in the specimen.

Treatment was begun 7 July 1977 with streptomycin 0.5 g, isoniazid 150 mg with pyridoxine 40 mg, and rifampicin 450 mg daily. The streptomycin treatment was withdrawn after 3 weeks. After a slight general improvement, draining fistulas appeared in both hip regions. Repeated attempts to excise the fistulas failed to ameliorate the symptoms.

Multiple cultures from the fistulas yielded slow-growing acid-fast bacteria without cord or pigment production. The strain was pathogenic for chicken but not for guinea pig and was lipid type A2. It was biochemically confirmed as *M. avium* (Runyon 1974). In serological identification (Dr A. Lazlo, Laboratory Center for Disease Control, Ottawa, Canada) the strain was found to react with antisera to *M. avium* 1 and *Mycobacterium intracellulare* Sero var, 6. *In vitro* the mycobacteria were resistant to all common antituberculosis drugs except cycloserine.

In December 1977 cycloserine (250 mg) and in January 1978 ethambutol (750 mg) were added to the daily medication, but the boy's health gradually deteriorated to a marasmic state. Body weight in January

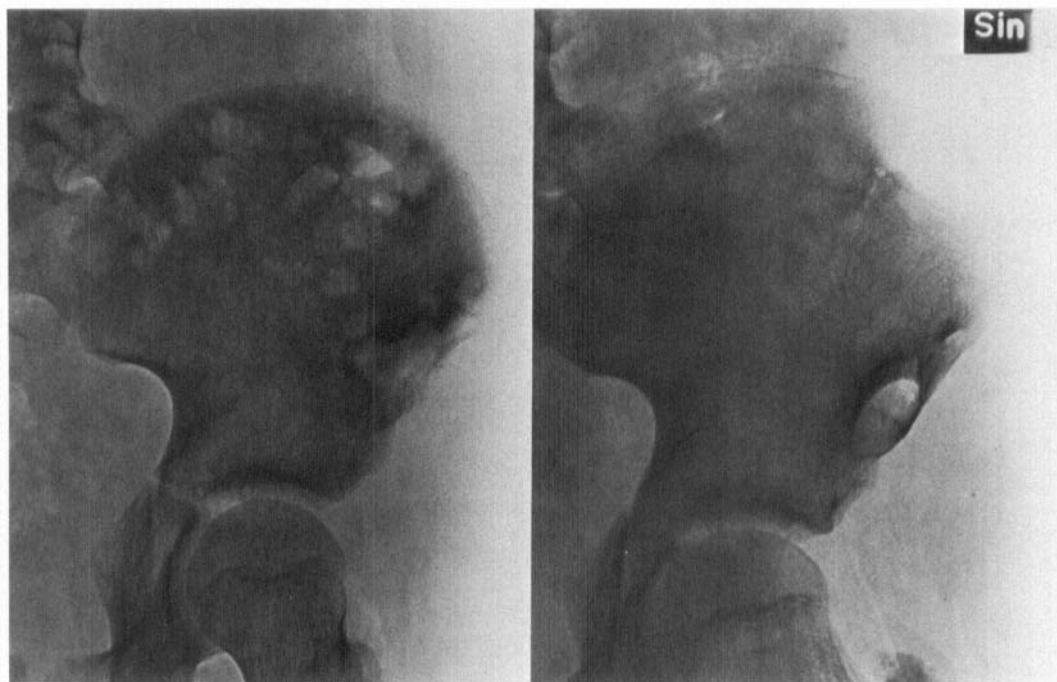


Figure 1. A, Radiograph showing multiple bone lesions in the left ileum, June 1977. B, The healed bone lesions, March 1979.

1978 was 30 kg. Blood analysis showed leukocytosis with lymphocyte counts $1.60\text{--}3.30 \times 10^9/\text{l}$ and T cells $0.60\text{--}0.83 \times 10^9/\text{l}$ (normal count $\geq 1 \times 10^9/\text{l}$). Lymphocytes *in vitro* showed high incorporation of ^{14}C -thymidine in the presence of PPD RT 23 and PPD *M. avium* (19×10^3 and 30×10^3 cpm, respectively). Lymphocyte activation with nonspecific T and B cell mitogens was normal.

Streptomycin (0.5 g three times weekly) was re-introduced 1 March 1978. The boy continued to receive rifampicin, cycloserine, ethambutol and isoniazid. From now onwards his condition improved dramatically. The haemoglobin, T cell counts and ESR rapidly normalized and serial roentgenograms showed gradual resolution of the skeletal lesions. In March 1979 all fistulas had closed (Figure 1B) and his body weight had increased to 46 kg.

In July 1982 following 30 months of continuous treatment with five drugs including streptomycin, followed by nearly 2 years without medication, the boy is in good health and his physical development is normal. The total streptomycin dose was 160 g. His hearing, balance and vision show no adverse influence of the chemotherapy. X-ray and laboratory tests have shown no signs of recurrence of the infection.

DISCUSSION

Skeletal infection due to *M. avium* is rare and has been fatal in many cases reported (Lincoln & Gilbert 1972, Jenkin & Dall 1975). The rising incidence of nontuberculous mycobacterial infections in Sweden since 1975 has been ascribed partially to the abolition of routine BCG vaccination in neonates (Wickman 1978). To our knowledge, however, this is the first case of skeletal *M. avium* infection reported from Scandinavia.

In the case presented here the first clinical sign of *M. avium* infection seems to have been the swollen neck glands 3 years after BCG vaccination. The disease showed slow progression and the possibility cannot be excluded that it had begun before BCG was given, in which case the vaccination offered no protection.

Bacteriologically, *M. avium* was previously included among the mycobacteria of Runyon's group III – nonphotochromogens. Nowadays *M. avium* is usually grouped with *M. intracellulare* and *M. scrofulaceum* in the MAIS complex. Like

M. tuberculosis it can produce skeletal destruction, especially in spongy bone. The bone lesions are often multiple. There is a strong tendency to formation of abscesses and fistulas (Lincoln & Gilbert 1972). Diagnosis is impossible clinically and can only be established by laboratory investigations.

Surgical intervention has little effect in these cases. Recovery from the protracted debilitating skeletal mycobacteriosis in our case may be attributable to several factors. The course of the disease, however, indicates that the intensive streptomycin treatment was of major importance, probably in concert with the other antimicrobial drugs. Although the mycobacterial strain was resistant to streptomycin *in vitro*, clinical experience with mycobacteriosis has shown that the correlation between *in vitro* and *in vivo* effect of antimicrobial agents may be poor (Davidson 1979). Moreover, the multidrug regimen could have permitted synergistic interaction between streptomycin and some of the other drugs. This possibility, however, was not investigated *in vitro*.

In previous reports it has been suggested that disseminated infection due to *M. avium* has occurred mainly in patients with some defect in host defences (Lakshminarayan & Sahn 1973, Lincoln & Gilbert 1972). In our case we could not find any such defect. The patient's skin reactivity to PPD was strong, and the specific reactivity of his lymphocytes was high, indicating that the cellular immune responses to mycobacteria were intact. Adequate immune functions presumably were a prerequisite for the cure. The low T-cell counts probably were secondary to the boy's poor general condition. The counts normalized with recovery. The PPD reactivity probably arose from the *M. avium* infection rather than from the BCG vaccination: Mycobacteria are known to possess cross-reacting antigens.

In generalized *M. avium* infection, aggressive multidrug therapy, including an aminoglycoside, may be essential to prevent a fatal outcome. With careful monitoring of serum aminoglycoside concentrations and of 8th cranial nerve function, high total doses of streptomycin may be given without adverse effects.

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