There are reports of clinical experience with complex diagnostic and therapeutic issues in HIV-infected children from sub-Saharan Africa where TB is endemic, drug-resistant TB is increasing and disseminated Bacille Calmette-Guérin (BCG) disease after immunisation is a recently recognised complication. We describe an infant with chronic lung disease, BCG adenitis due to the immune reconstitution inflammatory syndrome (IRIS), recurrent TB and suspected pulmonary embolism complicated by *Escherichia coli* sepsis, intracardiac thrombus and hepatotoxicity while receiving highly active antiretroviral therapy (HAART) and antituberculosis therapy. The second episode of TB was due to reinfection with an MDR *M. tuberculosis* strain. The purpose of this report is to broaden the experience of clinicians managing infants under similar circumstances.

**CASE PRESENTATION**

The infant presented at 3 months of age with *Pneumocystis jiroveci* pneumonia (PJP), multiple skin abscesses, oral candidiasis, chronic gastroenteritis and failure to thrive. An enzyme-linked immunosorbent assay for HIV antibodies and a polymerase chain reaction for HIV-1 RNA were positive. Both parents were also HIV-seropositive. Her HIV disease was classified as Centers for Disease Control (CDC) stage C-3. The absolute CD4+ T-lymphocyte count was $101/\mu l (10\%)$. Owing to financial constraints, plasma HIV RNA was not quantified. HAART, consisting of ritonavir (RTV), didanosine (ddI) and stavudine (d4T), was commenced at 4 months of age. Therapy was funded through a charitable donation as at the time (2002) HAART was unavailable for children in public hospitals. Three weeks after initiation, she developed BCG IRIS presenting as right axillary lymphadenitis. *M. tuberculosis* complex was cultured and *M. bovis* BCG identified by PCR. At the same time *M. tuberculosis*, susceptible to isoniazid and rifampicin, was cultured from gastric aspirates taken at 4 months of age because of a cavity noted on chest radiography. The Mantoux tuberculin skin test showed no reaction at 4 and 6 months of age. Her mother was subsequently discovered to have active TB. Antituberculosis treatment with rifampicin, isoniazid, pyrazinamide, and...
ethambutol and ethionamide was commenced. Three follow-up cultures for M. tuberculosis were negative following 6 months of treatment. Treatment with all 5 drugs was continued for 8 months and then stopped following a good clinical response, with increased weight for age standard deviation score increasing from –3 at 6 months to –1 at 15 months.

Two months later, at 16 months of age, the patient presented with acute pneumonia (cough and difficult breathing for 2 days). A chest radiograph showed new alveolar opacification and a large cavity in the apex of the right lower lobe. In addition to antibiotics, a second course of antituberculosis treatment was started with the same drugs as before, as both she and her mother had documented drug-susceptible TB.

At 19 months of age she presented with acute onset of severe dyspnoea. Medication at this stage consisted of co-trimoxazole prophylaxis, antituberculosis treatment and HAART. Adherence to all medications including HAART was excellent, with calculated adherence for HAART in the previous 6 months between 93% and 152% (mean 118%).

Physical examination showed an afebrile well-nourished, acutely ill child. Her systemic blood pressure was 100/62 mmHg. There was severe tachypnoea and dyspnoea and signs of long-standing lung disease (clubbing and Harrison’s sulci). The transcutaneous O2 saturation was 90% with 6 l O2/min administered by face-mask. Her chest was hyperinflated without adventitious sounds. Cardiovascular examination revealed a normal S1 and a loud S2. Peripheral circulation was adequate. There was mild hepatomegaly and splenomegaly. The neurological examination was normal.

M. tuberculosis was again confirmed on the gastric aspirate culture done at 16 months. As her weight gain had been good, current treatment was continued while awaiting mycobacterial drug susceptibility test (DST) results. The chest radiograph showed increased heart size compared with previous chest radiographs, new-onset hyperinflation and a bilateral diffuse nodular appearance in the lung fields, noted 3 months earlier, but no cavities. Laboratory investigations revealed a white blood cell count of 13.4 × 10^9/l (7.1 × 10^9 lymphocytes), haemoglobin 11.1 g/dl, platelets 203 × 10^9/l and C-reactive protein (CRP) 65 mg/l. There was a marked increase in levels of aspartate-aminotransferase (7 280 IU/l) and alanine-aminotransferase (2 283 IU/l). The urea level was 4.4 mmol/l (normal range 1.1 – 5 mmol/l) and the creatinine level 54 μmol/l (normal range 35 – 62 μmol/l). The blood gas showed a pH of 7.3, pCO2 of 6.28 kPa and base excess of –2.8 mmol/l. The anion gap was 18 mmol/l. Blood lactate was not measured. The bilirubin (total –57 mmol/l, unconjugated fraction 28 mmol/l) was mildly elevated. The CD4+ T-lymphocyte percentage was 26% (absolute number 1.2 × 10^9/l) with a CD4/CD8 ratio of 0.68:1. Urine was not cultured. Serology for hepatitis A, B and C was negative.

The differential diagnosis included pneumonia (bacterial, viral, tuberculosis or PJP) and pulmonary hypertensive crisis. The hepatitis was ascribed to hepatotoxicity secondary to HAART and antituberculosis medication, aggravated by sepsis and congestive cardiac failure.

Cefuroxime (100 mg/kg/d intravenously) was prescribed for bacterial pneumonia. Co-trimoxazole dosage was increased to 20 mg/kg/day of the trimethoprim component for possible PJP and hydrochlorothiazide (2 mg/kg/d) was commenced for pulmonary hypertension. HAART was discontinued due to hepatitis and antituberculosis therapy was changed to amikacin, ofloxacin and ethambutol.

E. coli was cultured from blood. An electrocardiogram showed sinus rhythm and right-sided ventricular enlargement. Echocardiography showed right atrial and ventricular enlargement. The pulmonary arterial systolic pressure was 76 mmHg, indicative of severe pulmonary hypertension. A round echogenic mass, diameter 6 mm, was visualised in the right atrium just below the superior vena cava, compatible with a thrombus. Identification of E. coli from blood implied that the mass might be infected. Amphotericin B and anticoagulation therapy (heparin and warfarin) were commenced. The liver enzymes normalised rapidly after discontinuation of the HAART and altered antituberculosis therapy, and the respiratory distress improved gradually.

Fundoscopy showed no signs of systemic fungal infection, and repeated blood cultures remained negative for fungi. A ventilation-perfusion scan of the lung performed 9 days after admission showed low intermediate probability (30%) of a pulmonary embolus in the anterior basal segment of the left lower lobe. Repeat echocardiography a day later still showed pulmonary hypertension, but the right atrial mass had disappeared. Eight weeks later the pulmonary hypertension had also resolved. Oxygen therapy was discontinued.

After the hepatitis resolved, the original antituberculosis drugs were gradually re-introduced. This was changed to MDR TB treatment with ethambutol, ethionamide, ofloxacin, amikacin and terizidone after the drug susceptibility test pattern confirmed resistance to isoniazid and rifampicin after 3 months. Thereafter, HAART was restarted uneventfully. Coagulation studies 12 weeks after admission were normal except for a marginally low protein C. MDR TB treatment was continued for 15 months. The patient was clinically cured, confirmed by several negative cultures and calcification on chest radiograph.

Strain identification by standardised DNA-spoligotyping confirmed re-infection with a different strain of M. tuberculosis to the initial isolate.

**DISCUSSION**

This case illustrates the difficulty of diagnosing and managing TB in HIV-infected children, even in a region where TB is endemic and physicians have a high index of suspicion for TB. The case also emphasises the importance of regular DSTs for M. tuberculosis isolates. The diagnosis of TB was first made in the infant a month after the gastric aspirate was taken.
Because BCG adenitis was clinically suspected and M. bovis BCG is intrinsically resistant to pyrazinamide, ethambutol and ethionamide were added to the treatment regimen. These decisions were vindicated by detection of both M. bovis BCG and M. tuberculosis infection.

The patient presented with a second episode of pulmonary TB due to reinfection with an MDR M. tuberculosis strain. At this time there was no reason to suspect MDR TB, as the previous isolates were susceptible. Inappropriate treatment of MDR TB initially may have contributed to the complicated course during the most recent admission. Confirmation of susceptibility may take 2 – 3 months, during which treatment decisions are required. Recurrence of TB is not uncommon in HIV-infected children in this highly TB endemic area, where the annual notification rate was 638 cases/100 000 population in 2003. Both reinflection and relapse occur. In this patient, reinflection with an MDR M. tuberculosis strain was confirmed by DNA fingerprinting.

The management of MDR TB cases is difficult and mortality is usually high, especially in HIV-infected patients. Although the DST pattern only showed resistance to isoniazid and rifampicin and was susceptible to ethambutol, the treatment regimen included all available second-line antituberculosis drugs, as she had previously received 5-drug treatment and now presented with cavitating disease, indicating higher organism load and the danger of development of further drug resistance if not managed appropriately. Treatment was continued with all drugs except amikacin for 12 months after initiation of HAART. TB and its complications require vigilance in HIV-infected children and clinical decisions may precede laboratory confirmations.

This case reflects the difficulties in management of children with advanced HIV disease. The patient had an especially complicated course preceding and after the introduction of HAART. TB and its complications require vigilance in HIV-infected children and clinical decisions may precede laboratory confirmations.

REFERENCES