

# AN HIV-INFECTED INFANT WITH BACILLE CALMETTE-GUÉRIN DISEASE, RECURRENT AND MULTIDRUG-RESISTANT TUBERCULOSIS COMPLICATED BY ACUTE COR PULMONALE AND HEPATITIS WHILE ON ANTIRETROVIRAL THERAPY

**J M van Montfrans**<sup>1,4</sup>, MD, PhD

**H Rabie**<sup>1</sup>, MB ChB, MMed, FCP

**H S Schaaf**<sup>1</sup>, MB ChB, MMed (Paed), DCM, MD Paed

**A C Hesselning**<sup>1</sup> MB ChB, MSc

**M F Cotton**<sup>1</sup>, FCPaed (SA), MMed (Paed), PhD

**S E Shipton**<sup>2</sup>, MB ChB, MRCP, FCPaed (SA), MMed (Paed)

**T Victor**<sup>3</sup>, PhD (Med Biochem)

<sup>1</sup>Department of Paediatric Infectious Diseases, Tygerberg Children's Hospital, Tygerberg, W Cape

<sup>2</sup>Department of Paediatric Cardiology, Red Cross War Memorial Children's Hospital, Cape Town

<sup>3</sup>MRC Unit for Cellular Biochemistry, Faculty of Health Sciences, Stellenbosch University, Tygerberg, W Cape

<sup>4</sup>Present address: Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht, The Netherlands

We describe the management of an HIV-infected infant with multisystem disease. The infant presented with severe disease at 3 months of age. Initiation of antiretroviral therapy (ART) was delayed through initial lack of access, after which she developed immune reconstitution inflammatory syndrome to BCG. At this time she was also infected with *Mycobacterium tuberculosis*, with a later recurrence due to multidrug-resistant (MDR) tuberculosis (TB). During this episode she presented with acute cor pulmonale, possibly due to a pulmonary embolus and also transaminitis. Although such infants are seen frequently in sub-Saharan Africa, there are few guidelines or case descriptions to assist clinicians.

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.

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.<sup>1</sup> The absolute CD4+ T-lymphocyte count was  $101 \times 10^9/l$  (10%). Owing to financial constraints, plasma HIV RNA was not quantified. HAART, consisting of ritonavir (RTV), didanosine (ddI) and stavudine (d4T), was commenced at 4½ 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.<sup>2,3</sup> The lymph node developed into a massive local abscess, which was eventually drained.<sup>4</sup> 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,

## 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

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 O<sub>2</sub> saturation was 90% with 6 l O<sub>2</sub>/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  $13.4 \times 10^9/l$  ( $7.1 \times 10^9$  neutrophils and  $4.8 \times 10^9$  lymphocytes), haemoglobin 11.1 g/dl, platelets  $203 \times 10^9/l$  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  $\mu$ mol/l (normal range 35 - 62  $\mu$ mol/l). The blood gas showed a pH of 7.3, pCO<sub>2</sub> 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  $1.2 \times 10^9/l$ ) 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-spiligotyping<sup>5</sup> 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.<sup>6</sup> Both reinfection and relapse occur.<sup>7</sup> In this patient, reinfection 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 the first negative culture.

BCG IRIS-related suppurative adenitis occurs fairly commonly after initiation of HAART.<sup>8</sup> The BCG abscess responded well to the combination of surgical drainage by aspiration of the abscess, antituberculosis treatment and continuation of HAART. Dual infection with *M. tuberculosis* and BCG has also been described<sup>4</sup> and this case illustrates the importance of retaining pyrazinamide until *M. tuberculosis* has been excluded.

While on HAART and treatment for the second TB episode, the infant developed hepatotoxicity. Both regimens contain hepatotoxic drugs and physicians should be alert to this complication. As drug hepatotoxicity could be fatal, all potentially hepatotoxic drugs were discontinued and

reintroduced sequentially after hepatic enzymes had normalised. At the same time, *E. coli* sepsis and acute cor pulmonale possibly due to a pulmonary embolus was diagnosed. The disappearance of the mass could have been due to dislodgement or fibrinolytic activity (either intrinsic or exogenous). Its disappearance in 10 days excluded a malignancy, and the multiple negative fungal blood cultures make a fungal aetiology unlikely. We could not definitively diagnose pulmonary embolism as the VQ scan showed only a 30% probability. A pulmonary embolus is compatible with the clinical course, showing gradual improvement of respiratory distress and eventual normalisation of pulmonary pressures. Hypercoagulability has been described in patients with HIV and also tuberculosis.<sup>9,10</sup>

## CONCLUSION

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

- Centers For Disease Control and Prevention (CDC). Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994; 36: 225-230.
- Parsons LM, Brosch R, Cole ST, et al. Rapid and simple approach for identification of *Mycobacterium tuberculosis* complex isolates by PCR-based genomic deletion analysis. *J Clin Microbiol* 2002; 40(7): 2339-2345.
- Talbot EA, Williams DL, Frothingham R. PCR identification of *Mycobacterium bovis* BCG. *J Clin Microbiol* 1997; 35(3): 566-569.
- Hesseling AC, Schaaf HS, Hanekom WA, et al. Danish bacille Calmette-Guérin vaccine-induced disease in human immunodeficiency virus-infected children. *Clin Infect Dis* 2003; 37(9): 1226-1233.
- Kamerbeek J, Schouls L, Kolk A, et al. Simultaneous detection and strain differentiation of *Mycobacterium tuberculosis* for diagnosis and epidemiology. *J Clin Microbiol* 1997; 35(4): 907-914.
- Cape Town TB Control. Progress report 1997 - 2003. <http://www.hst.org.za/publications/618> (accessed 6 January 2006).
- Schaaf HS, Krook S, Hollemans DW, Warren RM, Donald PR, Hesseling AC. Recurrent culture-confirmed tuberculosis in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2005; 24(8): 685-691.
- Puthanakit T, Oberdorfer P, Akarathum N, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J* 2006; 25(1): 53-58.
- Saif MW, Greenberg B. HIV and thrombosis: a review. *AIDS Patient Care STDs*. 2001; 15(1): 15-24.
- Turken O, Kunter E, Sezer M, et al. Hemostatic changes in active pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2002; 6(10): 927-932.

