CASE REPORT

BREAKTHROUGH NEUROLOGICAL MANIFESTATION DURING APPROPRIATE ANTITUBERCULOUS THERAPY OF MILIARY TUBERCULOSIS

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Abstract. We report a 20-month-old girl with miliary pulmonary tuberculosis and normal neurological findings. While on treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol for 1 month, she developed weakness of the lower extremities without meningism or altered consciousness. A computerized tomogram revealed tuberculomas and basal arachnoiditis. The cerebrospinal fluid findings were compatible with tuberculous meningitis. She responded well to systemic corticosteroids.

Treatment of pulmonary tuberculosis with anti-tuberculous drugs usually results in resolution of the illness. However, killed mycobacteria may trigger a hypersensitivity reaction and result in development of symptoms in organs that were silently infected. Here we report a case with this phenomenon in a child with miliary tuberculosis, who developed central nervous system manifestations during effective antituberculous treatment.

A 20-month-old girl presented with fever and cough for two weeks. Her grandmother, who had stayed with her during infancy, had tuberculosis. Physical examination showed her weight to be 10 kg, body temperature 39℃, respiratory rate 40/minute, heart rate 120/minute and blood pressure 90/60 mmHg. She was active and well-nourished. Chest examination was normal as was the remaining physical examination. Initial laboratory tests gave a hemoglobin of 11 g/dl, hematocrit of 35%, white blood count of 14,900/mm^3 (54% polymorphonuclear cells, 37% lymphocytes, 8% monocytes) and a platelet count of 534,000 /mm^3. Urine analysis, blood chemistry and liver function tests were normal. A chest roentgenogram (CXR) revealed a bilateral diffuse reticulonodular infiltration (miliary pattern). The purified protein derivative (PPD) skin reaction was 15 mm in diameter. Gastric washings for acid-fast bacilli were negative for three days. Due to abnormal CXR, positive PPD skin test and a history of tuberculosis exposure, antituberculous therapy was started with INH 100 mg, rifampicin 100 mg, pyrazinamide 250 mg, and streptomycin 200 mg intramuscularly. Corticosteroids were not considered due to the mild degree of symptoms. Her temperature declined gradually and she was afebrile within ten days. One month later, she developed weakness of both legs. Physical examination showed motor power of grade 3 in both legs, hyperreflexia, and a dorsal response to Barbinski's test. She had gained 800 grams over the month and had been afebrile. The streptomycin injection site was unremarkable. The CXR was unchanged compared with the previous film. A computerized tomogram (CT) of the brain showed hyperdensity with contrast enhancing lesion at the left side of the circle of Willis. This lesion was enhanced along the course of the middle cerebral artery and sylvian cistern. Other small enhancing nodules at the right ambient cistern and at the right prepontine cistern were also noted. Borderline enlargement of the ventricular system was observed. The cerebrospinal fluid (CSF) was clear with 35 white blood cells/mm^3 (lymphocyte 100%), no red blood cells, protein of 932 mg/dl, and glucose of 18 mg/dl (concurrent blood glucose was 85 mg/dl). The CSF culture showed no growth. She was put on prednisolone 2 mg/kg/day with a remarkable improvement. After three weeks of

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corticosteroid therapy, the CSF showed a pressure of 30/28 mmHg, white blood cell count of 19 cells/mm^3 (lymphocyte 99%), red blood cells 2 cells/mm^3, protein 22 mg/dl, and glucose 50 mg/dl. At two months of treatment, she was active and her motor function had returned to normal. Steroids and diamox were tapered off. Gastric washing, collected before antituberculous therapy was started, grew *Mycobacterium tuberculosis*. The isolate was resistant to streptomycin, but sensitive to isoniazid, rifampicin and ethambutol. Streptomycin was changed to ofloxacin and was continued for two months. Pyrazinamide was discontinued after two months of treatment, and then isoniazid and rifampicin were continued to complete one year's treatment (1IRZS/1IRZO/10IR).

Tuberculosis in children has been recognized as having a tendency to be more severe, with more extrapulmonary involvement than in adults. Because of unreliable physical findings and strong possibility of CNS involvement, lumbar puncture is always performed in infants with tuberculosis, regardless of neurological findings. However, children more than one year old usually show neurological symptoms and signs if CNS involvement occurs. This patient had no neurological deficit and therefore was not evaluated for CNS involvement when she presented.

In miliary tuberculosis, pleural effusion, peritonitis and meningitis occur in as many as 2/3 (David and Roger, 1995). A study in adults found an abnormal magnetic resonance imaging (MRI) scan in four out of seven patients with miliary tuberculosis who had no CNS symptoms (Gupta *et al*, 1997). This information underscores the necessity of investigating CNS involvement in all cases of miliary tuberculosis. The pitfalls of not investigating CNS involvement in this patient resulted in the missed opportunity of treatment with corticosteroids from the beginning, which would have prevented the late CNS manifestations. We believe that the CNS lesions in this patient had been present silently before treatment was started, similar to that found in adults (Gupta *et al*, 1997). Treatment with antituberculous drugs induced an immunologic hypersensitivity reaction against the protein released by the lysis bacilli and resulted in the development of symptoms (Afghani and Lieberman, 1994). The prompt response to steroids supports this hypothesis. The PPD reaction to 15 mm in our patient was evidence of a strong immunologic response to the organism. A few earlier reports have noted the development of CNS tuberculosis during appropriate antituberculous treatment, or after the resolution of miliary tuberculosis (Afghani and Lieberman, 1994; Chang *et al*, 1998). Our patient is further evidence confirming this phenomenon and the importance of steroid therapy in CNS tuberculosis, regardless of symptoms. Corticosteroids improve the survival rate and intellectual outcome in tuberculous meningitis by enhancing the resolution of basal exudate and tuberculomas (Schoeman *et al*, 1997).

In severe miliary tuberculosis, corticosteroids also help mitigate alveolocapillary block (Larry *et al*, 2000). However, in milder cases, steroids are not necessary except as in this patient, when CNS involvement occurs.

In conclusion, CNS tuberculosis may flare up during appropriate antituberculous therapy where cases of miliary tuberculosis if corticosteroids are not used. Work-ups for CNS involvement are indicated in cases of miliary tuberculosis, regardless of CNS symptoms or age, and corticosteroids are indicated if CNS involvement occurs.

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