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Mycobacterium tuberculosis infection in immunocompetent children

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Abstract *Objective.* The purpose of this paper is to present our experience with *Mycobacterium tuberculosis* infections in immunocompetent children.
Subjects and methods. Radiology, pathology, microbiology, and discharge records at two institutions identified the study population. Children who were immunocompromised and those with a positive skin test and no radiological or clinical evidence of active infection were excluded. Active mycobacterial infection was defined by a positive culture, biopsy, or a reactive purified protein-derivative skin test (PPD) with an appropriate clinical presentation and response to therapy and/or known exposure to an adult with active tuberculosis.
Results. There were 22 children in whom *Mycobacterium tuberculosis* (MTb) was identified. Fourteen of the patients with MTb were 5 years of age or younger. The most common sites of radiological involvement were the lungs (15 cases) and the hila (eight cases). Four patients had evidence of extrathoracic MTb infection. Three cases of miliary tuberculosis were identified, all in children less than 9 months of age.
Conclusion. Although pulmonary and/or hilar disease remains the most common radiological presentation of childhood tuberculosis, the radiologist must be aware of the many radiological presentations of childhood *Mycobacterium tuberculosis* infection, and should have a high index of suspicion with the increasing incidence in both normal and immunocompromised children.

Introduction

In 1990, 25 701 new cases of tuberculosis were diagnosed in the United States, representing a 15.8 % increase from 1985 [1]. The largest increase occurred in 25 to 44-year-olds, attributed to the increasing prevalence of HIV infection in this age-group. Significant increases in incidence were also reported in children 0–4 years of age (up 18.6 %) and in those 5–14 years of age (up 39.8 %). Populations at risk include the homeless, intravenous drug abusers, immigrants from countries with endemic tuberculosis, prisoners, nursing home residents, and those with HIV infection [2]. The HIV epidemic, a decline in public health services with a concomitant increase in homelessness, and increasing immigration have been cited as factors in the increase in the incidence of both new cases and reactivation tuberculosis [3].

The increasing incidence of tuberculosis in childhood is particularly worrisome, since each case of childhood tuberculosis represents a new infection from a contagious source, as opposed to adults, in whom infection is due both to reactivation and new infections. As Starke

Table 1 Summary of MTb cases (*N* no PPD testing, + reactive PPD, – nonreactive PPD, – > + converted from nonreactive to reactive PPD during course, *A* active pulmonary tuberculosis, + *PPD* reactive PPD test without evidence of active pulmonary tuberculosis)

Patient	Age	Positive sites (s)	PPD	Biopsy/cultures	Contact(s)
1	2 m	Lungs (miliary), kidneys, liver	+	Sputum/ gastric/urine	Mother (+ PPD)
2	3 m	Lungs (miliary)	N	Sputum/ gastric/lung	Mother (A), Father (A), Brother (A, Patient 10)
3	4 m	Lungs/hila	+	Gastric	Grandfather (A), Multiple others (+ PPD)
4	8 m	Lungs (miliary)/hila	+	Gastric	Family friend (A), Mother (+ PPD), Father (+ PPD)
5	9 m	Lung/hila	–	[a]	Mother (+ PPD)
6	1 y	Hila	+	[a]	–
7	2 y	Lung/hila	– > +	Sputum	Grandparent (A)
8	2 y	Hila	– > +	[b]	Grandmother (A)
9	2 y	Lung/hila	– > +	[a]	Father (+ PPD)
10	3 y	–	+	Urine	Mother (A), Father (A), Brother (A, Patient 2)
11	4 y	Meninges/brain	+	CSF	–
12	4 y	Lungs/hila	+	[a]	–
13	5 y	Lungs	+	[a]	–
14	5 y	Meninges	– > +	CSF	–
15	6 y	Lung	+	[a]	–
16	9 y	Lung	+	[a]	Father (A)
17	12 y	Liver/spleen/kidneys	–	Liver	Father (+ PPD)
18	14 y	Lung	+	Sputum	Mother (+ PPD) Aunt (A)
19	16 y	Lungs	N	Sputum	–
20	17 y	Lungs	+	[a]	–
21	19 y	Pleura	+	[a]	–
22	20 y	Lungs	N	Sputum	Mother (A)

[a] Diagnosis of MTb based on reactive PPD, clinical course, and response to therapy

[b] Diagnosis of MTb based on reactive PPD, clinical course, and exposure to adult with active pulmonary MTb

et al. write, "Each case of tuberculosis in a child is a sentinel health event representing recent transmission of tuberculosis within the community and a failure of our ability to control tuberculosis" [3].

In recent years, we have noted several cases of advanced mycobacterial disease in immunocompetent children, who are not at increased risk for the disease. This paper presents our experience with *Mycobacterium tuberculosis* (MTb) infections in the immunocompetent pediatric population.

Patients and methods

Pediatric patients with clinically documented cases of MTb infection without evidence of immune deficiency were identified at two institutions in close proximity. One institution is a large urban hospital with both an indigent care base and a suburban satellite system, and the other is a large tertiary referral university hospital. Records were reviewed from 1986 through 1993. Combined, the two institutions average approximately 6000 non-neonatal pediatric admissions and 85000 on-site outpatient/emergency room pediatric patient visits per year. Patients were identified by discharge diagnosis data base, radiology reports, and microbiology laboratory records. Particularly helpful were files maintained by the microbiology departments of positive mycobacterial cultures reported to the state health department. Two patients were seen for initial workup during the study.

Twenty-two immunocompetent children (14 girls, 8 boys) were identified as having mycobacterial infection. Their ages ranged from 2 months to 20 years (mean: 6.5 years, median: 4 years). Sixteen patients (64 %) were 5 years or younger.

Patients included in our series had clinical evidence of mycobacterial infection. In 12 patients cultures and/or biopsies were diagnostic. Nine additional patients had reactive purified protein-derivative skin tests (PPD) and appropriate clinical presentation and response to antituberculous therapy. One other patient was included with conversion of PPD testing and exposure to an adult with active tuberculosis. Patients with a non-reactive PPD test were not included unless there was culture proof of MTb and/or subsequent conversion to a reactive PPD. Asymptomatic patients with a reactive PPD and no radiographic findings were excluded from the study; although this constitutes a substantial number of patients, an accurate prevalence could not be calculated as these patients are seen as outpatients, documentation is frequently incomplete, and reporting to the state health department is not required. All medical records, imaging studies, and histological and microbiological results were reviewed.

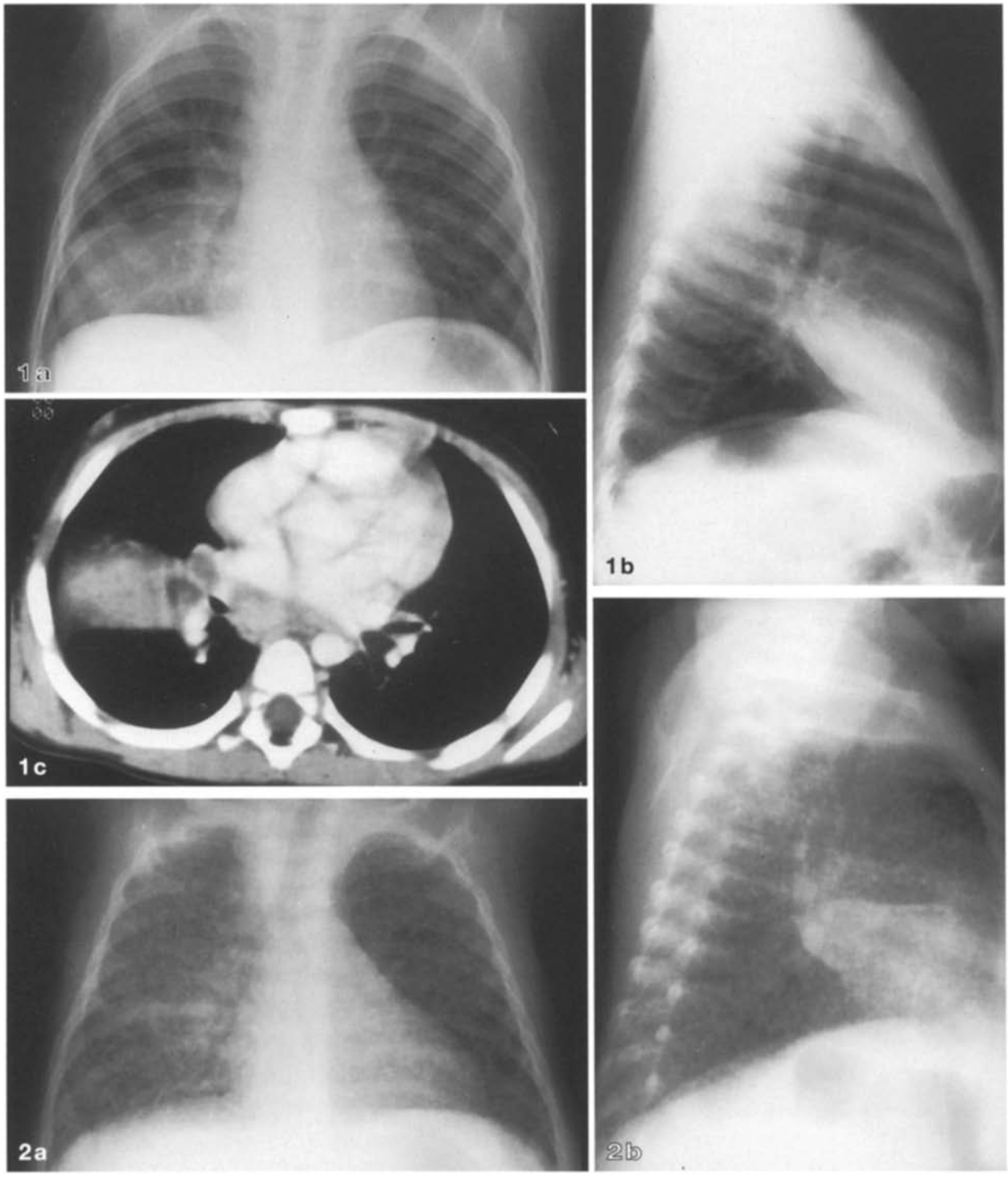

Fig. 1a–c Primary pulmonary tuberculosis in a 2-year-old boy. **a** Anteroposterior chest radiograph shows right paratracheal lymph node enlargement and right middle lobe opacity. **b** Lateral chest radiograph confirms right middle lobe opacity with some volume loss. **c** CT scan demonstrates low-attenuation, enlarged right hilar lymph nodes and opacity in lateral segment of right middle lobe. Peripheral nodal enhancement is seen

Fig. 2a, b Miliary tuberculosis in a 2-month-old female infant. Anteroposterior (**a**) and lateral (**b**) chest radiographs demonstrate innumerable tiny nodular opacities throughout both lungs

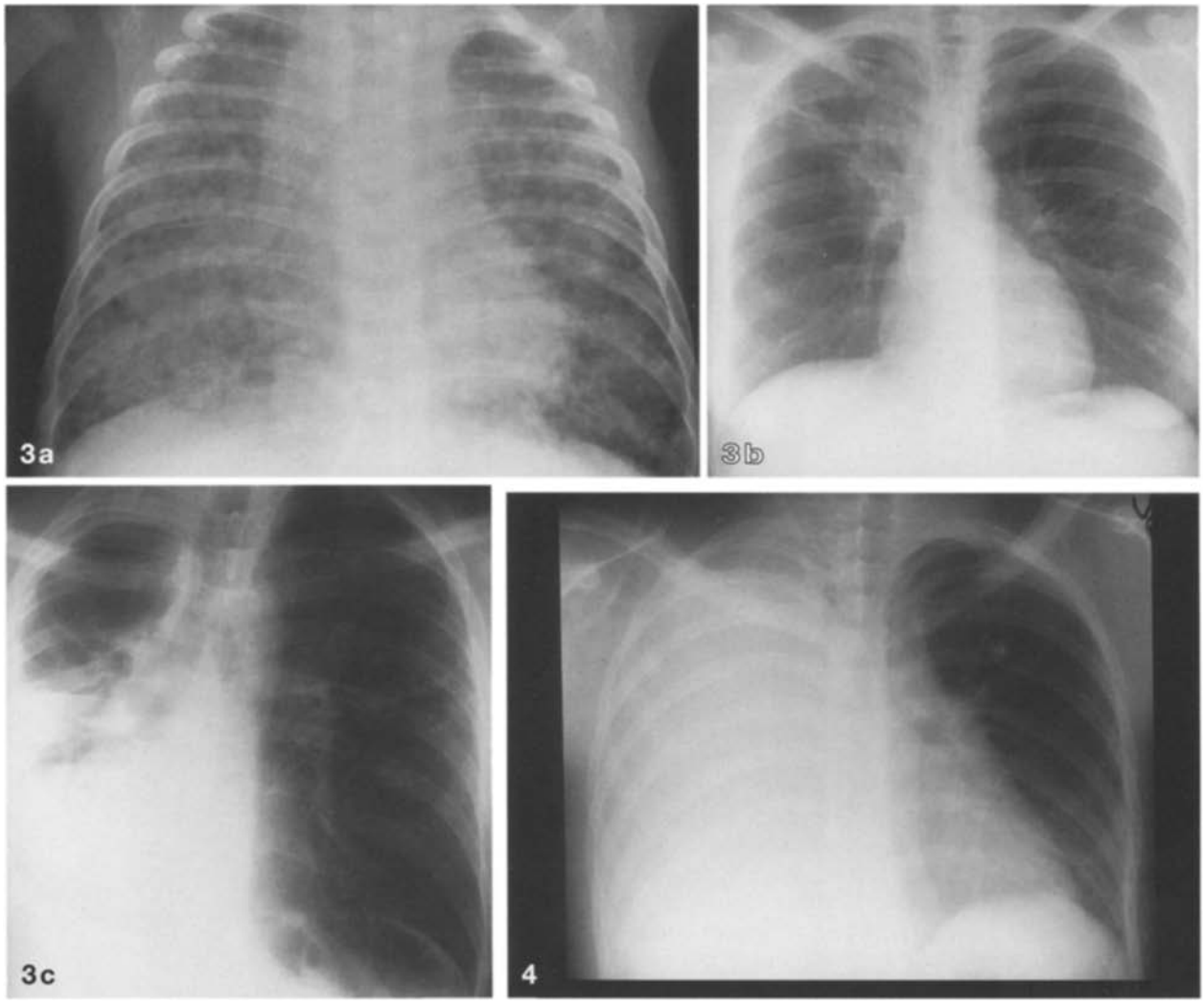

Fig. 3a–c Transmission of MTb within a family. **a** Anteroposterior chest radiograph of a 3-month-old male infant shows innumerable small ill-defined nodular opacities throughout both lungs, consistent with miliary tuberculosis. **b** Posteroanterior chest radiograph of the child's mother shows patchy opacity in the right upper lobe with strands of opacity extending to the hilum. **c** Posteroanterior radiograph of the child's father shows severe cavitation and destruction of the right lung

Fig. 4 Tuberculous pleural effusion in a 19-year-old girl. Posteroanterior chest radiograph shows near complete opacification of the right hemithorax by pleural effusion. The trachea is slightly shifted leftward

Results

Results are summarized in Table 1. Patients are listed by age at the time of diagnosis.

Of the 19 children who underwent PPD testing, 13 (68 %) were reactive and six (32 %) were nonreactive. Four (21 %) of the latter group subsequently converted to reactive; the other two children had no further PPD testing recorded. Three children did not undergo PPD testing.

Twenty-one of the 22 children had findings on imaging studies. One child, with a reactive PPD and a positive urine culture, had a normal chest radiograph and renal ultrasound; this child was the sibling of another child in this series. Fifteen children had pulmonary disease, including 12 with air space consolidation or atelectasis (Fig. 1, Table 1) and three children, all less than 9 months of age, with miliary tuberculosis (Figs. 2 and 3). Eight children had radiographic evidence of enlarged hilar or mediastinal lymph nodes (six with associated pulmonary abnormality). There was a single case of massive tuberculous pleural effusion (Fig. 4).

Two patients had tuberculous meningitis (Fig. 5) and two cases revealed hepatic and renal involvement on imaging. A 2-month old with miliary disease had hepatomegaly and an ill-defined hyperechoic renal lesion, with elevated liver enzymes and a positive urine

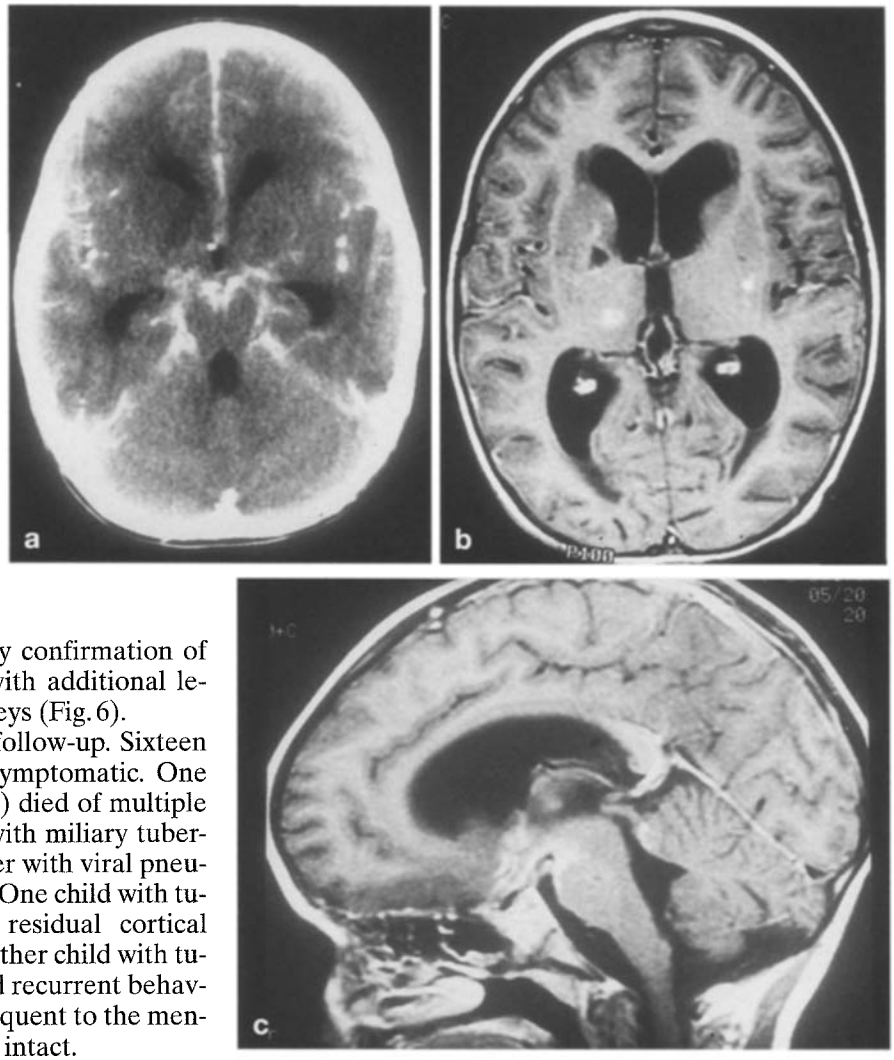

Fig. 5a–c Tuberculous meningitis in a 4-year-old girl. **a** Contrast-enhanced CT of the head shows extensive leptomeningeal enhancement within the basilar cisterns circumferential to the midbrain. The cerebral ventricles are diffusely dilated. **b** Gadolinium-enhanced axial T1-weighted MR image (TR = 616 ms, TE = 11 ms) shows several enhancing lesions and a single low-signal lesion within the basal ganglia. Ventricular dilatation is again noted. **c** Gadolinium-enhanced sagittal T1-weighted MR image (TR = 566 ms, TE = 11 ms) shows leptomeningeal enhancement within the basal cisterns

culture. A 12-year-old boy had biopsy confirmation of macronodular hepatic tuberculosis, with additional lesions identified in his spleen and kidneys (Fig. 6).

Two children were lost to clinical follow-up. Sixteen of the other 20 are now clinically asymptomatic. One child with miliary tuberculosis (case 1) died of multiple organ system failure. Another child with miliary tuberculosis (case 8) returned 4 months later with viral pneumonia and presumed viral meningitis. One child with tuberculous meningitis (case 11) has residual cortical blindness and right hemiparesis. The other child with tuberculous meningitis (case 14) has had recurrent behavioral problems which developed subsequent to the meningitis, but is otherwise neurologically intact.

Illustrative cases

Case 7. Primary pulmonary tuberculosis. A 2-year-old boy with a 6-week history of intermittent fever had an abnormal chest radiograph (Fig. 1a, b). Extensive lymph node enlargement with compression of the right middle lobe bronchus was shown on CT (Fig. 1c). The PPD test was initially nonreactive; it converted to reactive 1 month later. The child had contacted MTb from a grandparent from India with reactivation MTb. The child returned to normal on antituberculous medication; his chest radiograph also reverted to normal.

Case 1. Miliary tuberculosis. A $2^1/_2$-month-old girl was transferred from another hospital with increasing respiratory distress and an abnormal chest radiograph (Fig. 2). The patient had been febrile for 5 days, was lethargic, and, by history, had a significant weight loss. Laboratory tests demonstrated anemia, elevated liver enzymes, and an elevated prothrombin time. A PPD test was reactive, and urine, tracheal, and gastric aspirate cultures all eventually grew MTb. Fundoscopic examination demonstrated tuberculous chorioretinitis. An abdominal ultrasound showed hepatomegaly and a poorly circumscribed hyperechoic lesion at the upper pole

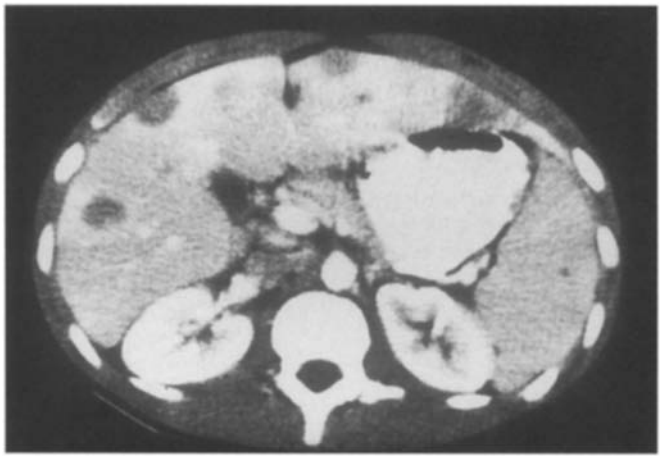

Fig. 6 Macronodular hepatic tuberculosis in a 12-year-old boy. Contrast-enhanced CT scan shows low-attenuation lesions with peripheral enhancement within the liver. Two small splenic lesions are also seen

of the left kidney. Despite aggressive antituberculous and supportive therapy, the patient died 8 weeks after diagnosis with multiple organ system failure. The mother was PPD reactive but had a normal chest radiograph. Both parents were prison inmates.

Cases 2 and 10. Transmission of MTb within a family. A 3-month old boy (case 2) had a 3-week history of intermittent fever, cough, and sneeze. A chest radiograph was abnormal (Fig. 3a). Lung biopsy confirmed miliary tuberculosis, and sputum and gastric aspirate cultures grew MTb. The patient responded well to antituberculous medication with no known sequelae. Both parents had radiographic evidence of active pulmonary tuberculosis (Fig. 3b, c), and were not compliant in taking antituberculous medication. The 3-year-old brother (case 10) had a reactive PPD test, and urine cultures grew MTb; however, chest radiograph and renal ultrasound were normal.

Case 11. Tuberculous meningitis. A 4-year-old girl with 9 days of progressive somnolence demonstrated papilledema on fundoscopy. CT and MR examinations revealed extensive basilar leptomeningeal enhancement and probable areas of infarction in the basal ganglia (Fig. 5). A chest radiograph was normal. Cerebrospinal fluid (CSF) studies confirmed meningitis, and cultures subsequently grew MTb. A PPD test was reactive. The child completed a four-drug treatment regimen but has residual cortical blindness and right hemiparesis.

Case 17. Macronodular hepatic tuberculosis. A 12-year-old boy presented with a 2-week history of night fever and abdominal pain. A chest radiograph was normal. An abdominal CT showed several hepatic lesions (Fig. 6); additional smaller lesions were present within the spleen and kidneys. A PPD test was nonreactive. Open liver biopsy revealed caseous granulomas which stained positive for MTb. The child's father had been PPD reactive for many years but was without evidence of active disease. The patient recovered completely on a two-drug regimen.

Discussion

Tuberculosis is again becoming an important infectious disease in the 1990s. Although increasing homelessness, an increasing immigrant population, and an increasing prevalence of AIDS and other forms of immune compromise have been cited as contributing to the resurgence of the disease, tuberculosis is not relegated to these segments of the population. This is particularly true among children. This series of immunocompetent children confirms pulmonary disease as the most common radiological manifestation of MTb in childhood; however, miliary disease or other forms of extrapulmonary disease can be seen in the immunocompetent child [4].

Miliary tuberculosis is particularly worrisome, since it affects the very young [5, 6]. When the classic miliary pattern is present the radiologist is frequently the first to entertain the diagnosis of tuberculosis, as presenting signs and symptoms are nonspecific. If diagnosed early, miliary tuberculosis can be treated, with excellent outcome. If undiagnosed, development of tuberculous meningitis or multisystem disease portends a poor prognosis, as seen in the sole fatality in our series [5, 7]. Tuberculous meningitis and macronodular hepatic tuberculosis are other less common forms of infection which can carry significant morbidity and mortality if not diagnosed and treated promptly [8–13].

Fourteen of our patients with MTb were 5 years of age or younger. This age distribution, with a high prevalence in the very young and a general paucity of new cases in the 5- to 15-year age-group, is similar to those in previously published series [1, 5, 7, 14, 15]. Family members or close household contacts are usually the source of exposure for younger children, while teenagers tend to be exposed outside of the home [4, 15].

Mycobacterial infection is increasing in frequency in all children, not just the immunocompromised. As childhood tuberculosis is usually primary disease, each case indicates recent transmission of MTb within the community. Prompt diagnosis is important for adequate treatment of the patient and prevention of permanent morbidity or death. Prompt diagnosis is also important for expedient involvement of the appropriate medical, public health, and social professionals in identifying and treating concomitant cases and preventing further spread of disease. The many different sites of involvement with varying clinical presentations pose a significant challenge to the clinician. The radiologist may be the first to suspect tuberculosis. Knowledge of both the common and the unusual manifestations of tuberculosis, combined with a high index of suspicion, will enable the radiologist to suggest the diagnosis of tuberculosis in a timely manner.

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