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INTERMITTENT CHEMOTHERAPY FOR MILIARY TUBERCULOSIS IN CHILDREN*

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SUMMARY: Anadol D, Kiper N, Göçmen A, Özçelik U. (Chest Disease Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Intermittent chemotherapy for miliary tuberculosis in children. Turk J Pediatr 1999; 41: 53-59.

Miliary tuberculosis is a severe manifestation of tuberculosis. Six children aged between two months and 10 years with the diagnosis of miliary tuberculosis were treated with intermittent antituberculous therapy for six, nine or 12 months. All the patients showed clearance of both clinical and radiological symptoms; there was no drug toxicity or resistance and no relapses were seen in the follow-up period ranging from nine months to nine years. Intermittent therapy is safe and effective in miliary tuberculosis and it may be an alternative therapy because of its minimal toxicity and lower cost. *Key words: miliary tuberculosis, intermittent chemotherapy, children.*

Tuberculosis remains a major problem for the world because of its high morbidity and mortality. Although significant progress in the control of this disease has been made in Turkey it is still one of the most important public health problems[1].

Miliary tuberculosis is a severe manifestation of tuberculosis, especially in children[2]. It is characterized by marked variation in clinical presentation and often significant delay in diagnosis[3]. During the prechemotherapy era, it was a common complication of primary tuberculosis with a very high mortality rate, but with the advent of treatment mortality declined[2]. The official recommendation in miliary tuberculosis is 12 months of treatment, with 10 months of isoniazid (INH) and rifampin (RIF) following the initial two months of daily multidrug therapy[4]; However, the therapy for tuberculosis has undergone major changes in the past 10 years[5, 6]. We hearby present our data with intermittent therapy for miliary tuberculosis.

Material and Methods

Patients with the diagnosis of miliary tuberculosis between January 1982 and December 1995 were included in this retrospective study. A presumptive diagnosis of miliary tuberculosis was made by typical miliary pattern on chest radiogram and clinical findings like fever and weight loss[7].

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The age and sex of the patients, their contact with another case of tuberculosis, results of their Mantoux test with 5 TU purified protein derivative (ppd) skin tests, and whether or not they had a BCG vaccine were recorded. An induration of ≥ 15 mm on the Mantoux test in vaccinated patients and > 10 mm in patients without a BCG vaccine was considered positive. The presenting symptoms, the duration of the symptoms and the clinical findings were noted.

Wellcome classification was used for the diagnosis of protein-energy malnutrition[8]. Hepatomegaly was defined as palpation of the lower edge of the liver 2 cm below the inferior costal margin in the midclavicular line. Splenomegaly was defined as the palpation of the splenic margin > 0.5 cm below the inferior costal margin.

The results of the mycobacterial culture from the gastric aspirates of all children were noted. Chest x-ray findings, microbiological findings, drug regimens, drug toxicity, time for complete clinical remission and radiological clearance, and the results of the treatment were also recorded. Clinical and radiological evaluations were made on the 15th day of the treatment and every three months during the therapy. Improvement in appetite and weight gain, normalization of body temperature, and cessation of sweating were accepted as criteria for recovery during the course of treatment. Resolution of infiltrates and miliary pattern on chest radiograph were accepted as criteria of radiological recovery. In order to estimate the compliance of the patients, the drugs were counted and the color of the urine was examined on every visit. Liver function tests were made if indicated in this period. After the treatment was discontinued, clinical and radiological outcome was assessed every three months in the first year, every six months in the second year and every 12 months in the following years.

Results

From January 1982 to December 1995, 19 cases were diagnosed with miliary tuberculosis. Only the six who we could be sure would be closely followed up, come regularly to hospital visits, and have a good compliance were treated with intermittent chemotherapy.

There were four boys and two girls and the ages of the patients ranged between two months and 10 years with a mean age of three years. The majority of patients (67%) were younger than six years, while half of the children were less than two years old.

Three patients (50%) had a history of contact with a tuberculous patient, with all infections occurring from household contact (one from mother, one from uncles, and the other from a distant relative).

The most common presenting symptoms were cough and fever, each noted in four and three patients respectively. One patient complained of vomiting, headache and convulsions. Weight loss, hemoptysis and reduced range of hip

motion were other presenting symptoms. The duration of time between the initiation of symptoms and diagnosis ranged from two weeks to seven months; the mean duration of time was seven weeks.

As for the predisposing conditions, two of our cases already had malnutrition. Only one patient was vaccinated with the BCG vaccine.

On clinical evaluation, five patients were found to have crackles and all but two had hepatosplenomegaly. One patient had reduced range of hip motion with pain.

Tuberculin test was positive in only two (33%) patients -both were unvaccinated. Four patients- one vaccinated- had a negative test.

On chest radiograms, all patients had miliary lesions; two had consolidation and one had pulmonary infiltration in addition to miliary opacifications.

One or more gastric aspirates were submitted for culture from all the children evaluated. A positive culture of Mycobacterium tuberculosis was obtained from gastric aspirates of four children (67%); there was no resistance to drugs. The characteristics, and clinical, radiological and bacterial findings of the patients are shown in Table I.

Table I: Characteristics and Clinical, Radiological and Bacteriologic Findings of the Patients

Case	Age*	Sex	Contact with tbc	BCG	ppd	Predisposing Factor	Clinical Findings	Radiological Findings	Culture
1	8 m	Male	+	–	>15 mm	–	Crackles, hepatosplenomegaly	Miliary lobar consolidation	+
2	2.5 y	Male	+	–	negative	–	Crackles, hepatosplenomegaly	Miliary	–
3	2.5 m	Female	–	–	>15 mm	–	Crackles, hepatosplenomegaly	Miliary, lobar consolidation	+
4	10 y	Male	–	–	negative	–	Hip pain	Miliary	+
5	6 y	Female	+	–	5 mm	malnutrition	Crackles	Miliary	–
6	2 m	Male	–	+	negative	malnutrition	Crackles hepatosplenomegaly	Miliary, Lobar infiltration	+

*m: months, y: years.

The dose for INH was 10 mg/kg/day to a maximum of 300 mg, for RIF was 10-15 mg/kg/day to a maximum of 600 mg and for streptomycin (SM) was 30 mg/kg/day to a maximum of 1 g. Medication was given once daily, preferably in the morning before breakfast. The drug regimen and the prognosis of the patients are shown in Table II. The difference in the regimens is a result of changes in protocols used in our department.

Table II: Drug Regimens and the Prognosis of the Patients

Case	Drug Regimen	Clinical Recovery	Radiological Recovery	Time of Follow-up
1	INH, RIF daily for 15 days, twice a week for the next 8.5 months	5 months	8 months	7 years
2	INH, RIF daily for 15 days, twice a week for the next 8.5 months	2 months	8 months	9 years
3	INH, RIF daily for 15 days, INH, RIF twice a week for 5.5 months	3 months	3 months	16 months
4	INH, RIF, SM daily for 15 days, INH, RIF twice a week for the next 8.5 months	3 months	6 months	9 years
5	INH, RIF, SM daily for 15 days, INH, RIF twice a week for the next 8.5 months	4 months	8 months	9 months
6	INH, RIF, SM daily for 15 days, INH, RIF twice a week for the next 11.5 months	5 months	10 months	13 months

Results of therapy were judged on the basis of elimination of symptoms, disappearance of extrapulmonary findings and clearing of chest roentgenogram abnormalities. Clearance of symptoms occurred between two and five months. The miliary findings on the chest radiograms were cleared between three and ten months (Figs. 1 and 2).

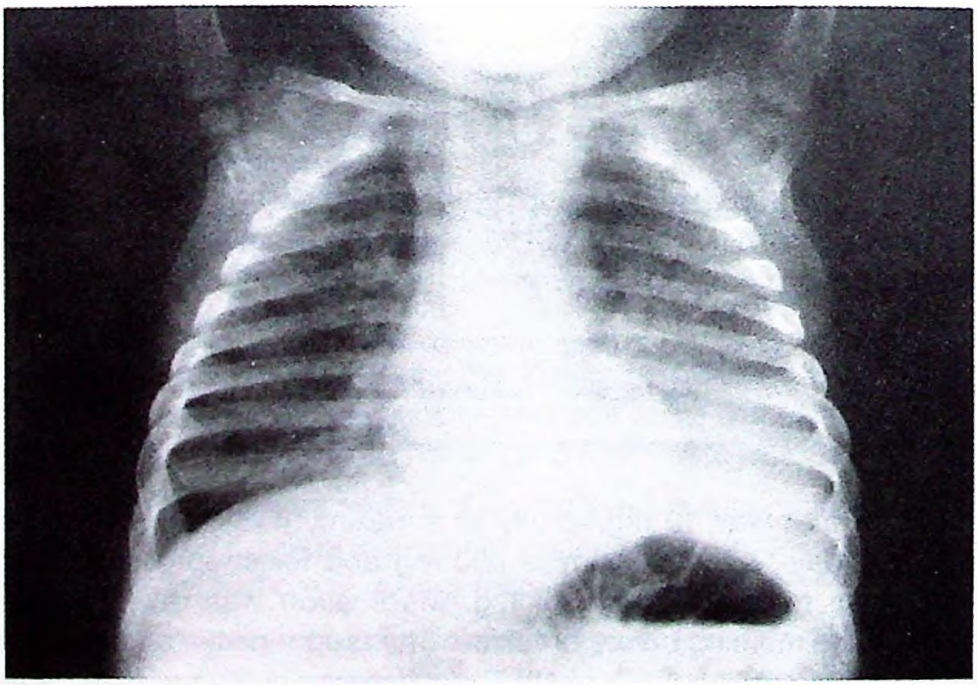

Fig. I: Miliary lesions on the chest radiogram of one of the patients before treatment.

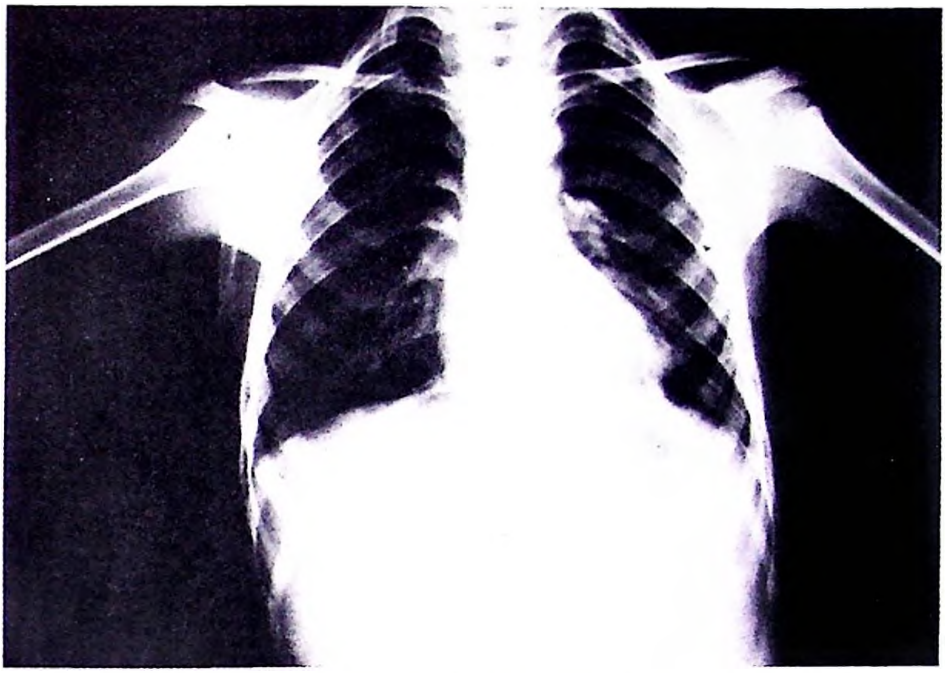

Fig. 2: Chest radiogram of the same patient after the treatment; miliary lesions are cleared and calcifications are seen.

As a result of therapy, all the patients diagnosed with miliary tuberculosis showed clearance of both clinical and radiological symptoms. They were followed up for a period ranging from nine months to nine years (mean, 4 years); no relapses were seen in this period.

No adverse reactions were noted among any patients except the elevation of SGPT in one patient up to 91 IU/L as a mild side effect.

Discussion

Miliary tuberculosis is the most commonly recognized form of disseminated infection. It occurs when a large number of bacilli invade the blood stream from a caseating focus, often a lymph node which ruptures into a blood vessel. It differs from other forms of tuberculosis in some ways: the clinical manifestations of miliary disease are generally nonspecific, including low-grade fever, anorexia, weight loss and night sweats[7]. The most common presenting symptoms of our patients were cough and fever. In this disease, hepatomegaly, splenomegaly and lymphadenopathy are common, as was seen in our patients. It is also well known that preexisting malnutrition is a predisposing factor to miliary tuberculosis.

Most of our patients were less than six years old, while half were less than two years old. These results emphasize the importance of paying much more attention to infants and younger children with tuberculosis in aspects of complications

like hematogenous dissemination. Results reveal that the diagnosis of miliary tuberculosis was made after as long as approximately seven months after the initiation of symptoms. Therefore, symptoms like fever, cough and weight loss must be taken into consideration for tuberculosis in children.

Many patients with miliary tuberulosis are anergic to tuberculin. Tuberculin skin tests are positive in about three quarters of patients with acute miliary tuberculosis[7]. In our study the test was positive in only two out of six patients (33%).

It is known that BCG does not prevent infection but it does decrease the incidence of serious disease and prevent severe complications such as tuberculous meningitis and miliary tuberculosis[2, 4]. However, considering the fact that only one of our patients was vaccinated with BCG, it was nevertheless disturbing to note the failure of the vaccine to prevent the disease. On the other hand, it is striking to see that five out of six children in our study were unvaccinated, as the policy of Turkey is to administer the BCG vaccination to every infant. This situation demonstrates that there is a great public health problem in controlling this disease in our country.

The radiological hallmark of acute disseminated tuberculosis is the miliary pattern on chest radiogram[7]. Our patients' diagnoses were also based primarily on this finding, and all of them had the miliary appearance on their chest x-ray.

The most definitive laboratory test for the diagnosis of tuberculosis is the mycobacterial cluture. However, sputum smears and culture for acid-fast bacilli are often negative, because relatively few organisms are involved despite widespread dissemination[7]. In our study, a positive culture for Mycobacterium tuberculosis was obtained from gastric aspirates of four children (67%); In our study only mycobacterial cultures were used. Newer culture methods like the BACTEC radiometric system, which can grow mycobacteria from sputum specimens in seven to 10 days, or polymerase chain reaction (PCR), which is a very rapid but not sufficiently reliable method, were not used for the diagnosis[4].

The official recommendation is that children who have miliary tuberculosis receive a total of 12 months of INH and RIF following an initial two months of daily multidrug therapy[4]. However, we gave our patients an alternative therapy, an intermittent regimen with two or three drugs daily for 15 days followed by two drugs twice weekly completed in up to six, nine or 12 months, which appears to have been successful in all the patients. The drug regimens differed from each other depending on the protocols we used in our department. There was no drug resistance reported in our study. In addition, there were no significant clinical or biochemical adverse effects except mild and transient elevation of liver enzymes in one patient. No relapses within our follow-up time of up to nine years suggests the effectiveness of this therapy.

Short-course intermittent chemotherapy has also been shown to be effective in controlling tuberculosis in young infants aged less than six months[9]. Compared to conventional regimens, an intermittent regimen has several advantages: shorter treatment time, fewer doses of medication, lower cost and minimal toxicity[10]. But, compliance is the most important factor in this type of therapy. It remains the single biggest problem in treating children with tuberculosis, many of whom live in a social environment not conducive to consistency or completeness of care. So, the ability to administer twice-weekly antituberculosis medications by a health care professional using directly observed therapy (DOT) is a necessary part of treatment programs. The adoption of DOT has been associated with a reduced rate of treatment failure, relapse an drug resistance[11]. Even though noncompliance with DOT was reported in an urban tuberculosis control program, it was found to be closely associated with alcoholism and homelessness[11].

To the best of our knowledge, this is the first report on intermittent therapy in miliary tuberculosis in children. Intermittent therapy seems to be safe and effective in miliary tuberculosis in children and it may be an alternative therapy, especially in developing countries, because of its minimal toxicity and lower cost.

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