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Full Length Research Paper

Clinical and laboratory characteristics of 48 patients with miliary tuberculosis

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Miliary tuberculosis (TB) is a progressive form of TB, indicating disseminated hematogenous spread. Data were collected by scanning the Dicle University Hospital records between January 1990 and December 2010. Forty eight adult patients which were diagnosed miliary TB and followed by hospitalization were enrolled in this study. The mean age was 41.2 ± 14.1 years. Twenty-four patients (50%) had history of contact with TB patients; six patients (12.5%) had a history of previous TB disease. The most common presenting symptoms were loss of appetite (77.1%), cough (70.8%) and weight loss (64.5%), respectively. Typical miliary pattern were diagnosed radiologically on chest radiographs of all patients. There was cavity at Thoracic tomography in six of 31 patients (12.5%). The most common laboratory finding was elevated erythrocyte sedimentation rate (83.3%). The patients were diagnosed by microbiological (10%), histological (29%) and clinical-radiological (61%) methods. 10 patients (20.8%) had a history of an additional disease accompanying TB. Five patients (10.4%) died during hospitalization. As a result, miliary TB is a form of TB that is more frequent and severe in risk groups with co morbid disease. After clinical suspicion, the use of microbiological and histopathological methods up to radiological methods thought to be useful for fast and accurate diagnosis.

Key words: Tuberculosis, miliary, diagnosis.

INTRODUCTION

The term miliary tuberculosis (TB), regardless of pathologic type, expresses all TB forms that showing progressive disseminated hematogenous spread. In a classical textbook, the terms miliary and disseminated TB was used interchangeably, however the title was 'miliary TB' (Baker and Glassroth, 2004).

Miliary TB was described because of simulating the 1-2 mm lesions in the lungs to the millet grain for the first time in the year 1700 by John Jacob Manget. These lesions often contain caseation necrosis (Kim et al., 1990).

Approximately one third of the patients are smear positive. Histopathological tissue examination is necessary for rapid diagnosis (Kim et al., 1990; Maartens et al., 1990; Baker and Glassroth, 2004).

Miliary TB is a severe form of TB infection and the rate of 3-7% in all TB cases. Mortality can be high, especially in children and can reach 25% (Dunlap et al., 1999). In Turkey, 15,943 new TB cases were reported and 150 (0.94%) miliary TB cases were reported among these TB cases (Bozkurt, 2011).

In this study, we aimed to investigate the clinical, radiological and laboratory findings, diagnostic methods, therapeutic approaches, and outcome in patients with miliary TB in an endemic area.

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Abbreviations: BCG, Bacille calmette guerin; **CSF,** cerebro spinal fluid; **CXR,** chest X-Ray; **ESR,** erythrocyte sedimentation rate; **LDH,** lactate dehydrogenase; **TB,** tuberculosis; **TST,** tuberculin skin test.

MATERIALS AND METHODS

Study data were collected by scanning the Dicle University Hospital records retrospectively between January 1990 and December 2010.

The data, obtained from patient files of 48 adult patients that were diagnosed miliary TB and followed by hospitalization, and then recorded in standard forms.

Inclusion criteria

Patients who were diagnosed with miliary TB in our hospital were included in the study. Miliary TB was diagnosed by bacteriological, histopathological or clinical-radiological findings. Smear and culture were performed for TB in sputum, fasting gastric juice, cerebrospinal fluid (CSF) of patients.

Exclusion criteria

Patients with history of other tuberculosis forms: lung cancer, chronic obstructive pulmonary disease, asthma, chronic renal and liver failure as well as children (<18 years) were excluded of this study.

Patients' age, gender, the presence of TB history in the family and itself, affected organs, symptoms, duration of symptoms, physical findings, diagnostic method, the tuberculin skin test (TST), microbiological tests, white blood cell count, hemoglobin level, erythrocyte sedimentation rate (ESR), liver enzymes, serum lactate dehydrogenase (LDH) level, serum albumin level, treatment regimen, the presence of death during hospitalization, were recorded.

Symptom duration, were defined as the time between onset of symptoms of patients and diagnosis.

Positivity of human immune deficiency virus (HIV) was not found in study population. Invasive diagnostic method was not performed to all because of patients were followed for a variety of clinics. Transbronchial biopsy was not performed because of the majority of our patients have not good general condition. Lumbar puncture and CSF analyze was performed in all patients with suspected meningitis. TST, was considered positive above 15 and 10 mm in vaccinated and unvaccinated patients respectively (as the case may Bacille Calmette Guerin (BCG) vaccination). The standard postero-anterior chest X-rays (CXR) of patients were evaluated in detail, in terms of miliary TB. Chest tomography scans of 31 patients at the time of hospitalization and control examination were reviewed.

RESULTS

The study included 48 patients (22 males, 26 females). The median age was 42 years (19-67 years). Twenty-four patients (50%) had a history of contact with TB patients. six cases (12.5%) had a history of previous TB disease.

A total of 19 patients (39.5%) had a BCG scar. Positi-vity of TST was found 10 (20.8%) patients. Demographic data are presented in Table 1.

The most common presenting symptoms were loss of appetite (77.1%), cough (70.8%) and weight loss (64.5%) (Table 2).

The most common findings on physical examination were fever (64.5%), pulmonary crackles (43.7%) and hepatomegaly (29.1%), respectively (Table 2).

All patients had typical military pattern on chest radiographs. There were typical miliary pattern and micronodularity at tomography scans of 31 patients during hospitalization and at controls and six patients (12.5%) had cavity.

The most common laboratory finding was elevated ESR (83.3%). Other common laboratory findings were leukocytosis (79.1%), elevated LDH (75%), anemia (66.6%), elevated liver enzymes (52.1%), and hypoalbuminemia (39.6%), respectively.

A total of 14 patients specimens were sent to Mycobacterial culture. Five patients were diagnosed by microbiological methods. Four of them had positive sputum smear and culture for TB. Cerebrospinal fluid smear was TB positive in one patient.

Seven patients accompanied by TB meningitis and all of them were diagnosed by lumbar puncture. CSF was fuzzy and had increased amount, pressure and cell contents in this patients. In addition, lymphocyte predo-minance was observed at CSF smear. In 10 patients (20.8%) had a history of additional disease accom-panying to TB. We diagnosed diabetes mellitus in five, chronic renal failure in three and connective tissue disease in two of these 10 patients.

Standard anti-TB treatment was given to patients

INH (5 mg / kg / day, maximum 300 mg / day) and rifampisin (10 mg / kg / day, maximum 600 mg / day) treatment was performed to all of the patients for 9-12 months .

In addition, pyrazinamide (25 mg/kg/day, maximum 2 g/day) and ethambutol (15-25 mg/kg/day, maximum 1.5 g/day) or streptomycin (15 mg/kg/day, maximum 1000 mg/day) treatment was performed for two months in the initial phase of treatment.

Five (10.4%) patients died during hospitalization. All of these patients had died within the first two weeks of anti-TB therapy.

DISCUSSION

Pathogenesis of miliary TB and disseminated TB are similar: hematogenous spread of large amount of bacilli; however they result in different histological pictures. While tubercules form in military TB in the tissues, they are not present in disseminated TB: nonreactive generalized TB (Mert and Ozaras, 2005).

Miliary TB is a rare but a serious form of TB. In the United States about 1% of all TB cases reported as miliary TB (Rieder et al., 1990). In Turkey, 15,943 new TB cases were reported and 150 (0.94%) miliary TB cases were reported among these TB cases (Bozkurt, 2011).

Miliary TB cases are usually seen as the primary cases. Therefore, to investigate the source of contami-nation is required. Unfortunately, we cannot find probable

Table 1. The demographic data of patients with miliary tuberculosis.

Demographic feature	Patients (n=48) n (%)
Median age (years)	42
Gender	
Male	22 (45.8)
Female	26 (54.2)
Presence of previous tuberculosis history	6 (12.5)
Presence of contact with tuberculosis patient	24 (50)
Presence of BCG vaccine scar	19 (39.5)
Positivity of TST	10 (20.8)
Additional organ involvement excluding lung	
Lymph Node	6 (12.5)
Meningeal	7 (14.5)
Mean symptom duration (months)	2.4
Diagnostic method	
Microbiological (smear and culture)	5 (10.4)
Histopathological	14 (29.1)
Clinical-radiological	29 (60.5)
Additional accompanying diseases	
Diabetes Mellitus	5 (10.4)
Chronic Renal Failure	3 (6.2)
Connective Tissue Disease	2(4.2)

TST= Tuberculin Skin Test BCG= Bacille Calmette Guerin.

source always. Berktas et al. (2002), reported series of 35 cases, 6 patients (17.1%) had history of contact with TB patients, while two patients had a history of previous TB. Mert et al. (2001) reported no history of contact with TB patients at their series of 38 cases. In our series, 50% of patients had a history of contact with TB patients and 12.5% of patients had a history of previous TB. Miliary TB symptoms and physical findings show variety.

Fever, anorexia, weight loss, pulmonary crackles and hepatosplenomegaly, are the most common findings (Starke, 1996), Maartens et al. (1990), was reported hepatomegaly and splenomegaly in 52 and 15% of 109 patients respectively. In our study, the most common symptoms in patients were anorexia and cough. The most common findings were fever and lung crackles. The results of this study are similar to literature. The average duration of symptoms was 2.4 months in our study.

We thought that suspicion from miliary TB might be useful for early diagnosis and a shorter duration of symptoms. Hematologic changes in miliary TB were defined as anemia, leukocytosis, leucopenia, and leukomoid reaction. However, the clinical significance of these parameters is controversial (Kim et al., 1990; Maartens et al., 1990; Baker and Glassroth, 2004; Sharma et al., 1995). Hyponatremia, high levels of alkaline phosphatase and transaminase, hyperbilirubinemia, and hypercalcemia occurs as biochemical abnormalities (Kim et al., 1990; Maartens et al., 1990; Sharma et al., 1995). We were detected leukocytosis, increased ESR, anemia, high LDH, hypoalbuminemia, and elevated liver enzymes in our study as similar to literature.

Appearance of radiographic signs after spreading of bacilli required a period of 4-6 weeks in miliary TB. Therefore, radiographic findings may not be seen in the first period of the disease. The incidence of classic miliary pattern at direct radiography has been reported between 40-100% (Kim et al., 1990; Maartens et al., 1990; Radosavljevic et al., 1993). Mert et al. (2001), were found classical miliary pattern as radiological in the 32 (84%) of 38 patients. Al-Jahdali et al. (2000) were reported classical miliary pattern in 89% of 47 patients. Hussey et al. (1991) have found classic miliary pattern at 91% of 94 patients in children's miliary TB series. Gurkan et al. (1998) have found the typical miliary pattern in all 23 patients.

Table 2. Symptoms and signs of patients.

Symptoms	n	%
Anorexia	37	77.1
Cough	34	70.8
Weight loss	31	64.5
Fatigue	31	64.5
Night sweats	29	60.4
Abdominal pain	23	47.9
Headache	17	35.4
Sputum	11	22.9
Hemoptysis	5	10.4
Signs		
Fever	31	64.5
Lung crackles	21	43.7
Hepatomegaly	14	29.1
Hypotension	11	22.9
Lymphadenopathy	10	20.8
Splenomegaly	5	10.4

Miliary pattern rate was found as 100% in our study. There were typical miliary pattern and micronodularity at thoracic tomography of 31 patients and the cavity was detected in 6 patients. We thought that, because of our patients do not resort a doctor until the disease pro-gresses and this disease was not considered in patients with no radiological findings, radiological features are clear.

Miliary TB is difficult to diagnose. Radiologically classic miliary pattern may not be in each patient. Microbiological diagnosis rates ranged from 76 to 21.7% in the literature (Kim et al., 1990; Mert et al., 2001; Radosavljevic et al., 1993; Gurkan et al., 1998). Microbiological diagnosis rate was found as 10.4% in our study. In addition, the histopathological diagnosis rate was 29.1%.

Possible causes of these low rates are; inappropriate general conditions of patients, starting treatment radio-graphic signs because of TB is a serious problem in our region, biased approach of people to invasive diagnostic methods in our region and to see radiological methods enough for miliary TB diagnose.

Miliary TB develops more easily in the presence of some predisposing factors. In particular, in the presence of diseases that distorting the host immune response, miliary TB has a more rapid course. Miliary TB rates that accompanied by a predisposing factor is varies between 23% and 76% in published series (Kim et al., 1990; Maartens et al., 1990; Berktas et al., 2002; Mert et al., 2001; Radosavljevic et al., 1993; Prout and Benatar, 1980; Nagai et al., 1998; Stenius-Aarniala and Tukiainen, 1979).

The most common predisposing factors are pregnancy, diabetes, kidney failure, malignancies, connective tissue disease, and a previous history of TB, alcoholism, and hematologic diseases.

In our study, 20% of patients were accompanied with predisposing factors. The most common disease was determined as diabetes mellitus.

Predisposing factors identified lower than the literature (Mert, 2001; Sharma, 1995). That can be explained by human immunodeficiency virus (HIV) infection is not common in our country.

Anti-HIV antibody studied and it was negative in all patients in a study of 300 TB patients in our country (Buket et al., 1993). Miliary TB is a disease with high mortality.

The mortality rate has been reported between 7.7 and 23.9% in several series (Kim et al., 1990; Maartens et al., 1990; Berktas et al., 2002; Mert et al., 2001; Al-Jahdali et al., 2000; Gurkan et al., 1998; Nagai et al., 1998; Stenius-Aarniala and Tukiainen, 1979). Prout and Benatar (1980) reported 40 (64%) deaths from 62 cases. An additional disease was found in 25 cases of them. The death of 31 patients directly linked to disseminate TB. Mortality rate was 10.4% in our study. We thought that low levels of accompanying disease rate, might be effective in this low levels of mortality.

TB continues to be a serious health problem in our region because of different reasons such as lower socioeconomic status, inadequate knowledge level, and late referral to hospital.

Individuals who share the same environment are at risk because of source cases cannot be isolated enough. Miliary TB is common in this type of family members. 50% of patients have a history of contact with TB patients in our study.

In conclusion, the appearance of miliary infiltrates on chest roentgenogram associated with fever suggests miliary TB, and every effort should be made to obtain confirmatory cultures and biopsies.

Effective treatment should be started immediately at the same time. Complete conducted screening is also important. Therapy must be started as soon as the diagnosis is suspected because of high mortality from this disease.

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