

# Miliary tuberculosis

## Epidemiological and clinical analysis of large-case series from moderate to low tuberculosis endemic Country

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### Abstract

The aim of this study was to determine the clinical features, and outcome of the patients with miliary tuberculosis (TB).

We retrospectively evaluated 263 patients (142 male, 121 female, mean age: 44 years, range: 16–89 years) with miliary TB. Criteria for the diagnosis of miliary TB were at least one of the followings in the presence of clinical presentation suggestive of miliary TB such as prolonged fever, night sweats, anorexia, weight loss: radiologic criterion and pathological criterion and/or microbiological criterion; pathological criterion and/or microbiological criterion.

The miliary pattern was seen in 88% of the patients. Predisposing factors were found in 41% of the patients. Most frequent clinical features and laboratory findings were fever (100%), fatigue (91%), anorexia (85%), weight loss (66%), hepatomegaly (20%), splenomegaly (19%), choroid tubercules (8%), anemia (86%), pancytopenia (12%), and accelerated erythrocyte sedimentation rate (89%). Tuberculin skin test was positive in 29% of cases. Fifty percent of the patients met the criteria for fever of unknown origin. Acid-fast bacilli were demonstrated in 41% of patients (81/195), and cultures for *Mycobacterium tuberculosis* were positive in 51% (148/292) of tested specimens (predominantly sputum, CSF, and bronchial lavage). Blood cultures were positive in 20% (19/97). Granulomas in tissue samples of liver, lung, and bone marrow were present in 100% (21/21), 95% (18/19), and 82% (23/28), respectively. A total of 223 patients (85%) were given a quadruple anti-TB treatment. Forty-four (17%) patients died within 1 year after diagnosis established. Age, serum albumin, presence of military pattern, presence of mental changes, and hemoglobin concentration were found as independent predictors of mortality. Fever resolved within first 21 days in the majority (90%) of the cases.

Miliary infiltrates on chest X-ray should raise the possibility of miliary TB especially in countries where TB is endemic. Although biopsy of the lungs and liver may have higher yield rate of organ involvement histopathologically, less invasive procedures including a bone marrow biopsy and blood cultures should be preferred owing to low complication rates.

**Abbreviations:** AFB = acid fast bacillus, CSF = cerebrospinal fluid, EMB = ethambutol, EZN = Ehrlich-Ziehl-Neelsen, FUO = fever of unknown origin, HRCT = High resolution computed tomogram, INH = isoniazid, PR = paradoxical reaction, PZA = pyrazinamid, RIF = rifampicin, SM = streptomycin, TB = tuberculosis, TST = tuberculin skin test.

**Keywords:** diagnosis, miliary tuberculosis, prognosis

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## 1. Introduction

Although the global incidence of tuberculosis (TB) has been slowly decreasing, the worldwide disease burden remains a major health problem. One-third of the world population is estimated to be infected with *Mycobacterium tuberculosis* (latent TB infection) and 10% of these individuals will develop active TB in their lifetime.<sup>[1]</sup> In 2014, an estimated 9.6 million people developed TB and 1.5 million died from the disease.<sup>[2]</sup> It is also a low endemic disease in our country (annual incidence in 2014 = 18/100,000).<sup>[2]</sup> Miliary TB accounts for ~1% of all TB cases and is a clinical picture resulting from massive lymphohematogenous dissemination of bacilli-laden focus.<sup>[3–10]</sup> Characteristic histopathological feature of miliary TB is a tubercle (granuloma) measuring ~2 mm in ≥2 noncontiguous organs. Although clinical features of the disease are not diagnostic, some findings may imply it.<sup>[11–15]</sup> The definite diagnosis is established by radiological and histological, and microbiological findings. To the best of our knowledge, this study evaluated the largest number of cases with miliary TB to date. In this study, we aimed to evaluate clinical features, diagnosis, treatment, and prognosis of the patients with miliary TB followed during the last 34 years. Initial 38 cases (those detected before 1988) have been published previously.<sup>[11]</sup>

## 2. Patients and method

Medical records of 15 tertiary care centers in Turkey were searched retrospectively for adult miliary TB cases diagnosed between 1981 and 2015. Radiologic criterion for miliary TB was defined as miliary pattern on chest X-ray and/or on high-resolution computed tomography (HRCT).

Pathological criterion for miliary TB was defined as detection of miliary organ involvement of ≥2 separate organs by any biopsy or autopsy.

Microbiological criterion for miliary TB was defined as recovery of *Mycobacterium tuberculosis* from blood specimen.

Criteria for the diagnosis of miliary TB were at least one of the followings in the presence of clinical presentation suggestive of miliary TB such as prolonged fever, night sweats, anorexia, and weight loss:

- (1) Radiologic criterion and pathological criterion and/or microbiological criterion.
- (2) Pathological criterion and/or microbiological criterion.

Miliary infiltrates on chest X-ray were classified as typical (multiple 1–3-mm well-defined nodules throughout all lung fields) or atypical (predominant nodules that measured >3 mm or reticulonodular pattern) miliary pattern.<sup>[11]</sup>

Patients fulfilling the diagnostic criteria of fever of unknown origin (FUO) and paradoxical reaction (PR) were also determined.<sup>[16–18]</sup> Paradoxical reaction (PR) is defined as a transient expansion (worsening) of a pre-existing tuberculous lesion or the development of new lesions under appropriate anti-TB therapy.

Ehrlich-Ziehl-Neelsen (EZN) method was used to stain acid-fast bacilli (AFB) from clinical samples (fluid or solid tissue). *M tuberculosis* was cultured in Löwenstein–Jensen media. Blood obtained from 97 patients was cultured in nonradiometric automated TB blood culture system (BACTEC™ Myco/F Lytic culture medium). *M tuberculosis* DNA was investigated by polymerase chain reaction (PCR). IS 6110-specific primers were used to amplify *M tuberculosis* complex.<sup>[19]</sup> In addition, paraffin-embedded granulomatous tissue samples of 21 patients were available during this review and sections of these samples were

stained by a pathologist by EZN to detect AFB. *M tuberculosis* DNA was studied by PCR in 15 of them.

Age, sex, previous history of TB, exposure to active TB, the predisposing factors to TB, and tuberculin skin test (TST) were noted. Induration at the TST site was measured in millimeters after 48 to 72 hours by experienced people. A positive TST was defined as an induration of ≥5 mm in immunosuppressive patients and ≥10 mm in immunocompetent patients.

Clinical and laboratory data and their prognosis were evaluated. Anti-TB drug combinations, their side effects, and complications of the disease were also noted.

The diagnosis of hepatotoxicity from anti-TB drugs was established by the presence of at least one of the followings:<sup>[20]</sup> increased Alanine transaminase (ALT) and/or Aspartate transaminase (AST) 5 times of upper limit of normal (40 IU/L), increased total bilirubin level of >1.5 mg/dL, presence of clinical signs and symptoms suggesting acute hepatitis such as anorexia, nausea, vomiting, and jaundice associated with increased ALT and/or AST 3 times of upper limit of normal.

Institutional ethics committee approval and informed consent are obligatory parts in all interventional studies (human or animal) without any doubt. However, recently published The National Code on Clinical Trials has declared that ethics approval is not necessary for real retrospective studies.<sup>[21]</sup>

Clinical and laboratory features of surviving and dead patients were compared by univariate analysis. Categorical and continuous variables are compared by using  $\chi^2$  and Mann–Whitney *U* tests, respectively. A “*P*” value of <0.05 (2-sided test) was considered to indicate significance. To evaluate the prognostic value of significant variables, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox Regression Model.

## 3. Results

Our research yielded 263 cases of miliary TB (142 males), mean age 44 years (range: 16–89 years). Totally, 44 (17%) patients died within 1 year after diagnosis established.

**Table 1**  
Signs and symptoms of 263 patients with miliary TB.

	Number of cases	%
Complaints		
Fever	263	100
Fatigue	238	90.5
Anorexia	223	84.8
Weight loss	177	66.2
Night sweats	159	65
Cough	159	60.5
Headache	144	43.3
Dyspnea	79	30
Abdominal pain	38	14.4
Hemoptysis	16	6.1
Findings		
Fever	263	100
Lymphadenopathy	56/221	21.3
Hepatomegaly	54	20
Splenomegaly	51	19.4
Mental changes	48	18.3
Pleural effusion	48	18
Neck stiffness	46	17.5
Choroid tubercules	20/159	7.6
Skin involvement*	4	1.5
Altered consciousness (delirium, psychosis)	3	5

TB = tuberculosis.

\* 3 cellulitis, 1 subcutaneous abscesses.

**Table 2****Predisposing factors in 263 patients with miliary TB.**

Factor	No. (%)	Remarks
Collagen vascular disorder	22	Given steroid, azathioprine, cyclophosphamide
Type 2 diabetes mellitus	22	
AIDS	16	All CD4 <100 cells/mm <sup>3</sup>
Cancer	12	Hairy cell leukemia (2), ectopic ACTH syndrome (1), immunoblastic sarcoma (1), NHL (3), CML (2), AML (1), MDS (1), MM (1)
Chronic renal failure	10	
Pregnancy	6	
Renal transplantation	2	
Inflammatory bowel diseases	2	
Addison disease	2	
Total	94 (41)	

ACTH=adrenocorticotropic hormone, AML=acute myelogenous leukemia, CML=chronic myelogenous leukemia, HCL=hairy cell leukemia, MDS=myelodysplastic syndrome, MM=multiple myeloma, NHL=non-Hodgkin lymphoma.

Signs and symptoms of the patients are given in Table 1. Most frequent complaints were fever (100%), fatigue (91%), anorexia (85%), and weight loss (66%). The findings were fever (100%), lymphadenopathies (21.3%), hepatomegaly (20%), and splenomegaly (19%). Fundoscopic examination was performed in 159 patients; 20 (12%) showed choroid tubercles. Meningitis and acute respiratory distress syndrome (ARDS) developed in 17% (46/263) and 10% (26/263) of the patients, respectively.

Twenty-four (9%) patients described exposure to patients with active TB. Twenty-three (9%) patients described previous history of TB and all patients were given the treatment for the appropriate period. A predisposing condition for TB was described in 94 (41%) (Table 2). F.U.O criteria were fulfilled in 131 (50%) patients. Hematological and biochemical findings are given in Table 3.

Anemia, lymphopenia, and pancytopenia developed in nearly 86%, 48%, and 12% of the patients, respectively. Elevated transaminase levels (38%) are more frequently encountered than that of alkaline phosphatase (19%). Elevations in transaminase and bilirubin levels did not exceed 6 times of upper limit of

**Table 3****Hematological and biochemical findings of 263 patients with miliary TB.**

	Number of cases	%
<b>Hematological</b>		
Anemia (Hct male <42%, female <37%)	227	86,3
Leukopenia <4.000 cells/mL	47	18
Leukocytosis >11.000 cells/mL	30	11,4
Lymphopenia <1.500 cells/mL	126	48
Monocytosis >800/ml <4000	30	11,4
Eosinophilia >400/ml 4000–11000	0	0
Thrombocytopenia <150.000 cells/mL	59	22,4
Thrombocytosis >400.000 cells/mL sit, /mL	29	11
Pancytopenia	32	12,2
<b>Biochemistry</b>		
Hypertransaminasemia	99	37,6
Alkaline phosphatase increase	49/151	32
Gamma-glutamyltransferase increase	9/37	24
Hyperbilirubinemia	8	3
Hypoalbuminemia (<3.5 g/dL)	183/244	75
Hyponatremia (<135 mmol/L)	32	12
<b>ESR, mm/h</b>		
<20	30	11,4
20–100	193	74
>100	40	15
<b>CRP (n=190)</b>		
Normal	10	6
Normal to 6 times increase	50,	20
6–12 times increase	45	24
>12 times increase	85	45

CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, TB=tuberculosis.

normal. Erythrocyte sedimentation rate was usually accelerated (normal in 11%).

TST positivity was seen in 29% (61/210) of the cases.

A miliary pattern was seen on chest X-ray and/or HRCT in 232 (88%) patients. Miliary pattern developed approximately 50 days (range 21–150) after the emergence of fever.

The results of microbiological studies (EZN, TB culture, and PCR) and histopathological results were given in Table 4. EZN staining was applied to 195 samples and 81 (41%) remained

**Table 4****Microbiological and histopathological findings of tissue and clinical samples from miliary tuberculosis.**

Tissues	EZN (%)	PCR (%)	Granuloma (%)	Caseation (%)	TB culture positivity rate (%)
Bone marrow*	4/25	4/11	23/28 (82)	13/23 (56)	—
Lungs†			18/19 (95)	10/18 (56)	—
Liver†	2/16	4/7	21/21 (100)	19/21 (90)	—
Lymphadenopathy	6/23	2/11	12/16 (75)	11/12 (92)	—
Pleura	2/3	0/5	—	—	—
Gut	3/7	1/4	—	—	—
Skin	2/2	1/1	—	—	—
Total	19/76 (25)	12/39 (31)	74/84 (88)	53/74 (72)	
<b>Clinical samples</b>					
Sputum	32/101	—	—	—	68/101
Blood	—	—	—	—	19/97
Gastric fluid	6/10	—	—	—	5/10
CSF	25/46	—	—	—	29/46
Bronchoalveolar lavage	18/38	—	—	—	27/38
Total	81/195 (41)				148/292 (51)

CSF=cerebrospinal fluid, EZN=Ehrlich-Ziehl-Neelsen, PCR=polymerase chain reaction.

\*5 from autopsy.

†6 from autopsy.

**Table 5**  
Autopsy findings of 7 patients died of miliary TB who could not be diagnosed clinically.

Age/sex	Duration of disease before death, days	Duration of hospitalization before death, days	Duration of anti-TB therapy	Predisposing factor	TST	Chest X-ray	Presumed diagnosis	Autopsy findings
25/M	150	30	25	No	(+)	Normal	TB meningitis	TB meningitis. Granulomas in lungs, liver, spleen*, and lymph nodes
53/F	28	8	No therapy	No	(-)	Reticulonodular infiltrates	FUO	Granulomas in lungs*, liver*, spleen*, lymph nodes, kidneys, adrenal, pancreas, and endometrium
28/M	40	10	No therapy	No	(-)	Nodular infiltrates	FUO	Granulomas in lungs*, liver*, spleen*, lymph nodes*, and bone marrow.
51/M	57	9	No therapy	No	(-)	Reticulonodular infiltrates	FUO	Granulomas in lungs*, liver*, spleen*, lymph nodes*, bone marrow, kidneys, colon, and prostate
16/M	28	2	No therapy	No	(-)	Normal	TB meningitis	TB meningitis. Granulomas in lungs*, liver*, spleen*, and lymph nodes
74/M	76	16	7	Immunoblastic sarcoma	(-)	Apical infiltration and caverns	FUO	Casating pneumonia. Immunoblastic sarcoma in lymph nodes. Granulomas in liver*, spleen*, and lymph nodes.
52/F	67	7	No therapy	No	(-)	Nodular infiltrates	SLE	Granulomas in lungs*, liver*, spleen*, lymph nodes*, and bone marrow.

F = female, FUO = fever of unknown origin, M = male, TB = tuberculosis, TST = tuberculin skin test.  
\* caseating granuloma, SLE = Systemic lupus erythematosus.

positive. Culture positivity was found in 148 of 292 (51%) samples. TB blood culture yielded *M tuberculosis* in a rate of 20% within 16 to 39 days. Eighty-nine tissue samples including mainly bone marrow samples were studied and granulomas were detected in 74 (88%). Caseating necrosis was noted in 53 (72%). AFB were seen in 25% in granulomatous tissues, whereas 7 of 39 (31%) were positive for *M tuberculosis* DNA by PCR.

The most frequently used drug combination was isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) or streptomycin (SM) (227 patients; 86%). Steroids in addition to anti-TB therapy were also given to 72 patients (46 with meningitis and 26 with ARDS). Fever resolved in a mean duration of 14 days (range: 2–90 days, interquartile range: 7–21 days), and radiological improvement was noted in mean duration of 3 months (range: 3 weeks–6 months). Fever resolved within first 21 days in the majority (90%) of the cases. Fever resolved in 6th month and radiological improvement was noted in 24th month in 1 patient. Surviving cases were followed-up for 1 year. Forty-four (17%) of the patients died: 8 before initiation of treatment and 36 during treatment. The diagnosis of miliary TB was confirmed with autopsy in 7 patients (Table 5).

Forty-two patients (16%) developed hepatotoxicity in days 3 to 10 and improved within 10 days (median 5–60 days) of discontinuation. Liver enzymes did not increase after initiating again. A total of 116 patients (44%) developed complications. The organ system involvements in decreasing order were meningitis (71 cases), cellulitis (3 cases), and 1 subcutaneous abscess, ARDS (26 cases), convulsions (3 cases), spontaneous pneumothorax (5 cases), small bowel perforation (5 cases), 6th cranial nerve palsy (1 case), and paradoxical expansion in the miliary lesions (1 case). Twelve (10%) of these complications were paradoxical reactions (5 spontaneous pneumothorax, 5 small bowel perforation, 1 subcutaneous abscess, 1 paradoxical expansion in the miliary lesions). A univariate analysis was used for the detection of the factors associated with mortality (Table 6). Multivariate Cox regression analysis revealed that older age (hazard ratio [HR] 1.019, confidence interval [CI] 1.002–1.036,  $P=0.029$ ), low albumin level (HR 0.440, CI 0.269–0.721,  $P=0.001$ ), hemoglobin concentration, (HR 0.825, CI 0.712–0.957,  $P=0.011$ ) existence of miliary pattern (HR 2.203, CI 1.060–4.579,  $P=0.034$ ) and mental change alterations (HR 2.734, CI 1.398–5.347,  $P=0.003$ ) at the diagnosis were independent clinical determinants of survival.

#### 4. Discussion

Although the global incidence of TB has been slowly decreasing with globally conducted program, miliary TB incidence will relatively increase owing to widespread use of immunosuppressive drugs and HIV/AIDS pandemicity. Large amounts of bacillemia in miliary TB involve organs with high blood supply including lungs, liver, bone marrow, eyes, kidneys, and adrenals.<sup>[5,7,8]</sup> Miliary TB is a form of extrapulmonary TB and corresponds to ~1% of all TB.<sup>[6]</sup>

Clinical findings (sign and symptoms) and routine laboratory data of the patients with miliary TB may imply this diagnosis but are not diagnostic.<sup>[3,4,6,7,12–14]</sup> This disease has a wide range of clinical spectra from ARDS to FUO. The patients generally present with fever, malaise, night sweats, cough, dyspnea, poor appetite, and weight loss lasting for weeks (generally >3). Clinical signs and symptoms of our patients with miliary TB (except the one with TB cellulitis) are compatible with the results of the previous studies.<sup>[5,8,9,12,22–24]</sup> Among the findings from



**Table 6****Comparison of continuous and categorical variables in patients surviving or died.**

Continuous variables	Surviving (n=219) (mean±SD)	Died (n=44) (17%) (mean±SD)	P
Age, y	42±17	51±17	0.005
Hemoglobin	11±2	9±2	0.000
Leukocyte, mm <sup>3</sup>	7228±5488	7525±5735	0.746
Platelets, mm <sup>3</sup>	252±124	182±119	0.001
Albumin, g/dL	3±0,6	2±0,6	0.000
ALT, U/L	51±69	48±40	0.750
AST, U/L	60±111	60±86	0.979
ESR, mm/h	61±34	64±37	0.632
Categorical variables	Surviving (n=219) n (%)	Died (n=44) n (%)	
Male gender	114 (52)	28 (62)	0.253
Predisposing factor	72 (33)	22 (49)	0.044
Miliary pattern	127 (58)	35 (78)	0.014
Mental change	34 (16)	14 (31)	0.020
Meningitis	58 (27)	13 (29)	0.767
FUO	103 (47)	28 (62)	0.072
Leukopenia	37 (17)	10 (22)	0.393
Thrombocytopenia	41 (19)	18 (43)	0.002
Pancytopenia	24 (11)	8 (18)	0.211

ESR=erythrocyte sedimentation rate, FUO=fever of unknown origin.

physical examination, choroidal tubercles in the eye are pathognomonic for miliary TB.<sup>[9]</sup> The rate of choroidal tubercles was reported between 2% and 21% in miliary TB series.<sup>[14,22,23,25]</sup> In our study, this figure was found to be 8%. Choroidal tubercles are reported to be less frequent in adults<sup>[26]</sup> than autopsy probably because of not performing a routine eye examination and not using midriatics during this examination.<sup>[8,13,22,23,25]</sup> In an autopsy series, choroidal tubercles are found in nearly 50% of the cases.<sup>[7]</sup> Therefore, a systematic ophthalmoscopic examination after mydriatic administration is recommended in all patients suspected of having miliary TB. Meningitis has been described in 10% to 30% of patients with miliary TB.<sup>[4,5,9,22,23,25]</sup> We found 18% rate of meningitis. Skin involvement, which is generally subcutaneous abscess, is seen in 1% to 9% of cases reported in the miliary TB series.<sup>[4,8,12,22,23,25]</sup> In our series, it was 1.5%. Although TB cellulitis is not reported in those series, we have seen 3 such cases. In miliary TB series, pleurisy was seen in 5 to 38%, we found it in 18% of the cases.

The clinical significance and predicting role of hematological changes seen in miliary TB (anemia, leukopenia, leukocytosis, monocytosis, leukomoid reaction, thrombocytopenia, agranulocytosis, and pancytopenia) are controversial.<sup>[4,8,12-14,23,25,27]</sup> The most frequently encountered one is anemia of chronic illness. Pancytopenia is rare and leukopenia and thrombocytopenia are more frequent. Pancytopenia associated with FUO should raise the suspicion of miliary TB. Although the correlation of hematological findings with prognosis could not be shown in previous case series, our cases were generally anemic (86%) and pancytopenia was seen in 12%.<sup>[4,22]</sup>

In nearly half of the cases, an elevation in alkaline phosphatase and/or transaminase level is seen.<sup>[8,12,23-25]</sup> Liver function tests are not correlated with the liver histology.<sup>[8,23]</sup> Transaminase and alkaline phosphatase levels were elevated in nearly one-third of our cases. ESR, an acute phase reactant, is accelerated in miliary TB, whereas level of albumin, a negative acute phase reactant, decreases. An accelerated ESR and hypoalbuminemia were seen in the majority of our cases (90% and 75% respectively).

Previous studies reported an underlying disorder making the host vulnerable to miliary TB (HIV infection, collagen-vascular

disorder, diabetes mellitus, neoplasm, chronic renal failure, pregnancy, steroid use, and alcoholism) in nearly half (30%–66%) of the cases.<sup>[4,12,13,23,26]</sup> A predisposing factor was determined in nearly half of our cases as well, and these factors did not correlate with the mortality. Although TB is endemic in our country, HIV infection is rare. Among our series, miliary TB developed in 16 HIV-infected cases.

Anergy to TST is a more frequent event in miliary TB when compared to pulmonary or other forms of extrapulmonary TB cases.<sup>[3,9]</sup> This observation can be supported by the finding that it often turns positive following improvement during treatment. The rate of TST positivity decreased gradually from 80% to 32% during the last 30 years.<sup>[8,12-14,22,25]</sup> This decrease remains to be explained. A negative TST (owing to anergy) does not necessarily show a poor prognosis.<sup>[22,23]</sup> Nearly ~two-third of our cases had negative TST results and did not correlate with the mortality. The test was repeated after improvement with the therapy and turned positive in nearly half of the cases.

Although miliary TB is known to cause FUO, except from the series of Proudfoot et al,<sup>[14]</sup> FUO was not discussed in miliary TB series.<sup>[4,8,22-25]</sup> Proudfoot et al reported that their 25% of the cases with miliary TB fulfilled the criteria of FUO. Nearly half of our cases had FUO. In FUO series, miliary or disseminated TB seems to be a major cause of prolonged fever.<sup>[28-36]</sup> Therefore, miliary TB should be considered in the differential diagnosis list in a patient with FUO in the countries where TB is endemic.

Miliary nodules are either micro (1–3 mm) or macronodules (3–10 mm) radiologically.<sup>[37]</sup> The classical miliary nodules are micronodules and are seen as typical miliary pattern on chest X-ray. Macronodules are seen as atypical miliary nodules. The clinical miliary TB form which does not associate miliary foci on chest X-ray is called cryptic miliary TB and seen in a rate of 30% in clinical series.<sup>[11,14]</sup> Before naming it as cryptic miliary TB, an HRCT should be obtained since the sensitivity of HRCT for micronodules is higher than chest X-ray.<sup>[37,38]</sup> Miliary nodules were seen on chest X-ray in rates of 40% to 100% in the previous studies.<sup>[8,12-14,24,27]</sup> Absence of the miliary infiltrations on admission cannot exclude the diagnosis.<sup>[8,12-14,24,28]</sup> For detecting the lesions radiologically, at least 2.5 weeks after the initiation

of fever are required.<sup>[39]</sup> For this reason, if miliary TB is a concern, sequential chest X-ray studies should be obtained. The diagnosis was established by detection of miliary pattern on chest X-ray and/or HRCT in ~90% of our cases. The diagnosis was established by culture positivity, laparotomy, and autopsy in patients without a miliary pattern on chest X-ray (cryptic miliary TB).

Yielding the causative agent is important in the exact diagnosis. Routine mycobacterial blood culture and/or bone marrow culture is recommended during evaluations for mycobacterial infections in miliary TB patients. Nonradiometric automated TB blood culture systems effectively yield *Mycobacterium* species. In Wang et al's miliary TB series, the sensitivity of blood and bone marrow mycobacterial culture is found to be 64.7% and 38.5%, respectively.<sup>[4]</sup> In the same study, combined results of bone marrow culture and histopathologic examination are much higher than that of only blood culture (93% vs. 65%). In addition, bone marrow biopsy results can be obtained within 1 week, allowing anti-TB therapy to be started early. The bone marrow biopsy procedure is safer than the others. We have obtained BACTEC™ Myco/F Lytic culture medium in 97 patients, 19 (20%) yielded *M tuberculosis* in days 16 to 39. Previous studies showed the rate of AFB in granulomas as 0% to 44%.<sup>[40–43]</sup> New molecular diagnostics such as PCR contributed much to the diagnosis of TB. This method detects *M tuberculosis* DNA in fluid and tissue samples in a sensitivity ranging from 37% to 100%.<sup>[3,19,44,45]</sup>

Detection of granulomas in several tissue samples including lungs, liver, bone marrow, and lymph node is important in the diagnosis of miliary TB. Three studies reported the rate of granulomas in transbronchial biopsy samples as 10%, 63%, and 75%.<sup>[4,12,23]</sup> We found this figure as 95% in tissue samples of lungs (6 from autopsy). In miliary TB series, hepatic granulomas were detected in a range of 67% to 100%.<sup>[4,12,14,23,41]</sup> Absence of hepatomegaly or normal liver function tests cannot rule out the presence of granulomas.<sup>[8,25]</sup> Although liver function tests were normal and hepatomegaly was not present in nearly one-third of the cases, liver biopsy showed granulomas in all of 21 patients experienced this procedure. Although liver biopsy has a high diagnostic rate, as its complications are more frequent than bone marrow biopsy, the latter is recommended to perform initially. In the studies, diagnostic rate of bone marrow biopsy is reported ~50%.<sup>[4,8,12,14,19,40]</sup> We found this rate as 82% (5 from autopsy). A caseating granuloma should be remembered to be specific for TB.

Paradoxical reaction (PR) is not a rare event. A PR can be encountered at varying rates of 6% to 30% according to given clinical forms of TB.<sup>[18]</sup> This reaction may develop during 2nd week to 9th month (~3rd month). When PR develops, the treatment is continued. Steroids may be added or surgical treatment can be applied when needed. PR was not mentioned in miliary TB series. We have noted PR in 2% of our cases on treatment (2 pneumothorax, 2 bowel perforation, 1 expansion of a preexisting lesion, 1 subcutaneous abscesses). Three of these cases have been published previously.<sup>[46–48]</sup>

Miliary TB cases die within 1 year if they remain untreated.<sup>[3,9]</sup> Anti-TB therapy is essential for survival. A consensus for optimum duration of therapy is lacking in the published miliary TB series. The duration is given as 24 months in one,<sup>[25]</sup> 6 and 9 months in the 2 others.<sup>[4,24]</sup> American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America,<sup>[49]</sup> and British Thoracic Society<sup>[50]</sup> guidelines recommended 6 months' therapy for miliary TB without meningitis. If meningitis associates, the duration should be 12 months. Radiological improvement generally takes 2.5 to 5

months.<sup>[14,23,24]</sup> Steroids are recommended to add when complications such as meningitis, pericarditis, ARDS, and adrenal insufficiency associate.<sup>[1,3,8,25]</sup> Main risk factors predicting the mortality are advanced age, dyspnea, mental changes, meningitis, and failure to initiate therapy quickly.<sup>[12,23,24]</sup> The main factor among these ones is failure to diagnose and treat quickly. The mortality rate is ~25% (14%–30%), and seemed to remain unchanged during last 25 years.<sup>[3,4,8,9,12,14,23–25]</sup> According to Cox Regression analyses, age, albumin level, miliary pattern, presence of mental changes, and hemoglobin level were significantly associated with mortality with negative correlation.

Fever resolved in a mean duration of 24 days (range: 2–90 days, interquartile range: 7–21 days) and radiological improvement was obtained within 3 months (3 weeks to 6 months) with anti-TB therapy in our patients. Fever disappeared within first 21 days in the majority (75%). Surviving cases were followed-up for a mean duration of 2.5 years (range: 1–10 years) and 1 recurred.

Our study has several limitations. The main limitation of our study is its retrospective design; however, miliary TB is very rare presentation of TB even in highly endemic countries. Therefore, it is time consuming and difficult to perform a prospective cohort study. Second limitation is that information on variables may potentially be incomplete as this was a retrospective chart review; however, statistical adjustment (data completion) could be done with appropriate techniques by competent statistician. Third limitation is the low rate of positive blood cultures. It is expected to have higher rates of mycobacterial growth in cultures obtained using procedures that are up to the standards.

In conclusion, prolonged fever (>21 days) and miliary infiltrates on chest X-ray and/or HRCT support the diagnosis of miliary TB. Although biopsies obtained from lungs and liver have a higher yield rate, owing to low complication rate, bone marrow biopsy can be performed initially. In patients with FUO, miliary TB should be considered in the differential diagnosis especially in countries where TB is endemic. As mortality is high in this disease, when suspected, after a quick diagnostic work-up, therapy should be administered immediately.

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