

Original Article

Disseminated Tuberculosis: A 3-Year Case-Series Experience in a Tertiary Care Center

Canan Gunduz Gurkan^{ID}, Hamide Şekerbey^{ID}, Aylin Babalık^{ID}

Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

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Abstract

OBJECTIVE: Disseminated tuberculosis (dTB) is an important health issue resulting from the hematogenous spread of *Mycobacterium tuberculosis*, and is associated with a globally significant burden of morbidity and mortality. Despite several studies from various countries, there are no data from Turkey specifically evaluating this special population. Our study aimed to evaluate the characteristics and treatment outcomes of dTB patients followed in our institution.

MATERIAL AND METHODS: In the current case series, patients with dTB followed between 2017 and 2020 in our institution were retrospectively examined. Data regarding patient characteristics, diagnostic methods, organ involvement, radiological patterns, treatment regimen, and outcomes were recorded. Descriptive statistics were performed.

RESULTS: In the present study, 23 dTB patients (median age 36, 56.5% male) were evaluated. The most common extrapulmonary manifestations were observed in the skeletal ($n = 13$) and genitourinary systems ($n = 5$). Multidrug-resistant TB was detected in 3 patients. The most common risk factors for dTB were living in a country with a high TB burden, and HIV infection.

CONCLUSION: Foreign-born patients were at high risk for disseminated TB in our study. HIV infection was also defined as the most important risk factor. Our data contribute to the current knowledge on the characteristics and outcomes of dTB patients in Turkey.

KEYWORDS: Extrapulmonary tuberculosis, disseminated tuberculosis, HIV, migration, multidrug-resistant tuberculosis

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INTRODUCTION

Tuberculosis (TB), being one of the most important communicable diseases with high mortality globally, is regarded as a major global health problem. According to the WHO global TB report, there were 10 million incident TB cases worldwide in 2018, with Turkey alone contributing to 0.13% of the global burden.¹ Although the term TB is commonly used to define pulmonary TB, multisystemic manifestations of TB are also frequently seen.

Extrapulmonary TB (EPTB) represents 15% of the 7 million incident cases reported in 2018, with a range of 8-24% across the Western Pacific Region and the Eastern Mediterranean Region.¹ In Turkey, 35% of incident TB cases are reported as EPTB.² Extrapulmonary locations of TB have become frequent over the last decade, correlating with the increased prevalence of acquired immune deficiency syndrome and the increased number of organ transplants.^{3,4} The most common anatomic sites involved in EPTB are the lymph nodes, pleura, bone and joints, urogenital tract, and meninges.⁵ Disseminated tuberculosis (dTB) results from the hematogenous spread of *Mycobacterium tuberculosis*. Since dTB is defined as a form of pulmonary TB or EPTB, in most studies, patients with dTB have not been evaluated separately. However, dTB cases represent a special group with more severe diseases and with a worse prognosis than other forms of TB, requiring special attention.⁶

Despite substantial data regarding pulmonary and extrapulmonary TB in the literature, current knowledge on dTB is limited, with a few studies from countries with intermediate burden settings.^{7,8} Although there are previous studies from Turkey presenting the regional TB data, dTB was not evaluated separately in these studies.^{9,10} Furthermore, the current data lack information regarding the potential association of TB and population dynamics, including the effects of migrating populations in Turkey over the last few years.

Istanbul is Turkey's largest city, with 15.5 million inhabitants, and has also been an important destination for the influx of migrating populations. Our institution is one of the 4 reference centers for TB in Turkey, with a broad spectrum of TB patients. The present study aimed to evaluate the clinical and radiological features of dTB patients, as well as their potential roles in predicting disease severity and treatment outcomes.

Corresponding author: Canan Gunduz Gurkan, e-mail: canangunduz@yahoo.com

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MATERIAL AND METHODS

In this retrospective study, patients diagnosed with dTB and followed between 2017 and 2020 in a tertiary referral hospital in Istanbul, have been evaluated. Data regarding patient characteristics, methods used in establishing the definitive diagnosis, radiological patterns in chest X-rays, extrapulmonary sites involved, antituberculosis treatment regimens received, medication side effects, treatment outcomes, and drug resistances have been examined from medical recordings. Among patient characteristics, age, sex, comorbidities including HIV, and use of immunosuppressive treatments were recorded.

Inclusion/Exclusion Criteria

Patients ≥ 18 years old, with dTB diagnosis were included in the study.

Disseminated TB was defined when: thoracic X-ray or computed tomography scan showed a pattern that indicated miliary pattern/dissemination; 2 non-contagious organ sites were involved; or *M. tuberculosis* was isolated in the bloodstream.⁸ In the biopsy specimen, either *M. tuberculosis* was obtained in culture isolation, or caseous granuloma formations were demonstrated in histopathological examinations. Furthermore, disseminated TB was also defined in patients with bacteriologically or histopathologically confirmed TB in a single organ with compatible clinical and radiological findings in other involved organs. Diagnosis and follow-up of these patients were performed concomitant with the specialists regarding the extrapulmonary systems involved.

Chest X-ray was assessed in all patients and the radiological evaluation of all chest X-rays were performed by 2 chest physicians. Drug-susceptible and drug-resistant antituberculosis treatment regimen and duration were managed as recommended in the WHO guidelines as well as the guidelines of the Ministry of Health.^{1,2} The BACTEC MGIT 960 system was used for culture isolation and drug susceptibility testing. Patients with missing data were excluded.

Directly observed treatment was applied to all patients. Treatment outcomes were evaluated in accordance with the guidelines, as follows^{1,2}:

Cure was reported in patients who were initially bacteriologically confirmed (culture or molecular test), who completed

treatment with at least 2 negative cultures in drug-susceptible TB in the end of the treatment, and 3 negative cultures in the last 8 months of treatment for multi-drug-resistant (MDR) TB. Treatment response in the extrapulmonary sites was evaluated according to clinical and radiological findings. *Death* was reported in patients who died during TB treatment or while awaiting TB treatment, irrespective of the cause of death. The treatment results were *not evaluated* in patients whose treatment outcome was unknown (including patients “transferred out” to another treatment center, for whom the outcome was unknown).

Descriptive statistics were performed. The study was approved by the Ethics Committee of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (116.2017.117). Informed consent was obtained from each patient.

RESULTS

Characteristics of the Patients

Clinical characteristics of 23 patients, with median age 36 (range: 21-80; 56.5% male) were evaluated in the present case-series study. The extrapulmonary manifestations of TB were most frequently seen in the skeletal system (*n* = 13), and were followed by the genitourinary system (*n* = 5), pleura (*n* = 4), central nervous system (*n* = 3), pericardium (*n* = 2), gastrointestinal system (*n* = 1), ocular system (*n* = 1), vasculitis (*n* = 1), and lymph node (*n* = 1). Involvement of more than 2 organs was seen in 8 subjects. Thirteen patients had Turkish citizenship, followed by 10 foreign-born patients who were citizens of Bangladesh (*n* = 1), Republic of Cote d’Ivoire (*n* = 1), Guinea (*n* = 1), Mali (*n* = 1), Nigeria (*n* = 1), Uzbekistan (*n* = 1), Pakistan (*n* = 1), Russia (*n* = 1), Tajikistan (*n* = 1), and Uganda (*n* = 1). Nine patients were older than 40 and all of them were Turkish citizens. Seven patients were ≤ 30 years old and were from Bangladesh, Guinea, Mali, Nigeria, Uzbekistan, Pakistan, and Russia. The comorbid diseases of the patients were HIV infection (*n* = 3), silicosis (*n* = 1), rheumatoid arthritis (*n* = 1), chronic obstructive pulmonary disease (*n* = 1), obstructive sleep apnea (*n* = 1), and coronary heart disease (*n* = 1). Our patient with rheumatoid arthritis was under anti-TNF treatment.

Among 23 patients, 9 had smear-positive pulmonary TB diagnosis followed by culture-positive TB (*n* = 6), molecular-test positive TB (*n* = 3), smear-negative culture-positive TB (*n* = 2), clinical radiological TB (*n* = 2) and histopathological TB (*n* = 1). The characteristics of the patients are demonstrated in Table 1.

The most common patterns seen in chest X-ray were infiltration (*n* = 12), cavity (*n* = 3), miliary pattern (*n* = 3), and pleural effusion (*n* = 3).

Drug Susceptibility and Treatment

Out of 23 patients, 10 patients were cured and 7 patients were still followed-up due to ongoing treatment. Death occurred in 1 patient. The treatment outcomes in 5 patients could not be evaluated due to loss in follow-up. Culture conversion was recorded in 10 patients and occurred in (mean ± SD) 2.9 ± 1.37 months.

MAIN POINTS

- Disseminated tuberculosis (dTB) is associated with a globally significant burden of morbidity and mortality.
- Foreign-born patients and HIV infection were defined as important risk factors in our study.
- Our case series may contribute to the literature since present studies do not focus on dTB, and there are no local data from Turkey either.
- Larger and multicenter studies on disseminated tuberculosis are needed to identify this special group of patients in the best manner.

Table 1. Characteristics of Study Patients (n = 23)

	Sex	Age	Country	Extrapulmonary Sites	Diagnosis	Comorbidities	Radiologic Pattern on Chest X-ray
1	F	59	Turkey	Skeletal system	Histopathological	N/A	Infiltration
2	F	38	Republic of Cote d'Ivoire	Pleura	Smear (-) Culture (+)	HIV (+)	Effusion Infiltration
3	F	31	Turkey	Central nervous system	Culture (+)	N/A	Infiltration
4	M	28	Guinea	Pleura	Clinical radiological	N/A	Effusion Miliary
5	F	36	Uganda	Pleura + Pericardium	Clinical radiological	N/A	Effusion
6	M	29	Bangladesh	Skeletal	Smear (-) Culture (+)	N/A	Infiltration
7	M	36	Turkey	Genitourinary	Culture (+)	HIV (+)	Infiltration
8	F	72	Turkey	Gastrointestinal	Culture (+)	N/A	Infiltration
9	M	30	Mali	Skeletal, Pleura	Culture (+)	N/A	Infiltration
10	F	58	Turkey	Skeletal, Lymph node	Culture (+)	N/A	Cavity
11	M	21	Nigeria	Skeletal, Genitourinary, CNS	Culture (+)	N/A	Infiltration
12	F	27	Uzbekistan	Skeletal	Molecular test (+)	N/A	Miliary
13	M	39	Tajikistan	Genitourinary, Skeletal	Molecular test (+)	N/A	Miliary
14	F	27	Russia	Ocular, vascular	Molecular test (+)	N/A	Miliary
15	F	68	Turkey	Genitourinary	Smear (+)	Diabetes Hypertension Asthma	Infiltration
16	M	47	Turkey	Skeletal	Smear (+)	HIV+	Infiltration Cavity
17	F	80	Turkey	Skeletal, joint	Smear (+)	COPD	Infiltration
18	M	71	Turkey	Genitourinary	Smear (+)	OSA+ DM	Miliary
19	F	65	Turkey	Pericardium	Smear (+)	Rheumatoid arthritis	Infiltration
20	M	34	Turkey	CNS	Smear (+)	Silicosis	Infiltration
21	M	22	Pakistan	Skeletal	Smear (+)	N/A	Cavity
22	M	34	Turkey	CNS, skeletal	Smear (+)	N/A	Miliary
23	M	44	Turkey	Skeletal	Smear (+)	N/A	Cavity Infiltration Bronchiectasis

CNS, central nervous system.

In the treatment, first-line anti-TB drug regimen (isoniazid, rifampicin, ethambutol, pyrazinamide) was initiated in all patients except for 2 MDR-TB patients initially diagnosed by a molecular test. Drug susceptibility for first-line anti-TB drugs was present in 12 patients. INH resistance was reported in 3 patients. Multidrug resistance was reported in 3 patients. In 2 of the patients with MDR, ethionamide resistance was also present in addition to isoniazid and rifampicin resistance. In MDR patients, side effects related to second-line drugs were observed. One of the patients with MDR was simultaneously undergoing HIV treatment. The remaining MDR-TB patients were from countries with high TB and MDR-TB prevalence and had arrived ≤ 2 years ago.¹¹

The most common side effects observed due to treatment were hepatotoxicity ($n = 2$), hallucination ($n = 2$), sight problems ($n = 1$), allergic reaction ($n = 1$), kidney failure ($n = 1$), and pancytopenia ($n = 1$). Alternative treatment regimen had to be initiated in 5 subjects due to medication side effects. One patient who died had MDR-TB, was from a country with a high MDR-TB burden; the patient also experienced a few side effects due to second-line anti-TB drugs.

DISCUSSION

Disseminated TB is a global health issue and is related to a significant burden of morbidity and mortality. Diagnosis of dTB can be challenging due to nonspecific clinical findings

(which reflects the underlying organ involvement in most cases) and the limited diagnostic tools.⁶ Furthermore, the low bacillary load in tissues also leads to poor sensitivity of microscopy for acid-fast bacilli.¹² Our case series of 23 dTB patients represents a mostly young population with the risk factors of immunosuppression (including acquired immune system deficiency) and being from high TB burden areas. The skeletal and genitourinary system were the most frequently affected extrapulmonary sites.

HIV infection, smoking, malnutrition, alcohol, and diabetes have been defined as the most common risk factors associated with TB.¹ Risk factors for EPTB and dTB have also been investigated previously in several studies. In a retrospective study conducted in Southern Taiwan, Lin et al.¹³ have reported female gender, not being diabetic, having an end-stage renal disease, and not smoking as independent risk factors for EPTB.¹³ In a study from Turkey examining EPTB in 2 provinces, any gender and age were described as potential risk factors.⁹ Since our population was mostly young and had a similar distribution of sexes, we could not assess the effect of age and gender. In a study evaluating 145 dTB patients in Porto, HIV infection and pharmacological immunosuppression, chronic liver failure or cirrhosis, and longer duration of symptoms were defined as risk factors for dTB.⁷ Furthermore, in the study by the British Society for Rheumatology Biologics Register,¹⁴ a higher prevalence of EPTB and dTB compared to TB has been reported in patients with rheumatoid arthritis treated with anti-TNF therapy. Although the number of cases in our series limited our ability to establish a causal relationship between dTB and related risk factors, HIV and pharmacological immunosuppression related to rheumatoid arthritis were also observed as medical risk factors in our study.

Co-infections of HIV and TB occur frequently, and they are associated with greater mortality and worse outcomes than TB alone. Extrapulmonary and disseminated TB are more common in HIV-infected patients and the extrapulmonary involvement is negatively correlated with the CD4 count.¹⁵ Management of co-infected patients can be difficult due to overlapping drug toxicities and interactions. On the other hand, the initiation of antiretroviral therapy after starting TB treatment is highly recommended in HIV-infected patients.¹⁵ Spreading of HIV infection and TB drug resistance have negative effects on the control of TB, and TB has also re-emerged in some parts of the world.⁹ In a rural sub-Saharan African cohort of HIV-infected patients, EPTB prevalence of 5.6% with a high mortality rate of 14.3% has been reported.¹⁶ In a study from Romania, 4.39% of 956 HIV patients were reported for a history of TB in the preceding 2 years and 38% of them were dTB cases.¹⁷ Besides, most of the patients with HIV and severe immunosuppression are reported as commonly presenting with dTB.¹⁸ Among our case series, 3 (13%) patients had HIV infection and one of them had an MDR diagnosis. According to the data of the Republic of Turkey Ministry of Health (TR MoH), HIV-positive patients constitute 0.6% of patients diagnosed with TB.¹⁹ Although higher rates of HIV infection in dTB

patients compared to the TB population may be expected, the higher rates in our study can also be related to the small sample size in our study as well as the impact of possible referral bias.

The organ involvement in EPTB and dTB vary greatly depending on the geographical region. Yang et al.²⁰ have suggested that the skeletal system and joints were involved more commonly in EPTB, while Noertjojo et al.²¹ have reported that the genitourinary system was more frequently affected.^{20,21} The frequency of musculoskeletal system involvement has been reported as 20% of patients diagnosed with TB in Turkey.²² Similarly, most of our cases involved the musculoskeletal system, followed by the genitourinary system.

The sociocultural dynamics in the cosmopolitan city of Istanbul and the effects of immigration also have important influences. The migrants from countries with a high burden of TB may constitute difficulties in the control of TB in the influx regions.²³ Throughout the last decade, there has been a significant increase in the migrant population both in Turkey and in Istanbul. Individuals from TB-endemic countries are also included in the migrant population.²⁴ As indicated by the TR MoH, foreign-born TB patients are reported to constitute 10.8% of all patients with TB.¹⁹ Our data demonstrate higher rates of foreign-born dTB patients ($n = 10$, 45.5%) compared to the global TB data of TR MoH. Higher rates can be associated with the characteristics of our study population, since dTB represents severe TB cases. Additionally, our hospital is a tertiary reference center for TB patients where medical care for TB is provided without any charge, including for patients without social security. Seven patients in our study were from high-burden TB countries and 4 of them were from high-burden MDR countries (Bangladesh, Uzbekistan, Pakistan and Tajikistan). The Republic of Cote d'Ivoire and Mali were recently moved from the high-burden HIV-TB list in the latest WHO report.¹¹ We believe that the migration dynamics in Istanbul were reflected in our study population, which also affected our outcomes. Since most of our foreign-born patients did not have social security, they were not able to apply to a health institution. Thus, the diagnosis of TB as well as the initiation of treatment were delayed. Consequently, we also observed that being from countries with a high TB burden was an important risk factor for TB and MDR, independent of age and other comorbid diseases as previously reported.^{1,11} On this background, a high index of suspicion and a low threshold for investigating for TB has been recommended for the diagnosis of TB as well as for prompt treatment and decrease in mortality.²⁵

In our study, 5 (21.7%) dTB cases were lost to follow-up and treatment outcomes could not be evaluated. Data of TR MoH indicate a rate of 3.2% for all TB patients who were lost to follow-up, excluding patients transferred abroad. The higher rate in our data can be related to the lower treatment adherence in our population of dTB patients. Since patients who were transferred abroad could not be sorted out, this could have also affected outcomes.

To the best of our knowledge, this the first study from Turkey evaluating the characteristics of dTB patients as well as examining anti-TB drug susceptibilities. Although there are studies regarding patients with pulmonary TB and EPTB in Turkey, dTB subjects have not been examined separately. The present study also has several limitations. Our hospital is a tertiary referral center for TB patients. This clinical referral bias has a potential effect on the characteristics of our study population. Besides, our study design as a clinical series lacks a control group and causes certain limitations. These facts partially limit our ability to generalize the findings. Two of the patients were diagnosed as dTB according to clinical and radiological findings, accompanied by a confirmed TB diagnosis in 1 organ. The diagnoses were confirmed by the significant clinical and radiological responses following empirical treatment. Besides, 1 patient was diagnosed according to histopathological findings. Although treatment responses were obtained in these patients, anti-TB drug susceptibilities could not be assessed. Thus, the relative lack of access to adequate diagnostic specimens in EPTB from sites such as the nervous system, bone, and joints, or eyes, is also reported as a common problem in the literature.²⁶

CONCLUSION

Disseminated tuberculosis presents a severe form of EPTB and requires exclusive care as well as a specific approach regarding comorbid diseases, including the HIV infection existing in most cases. Foreign-born patients were found to be at higher risk for disseminated TB in our study. The present case-series, displaying the clinical and microbiological characteristics of dTB patients as well as the evaluation of the treatment outcomes, contributes to the current knowledge on the topic. Larger and multicenter studies with control groups on dTB are needed to identify this special group of patients in the best manner.

Ethics Committee Approval: The study was approved by the Ethics Committee of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (116.2017.117).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer Review: Externally peer-reviewed.

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