JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Clinical misconceptions and diagnostic delays in extrapulmonary tuberculosis: an evaluation on 89 cases

Emel Gürcüoglu[1]

[1] *Department of Infectious Diseases, Bursa City Hospital, Bursa, Türkiye*

Abstract

Introduction: Extrapulmonary tuberculosis (EPTB) has highly variable clinical findings, and has a more difficult diagnostic process than pulmonary tuberculosis (PTB). The aim of this study was to examine the difficulty of the diagnostic process in 89 cases that applied to different clinics in our hospital, with different complaints.

Methodology: A total of 89 patients diagnosed with EPTB between March 2020 and March 2024 were included in the study. EPTB diagnosis was determined by excluding patients with primary PTB.

Results: The mean age of the cases was 47.84 ± 19.23 years, and 52 (58.4%) of the patients were women. There was a significant relationship between the affected area and gender ($p < 0.001$). The rate of peripheral lymphadenopathy (LAP) involvement was much higher in women than that in men (85.2% vs. 14.8%). Pleural involvement was 6.5-fold higher in men than in women (51.4% vs. 7.8%). There was also a significant relationship between the affected area and the time to diagnosis ($p < 0.001$). While peripheral LAP cases were diagnosed late, patients with pleural involvement were diagnosed more quickly ($p < 0.001$). The rate of smoking addiction was high in males with pleural involvement (79.9%). Quinolone use was 77.4% in the early-diagnosed group and 54.9% in the late-diagnosed group ($p = 0.110$).

Conclusions: Due to the difficulty of diagnosis, EPTB should be included in the differential diagnoses of all relevant medical specialties, and insistence should be made for the diagnosis in the presence of clinical suspicion.

Key words: tuberculosis; extrapulmonary; endemia; diagnosis.

J Infect Dev Ctries 2025; 19(7):1074-1082. doi:10.3855/jidc.20731

(Received 16 August 2024 – Accepted 27 January 2025)

Introduction

Extrapulmonary tuberculosis (EPTB) is a disease that develops as a result of the settlement of tubercle bacilli in organs other than the lungs. The prevalence of EPTB is increasing day by day due to reasons such as human immunodeficiency virus (HIV), immunosuppressive treatments, migration, and economic crisis. EPTB affects all organs and systems outside the lungs (except hair, nails, and teeth). Different approaches and different diagnostic methods are required for each organ and system affected; therefore a standard method and algorithm cannot be described [1–3]. Even when no positive findings are detected with any method, it is a challenging picture that requires returning to EPTB research when other preliminary diagnoses are excluded. While bacteriological confirmation or histopathological findings are effective in the diagnosis of pulmonary tuberculosis, they may not be guiding in this patient group due to low bacilli load and difficulties in accessing the samples. Since EPTB cases present with misleading findings and tests are not sufficiently helpful in making a diagnosis, cases may be diagnosed incorrectly or late [1–4].

The aim of this study was to examine the difficulty of the diagnostic process in 89 cases that applied to different clinics in our hospital with different complaints.

Methodology

Demographic data, risk factors, organ and tissue involvement, affected area, and diagnosis time of 89 adult patients diagnosed with EPTB in Bursa City Hospital between March 2020 and March 2024 were defined in terms of the basic characteristics of the patients.

EPTB diagnosis was established by excluding those with primary pulmonary tuberculosis (PTB). Among the patients diagnosed with tuberculous lymphadenitis, those with intraabdominal and intrathoracic lymph node involvement were not included in the study group.

We started empirical treatment in cases without Erlich-Ziehl-Neelsen (EZN) staining, culture, or polymerase chain reaction (PCR) positivity; histopathology not interpreted as necrosis or caseation; without adenosine deaminase activity (ADA)

positivity; and in cases where we thought that there was a high probability of clinical diagnosis of tuberculosis. Patients whose treatment was completed and who recovered during the study period were included in the study as cases receiving empirical treatment.

The EPTB treatment protocol consisted of pyridoxine-supplemented isoniazid (INH) 10–20 mg/kg/day (maximum single dose 300 mg), rifampicin (RIF) 8–12 mg/kg/day (maximum single dose 600 mg), ethambutol 15–25 mg/kg/day, and pyrazinamide (PZA) 15–30 mg/kg/day (maximum single dose 2000 mg). Following completion of the second month, therapy was continued with INH + RIF alone. When there was bone joint or intra-abdominal involvement, the treatment was decided on a patient-by-patient basis, and the average treatment duration was 12–18 months. In complicated cases with central nervous system involvement, dexamethasone/prednisolone was given for 4–6 weeks with a gradual decrease in dosage. Symptomatic or asymptomatic patients with drug side effects were evaluated on a case-by-case basis; and if re-treatment was planned, it was started gradually or all at the same time depending on patient compliance.

Patients diagnosed within 1 month after the onset of symptoms were included in the early diagnosis group. Those diagnosed after more than 1 month were included in the late diagnosis group.

Those who used quinolones within 30 days before diagnosis were taken into account while investigating the effect of quinolone use and whether it complicated diagnosis. Granulomas containing caseation and/or necrosis were accepted as characteristic histopathological lesions of the disease.

Statistical analysis

All statistical analyses in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were presented as mean and standard deviation, and numerical data as number and percentage for nominal or ordinal variables. t test, analysis of variance (ANOVA), Chi-square test, and logistic regression were used to determine significant differences between groups in terms of some of the variables.

Table 1. Distribution of demographic characteristics.

Characteristics	n (%)
Gender	
Male	37 (41.6)
Female	52 (58.4)
Age (years) (mean ± SD)	47.84 ± 19.23
Involved area	
GIT/Periton	14 (15.7)
Vertebrae / muscle / skeleton	10 (11.2)
GUS	9 (10.1)
Peripheral LAP	27 (30.3)
CNS	1 (1.1)
Miliary	5 (5.6)
Pleura	23 (25.8)

SD: standard deviation; GIT: gastrointestinal tract; GUS: genitourinary system; LAP: lymphadenopathy; CNS: central nervous system.

Results

Out of the 89 patients, 52 (58.4%) were female. The mean age of the women was 46.46 ± 18.89 years and the mean age of the men was 49.78 ± 19.78 years ($p <$ 0.425). The distribution of the patients according to the affected areas is presented in Table 1.

The most frequently affected areas were peripheral lymphadenopathy (LAP) (85.2%) among the women and pleura (82.6%) among the men. When the genitourinary system (GUS) involvement was examined, genital system involvement was prominent among the women (55.6%) and the urinary system was prominent among the men (44.4%). There was a significant relationship between the affected area and gender ($p < 0.001$). The rate of smoking addiction was high among the male cases with pleural involvement (79.9%). The patients with miliary involvement were immunosuppressed. Cases other than miliary tuberculosis diagnosed with immunosuppression were

Table 2. Distribution of immunosuppression and affected area by gender.

	Involved area						*p* value
	GIT/Periton	Vertebrae / muscle / skeleton	GUS	Peripheral LAP	Miliary	Pleura	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gender							
Male	5 (35.7)	2 (20)	4 (44.4)	4 (14.8)	3 (60)	19 (82.6)	**< 0.001**
Female	9 (64.3)	8 (80)	5 (55.6)	23 (85.2)	2 (40)	4 (17.4)	
PPD							
Negative	5 (38.5)	4 (50)	1 (14.3)	7 (29.2)	2 (66.7)	3 (15.8)	0.244
Positive	8 (61.5)	4 (50)	6 (85.7)	17 (70.8)	1 (33.3)	16 (84.2)	
Immunosuppression							
None	14 (100)	10 (100)	9 (100)	23 (85.2)	0 (0)	19 (82.6)	**< 0.001**
Present	0 (0)	0 (0)	0 (0)	4 (14.8)	5 (100)	4 (17.4)	

PPD: purified protein derivative; GIT: gastrointestinal tract; GUS: genitourinary system; LAP: lymphadenopathy. A statistically significant association was observed between gender and the involved anatomical site (indicated in **bold font**): pleural involvement was more common in male patients, while peripheral lymph node involvement predominated among females ($p < 0.001$).

Table 3. Immunosuppressed cases.

Diagnosis	Gender	Age (years)	IGRAT	Involved Area *	TBC culture	CD4 count	CD4/CD8 ratio
Multiple sclerosis	Female	41	Negative	4	Negative		
Chronic lymphocytic leukemia	Female	57	Negative	4	Absent		
Rheumatoid arthritis	Female	35	Positive	4	Positive		
HIV	Male	38	Negative	6	Positive	CD4: 16.3/μL	CD4/CD8: 0.32
HIV	Male	51	Negative	6	Negative	CD4: 60/μL	CD4/CD8:0,21
Thyroiditis	Female	70	Positive	6	Positive		
HIV + endometrium CA, septicemia	Female	58	Negative	6	Positive	CD4: 22/μL	CD4/CD8: 0.24
Rheumatoid arthritis	Female	65	Negative	4	Negative		
Bladder cancer	Male	73	Positive	7	Negative		
Bladder cancer	Male	46	Absent	7	Negative		
Lung cancer	Male	78	Absent	7	Positive		
Chronic lymphocytic leukemia	Female	85	Negative	7	Negative		
Bladder cancer	Male	64	Positive	3	Positive		

*Involved area: 1: gastrointestinal tract/peritoneum (GIT/peritoneum); 2: vertebrae/muscle/skeleton system; 3: genitourinary system (GUS); 4: peripheral lymphadenopathy (LAP); 5: central nervous system (CNS); 6: miliary involvement; 7: pleural involvement. IGRAT: interferon gamma release assay test; TBC: tuberculosis; HIV: human ımmunodeficiency virus; CA: cancer — "carcinoma".

tuberculous pleurisy and tuberculous lymphadenitis. Other laboratory tests did not contribute significantly to the diagnosis. Interferon gamma release tests (IGRT) and purified protein derivative (PPD) skin tests did not contribute to the diagnosis (Table 2).

Of the 89 patients, 70 had 1 or 2 Bacillus Calmette–Guérin (BCG) scars. The number and distribution of IGRT were as follows: 35 of 89 patients (39.3%) had a test, 54 patients were not tested; and 16 of the 35 cases were positive (45.7%). IGRT was performed in an external laboratory in another city.

PPD was performed in 74 of 89 cases, and 52 of them were positive. Most of the cases with pleural and lymph node involvement had positive PPD.

When the distribution of immunosuppressed cases was analysed, 3 of them were HIV positive and their interferon-gamma release assay (IGRA) tests were negative. Five of the other 10 cases were negative. None of the bladder cancer cases received intravesical BCG treatment and they were in advanced oncological stages. The immunosuppressed cases are listed in Table 3.

While the majority of tuberculous pleurisy cases were diagnosed early, patients with peripheral LAP, gastrointestinal tract (GIT)/peritoneum, and vertebral/musculoskeletal involvement were diagnosed late. 77.4% of the patients in the early diagnosis group, and 54.9% in the late diagnosis group were using quinolones ($p = 0.110$). Four of the 5 patients (80%) diagnosed with miliary tuberculosis were in the late diagnosis group. The affected area was a factor affecting the time to diagnosis ($p < 0.001$). The rate of requesting imaging was increased in those who were diagnosed late (Table 4).

Our peripheral lymph node involvement cases were mostly diagnosed by ultrasonographic methods. Contrast neck tomography was performed to rule out deep neck infection in only 8 cases with cervical lymph node involvement. However, in these cases, the interventional radiology unit was used to diagnose with ultrasound biopsy. Because of lymphoproliferative disorders, metastatic disease, and primary or secondary malignancies were considered in the differential diagnosis of every patient. Advanced imaging—namely computed tomography (CT) and magnetic resonance imaging (MRI)—was warranted during the diagnostic

Table 4. Distributions of early/late diagnosis according to involvement areas.

	Diagnosis		*p*
	< 1 month n (%)	**> 1 month n (%)**	
Involved area			
GIT/periton	0 (0)	14 (25)	**< 0.001**
Vertebrae/muscle/skeleton	0 (0)	10 (17.9)	
GUS	1 (3.2)	8 (14.3)	
Peripheral LAP	6 (19.4)	20 (35.7)	
Miliary	1 (3.2)	4 (7.1)	
Pleura	23 (74.2)	0 (0)	
Imaging method			
CT	25 (80.6)	20 (35.7)	< 0.001
MRI	1 (3.2)	17 (30.4)	
USG	5 (16.1)	19 (33.9)	

GIT: gastrointestinal tract; GUS: genitourinary system; LAP: lymphadenopathy; CT: computerized tomography; MRI: magnetic resonance imaging; USG: ultrasonography. The time to diagnosis in patients with gastrointestinal system/peritoneal involvement (GIT/periton) was significantly longer than in patients with other extrapulmonary involvement (indicated in **bold font**).

Table 5. Pathological findings according to involvement areas.

	Involved area						*p*
	GIT/periton n (%)	**Vertebrae/muscle/skeleton n (%)**	**GUT n (%)**	**Peripheral LAP n (%)**	**Miliary n (%)**	**Pleura n (%)**	
Caseifying infection	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)	1 (4.3)	0.044
Necrotizing infection	0 (0)	0 (0)	0 (0)	2 (7.4)	0 (0)	0 (0)	
Granulomatous infection	0 (0)	2 (20)	1 (12.5)	7 (25.9)	0 (0)	2 (8.7)	
Caseified granuloma	4 (28.6)	3 (30)	0 (0)	4 (14.8)	0 (0)	2 (8.7)	
Caseified necrotizing	3 (21.4)	0 (0)	1 (12.5)	5 (18.5)	0 (0)	1 (4.3)	
Necrotizing granuloma	3 (21.4)	3 (30)	5 (62.5)	5 (18.5)	2 (50)	3 (13)	
Atypical/Nonspecific	3 (21.4)	2 (20)	0 (0)	1 (3.7)	1 (25)	13 (56.5)	
None	1 (7.1)	0 (0)	1 (12.5)	2 (7.4)	1 (25)	1 (4.3)	

GIT: gastrointestinal tract; GUS: genitourinary system; LAP: lymphadenopathy.

work-up. In addition, positron emission tomography–computed tomography (PET-CT) was performed in 9 patients to delineate disease dissemination and to exclude non-infectious etiologies. Ultrasonography or CT accompanied sampling was done in these cases.

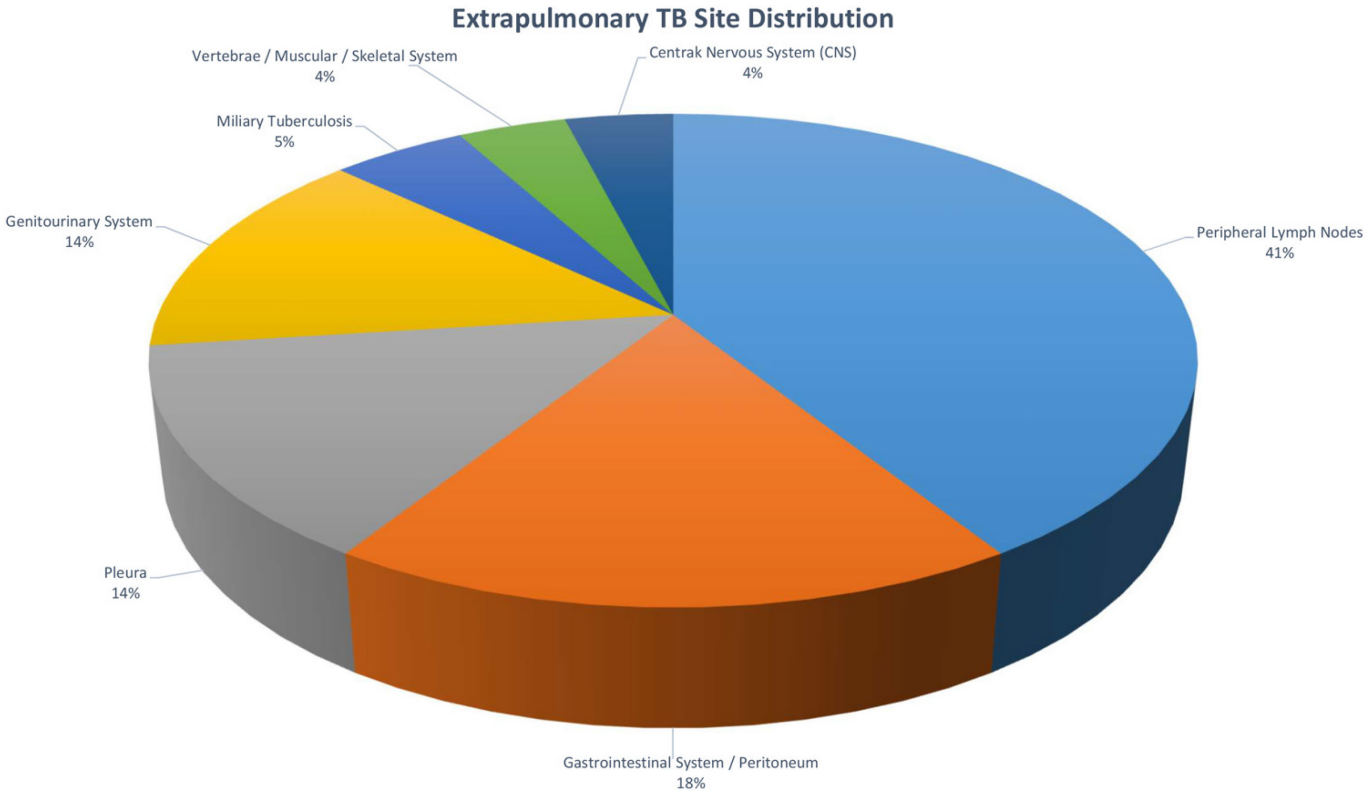
Contrast MRI of the vertebral musculoskeletal system was the primary method of imaging; and in these cases, open surgery sampling and interventional radiology unit tomography accompanied biopsy was performed.

A total of 173 clinical specimens from 60 of the 89 patients included in the study were subjected to microbiological culture. Growth was detected in 21 samples (12.1%), corresponding to 16 patients (26.67%). Only 2 (1.2%) samples were EZN positive, and 21 (12.1%) had growth. Only 7 (23.3%) of the 30 samples analyzed with PCR were positive, which was more significant than culture positivity. Four of these 7 cases had growth in their cultures simultaneously. Histopathologically, caseation necrosis was reported in only 10 of the 85 cases, and 5 (50%) were lymph node pathologies (Table 5).

The distribution of the affected areas in cases in which empirical treatment was initiated is presented in Figure 1.

The majority of patients who were initiated on empirical treatment within a therapeutic trial framework had lymph node involvement (41%). In these cases, multiple biopsy specimens were obtained prior to treatment, and both pathological and microbiological evaluations were performed; however, all results were reported as negative.

Figure 1. Distribution of cases in which empirical treatment was initiated according to the affected areas.



Patients with gastrointestinal intolerance; and asymptomatic patients with mild elevated liver enzymes, bilirubin, and uric acid elevations, were followed up without discontinuing treatment; especially in the first 2 months. They were followed up directly by tuberculosis dispensaries where supervised treatment was administered. In cases with severe toxicity, a treatment plan was made by our hospital. The treatment plans of a total of 4 cases were changed. After the treatment was initiated, 2 patients developed elevated uric acid levels along with joint pain and swelling. Therefore, PZA-induced hyperuricemia was suspected, and it was replaced with moxifloxacin.

One patient with endometrium ca and sepsis had liver failure and the treatment plan was adjusted accordingly (moxifloxacin 400 mg/day, ethambutol 15/mg/kg/day, cycloserin 1000mg/day in 2 divided doses, streptomycin 15 mg/kg/day).

Of the other 2 cases requiring treatment change, 1 was a case of chronic active hepatitis, and the other was a case of compensated cirrhosis due to hepatitis B; and in both cases, INH was replaced with moxifloxacin. Dolutegravir was double-dosed in HIV-positive cases. Rifabutin could not be obtained.

All treatments were carried out in the form of direct supervised treatments under the control of tuberculosis dispensaries. We did not have any patients who experienced hematologic side effects.

The retrospective study coincided with the coronavirus disease 2019 (COVID-19) pandemic and its aftermath, and BCG vaccination in our country was included in the national vaccination program for all individuals. The inclusion of only BCG-vaccinated individuals in this study limits the ability to establish a direct association between BCG vaccination and the development of COVID-19 infection. Nevertheless, the generally mild clinical course of COVID-19 observed in our cases and the absence of COVID-19–related mortality may suggest a potential protective effect of BCG vaccination. Further prospective, controlled studies are needed to reach more definitive conclusions on this subject.

Among the 89 cases included in the study, 19 had documented COVID-19 infection. Of these 19 cases, 12 (63.2%) contracted COVID-19 during active tuberculosis treatment; among these, 8 had received 1 or 2 doses of the COVID-19 vaccine. Six cases contracted COVID-19 prior to the tuberculosis diagnosis, and only 2 of them were vaccinated. One case contracted COVID-19 after completing tuberculosis treatment and had received 2 doses of the vaccine. Among the cases who had COVID-19 and underwent tuberculosis treatment, 5 died; however, these deaths were not directly related to COVID-19 (Table 6).

The lowest survival rate was observed in the miliary tuberculosis patient group (40%). There was a significant relationship between the affected area and survival status ($p = 0.021$). No mortality was observed in the patient group with vertebral/musculoskeletal and peripheral LAP involvement.

Discussion

Tuberculosis is a treatable disease with high morbidity and mortality. The development of the disease in the infected population is often reactivation tuberculosis, and approximately 15–20% of the disease is in the form of EPTB [1,2]. An increase in the frequency of active tuberculosis disease and EPTB rates is observed as a result of treatments that cause immunosuppression and increasing HIV infection [2–4]. Rolo *et al*. examined 398 tuberculosis cases between 2016 and 2021, and reported that the EPTB rate was 20.9% in 2016, and 27.9% in 2021, emphasizing the increase in EPTB rates over the years [5]. In our country, this rate was 19.6% in 1996, and it is 35% according to the latest data [1,6].

The distribution of affected areas in our cases was similar to that observed worldwide, and the most commonly affected areas were peripheral lymph node (30%) and pleural involvement (25.8%) [1,7]. The areas of involvement differed according to gender. In our study, 23 out of 27 patients (85.2%) with peripheral lymphadenopathy were female. and cervical lymph node involvement was the most common. Fine needle aspiration (FNA) biopsy was the first and frequently preferred method. The lymph node culture positivity rate in our cases was similar to the literature (11.1%) [8–10]. Growth was observed in cases with more repeated biopsies. The reason for repeated biopsies was

Table 6. Distribution of COVID-19 vaccinization status of the patients.

	Unvaccinated	One dose	Two doses	Total
TBC + COVID 19	4	6	2	12
Before the diagnosis of TBC	4	1	1	6
After TBC treatment	0	0	1	1
Total	8	7	4	19

COVID-19: coronavirus disease 2019; TBC: tuberculosis.

that it was known that the false-negative rate in FNA was high. Excisional biopsy was a less preferred method; because, in spite of being more efficient, it was an invasive method for detecting the pathogen.

In our cases pleural involvement was the second most frequent area of involvement, and the most common, symptoms were short-lived and noisy. The majority were male and the rate of smoking was high (79.9%) [11,12].

Given the exudative nature of the pleural fluid samples taken; ADA positivity, culture, and PCR positivity supported the diagnosis; but cytopathology results were not supportive. Our cytopathology results were nonspecific. There was growth in only one of the 23 cases (4.3%), and 1 case was PCR positive [13–15].

Tuberculosis is among the causes of secondary infertility. All female cases with genital involvement were diagnosed with tuberculosis while malignancy was being investigated. CA 125 values were found to be high in genital and GIT involvements of tuberculosis, correlating with the data in previous research studies [16,17]. In cases where treatment is started with a diagnosis of tuberculosis, simultaneous malignancy should be investigated. In addition, tuberculosis should be investigated in cases diagnosed with malignancy, keeping the possibility of co-incidence in mind [18,19].

The host's immune response primarily affects the dissemination of tuberculosis. The damage caused by the *Bacillus* in the immune system and its ability to prevent host defense cause it to develop a special defense mechanism against the agent. The factors affecting cellular immunity (HIV, etc.) increase the frequency and dissemination of tuberculosis infection [20,21]. We had 5 miliary tuberculosis cases, all of whom were immunosuppressed. Four of the cases were in the late-diagnosed group (80%), and their mortality was high.

Mortality in EPTB is mostly due to comorbidities, immunosuppression, and delayed treatment. The most important factor affecting the time to diagnosis was the affected area status ($p < 0.001$).

Quinolone, which has the potential to delay diagnosis, is widely used as a non-tuberculosis treatment. In applications with non-specific complaints, quinolones are one of the preferred groups in our country, after empirical beta-lactam antibiotics. It may be the second choice in cases with fever and lymphadenopathy of unknown origin, until the results of the tests for endemic diseases in our region are available.

Quinolone use was reported in 77.4% of the early-diagnosed group and in 54.9% of the late-diagnosed group ($p = 0.110$). It was observed that the use of quinolones did not cause delay in diagnosis in our cases.

The mean age of the surviving patients in our cases was 47 ± 19.28 years. The mean age of the patients who died was 57.67 ± 18.36 years. Mortality was high in our miliary tuberculosis cases (60%). Mortality was not observed in the patient group with vertebral/musculoskeletal and peripheral LAP involvement. There was a significant relationship between the affected area and survival status ($p = 0.021$). Yıldız *et al.* found that advanced age, high sedimentation rate, and miliarity increased the risk of death in 217 EPTB cases [22]. Four of the deceased patients were over 55 years old and immunosuppressed with additional diseases, had high sedimentation rate and CRP values, and were diagnosed late. Although it is thought that there were subclinical cases and/or undocumented COVID-19 among the 89 EPTB cases; except for 19 of the cases, there was no history of COVID-19 pneumonia or cytokine release syndrome requiring hospitalization during the tuberculosis diagnosis and treatment process. 70 of the 89 cases had 1 or 2 BCG scars. Those without scars had no documented COVID-19 infection. The only case who died without a scar was due to ileal obstruction/rupture as a result of gastrointestinal tuberculosis. BCG vaccination was not significant in terms of the relationship between COVID-19 and tuberculosis infection in the cases included in the study.

The number of PCR tests was quite low. This was primarly due to the following reasons; the first sample collections of the cases were made in different branches with different preliminary diagnoses., and the patients could not be convinced to take a second sample for differential diagnosis. Thus, insufficient samples were taken and a culture request was made from the existing sample. Another important reason for the low number was that our physicians tended to request more cultures, and the PCR test was done in an external laboratory which was expensive.

A tuberculosis drug susceptibility test was performed on all samples with growth. All of our cases were sensitive to rifampin. Only one case was resistant to streptomycin.

The institution to which PCR testing was outsourced, did not work on resistance at the molecular level; thus, resistance was not studied in PCR positive samples.

In this study, PCR positivity (23.3%) in a few samples were more significant than culture positivity. In a study by Timur *et al.* that included our central data

and covered pulmonary and EPTB, 8 (1.9%) of 432 clinical samples were EZN, 20 (4.6%) were culture positive, and the molecular method sensitivity was 42.9–83.3% and specificity was 99.1–97.9% [23]. Molecular methods may be better diagnostic tools in EPTB due to the difficulty of accessing the sample and the low bacilli load. The Centers for Disease Control and Prevention (CDC) recommended the use of at least one molecular method in 2009, due to its high specificity in the diagnosis of tuberculosis [7]. The population living in rural areas can be infected by direct contact and inhalation, or unpasteurized dairy products. Zoonotic strains usually show extrapulmonary involvement. Molecular methods are also superior to culture in distinguishing species of zoonotic strains [24,25].

Our hospital is the largest hospital in the southern Marmara region and was converted into a pandemic hospital with an intensive care unit and clinic during the pandemic. After the vaccine was available, it became the primary implementing hospital for the COVID-19 vaccination program. Our laboratories also adopted a work plan appropriate to this situation. Although we think that this may cause a decrease in the number of tests, the recommendation in our national guide to prefer tuberculin skin test (TST) in our country is also effective.

In our cases, the IGRA test and the PPD skin test, which were studied in small numbers, did not contribute to the diagnosis. Other nonspecific laboratory tests did not contribute significantly to the diagnosis. Biomarker studies are being conducted with the hope of providing more specific contributions. The use of new biomarkers such as microRNA (miRNA) in the diagnosis process is promising [26,27].

Imaging findings were not interpreted as supporting a specific diagnosis. This situation caused an increase in the number of requests for advanced imaging. Histopathology has an important place in EPTB. *M. tuberculosis* is an immunomodulatory microorganism that stimulates the formation of caseation necrosis [20,28].

Öztomurcuk *et al.* found the presence of tuberculosis in necrotic granulomatous tissues in 703 preparations to be statistically significantly high ($p < 0.001$). However, they particularly emphasized that the diagnosis should not be abandoned in cases where caseation necrosis was not described [29]. Only 10 (1.1%) of our 89 EPTB cases were interpreted as necrotizing caseous granulomatous inflammations.

The World Health Organization states that EPTB suspected cases should be treated even if the clinician does not have positive data within the scope of the prevalence of infected tuberculosis cases and the tuberculosis surveillance program. In cases where clinical and radiological findings raise suspicion of tuberculosis, a favorable response to anti-tuberculous therapy may be considered supportive of the diagnosis, even in the absence of microbiological confirmation [2,4,30].

The 21 cases in whom empirical treatment was initiated, were accepted as having tuberculosis at the end of the treatment. The most important reason for the need for an empirical treatment plan was the lack of patient consent for the invasive procedure required for tuberculosis in these cases, which were not initially examined for tuberculosis. The second important reason was that it was in anatomical regions where the possibility of resampling was difficult.

In addition, when resampling is performed, a negative result again is not a surprise for EPTB. In our country, where the incidence is high, the ex-adiuvantibus treatment approach can be selected with patient consent in highly probable cases.

The other 3 peripheral LAP cases with the same clinical and laboratory findings in whom empirical treatment was initiated received different diagnoses. Their treatments were discontinued. However, subsequent comprehensive evaluations revealed distinct diagnoses: bisphosphonate-related osteonecrosis of the jaw (BRONJ), low-grade lymphoma, and Q fever (coxiellosis). These revised diagnoses necessitated the discontinuation of the initial empirical treatments and the implementation of targeted therapeutic strategies.

Conclusions

The cases who frequently apply to healthcare facilities and where tuberculosis is not in their preliminary diagnosis, have the potential to be confused with other diseases with similar clinical presentations. Findings that are not specific to the disease, low bacilli load, and difficulty in accessing the sample are some reasons for delayed diagnosis. This situation is even more critical in countries with low incidence and prevalence of tuberculosis. Insistence should be made to make a correct diagnosis and patient-specific diagnostic processes should be designed in line with the current information and within the possibilities of the centers.

Corresponding author
Emel Gürcüoglu, MD.
Bursa Şehir Hastanesi, Doğanköy Mahallesi, 16110 Nilüfer / Bursa, Türkiye
Tel: +90-5325966317
Email: emelshen91@gmail.com

Conflict of interests
No conflict of interests is declared.

References
1. Government of Turkey (2021) Tuberculosis control in Turkey: 2021 report. Available: https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz-db/Dokumanlar/Raporlar/Turkiyede_Verem_Savasi_2021_Raporu.pdf. Accessed: 10 July 2024. [Article in Turkish].
2. WHO (2023) Global tuberculosis report 2023. Available: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023. Accessed: 10 July 2023.
3. Culqui-Lévano DR, Rodriguez-Valín E, Donado-Campos JM (2017) Analysis of extrapulmonary tuberculosis in Spain: 2007–2012 national study. Enferm Infecc Microbiol Clin 35: 82–87. doi: 10.1016/j.eimc.2016.06.002.
4. Dheda K, Barry CE, Maartens G (2016) Tuberculosis. Lancet 387: 1211–1226. doi: 10.1016/S0140-6736(15)00151-8.
5. Rolo M, González-Blanco B, Reyes CA, Rosillo N, López-Roa P (2023) Epidemiology and factors associated with extra-pulmonary tuberculosis in a low-prevalence area. J Clin Tuberc Other Mycobact Dis 32: 100377. doi: 10.1016/j.jctube.2023.100377.
6. Government of Turkey (2007) Tuberculosis control in Turkey: 2007 report.. Available: https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz-db/Dokumanlar/Raporlar/Turkiyede_Verem_Savasi_2007_Raporu.pdf. Accessed: 10 July 2024. [Article in Turkish].
7. Centers for Disease Control and Prevention, CDC (nd) Clinical overview of tuberculosis. Available: https://www.cdc.gov/tb/hcp/clinical-overview/index.html. Accessed: 10 July 2024.
8. Xu JC, Shi X, Ma X, Gu WF, Fang ZX, Zhang H, Fan XY (2023) Diagnosis of extrapulmonary tuberculosis by ultrasound-guided biopsy: a retrospective comparison study. Front Cell Infect Microbiol 13: 1154939. doi: 10.3389/fcimb.2023.1154939.
9. Assefa W, Eshete T, Solomon Y, Kassaye B (2022) Clinicoepidemiologic considerations in the diagnosis of tuberculous lymphadenitis: evidence from a high burden country. Int J Infect Dis 124: 152–156. doi: 10.1016/j.ijid.2022.09.030.
10. Pang Y, An J, Shu W, Huo F, Chu N, Gao M (2019) Epidemiology of extrapulmonary tuberculosis among inpatients, China, 2008–2017. Emerg Infect Dis 25: 457–464. doi: 10.3201/eid2503.180572.
11. Wang EY, Arrazola RA, Mathema B, Ahluwalia IB, Mase SR (2020) The impact of smoking on tuberculosis treatment outcomes: a meta-analysis. Int J Tuberc Lung Dis 24: 170–175. doi: 10.5588/ijtld.19.0002.
12. Feng Y, Xu Y, Yang Y, Yi G, Su H, Chen H, Guo R, Jia J, Wang P (2023) Effects of smoking on the severity and transmission of pulmonary tuberculosis: a hospital-based case control study. Front Public Health 11: 1017967. doi: 10.3389/fpubh.2023.1017967.
13. Pandey PP, Jaiswal V, Sharma TN, Vaidhya S, Karki A, Dahal B (2024) Evaluation of efficacy of serum adenosine deaminase values for detection of pulmonary and extra pulmonary tuberculosis. J Coll Med Sci — Nepal 20: 114–118. doi: 10.3126/jcmsn.v20i2.66324.
14. Sarkar K, Kashyap B, Jhamb R, Madhu SV, Avasthi R, Hyanki P (2024) Correlation of serum adenosine deaminase levels with microbiological parameters in pulmonary tuberculosis. Indian J Clin Biochem 39: 380–386. doi: 10.1007/s12291-023-01116-5.
15. Ninghot A, Mohod K, Kumar S (2017) Evaluation of serum adenosine deaminase (ADA) values for detection of pulmonary and extra-pulmonary tuberculosis. Int J Clin Biochem Res 4: 106–110.
16. Fahmi MN, Harti AP (2019) A diagnostic approach for differentiating abdominal tuberculosis from ovarian malignancy: a case series and literature review. BMC Proc 13 Suppl 11: 13. doi: 10.1186/s12919-019-0180-y.
17. Wagner A, Arsenić R, David M, Sehouli J, Vidosavljević D, Rohr I (2020) Peritoneal and upper genital tract tuberculosis. Med Glas (Zenica) 17: 86–91. doi: 10.17392/1023-20.
18. Gupta A, Gupta S, Manaktala U, Khurana N (2016) Coexisting genital malignancies with tuberculosis: a case series with review of literature. J Midlife Health 7: 159-162. doi: 10.4103/0976-7800.195693.
19. Önal U, Taşbakan M, Sipahi R, Taşbakan S (2015 Case report: five cases with tuberculosis peritonitis and elevated serum CA-125 levels. ANKEM Derg 29: 126–130. [Article in Turkish]. doi: 10.5222/ankem.2015.126.
20. Moule MG, Cirillo JD (2020) *Mycobacterium tuberculosis* dissemination plays a critical role in pathogenesis. Front Cell Infect Microbiol 10: 65. doi: 10.3389/fcimb.2020.00065.
21. Kaufmann SH (2014) Introduction. Semin Immunol 26: 429–430. doi: 10.1016/j.smim.2014.09.007.
22. Aysert Yıldız P, Karamanlıoğlu D, Özger HS, Katı H, Güzel Tunçcan Ö, Dizbay M (2022) Extrapulmonary tuberculosis: clinical and diagnostic features and risk factors for early mortality. Acta Medica 53: 367–374. doi: 10.32552/2022.ActaMedica.844.
23. Timur D, Parkan Ö, Kılıç H, Atalay A, Tekinşen FF, Koç AN (2023) Evaluation of two different real-time PCR methods in the diagnosis of *Mycobacterium tuberculosis*. Med Res Rep 6: 12–18. doi: 10.55517/mrr.1215658.
24. Çavuşoğlu C, Yılmaz FF (2017) Molecular epidemiology of human *Mycobacterium bovis* infection in Aegean Region, Turkey. Mikrobiyol Bul 51: 165–170. [Article in Turkish]. doi: 10.5578/mb.53963.
25. Causse M, Ruiz P, Gutiérrez-Aroca JB, Casal M (2011) Comparison of two molecular methods for rapid diagnosis of extrapulmonary tuberculosis. J Clin Microbiol 49: 3065–3067. doi: 10.1128/JCM.00491-11.
26. Agrawal P, Upadhyay, A, Kumar A (2024) microRNA as biomarkers in tuberculosis: a new emerging molecular diagnostic solution. Diagn Microbiol Infect Dis 108: 116082. doi: 10.1016/j.diagmicrobio.2023.116082.
27. Nogueira BMF, Krishnan S, Barreto-Duarte B, Araújo-Pereira M, Queiroz ATL, Ellner JJ, Salgame P, Scriba TJ, Sterling TR, Gupta A, Andrade BB (2022) Diagnostic biomarkers for active tuberculosis: progress and challenges. EMBO Mol Med14: e14088. doi: 10.15252/emmm.202114088.
28. Russell DG, Cardona PJ, Kim MJ, Allain S, Altare F (2009) Foamy macrophages and the progression of the human

tuberculosis granuloma. Nat Immunol 10: 943–948. doi: 10.1038/ni.1781.

29. Öztomurcuk D, Terzi Ö, Demirci C, Kılıçaslan Z (2022) Investigation of granulomatous inflammations in terms of tuberculosis diagnosis: a 5-year multi-center laboratory study. Turk Thorac J 23: 11–16. doi: 10.5152/TurkThoracJ.2022.20314.

30. Barreto-Duarte B, Araújo-Pereira M, Nogueira BMF, Sobral L, Rodrigues MMS, Queiroz ATL, Rocha MS, Nascimento V, Souza AB, Cordeiro-Santos M, Kritski AL, Sterling TR, Arriaga MB, Andrade BB (2021) Tuberculosis burden and determinants of treatment outcomes according to age in Brazil: a nationwide study of 896,314 cases reported between 2010 and 2019. Front Med (Lausanne) 8: 706689. doi: 10.3389/fmed.2021.706689.