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Original Article

Diagnostic approach of tuberculous lymphadenitis in a multicenter study

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Abstract

Introduction: Tuberculous lymphadenitis (TBLN) is the most common infectious etiology of peripheral lymphadenopathy in adults, in Turkiye. This study aimed to identify the demographic, clinical, and laboratory variables that differentiate TBLN from non-tuberculous lymphadenitis (NTBLN), as well as the etiology of lymphadenopathy in adults.

Methodology: Patients who were over 18 years old and were referred to the infectious disease outpatient clinics with complaints of swollen peripheral lymph nodes, and who underwent lymph node biopsy between 1 January 2010 and 1 March 2021, were included in this multicenter, nested case-control study.

Results: A total of 812 patients at 17 tertiary teaching and research hospitals in Turkiye were included in the study. TBLN was the most frequent diagnosis (53.69%). The proportion of patients diagnosed with TBLN was higher among females; and among those who had a higher erythrocyte sedimentation rate, positive purified protein derivative test, and positive interferon-gamma release test result ($p < 0.05$). However, TBLN was less frequent among patients with generalized lymphadenopathy, bilateral lymphadenopathy, axillary lymphadenopathy, inguinal lymphadenopathy, hepatomegaly, splenomegaly, leukocytosis, and moderately increased C reactive protein levels ($p < 0.05$).

Conclusions: Identifying the variables that predict TBLN or discriminate TBLN from NTBLN will help clinicians establish optimal clinical strategies for the diagnosis of adult lymphadenopathy.

Key words: lymphadenopathy; tuberculous lymphadenitis; lymph node biopsy; adult; etiology; Turkey.

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Introduction

Mycobacterium tuberculosis, the leading cause of death by a single infectious agent—excluding other pandemic periods like COVID-19—is estimated to infect more than 1.7 billion people worldwide [1,2]. According to the World Health Organization (WHO), in 2020, 9.9 million people were diagnosed with tuberculosis (TB), and 1.5 million died [3]. Turkiye is in the second lowest category on the WHO TB-endemicity map, with a TB incidence of 15 cases per 100,000 population [4]. Extrapulmonary TB comprises of approximately 16% of all TB cases, and tuberculous

lymphadenitis (TBLN) is the most common manifestation of extrapulmonary TB [1]. Of the 11,786 TB cases reported in Turkey in 2018, approximately 65% had pulmonary TB and 35% had extrapulmonary TB [5].

The incidence of lymphadenopathy (LAP), etiological spectrum, and clinical manifestations of LAP may differ by geographical region due to factors including socioeconomic factors, rate of the elderly population, people living with human immunodeficiency virus (HIV), or improvement in diagnostic procedures. However, excluding unidentified cases or non-specific etiologies, TBLN is the leading cause of LAP, especially in developing countries [6-8]. Other possible causes of LAP include infectious diseases; immunological, neoplastic, and metabolic disorders; medications; and iatrogenic causes.

A good medical history and physical examination—including patient age, duration and location of LAP, exposures, associated symptoms, travel history, and occupation—usually help identify the cause of LAP [9]. However, it is always a long and challenging process to reach a definitive differential diagnosis, especially in patients who represent generalized LAP, and, it is not possible to have a definitive diagnosis in a considerable proportion of these patients [6]. Peripheral LAP, including TBLN, is generally asymptomatic and TBLN mimics various infectious and non-infectious diseases, including mycobacterial or bacterial adenitis, fungal diseases, toxoplasmosis, tularemia, cat-scratch disease, sarcoidosis, non-specific hyperplasia, and primary or metastatic neoplasms; therefore, diagnosis often requires lymph node biopsy for both pathological and microbiological investigations [10-12]. Microbiological investigations include traditional methods such as lymph node tissue culture, which is still the gold standard method, and novel molecular methods such as polymerase chain reaction (PCR). Due to the low sensitivity of microbiological tests of lymph node specimens, the diagnosis of TBLN is mainly based on lymph node histopathological findings. In TB-endemic countries, the presence of necrotizing granulomatous findings in lymph node histopathology is generally considered to be associated with TBLN [12].

In this multicenter study, we aimed to identify demographic, clinical, and laboratory variables to differentiate TBLN from other infectious and non-infectious etiologies. In addition, we aimed to determine the ratio of TBLN and all etiologies among patients with peripheral LAP who underwent lymph node biopsy, as well as the lymph node histopathological findings in the adult population with peripheral LAP.

Methodology

Patients who were > 18 years of age, were referred to infectious disease outpatient clinics with complaints of swollen peripheral lymph nodes, and had a lymph node biopsy histopathological workup between 1 January 2010 and 1 March 2021, were included in this multicenter, retrospective nested case-control study. The study was carried out in 17 tertiary teaching and research hospitals in 7 different regions of Turkey. The medical records of these patients were retrospectively obtained from the hospital database systems, and the data were recorded in Excel. The data consisted of medical data that included demographic data, history, and clinical characteristics of patients; as well as diagnostic workup data, including laboratory tests and radiological, microbiological, and histopathological procedures.

The etiological spectrum in the study was categorized into five main groups: (1) infectious, (2) malignant, (3) autoimmune-inflammatory, (4) miscellaneous diseases, and (5) patients with no diagnosis or nonspecific etiology. In addition, the patients in the study were divided into two groups: patients diagnosed with TBLN and those with other infectious or non-infectious diseases (non-TBLN). Demographic, clinical, and laboratory variables related to the prediction of TBLN or the discrimination of TBLN from non-TBLN were analyzed. This study also revealed the essential histopathological features of adult LAP with infectious and non-infectious etiologies.

Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 15.0. Descriptive statistics are expressed as frequency, mean, median, standard deviation, minimum, and maximum values. Student's t-test was used to compare parametric variables. Difference analyses and risk estimation for categorical variables were performed using the Chi square test. The confidence level for statistical significance was set at 95 percent ($\alpha = 0.05$).

Results

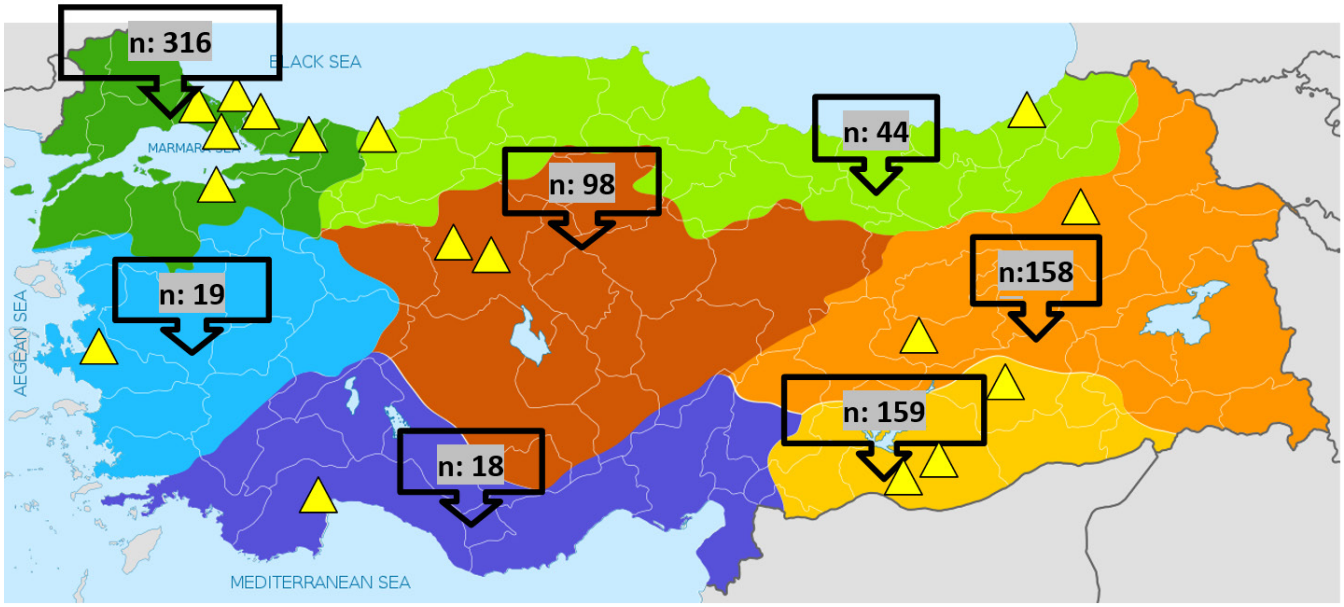
A total of 812 patients who underwent lymph node biopsy for peripheral LAP at 17 tertiary teaching and research hospitals from seven different regions in Turkiye were included in the study (Figure 1). The median age, duration of LAP, and lymph node size were 41 years (minimum 18; max 88 years), 60 days (min 3; max 12.775 days), and 25 mm (min 5; max 116 mm),

respectively; and there was no difference in these parameters between patients with and without TBLN. Of the patients, 63.18% were female, 88.13% lived in urban areas, and only 3.11% had a history of TB (Table 1). The proportions of fever, weight loss, and night sweats were 26.16%, 20.56%, and 24.65%, respectively. Dolor, color, and rubor in the lymph nodes were described in 36.15%, 12.17%, and 9.12% of patients, respectively. Of the patients, 29.88% presented with generalized, 69.81% with bilateral, and 79.75% with multiple LAP. Cervical LAP constituted the majority of patients (75.86%). Hepatomegaly and splenomegaly were detected in 10.32% and 8.33% of the patients, respectively. C reactive protein (CRP) levels were in the normal range at 56.4%, while the erythrocyte sedimentation rate (ESR) was normal in 38.55% of the patients. The ratio of Bacillus Calmette-Guerin (BCG) scar, purified protein derivative (PPD) positivity, interferon-gamma release assay (IGRA) positivity, and imaging findings indicating previous pulmonary TB were 81.06%, 46.71%, 71.84%, and 13.92%, respectively. The biopsy type was fine-needle in 47.9%, tru-cut in 12.35%, and excisional in 39.75% of the patients; repeated lymph node biopsy was performed in 19.58% due to various reasons, such as inadequate or non-diagnostic material. The proportions of acid-fast bacillus (AFB) test, TB PCR, and TB culture positivity were 17.2%, 30.43%, and 35.4%, respectively. Of all patients in the study, 26.35% (n = 214) had no specific diagnosis, while 53.45% (n = 434) were diagnosed with TBLN; 2.29% (n = 17) of them had concomitant pulmonary TB (Table 1).

Table 1. Demographic, clinical, and laboratory variables of the patients in the study.

Characteristics	n	%
Age (n: 812)*		
18- 40 years	382	47.04
40 - 59 years	290	35.71
≥ 60 years	140	17.24
Gender (n: 812)*		
Male	299	36.82
Female	513	63.18
Geograghic region (n: 812)*		
Marmara	316	38.91
Egean	19	2.34
Mediterranean	18	2.22
Central Anatolian	98	12.07
Black sea	44	5.42
Eastern	158	19.46
Sautheastern	159	19.58
Residence (n: 809)*		
Urban	713	88.13
Rural	96	11.87
History of pulmonary TB (n: 771)*	24	3.11
Fever > 38°C (n: 776)*	203	26.16
Weight loss (n: 681)*	140	20.56
Night sweat (n: 641)*	158	24.65
Lymph node		
Dolor (n: 697)*	252	36.15
Calor (n: 682)*	83	12.17
Rubor (n: 680)*	62	9.12
Lymhadenopathy (n: 773)*		
Generalized	231	29.88
Localized	542	70.12

Figure 1. Regional distribution of patients in the study (n: 812); yellow triangles indicate centers included in the study. The numbers in the boxed arrows indicate the number of the patients living in that region.



The ratio of patients diagnosed with TBLN was higher in patients who were female (*p*: 0.000, OR: 2.19, 95% Cl: 1.64 to 2.93), in patients who had a history of pulmonary TB (*p*: 0.019, OR: 3.11, 95% Cl: 1.15 to 8.41), patients whose sedimentation rate was higher than the upper limit of normal range (ULN) (*p*: 0.000, OR: 1.99, 95% Cl: 1.51 to 2.64), patients with PPD positivity (*p*: 0.005, OR: 1.53, 95% Cl: 1.53 to 2.06), IGRA positivity (*p*: 0.000, OR: 13.86, 95% Cl: 4.32 to 44.41), any imaging finding indicating previous pulmonary TB (*p*: 0.001, OR: 2.39, 95% Cl: 1.40 to 4.08), and excisional lymph node biopsy (*p*: 0.026, OR: 1.38, 95% Cl: 1.04 to 1.83) (Table 2). TBLN were less frequent in patients who had generalized LAP (*p* = 0.000, OR: 0.41, 95% Cl: 0.30 to 0.56), bilateral LAP (*p* = 0.004, OR: 0.60, 95% Cl: 0.43 to 0.85), axillary LAP (*p* = 0.002, OR: 0.61, 95% Cl: 0.45 to 0.83), inguinal LAP (*p* = 0.000, OR: 0.33, 95% Cl: 0.23 to 0.49), hepatomegaly (*p* = 0.001, OR: 0.40, 95% Cl: 0.23 to 0.69), splenomegaly (*p* = 0.000, OR: 0.21, 95% Cl: 0.11 to 0.41), leukocytosis (*p*: 0.000, OR: 0.25, 95% Cl: 0.16 to 0.40), and CRP level higher than five times that of ULN (*p*: 0.000, OR: 0.51, 95% Cl: 0.36 to 0.73). Among the lymph node specimen microbiological diagnostic workup, the AFB test positivity rate was the lowest, with a rate of 28.38% in patients with TBLN. Furthermore, TB PCR and TB culture rates were low, at 47.95% and 54.19%, respectively (Table 2). Other demographic, clinical, and laboratory variables used to differentiate TBLN from other infectious and non-infectious diseases in patients with peripheral LAP are summarized in Table 3.

Of all patients, 599 (73.77%) had a specific diagnosis, while 215 (26.48%) had a reactive LAP or

Table 1 (continued). Demographic, clinical, and laboratory variables of the patients in the study.

Lymhadenopathy (n: 646)*		
Bilateral	451	69.81
Unilateral	195	30.19
Lymhadenopathy (n: 810)*		
Multiple	646	79.75
Single	164	20.25
Lymph node region (n: 812)*		
Cervical	616	75.86
Axillary	231	28.45
Inguinal	142	17.49
Supraclaviculary	132	16.26
Duration of LAP (n: 640)*		
< 1 month	78	12.19
1–3 months	294	45.94
3–12 months	197	30.78
≥ 1 year	71	11.09
Size of LAP (n: 797)*		
10–19 mm	212	26.11
20–39 mm	480	59.11
≥ 40 mm	105	12.93
Hepatomegaly (n: 591)*	61	10.32
Splenomegaly (n: 588)	49	8.33
Leukopenia (n: 806)*	41	5.09
Leukocytosis (n: 806)*	98	12.07
Anemia (n: 806)*	196	24.32
Thrombocytopenia (n: 806)*	30	3.72
CRP (n: 757)*		
N	458	56.40
ULN–5x ULN	145	17.86
5x–10x ULN	94	11.58
≥ 10x ULN	60	7.39
Sedimentation rate (n: 750)*		
N	313	38.55
ULN–2x ULN	235	28.94
2x ULN–100 mm/h	189	23.28
≥ 100 mm/h	13	1.60
BCG scare (n: 264)*	214	81.06
PPD positivity (n: 715)*	334	46.71
IGRA Positive (n: 103)*	74	71.84
Imaging of lungs (n:810)*	582	71.85
Any imaging finding indicating previous pulmonary TB (n:582)*	81	13.92
Lymph node biopsy (n:812)*	812	100
Lymph node biopsy type (n:810)*		
Fine-needle	388	47.90
Tru-cut	100	12.35
Excisional	322	39.75
Repeated lymph node biopsy (n: 812)*	159	19.58
Lymph node specimen AFB test positivity (n: 378)*	65	17.20
Lymph node TB PCR positivity (n: 230)*	70	30.43
Lymph node TB culture positivity (n:275)*	97	35.40
Reactive lymphadenitis / Non-specific (n: 812)*	213	26.23
Diagnosis of TB lymphadenitis (n: 812)*	436	53.69
Concomitant pulmonary TB (n: 741)*	17	2.29

*Number in the brackets indicates the number of the patients in the study that have data in that category. AFB: acid-fast bacillus; BCG: bacillus Calmette-Guérin; CRP: C reactive protein; IGRA: ınterferon-gamma release assay; LAP: lymphadenopathy; PCR: polymerase chain reaction; PPD: purified protein derivative; TB: tuberculosis; ULN: upper limit of

Table 2. Etiological distribution of lymphadenopathy in all patients.

Etiology (n: 812)	**N**	**%**
Tuberculous lymphadenitis	436	53.69
Non-tuberculous infections	55	6.7
Toxoplasmosis	2	0.2
Tularemia	19	2.33
HIV-AIDS	1	0.12
Cat-scratch disease	10	1.23
EBV	1	0.12
CMV	1	0.12
Syphilis	1	0.12
Acute bacterial lymphadenitis / Local infections	19	2.33
Actinomyces	1	0.12
Malignancy	91	11.2
Lymphoma	65	8
Leukemia	3	0.3
Metastasis	22	2.7
Autoimmune/inflammatory	11	1.3
Sarcoidosis	11	1.3
Miscellaneous	4	0.7
Epidermal cyst	1	0.1
Kikuchi disease	1	0.1
Chronic sialadenitis	1	0.1
Vascular transformation of sinuses	1	0.1
Reactive lymphadenitis/non-specific *	215	26.48

*This group included patients who had reactive lymphoid hyperplasia or reactive lymphadenitis and benign changes or other non-specific findings in lymph node histopathology; AIDS: acquired immunodeficiency syndrome; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; HIV: human immunodeficiency virus.

non-specific etiology (Table 4). TBLN was the most frequent cause of both infectious and noninfectious etiologies (n = 436, 53.69%). Acute bacterial lymphadenitis or local infections (n = 19, 2.33%), tularemia (n = 19, 2.33%), and cat-scratch disease (n = 10, 1.23%) were the other most frequently diagnosed infective causes. Malignancies (n = 91, 11.2%), 65 (8%) of which were lymphomas; and sarcoidosis (n = 11, 1.3%); were the most frequent non-infectious etiologies. The other causes of LAP are listed in Table 2.

Lymph node histopathological features according to the etiology are summarized in Table 4. Necrotizing granulomas with or without caseification (n = 400; 49.26%), non-necrotizing granulomatous inflammation (n = 120; 14.78%), and normal/benign and/or reactive

Table 3. Demographic, clinical and laboratory variables to differentiate tuberculous from non-tuberculous lymphadenitis.

Characteristics	Tuberculous lymphadenitis	Non-tuberculous lymphadenitis	*p*	Odds Ratio	(95% Cl) Lower	Upper
Age ≥ 40 years (n: 812)*	230 (52.75%)	201 (53.46%)	0.841	0.97	0.74	1.28
Age ≥ 60 years (n: 812)*	75 (17.20%)	65 (17.29%)	0.974	0.99	0.69	1.43
Female gender (n: 812)*	312 (71.56%)	201 (61.17%)	0.000	2.19	1.64	2.93
History of pulmonary TB (n: 771)*	19(4.42%)	5(1.47%)	0.019	3.11	1.15	8.41
Fever > 38 °C (n: 776)*	102 (23.61%)	101 (29.36%)	0.070	0.74	0.54	1.03
Weight loss (n: 812)*	78(17.89%)	62 (16.49%)	0.598	1.10	0.77	1.59
Night sweat (n: 641)*	91 (24.33%)	67 (25.09%)	0.825	0.96	0.67	1.38
Lymph node						
Dolor (n: 697)*	145 (35.80%)	107 (36.64%)	0.820	0.96	0.71	1.32
Calor (n: 682)*	53 (13.15%)	30 (10.75%)	0.346	1.26	0.78	2.02
Rubor (n: 680)*	39 (9.73%)	23 (8.24%)	0.509	1.20	0.70	2.06
LAP						
Generalized (n: 773)*	90 (21.43%)	141 (39.94%)	0.000	0.41	0.30	0.56
Bilateral (n: 646)*	226 (64.94%)	225 (75.50%)	0.004	0.60	0.43	0.85
Multiple (n: 810)*	349 (80.05%)	297 (79.41%)	0.823	1.04	0.74	1.47
Lymph node region (n: 812)*						
Cervical	330 (75.69%)	287 (76.06%)	0.845	0.97	0.70	1.34
Axillary	104 (23.85%)	127 (33.78%)	0.002	0.61	0.45	0.83
Inguinal	45 (10.32%)	97 (25.80%)	0.000	0.33	0.23	0.49
Supraclaviculary	79 (18.12%)	53 (14.10%)	0.121	1.35	0.92	1.97
Duration of LAP (n: 640)*						
≥ 1 month	319 (88.86%)	243 (86.48%)	0.361	1.25	0.78	2.00
≥ 3 months	225 (62.67%)	167 (59.43%)	0.403	1.15	0.83	1.58
≥ 1 year	34 (9.47%)	37 (13.17%)	0.139	0.69	0.42	1.13
Size of LAP (n: 797)*						
≥ 20 mm	320 (74.77%)	265 (71.82%)	0.347	1.16	0.85	1.59
≥ 40 mm	62 (14.49%)	43 (11.65%)	0.238	1.28	0.85	1.95
Hepatomegaly (n:591)*	23 (6.73%)	38 (15.26%)	0.001	0.40	0.23	0.69
Splenomegaly (n:588)*	12 (3.53%)	37 (14.92%)	0.000	0.21	0.11	0.41
Leukopenia (n:806)*	21 (4.84%)	20 (5.38%)	0.729	0.89	0.48	1.68
Leukocytosis (n:806)*	25 (5.76%)	73 (19.62%)	0.000	0.25	0.16	0.40
Anemia (n:806)*	107 (24.65%)	89 (23.92%)	0.810	1.04	0.75	1.44
Thrombocytopenia (n:806)*	13 (3%)	17 (4.57%)	0.239	0.64	0.31	1.35
CRP (n: 757)*						
≥ ULN	252 (60.72%)	197 (57.60%)	0.384	1.14	0.85	1.52
≥ 5x ULN	64 (15.42%)	90 (26.32%)	0.000	0.51	0.36	0.73
≥ 10x ULN	24 (5.78%)	36 (10.53%)	0.16	0.52	0.30	0.89
Sedimentation rate (n: 750)*						
≥ ULN	269 (61.70%)	168 (44.68%)	0.000	1.99	1.51	2.64
≥ 2x ULN	111 (26.68%)	91 (27.25%)	0.863	0.97	0.70	1.34
≥ 100 mm/h	6 (1.44%)	7 (2.10%)	0.496	0.68	0.23	2.05
BCG scar (n: 264)*	169 (83.66%)	45 (72.58%)	0.051	1.93	0.99	3.79
PPD positivity (n: 715)*	209 (51.23%)	125 (40.72%)	0.005	1.53	1.13	2.06
IGRA (n: 103)*	51 (92.73%)	23 (47.92%)	0.000	13.86	4.32	44.41
Any imaging finding indicating previous pulmonary TB (n:582)*	61 (17.84%)	20 (8.33%)	0.001	2.39	1.40	4.08
Lymph node biopsy type (n: 810)*						
Fine-needle	194 (44.70%)	194 (51.60%)	0.050	0.76	0.57	1.00
Tru-cut	52 (11.98%)	48 (12.77%)	0.735	0.93	0.61	1.41
Excisional	188 (43.32%)	134 (35.64%)	0.026	1.38	1.04	1.83
Lymph node specimen AFB test positivity (n: 378)*	65(28.38%)	0(0%)	0.000	N/A	N/A	N/A
TB PCR positivity (n: 230)*	70(47.95%)	0(0%)	0.000	N/A	N/A	N/A
TB culture positivity (n:275)*	97(54.19%)	0(0%)	0.000	N/A	N/A	N/A

*Number in the brackets indicates the number of the patients in the study that have data in that category. AFB: acid-fast bacillus; BCG: bacillus Calmette-Guérin; CI: confidence interval; CRP: C reactive protein; IGRA: ınterferon gamma release assay; LAP: lymphadenopathy; PCR: polymerase chain reaction; PPD: purified protein derivative; TB: tuberculosis; ULN: upper limit of normal.

lymph node findings (n = 83; 10.22%) were the most common histopathological findings in the study population. Additionally, necrotizing granuloma with or without caseification (n = 361 436; 82.8%) and non-necrotizing granulomatous inflammation (n = 63 436; 14.45%) were the most frequent histopathological findings in patients with TBLN (Table 4).

Discussion

Many infectious and non-infectious diseases have been identified as a cause of LAP, and the spectrum of etiology varies based on many factors, including geographic region; socioeconomic status; and demographic factors, including age and HIV incidence. Because patients with LAP are mostly asymptomatic or the clinical findings often do not have diagnostic efficacy, reaching a definitive diagnosis in LAP etiology, including TBLN, is always a long and challenging process and requires state-of-the-art diagnostic laboratory capability. Lymphadenitis is the most frequent form of extrapulmonary TB. Cervical LAP is the most common form, but other lymphatic sites, including inguinal, axillary, and mesenteric or mediastinal lymph nodes, can be involved [11]. This multicenter study aimed to identify demographic, clinical, and laboratory variables to predict TBLN, and differentiate TBLN from non-TBLN.

In developing and TB-endemic countries, TBLN is still the most common cause of adult peripheral LAP etiology among cases with a definite diagnosis. In developed countries, although the incidence of TB has decreased, there is an increasing trend in the proportion of extrapulmonary TB, including TBLN, mainly because of increasing HIV incidence [13,14]. Although Turkiye is in the second lowest category in the WHO TB-endemicity map with a TB incidence of 15 cases per 100,000 population, uncontrolled migration to Turkiye due to civil wars and conflicts in the Middle East and Asia exposes additional risks for emerging or re-emerging infectious diseases such as TB, and consequently TBLN [4,15].Our multicenter study with the maximum number of patients from 17 different centers located in different regions, is an important study in the literature revealing epidemiological and clinical aspects of both LAP and TBLN.

TBLN was the most frequent diagnosis, including infectious and noninfectious etiologies of LAP in our study. As the second most frequent cause, approximately one-quarter of the cases were considered to have reactive LAP or a non-specific etiology. The proportions of this group in our previous multicenter study including 1,401 cases were 44.3% and 77.2% in patients with and without histopathology, respectively [6]. The ratio of reactive and/or non-specific lymphadenitis ranges from 28.4% to 52.2% in histopathology-based studies in the literature [7,16,17]. In a histopathology-based study from Turkiye, Gul *et al.* reported that 29.9% of adult patients had TBLN, while 28.4% had non-specific lymphadenitis [18]. Mohan *et al.* identified TBLN in 31.3% of 1,724 lymph node histopathological specimens, and the TBLN ratio was 58% in the study of Ashfaq *et al.* including patients with cervical LAP [7,8].

The ratio of TBLN, as well as other infectious etiologies among patients with LAP, is higher at younger ages, and TBLN peaks from 20 to 40 years of age [8,19.20]. However, our results did not show any differences according to age group and were not concordant with the literature. Female gender constituted almost two-thirds of all patients in our study, and in agreement with previous data in the literature, the odds of TBLN in patients with peripheral LAP were higher among females in comparison to that among males [11,21]. In contrast, the male gender was reported to be a risk factor for lymph node TB by Al-Ghafli*et al.* [22].

Table 4. Lymph node biopsy histopathological features of patients in the study (n: 812).

	Lymphoma (n: 66)	Leukemia (n:3)	Malign/ metastasis (n:22)	Suppurative (n: 38)	Necrotizing (n: 5)	Non-necrotizing granulomatous (n: 120)	Necrotizing granuloma (n: 400)	Normal/ benign/ reactive (n: 83)	In-adequate/ non-diagnostic (n: 75)
TB lymphadenitis (n: 436)	0	0	0	8	1	63	361	1	2
Other infections (n: 55)	0	0	0	30	0	10	9	3	3
Malignancies (n: 91)	66	3	22	0	0	0	0	0	0
Autoimmune/ Inflammatory (n: 11)	0	0	0	0	0	9	2	0	0
Miscellaneous (n: 4)	0	0	0	0	0	0	0	3	1
Reactive or non-specific diagnosis (n: 215)	0	0	0	0	4	38	28	76	69

TB: tuberculosis.

According to our study results, patients who had localized and unilateral LAP were more likely to have TBLN. In contrast, patients with axillary or inguinal LAP, hepatomegaly and splenomegaly were unlikely to have TBLN. In our previous study, including patients with and without lymph node histopathology, the probability of having an infectious etiology was significantly higher in patients with localized and unilateral LAP, while hepatomegaly and splenomegaly were not associated with increased risk in terms of infectious or non-infectious diseases; however, we did not evaluate these results in terms of TBLN [6]. The duration or size of the lymph node revealed no importance in the differential diagnosis of LAP in the discrimination of TBLN from other causes [23].

Inflammatory markers such as CRP, ESR, and leukocyte count are commonly used in clinical practice for the differential diagnosis of both infectious and non-infectious diseases. Based on our study results, TBLN was less frequent in patients with leukocyctosis and moderate increase in CRP (> 5 times ULN but < 10 times ULN); on the other hand, minimal increase in sedimentation rate was associated with TBLN. PPD and IGRAs are widely used in TB screening and diagnostic workup, with especially high sensitivities in chronic forms of TB, such as TBLN. In a meta-analysis, IGRAs revealed high diagnostic accuracy with a sensitivity of 0.89, specificity of 0.81, positive likelihood ratio (PLR) of 4.25, negative likelihood ratio (NLR) of 0.16, and area under the curve (AUC) was 0.93 [24]. According to our results, parameters related to latent TB, including any pulmonary imaging finding, PPD, or IGRA positivity, revealed statistically significant results in the differential diagnosis of TBLN. However, negative IGRA results, in comparison with the absence of any pulmonary imaging findings, revealed a much more significant effect in excluding TBLN. Similar observations were made by Khajanchi *et al*., although few patients in their study had a history of contact with TB (13/74), and a history of contact with a patient with TB was found to be a significant risk factor for TBLN in patients with cervical LAP [25].

In our analysis of lymph node biopsy type for the diagnosis of TBLN, the odds of TBLN were higher with excisional biopsy than with fine-needle aspiration and tru-cut. However, the AFB, TB PCR, and TB culture rates in patients with TBLN were low. In another study, the diagnostic sensitivity of histology in excision biopsy (95.8%) was significantly higher than that of cytology in fine-needle aspiration (38.5%), whereas the diagnostic sensitivity of AFP microscopy was similar in fine-needle aspiration and excision biopsy [26]. According to a systematic review, pathological and microbiological results performed on excision biopsy specimens have the highest diagnostic performance, whereas fine-needle aspiration is less invasive. If fine-needle aspiration examination results are inconclusive, an excision biopsy may need to be performed; however, this approach may cause a delay of 2–8 weeks in the diagnosis [27].

In our study, necrotizing granuloma, with or without caseification, constituted the vast majority (82.8%) of the histopathological examination of patients with TBLN. In addition, 361 of the 400 patients with necrotizing granuloma (90.25%) were diagnosed with TBLN, whereas the rest did not have a specific diagnosis. According to the results reported by Khajanchi*et al.*, the most common diagnosis based on fine needle aspiration cytology was reactive nodes (39%), followed by TBLN (26%), metastasis (8%), and lymphoma (2%) [25]. Furthermore, 17% of patients had granulomatous disease with an unspecified diagnosis, and inconclusive results on fine needle aspiration cytology were reported in 7% of patients. In our study, among patients with TBLN, the AFB test positivity rate was the lowest at 28.38%, and the TB PCR and TB culture rates were relatively higher at 47.95% and 54.19%, respectively. These results were consistent with those in the literature [27]. Because of the low positivity rates and limitations of the diagnostic performance of microbiological tests, the diagnosis of TBLN is mainly based on cytomorphological analysis of lymph node specimens [28]. To overcome this problem, it is important to concurrently perform TB AFB, PCR, and culture. However, these tests can be performed in less than half of the patients with LAP because clinicians in surgical units or interventional radiology departments in Turkiye are not inclined to send the lymph node specimens for microbiological workup. Therefore, patients generally had to be referred to the infectious disease departments only with pathological reports. To overcome this problem, there is a need to organize training activities among these groups of clinicians, both for the etiology and diagnostic workup for LAP etiology. As our study results support, diagnosis of TBLN is mainly based on histopathological findings in Turkiye; however, the findings vary with the phase of the disease. Non-specific reactive hyperplasia in the early phase, formation of abscesses, Langerhans giant cells, caseating necrosis, granulomatous inflammation, and calcification can be observed. Although non-caseating granulomas are more prominent in non-TBLN, they can also be observed in TBLN [12,13].

The present study was carried out among patients with suspected infectious causes of LAP, including TBLN, who were referred to infectious disease outpatient clinics in Turkiye. In addition, this study included only patients who underwent lymph node biopsy. Thus, the results may not reflect the actual incidence of infectious or noninfectious causes of LAP.

Conclusions

TBLN was the cause for the vast majority of LAP casesin Turkiye patients with a lymph node histopathological workup. Among these populations, female gender, history of pulmonary TB, minimally increased sedimentation rate, IGRA positivity, imaging findings indicating previous pulmonary TB, and excisional lymph node biopsy were parameters with increased risk of TBLN. However, generalized LAP, bilateral LAP, axillary LAP, inguinal LAP, hepatomegaly or splenomegaly, leukocytosis, and moderately increased CRP levels were clinical parameters related to an increased risk of non-TBLN. A definitive differential diagnosis of LAP is challenging; despite developments in microbiological work-up, histopathology still plays the most important role in the diagnosis of TBLN. Having comprehensive knowledge of the etiology in the geographical region, a high index of suspicion, detailed medical history, thorough clinical examination, and appropriate diagnostic workup should be provided to reach a definitive diagnosis of TBLN and non-TBLN. Our study is unique because it includes clinical, histopathological, and etiological data; and the maximum number of patients with LAP who underwent lymph node biopsy in Turkey. Thus, our results may help clinicians establish optimal clinical strategies for the diagnostic approach to TBLN and adult lymphadenopathy.

Previous presentation of this study

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