ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2022;(3):434-443 // 10.5505/amj.2022.39214

PERIPHERAL LYMPHADENOPATHY AND INFECTIONS: EVALUATION OF 197 CASES

Özlem Aydın[1], Begüm Bektaş[1], Pınar Ergen[1]
Bengu Cobanoglu[2]

[1]Department of Infectious Diseases and Clinical Microbiology, Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey
[2]Department of Pathology, Istanbul Medeniyet University Faculty of Medicine, Istanbul, Turkey

Correspondence:
Özlem Aydın (e-mail: ozlemsenaydin@hotmail.com)

Submitted: 08.06.2022 // Accepted: 08.09.2022

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: In our study, we aimed to evaluate the causes of peripheral lymphadenopathy (LAP).

Materials and Methods: Patients older than 18 years old who were diagnosed with LAP and underwent peripheral lymph node biopsies between 01.11.2017 and 01.01.2020 were included in the study. The demographic data and histopathological findings of the patients were retrospectively reviewed on the computer database of the hospital.

Results: One hundred ninety-seven adult patients in total were included in the study, 51.27% (n=101) of whom were female. The rates of fever, night sweats, and weight loss symptoms were detected as 8.63%, 13.70%, and 20.30%, respectively. Excisional biopsy was performed in 93.40% of the patients, and the most frequently excised lymph node was the axillary node at a rate of 40.10%. According to the results of the histopathological analyses, the most common etiology was malignancy, and the second one was infectious, at 31.98% and 29.95%, respectively. Malignancy was caused by lymphoma in 93.65% of the cases, whereas the infectious etiology was caused by tuberculosis at 74.58%. A specific diagnosis could not be made for 26.90% of the cases, and their outpatient follow-up was continued.

Conclusion: Although LAP is often associated with infections, it also occurs as a manifestation of malignant diseases. In our study, the most common etiology was malignant diseases. Infections were the second most common etiology, and among infections, tuberculosis was the leading one. LAP is a frequently encountered clinical condition that is difficult to manage. To avoid delays in diagnosis, patients should be carefully evaluated and followed closely. Although a specific diagnosis cannot always be made, histopathology remains the gold standard for diagnosis.

Keywords: Lymphadenopathy, peripheral, etiology, tuberculosis.

Introduction

Lymphadenopathy (LAP) describes conditions in which lymph nodes are abnormal in size, consistency, or number, and it may be one of the symptoms of various diseases.[1,2] In general, the normal lymph node size is defined as less than 1 cm in diameter, albeit varying based on age and geography.[1-3]

Although peripheral LAP often develops due to self-limiting local or systemic infections, it can be a manifestation of an underlying malignant disease.[1] Autoimmune disease, drugs, and iatrogenic causes also play a role in its etiology.[2,3] Infectious etiologies include viral, bacterial, mycobacterial, fungal, and parasitic agents.[2-4]

Lymphadenopathy is a common clinical condition that causes concern in both patients and physicians.[3] Histopathological diagnosis with biopsy is the gold standard in determining its etiology.[1] The physician should make precise decisions on which patient should be followed observationally and which patient needs a quick workup to prevent possible delays in diagnosis.

We aimed in our study to review the histopathology findings and infectious causes that play a role in etiology in patients who presented with peripheral lymph node enlargement and underwent lymph node biopsy in their follow-ups.

Materials and Methods

Patients older than 18 years old, who presented to the infectious diseases outpatient clinic or were referred from other clinics for consultation between 01.11.2017 and 01.01.2020, and underwent lymph node biopsies after the detection of peripheral LAP, were included in the study. Patients with lymph node enlargement who were being followed up with the diagnosis of conditions such as malignancies or infectious diseases before their inclusion were excluded from the study.

The demographic information of the patients, the durations of their lymphadenopathy, their lymph nodal biopsy sites, the types of their biopsies, laboratory tests, imaging findings, and histopathological findings were retrospectively screened from the hospital's computer database. The obtained information was recorded in the data collection forms that were created by the researchers.

Statistical analysis

Descriptive statistics are expressed as frequency, percentage, and median values.

Results

One hundred ninety-seven adult patients in total were included in the study, 51.27% (n=101) of whom were female. The median age of the patients was 52 years (18-91). Generalized LAP was detected in 88.83% (n=175) of the patients. The time between symptom onset and admission was categorized as three months or shorter, 3-6 months, and six months or longer, and 58.89% (n=116) of the patients had complaints for three months or shorter. The rates of fever, night sweats, and weight loss symptoms among the patients were found as 8.63%, 13.70%, and 20.30%, respectively. Hepatomegaly was found in 24.87% (n=49) of the cases, and splenomegaly was found in 20.81% (n=41). It was found that 93.40% (n=184) of the biopsies were excisional. A history of animal contact was present in 9.14% of the cases (Table 1).

The median size of lymph nodes that was evaluated by ultrasound examination was 31 mm (10 mm-100 mm). Clinically, the most significant lymph node was removed in patients with generalized lymph node enlargement. In general, most biopsies were performed in the axillary region (Figure 1).

The histopathological findings of the lymph node biopsies are given in Table 2. The most common diagnosis was malignancy in 31.98% (n=63) of the patients. Reactive LAP was the second most common diagnosis, which was seen in 27.41% (n=54), followed by necrotizing granulomatous lymphadenitis and granulomatous lymphadenitis, at rates of 21.83% (n= 43) and 17.76% (n=35), respectively.

Table 1. Demographic, clinical and laboratory variables of patients followed up with lymph node biopsy

	n	%		n	%
Sex			**Animal Contact**		
Male	96	48.73	Yes	18	9.14
Female	101	51.27	No	179	90.86
LAP			**Organomegaly**		
Generalized	175	88.83	Hepatomegaly	49	24.87
Localized	22	11.17	Splenomegaly	41	20.81
LAP duration			**Laboratory findings**		
≤3 months	116	58.89	Leukocytosis	35	17.80
3-6 months	48	24.36	ESR>30	109	55.32
≥6 months	33	16.75	AST/ALT >ULN	20	10.15
Symptom			**Biopsy type**		
Fever	17	8.63	Excisional	184	93.40
Night sweats	27	13.70	Tru-cut	13	6.60
Weight loss	40	20.30			

(LAP: Lymphadenopathy, ESR: Erythrocyte Sedimentation Rate, ULN: upper limit of normal)

Table 2. Histopathological findings of lymph node biopsies

Findings	n	%
Lymphoma	59	29.95
Reactive Lymphadenitis	54	27.41
Necrotizing Granulomatous Lymphadenitis	43	21.83
Granulomatous Lymphadenitis	35	17.76
Metastasis	4	2.03
Histiocytic Necrotizing Lymphadenitis	1	0.51
Other	1	0.51

According to the overall evaluation results of the microbiological, radiological, and biochemical test results of the patients, along with their histopathological results, 73.09% (n=144) of the cases were associated with specific diagnoses. While malignancy was the most common diagnosis at a rate of 31.98% (n=63), infections were the second most common at a rate of 29.95% (n=59). Tuberculosis was the leading infectious cause, constituting 74.58% (44/59) of the infectious cases, followed by cat-scratch disease 13.56% (8/59). A specific diagnosis could not be made in 26.90% (n=53) of the cases, and their follow-ups continued (Table 3). One of the patients with the diagnosis of lymphoma and three of the patients with the diagnosis of tuberculosis were coinfected with the human immunodeficiency virus (HIV).

Table 3. Etiological distribution of LAP causes in patients with lymph node biopsy

Etiology	n	%	Percentage in the subgroup (%)
Malignancy	**63**	**31.98**	**100.00**
Lymphoma	59	29.95	93.65
Metastasis	4	2.03	6.35
Infections	**59**	**29.95**	**100.00**
TB	44	22.34	74.58
Cat-scratch Disease	8	4.06	13.56
EBV	3	1.52	5.09
Toxoplasmosis	2	1.01	3.39
CMV	1	0.51	1.69
Syphilis	1	0.51	1.69
Other	**22**	**11.17**	**100.00**
Sarcoidosis	20	10.15	90.90
Castleman Disease	1	0.51	4.55
Kikuchi-Fujimoto Disease	1	0.51	4.55
Non-specific	**53**	**26.90**	**100.00**

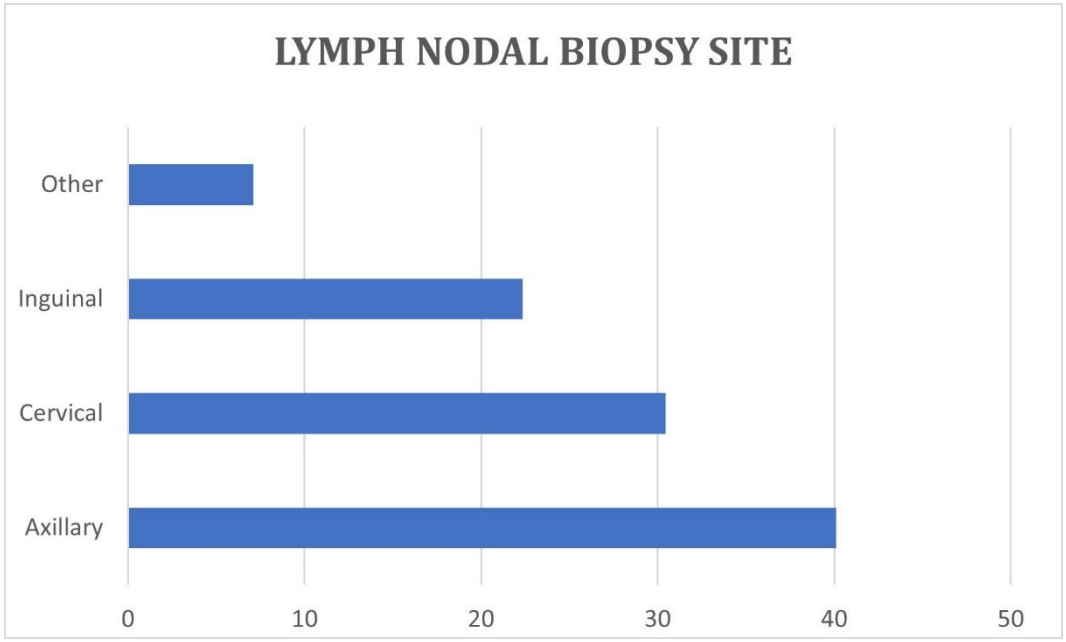

Figure 1. Distribution of lymph nodal biopsy site

Mycobacterium tuberculosis complex grew in the biopsy materials of four patients diagnosed with tuberculosis, bacilli were seen in the Ehrlich-Ziehl-Neelsen staining of the samples of two patients, and three patients had positive polymerase chain reaction (PCR) results for *Mycobacterium tuberculosis*. *Bartonella* indirect hemagglutination (IHA) tests were positive in 50% (n=4/8) of the patients who followed up with the diagnosis of cat-scratch disease. Three patients with EBV-VCA IgM positivity were diagnosed with Infectious mononucleosis, one with CMV IgM positivity was diagnosed with Cytomegalovirus infection, one with VDRL-TPHA positivity was diagnosed with syphilis, and two patients with toxoplasma IgM positivity were diagnosed with toxoplasmosis. Pathological and microbiological findings were evaluated together to determine the etiology in 33.89% (n=20/59) of the patients with LAP associated with infection.

Discussion

Lymph node biopsy is usually performed to investigate possible malignancy. However, some specific histopathological findings suggest infections at diagnosis.[5] In our study, 31.98% of the cases presenting with lymph node enlargement were diagnosed with malignancies, and lymphoma was the leading one among these malignancies. The second most frequent diagnosis was infections, at a rate of 29.95%. Gül et al. reported the rate of malignancies as 34.3%, and Akyüz Özkan et al. reported this rate as 66.5% in their studies examining

the excisional biopsy results of 67 and 185 patients, respectively.[6-7] Similar to our results, lymphoma was found to be the most frequently diagnosed malignant disease in both studies.[6,7] Mabedi et al. also reported malignancy as the most common etiology in patients over the age of 16 in their study, at a rate of 35%. Cetinkaya et al. reported the rate of malignancies as 6.7%, and Yenilmez et al. found this rate as 5% in their multicenter study, including 1401 patients, while the authors found the rates of infection to be 26.6% and 31.3%, respectively.[8-10] In both studies, malignancy rates were found to be lower than those in other studies in the relevant literature, including ours. This may be explained by the fact that patients with suspected malignancy are directed to oncology/hematology outpatient clinics and have fewer admissions to infectious diseases outpatient clinics.[9,10] In our study, patients diagnosed with non-infectious etiologies were directed to the relevant branches for their follow-ups and treatments.

Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis complex*, is one of the oldest known diseases and a significant cause of death worldwide.[11] According to the Turkey Tuberculosis Surveillance 2020 report, in 2018, a total of 11,786 TB patients were diagnosed. While pulmonary involvement is present in more than half of new TB cases, extrapulmonary presentation is mostly seen in the extrathoracic lymph nodes at a rate of 28.8%.[12] For lymphadenitis, the cervical region is the most common site, and cervical lymphadenitis is reported in 60-90% of TB lymphadenitis cases. Tuberculosis remains a problem in both diagnosis and treatment for clinicians, pathologists, and microbiologists.[11] Sunnetcioglu et al. evaluated extrapulmonary TB cases and reported that the disease progressed with lymph node involvement at a rate of 33.4%. In our study, we found *M. tuberculosis* to be the most prevalent among the infectious agents in patients presenting with lymph node enlargement.[13] This result was similar to those reported in previous studies.[6,9,10] In two different studies examining peripheral LAP biopsies in Nigeria and Nepal, TB was also found to be the most common etiology.[14,15]

Tuberculosis and HIV infections constitute the main burden of infectious diseases in countries with limited resources. HIV coinfection is the most significant risk factor for the development of active TB, which can cause both primary infection and TB reactivation in patients with latent TB. *M. tuberculosis* infection also has a negative effect on the immune response against HIV by accelerating the progression from HIV infection to acquired immune deficiency syndrome (AIDS).[16] According to the data of the World Health Organization, the frequency of tuberculosis in individuals living with HIV increases 18 times compared to those not infected with HIV.[17] It is recommended to investigate latent TB in patients diagnosed with HIV and perform prophylaxis when necessary to prevent reactivation.[18] In our study, we detected HIV coinfection in three of our patients diagnosed with TB.

Cat-scratch disease is a self-limited disease typically characterized by lymphadenopathy near a cat scratch or bite site. It is caused by the gram-negative bacterium *Bartonella henselae*. A few days after exposure, a papule

or swelling may develop in the area, followed by regional lymphadenopathy 1-2 weeks later. In most cases, it regresses spontaneously, but lymphadenopathy can persist for several months.[19,20] Cat-scratch disease, which is one of the causes of granulomatous lymphadenitis, should be considered in the differential diagnosis of acute, subacute, or chronic lymphadenopathy.[20] Enzyme immunoassay, indirect immunofluorescence assay, and molecular tests on tissue specimens have been evaluated for diagnosis.[19] We detected cat-scratch disease as the second most common infectious etiology in patients presenting with lymph node enlargement.

Epstein-Barr virus (EBV), the most common infectious disease in adolescents, is among the causes of LAP. The rate of seropositivity in the adult age group is around 90%.[21] The clinical condition is characterized by lymphocytosis, sore throat, lymphadenopathy, and fatigue, which can last for several weeks.[21,22] In our study, EBV, CMV, syphilis, and toxoplasmosis were among the other infectious etiologies.

Although LAP classically defines lymph nodes larger than 1 cm in diameter, supraclavicular, iliac, and popliteal lymph nodes that can be palpated at any size and epitrochlear lymph nodes larger than 0.5 cm in diameter are also considered abnormal.[1,2,23] In many LAP cases developing due to infections, it is often difficult to confirm the presence of microorganisms. In the evaluation of lymph node enlargement cases, first of all, a good anamnesis should be taken, and a physical examination should be performed.[1-3] Associated symptoms may be helpful for diagnosis. Fever, chills, night sweats, weight loss, and localized symptoms may be prodromal symptoms.[2-3] The most common symptom accompanying lymphadenopathy in our patients was weight loss, followed by night sweats and fever, at rates of 20.30%, 13.70% and 8.63%, respectively. Patients should be questioned regarding travel history, infectious agent exposure, animal contact, drug use, and high-risk sexual behaviors.[1-3] Animal contact was present in only 9.14% of our cases.

In cases where patients are evaluated as low-risk in terms of malignancy or serious disease, they can be followed up for 3-4 weeks to monitor whether the enlargement will regress. If the lymph node enlargement does not regress, a biopsy should be performed for diagnosis.[1,3] A specific diagnosis could not be made in 26.90% of our cases. In various studies conducted in Turkey, the rate of patients who could not get a specific diagnosis according to lymph node biopsy results has been reported as 28.4-63.3%.[6,9,10]

In addition to histopathological findings, clinical, serological, and microbiological investigations, especially molecular examinations, form the basis of diagnosis.[5] Molecular methods are recommended as the gold standard in the diagnosis of infectious lymphadenitis; culture remains critical in diagnosis, particularly for fastidious bacteria and mycobacteria. Clinicians should keep in mind that infection cannot be excluded even if molecular tests are negative.[24] Pathological and microbiological examinations were evaluated together in the diagnoses of 33.89% of our patients who were followed up for infection.

The major limitation of our study was its retrospective design. There are few studies on this subject, and they have been carried out mostly with the pediatric patient population. Although more comprehensive and prospective studies are required, we think that our study, in which we evaluated the etiology of LAP in terms of infectious diseases, will contribute to the literature.

In conclusion, we found tuberculosis in the first place among infectious etiologies. Tuberculosis continues to be a significant public health issue worldwide. As people living with HIV should be screened for TB, patients diagnosed with TB should also be screened for HIV infection. Although the cat-scratch disease cannot always be proven by serological tests, animal contact should be questioned and considered in the differential diagnosis of LAP. Even though infectious mononucleosis is frequently seen in pre-adolescent age groups, it should be kept in mind that it can be seen in any age group. LAP is a frequently encountered clinical condition that is difficult to manage. A specific diagnosis cannot always be made, but the gold standard for diagnosis is still histopathology. Close follow-up of patients with non-specific diagnoses should be continued.

Ethical Considerations: The study was approved by the Institutional Ethics Committee of the İstanbul Medeniyet University, Göztepe Training and Research Hospital (30.06.2021, 2021/0352).

Conflict of Interest: The authors declare no conflict of interest.

References

1. Mohseni S, Shojaiefard A, Khorgami Z, Alinejad S, Ghorbani A, Ghafouri A. Peripheral lymphadenopathy: approach and diagnostic tools. Iran J Med Sci. 2014;39(2):158-70.
2. Gaddey HL, Riegel AM. Unexplained Lymphadenopathy: Evaluation and Differential Diagnosis. Am Fam Physician. 2016;94(11):896-903.
3. Freeman AM, Matto P. Adenopathy. StatPearls, 2022 [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK513250/. (Accessed: 06.06.2022).
4. Weinstock MS, Patel NA, Smith LP. Pediatric Cervical Lymphadenopathy. Pediatr Rev. 2018;39(9):433-43 (doi: 10.1542/pir.2017-0249).
5. Lucas SB. Lymph node pathology in infectious diseases. Diagnostic Histopathology. 2017;23(9):420-30 (doi: 10.1016/j.mpdhp.2017.07.002).
6. Gül M, Aliosmanoğlu İ, Türkoğlu A et al. Peripheral lymphadenopathy in adults: Results of 67 cases of excisional biopsy. Dicle Medical Journal. 2013;40(2):245-49 (doi:10.5798/diclemedj.0921.2013.02.0263).
7. Özkan EA, Göret CC, Özdemir ZT, et al. Evaluation of peripheral lymphadenopathy with excisional biopsy: six-year experience. Int J Clin Exp Pathol. 2015;8(11):15234-9.
8. Mabedi C, Kendig C, Liomba G, et al. Causes of cervical lymphadenopathy at Kamuzu Central Hospital. Malawi Med J. 2014;26(1):16-9.
9. Çetinkaya RA, İlbak A, Yenilmez E. Etiology in Patients Presenting with Lymphadenopathy; Approach From the Perspective of Infectious Diseases. İKSSTD. 2019; 11(3):149-56 (doi:10.5222/iksstd.2019.66375).
10. Yenilmez E, Verdi Y, Ilbak A, et al. Demographic, clinical and laboratory characteristics for differential diagnosis of peripheral lymphadenopathy (LAP) and the etiologic distribution of LAP in adults; a multicenter, nested case-control study including 1401 patients from Turkey. Intern Emerg Med. 2021;16(8):2139-53 (doi: 10.1007/s11739-021-02683-2).
11. Natarajan A, Beena PM, Devnikar AV, Mali S. A systemic review on tuberculosis. Indian J Tuberc. 2020;67(3):295-311(doi: 10.1016/j.ijtb.2020.02.005).
12. Türkiye'de Verem Savaş 2020 Raporu. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Tüberküloz Daire Başkanlığı, 2020 [Internet]. https://hsgm.saglik.gov.tr/tr/tuberkuloz-haberler/turkiye-de-verem-savasi.html. (Accessed: 02.06.2022).
13. Sunnetcioglu M, Baran AI, Binici I, Esmer F, Gultepe B. Evaluation of 257 extra pulmonary tuberculosis cases at the Tuberculosis Control Dispensary, Van, Turkey. J Pak Med Assoc. 2018; 68(5):764-7.
14. Olu-Eddo AN, Ohanaka CE. Peripheral lymphadenopathy in Nigerian adults. J Pak Med Assoc. 2006;56(9):405-8.

15. Shrestha AL, Shrestha P. Peripheral Lymph Node Excisional Biopsy: Yield, Relevance, and Outcomes in a Remote Surgical Setup. Surg Res Pract. 2018; 2018:8120390 (doi: 10.1155/2018/8120390).
16. Bruchfeld J, Correia-Neves M, Källenius G. Tuberculosis and HIV Coinfection. Cold Spring Harb Perspect Med. 2015; 5(7): a017871(doi: 10.1101/cshperspect.a 017871).
17. Tuberculosis. WHO, 2022 [Internet]. https://www.who.int/health-topics/tuberculosis#tab=tab_1. (Accessed: 03.06.2022).
18. Latent tuberculosis. EACS, 2021 [Internet]. https://www.eacsociety.org/guidelines/eacs-guidelines. (Accessed: 04.06.2022).
19. Zangwill KM. Cat Scratch Disease and Bartonellaceae: The Known, the Unknown and the Curious. Pediatr Infect Dis J. 2021;40(5S):11-5 (doi: 10.1097/INF.0000000000002776).
20. Baranowski K, Huang B. Cat Scratch Disease. StatPearls, 2022 [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK482139/. (Accessed: 04.06.2022).
21. Dunmire SK, Verghese PS, Balfour HH Jr. Primary Epstein-Barr virus infection. J Clin Virol. 2018; 102:84-92 (doi: 10.1016/j.jcv.2018.03.001).
22. Naughton P, Healy M, Enright F, Lucey B. Infectious Mononucleosis: diagnosis and clinical interpretation. Br J Biomed Sci. 2021;78(3):107-16 (doi: 10.1080/09674845.2021.1903683).
23. Ferrer R. Lymphadenopathy: differential diagnosis and evaluation. Am Fam Physician. 1998; 58(6):1313-20.
24. Prudent E, La Scola B, Drancourt M, Angelakis E, Raoult D. Molecular strategy for the diagnosis of infectious lymphadenitis. Eur J Clin Microbiol Infect Dis. 2018;37(6):1179-86 (doi: 10.1007/s10096-018-3238-2).