

ORIGINAL ARTICLE

Medicine Science 2021;10(1):202-6

Evaluation of the patient with lymphadenopathy: Is it always easy to reach the correct diagnosis?

Adem Kose, Ahmet Dogan, Yasar Bayindir, Yasemin Ersoy, Mehmet Ozden,
Funda Memisoglu, Sibel Altunisik Toplu, Yakup Gezer

Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Inonu University, Malatya, Turkey

Received 03 February 2021; Accepted 21 February 2021
Available online 22.12.2021 with doi: 10.5455/medscience.2021.02.031

Copyright©Author(s) - Available online at www.medicinescience.org
Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



Abstract

Lymphadenopathy (LAP) is a common clinical problem in adult patients and should be thoroughly evaluated in a tertiary hospital to investigate its reasons. In this study, we aimed to present the demographic characteristics, etiology, diagnosis and follow-up results of the patients who applied with LAP symptoms and findings. This study was designed to include adult patients with neck, armpit, or groin swelling accompanied by symptoms, such as fever, night sweats, weight loss, cough and sputum between January 2010 and August 2017, retrospectively. Patients' data were collected from electronic files. Patients were diagnosed using radiological, histopathological, bacteriological, serological and other microbiological methods. Two hundred-thirty patients were included in this study. The mean age was 43.12 ± 17.06 SD in males and 45.74 ± 16.64 in females. On admission, the most common symptoms were night sweats (31%), fever (23%), weight loss (17%) and cough and/or sputum (13%) in order of frequency. However, 16% of the patients were asymptomatic. In this study, 157 (68.26%) patients were diagnosed. Tuberculosis (n=76; 33%), malignancies (n=28, 12.1%) and tularemia (N=14; 6.1%) were the most common diseases causing LAP that was most commonly located in the bilateral cervical chain. Lymphadenopathy should be evaluated comprehensively concerning diagnosing or ruling out many diseases that must be treated necessarily. Knowledge and awareness of the diseases as a cause of LAP may contribute to the early and correct diagnosis. Therefore, undiagnosed patients should be followed, and the institutions should develop policies for this purpose, such as telemedicine applications.

Keywords: Lymphadenopathy in adults, infectious diseases, diagnosis

Introduction

Lymphadenopathy (LAP) is defined as lymph nodes becoming abnormal in number, size, and consistency; and their normal size is less than 1 cm, but they have different sizes at different ages [1]. In primary care practice, the annual incidence of unexplained LAP is 0.6%, only 1.1% of these cases are related to malignancy, but this percentage increases with advancing age [2]. LAP occurs in two patterns: generalized and localized. Localized adenopathy occurs in contiguous groupings of lymph nodes. Generalized LAP entails LAP in two or more non-contiguous locations. It is

generally recognized that the majority of LAP, both localized and generalized, is of benign and self-limited etiology [3]. The most common causes in the etiology of lymphadenopathies are malignancies, infections, autoimmune diseases, iatrogenic reasons and various rare and unusual diseases [4]. Seventy-five percent of all lymphadenopathies are localized and more than 50% of them are located in the head and neck region. It is usually caused by a specific pathology located in the lymphatic drainage area and can be detected without an additional evaluation; the remaining 25% is generalized and may often be a sign of an underlying systemic disease [5].

The most critical step in evaluating lymphadenopathies is a careful history and a focused physical examination, the content of which should be determined according to the patient's clinic. The concomitant symptoms and the patient's epidemiology provide further clues to the diagnosis. A more comprehensive investigation of fever, chills, night sweats, weight loss and accompanying

*Corresponding Author: Adem Kose, Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Inonu University, Malatya, Turkey
E-mail: adem.kose@inonu.edu.tr

symptoms may contribute to the exhibition of the etiology. In addition, demographic characteristics, such as the patient's age, gender, exposure to infectious disease, toxins, drugs and habits, may also contribute more [6]. Since the cause is apparent in most cases (such as infection), no further studies of etiology are needed in primary evaluation. In cases where the cause cannot be explained, laboratory tests, imaging studies and tissue biopsy are recommended. Imaging can determine the size and distribution of the lymph node more accurately than a physical exam. Ultrasound is a non-invasive method to evaluate lymph nodes in superficial areas, such as the neck. On ultrasound (US) imaging, the cortex is usually hypochoic or even imperceptible, and the medulla is hyperechoic. Computed tomography (CT) is useful for detecting LAP in the thorax or abdominopelvic space. Tissue diagnosis by fine-needle aspiration biopsy or excisional biopsy is the gold standard assessment for LAP [7]. The underlying etiology in acute, soft and painful neck masses are usually localized or systemic viral and bacterial infections, subacute malignancies and chronic thyroid pathologies [8]. Systemic lymph nodes are more common in restricted viral infections. In lymphomas, the lymph nodes are usually elastic, conglomerate and painless. Metastatic lymph nodes are often painless, rigid and attached to the surrounding tissue [9]. Fine needle aspiration biopsy is useful to investigate benign/malignant differentiation in the etiology of LAP, but the state of inadequacy for diagnosis is often encountered. In addition, an excisional biopsy is required to diagnose lymphoma. Excisional biopsy is a diagnostic method that can be safely applied with minimal morbidity and mortality. An incisional biopsy is not recommended because it may lead to the formation of fistulas, especially in cases of tuberculosis (TB) [10]. Pathophysiology, treatment and prognosis vary significantly from patient to patient, but it is necessary to reach the correct diagnosis. In addition, delays in reaching the correct diagnosis can harm the patient. Moreover, impatience may be observed in patients during the prolonged diagnosis process.

In the current literature, studies on the clinical and etiological spectrum of lymphadenopathies are limited, especially outpatients in developing countries, which has remained under-researched. Therefore, in this study, we aimed to present the demographic characteristics, etiology, diagnosis and follow-up results of the patients who applied with LAP symptoms and findings.

Materials and methods

Study design and inclusion criteria

Between 01 January 2010 and 30 August 2017, 230 adult patients with having swollen in the regions where neck, axilla or inguinal and accompanied by any one of the symptoms, such as fever, night sweats, weight loss, cough and sputum, were included in our study. Patients were diagnosed using radiological, histopathological, bacteriological, serological and other microbiological methods.

Exclusion criteria

Only patients with one application and/or without regular clinical follow-up and pediatric patients were excluded from our study.

Ethical approval

Ethical approval was obtained from the Inonu University Non-Interventional Ethics Committee (Approval No: 2018/15-26).

Invasive procedures

According to the outcomes of the physical examination and radiological studies, the lesions with a diameter of >1 cm were performed excisional or incisional biopsy for diagnostic purposes by otolaryngology or general surgery.

Statistical analysis

The demographic data and follow-up results of the diagnosed patients were retrospectively scanned from the patient registration system and all the data were recorded in the patient record forms. IBM SPSS Statistics 17.0 software program was used for all data analyses.

Results

Two hundred-thirty patients were included in this study. Sixty-six (28.7%) of our patients were male and 164 (71.3%) were female. The mean age was 43.12 ± 17.06 SD in males and 45.74 ± 16.64 in females. One hundred fifty-two (66%) patients lived in the city center, 58 (25%) in the district and nine (4%) in the rural area. On the first admission, the most common symptoms were night sweats (31%), fever (23%), weight loss (17%), cough and/or sputum (13%), in order of frequency. However, 16% of the patients were asymptomatic. One or more members of the relatives of 32 patients and 13 cases had previous TB diagnosis. 15% cases had a history of consuming unpasteurized milk and milk products and 5% cases had unhygienic water consumption. LAP was observed in the regions of bilateral cervical, submandibular, submental and parotid gland (78%), axillary zone (7.4%), inguinal area (7.4%), supraclavicular region (3%), preauricular region (2.2%) and abdominal region (1.3%). Skin fistula was observed in 3% of the patients with LAP in the neck. Five patients had LAP in both the neck and inguinal regions.

Biopsy was performed in 145 (63%) of the cases. In this study, 157 (68.26%) patients were diagnosed, and an exact diagnosis could not be made in 73 (31.74%) cases. Histopathological examination was made in only 16 of 73 undiagnosed patients. The three most common diagnoses were TB (33%), malignancies (12.1%) and tularemia (6.1%). Of these, five (8.7%) patients had their clinical findings who were healed with antimicrobial therapy, which was initiated empirically for 14 days, and five (8.7%) patients have been still being followed up in the Department of Hematology. The diagnostic results of all patients are summarized in Table 1. Lymphadenopathies were the most commonly detected in the bilateral cervical chain, submandibular region, submental region and inside the parotid gland. Localizations and frequency of LAP are indicated in Table 2. Different antimicrobial treatments were applied to 14 patients diagnosed with tularemia for varying periods and MAT titers were monitored.

Table 1. Diagnostic results of all patients

Biopsy performed	Number (n)	Rate (%)	Biopsy unperformed	Number (n)
Tuberculous lymphadenitis	66	28.7	Undiagnosed	57
Malignancy / metastasis	27	11.7	Tuberculous lymphadenitis	10
Undiagnosed	16	6.95	Suppurative lymphadenitis	7
Tularemia	8	3.47	Tularemia	6
Suppurative lymphadenitis	7	3.04	Multiple Myeloma	1
Toxoplasmosis	6	2.6	Melkerson Rosenthal Syndrome	1
Chronic inflammation	5	2.17	HIV infection	1
Sarcoidosis	2	0.8	Toxoplasmosis	1
HSV type-1 infection	1	0.4	Rosai Dorfman disease	1
Reactive lymphadenitis	1	0.4		
Fibroadiopose tissue	1	0.4		
Spirochete infection	1	0.4		
Lymphocytic sialadenitis	1	0.4		
Castleman Disease	1	0.4		
Granulomatous mastitis	1	0.4		
Pleomorphic adenoma	1	0.4		
Total	145	63	Total	85

Table 2. Lymphadenopathy localization and frequency

Localisation	Number (n)	Ratio (%)
Bilateral cervical, submandibular, submental and parotid gland	181	78.7
Axillary zone	17	7.4
Inguinal area	17	7.4
Supraclavicular region	7	3
Preauricular area	5	2.2
Intraabdominal area	3	1.3
TOTAL	230	100

Discussion

Lymph node enlargement should be evaluated comprehensively in terms of diagnosing or ruling out many diseases that must be treated necessarily. However, especially in first and second-line health services, LAPs are either overlooked or not given the necessary attention [11]. Awareness and knowledge of the etiologies causing the disease in patients with LAP are the main keys in the diagnosis and management of these patients. However, the diagnostic procedures can be time-consuming in patients who have LAP with unknown etiology. Following carefully of these patients may contribute to correct diagnosis in the tertiary hospitals

providing health care to the undiagnosed cases [12]. In the current study, we aimed to retrospectively analyze the patients admitted to our center with LAP that had not been diagnosed in other centers.

In a retrospective study evaluating 925 patients who underwent lymph node biopsies from 1973 to 1977, 60% of the lymph nodes had benign lesions, 28% had carcinomas and 12% had lymphomas. For peripheral nodal biopsies (cervical, axillary, inguinal), 56% were related to benign lesions, 29% to carcinomas, and 15% to lymphomas [13]. In a study conducted by Gul et al., which included the five-year follow-up of 67 patients who applied for peripheral LAP and underwent excisional biopsy, the most common causes

were malignancies (n = 23; 34.3%) and TB (n = 20; 29.9%) [10]. In our study, we found that the three most common causes of lymphadenopathy were TB (33%), malignancies (12.1%) and tularemia (6.1%).

Tuberculous lymphadenitis is the most common form of extrapulmonary TB. In the diagnosis, demographic features, radiological imaging of LAP, physical examination findings, purified protein derivative (PPD) skin test, acid-resistant bacilli (ARB), molecular tests, TB culture and histopathological examination are the components that should be evaluated together for correct diagnosis [14]. The definite diagnosis is made with culture positivity, but culture negativity does not rule out the diagnosis. Because the agent can be isolated only in 10-69% of the cases, initiating treatment late is an important disadvantage because the culture result is expected for 6-8 weeks. Ziehl-Neelsen staining and microscopic evaluation is an easy, cheap and fast method, and it is a diagnostic method with 46-78% sensitivity and 100% specificity [15]. One of the most important diagnostic methods is the histopathological method characterized by Langerhans cells, caseous necrosis, granulomatous inflammation or calcifications [16]. In our study, among the patients diagnosed with tuberculous lymphadenitis, ARB was detected in 13 cases, polymerase chain reaction (PCR) positivity in 29 cases, and culture positivity in 40 cases. In twelve cases that received antituberculosis treatment, treatment was initiated according to the history, biopsy, PPD and Interferon Gamma Release Assay (IGRA). It was observed that culture, PCR and ARB tests were negative in these patients. Only nine of our cases had caseous necrosis. Extrapulmonary TB mostly involves the lymph nodes in the cervical chain with diffuse, multiple, fixed and painless character [17]. In our study, LAP was most often found in bilateral cervical, submandibular, submental and parotid gland in accordance with the literature.

In adult patients, LAP may develop largely due to metastatic carcinomas [18]. Biopsy of peripheral lymph nodes (cervical, supraclavicular, axillary) in the upper part of the body is more preferred, while biopsy of lymph nodes in the lower parts of the body (popliteal, inguinal, femoral) is usually less useful [19]. Ultrasonography, fine needle aspiration, CT and MRI are the most useful methods for diagnosis. In USG, round-shaped, homogeneous structure, extracapsular involvement is significant concerning irregular limited, central necrosis and non-hilum lap malignancy, but a lymph node or bone marrow biopsy is needed for a definite diagnosis [20]. In the study conducted by Rahman et al. [16], including 191 cases, 11 cases (5.7%) had Hodgkin lymphoma, 22 cases (11.5%) non-Hodgkin lymphoma, and 24 cases (12.5%) metastatic neoplasms. In the study of Gul et al. [10] mentioned above, it was Non-Hodgkin lymphoma (n = 11; 16.4%), Hodgkin lymphoma (n = 7; 10.4%) and metastasis (n = 5; 7.5%). Saraswat et al. [21] reported a 63% specific diagnosis rate, excluding patients with known malignancies, systemic diseases, or abnormal chest radiographs. The most critical aspect in the clinical approach to adenopathy is determining which cases are associated with benign lesions and which are associated with malignant disorders. Then, it is important to distinguish carcinoma from lymphoma [22]. In our study, we achieved the rate of being able to make a definite diagnosis at the level of 68.26%, whether a biopsy is performed or not. We can say that the rate of undiagnosed patients is higher than previous similar studies, and this can be explained by that

our number of patients is less. However, in the diagnostic process that requires time, our patients may prefer not to come or go to another clinic or hospital because of their outpatient follow-up due to their expectation of rapid diagnosis or their mild symptoms. In this study, we realized that these outpatients should be followed up until the correct diagnosis, even if they do not come to the clinic.

Especially in endemic regions, one of the important causes of LAP is tularemia, a zoonotic infection caused by *Francisella tularensis* [23]. Transmission to humans occurs through direct contact with infected animals, through vectors (ticks and mosquitoes), contaminated water and inhalation of infected aerosols. The findings showed that the most common symptoms and findings in cases were fever and lymphadenopathy, and the most frequent form of oropharyngeal tularemia was observed [24]. In a retrospective study conducted by Erdem et al. [25], including 1034 patients from 41 centers, 713 cases received monotherapy, 299 cases received combined therapy, 11 cases received sequential treatment, and 11 cases were lacking data. Recurrence was observed in our 12 cases who received monotherapy, 10 cases who received combined therapy and one patient who received consecutive treatment among patients who received treatment for at least two weeks or more. In our study, it was observed that 14 of 15 cases were administered treatment in our center, and a case was diagnosed and treated at an external center and applied to our center for control. One case presented with recurrence one year later despite receiving ciprofloxacin treatment for two weeks in an external center, and it was observed that this patient was administered combined doxycycline + ciprofloxacin therapy for three weeks. In our study, a diagnosis of tularemia was made in six cases that were not administered a biopsy and were examined serologically. The findings showed that tularemia treatment was administered to these patients for two or three weeks, as the micro-agglutination test (MAT) titer was reported as $\geq 1/160$ in 11 of 68 patients who were suspected of tularemia with the history and physical examination findings and micro-agglutination test was studied. One case treated for tularemia was diagnosed in another center. In addition, serological data of two cases who received treatment could not be reached.

The most common causes of axillary LAP are carcinomas, lymphomas, benign reactive hyperplasia, tuberculosis, atypical mycobacterial infections, cat-scratch disease and granulomatous infections, such as HIV, syphilis, toxoplasmosis and hepatitis, non-infectious granulomatous diseases, such as sarcoidosis and autoimmune diseases, such as lupus, rheumatoid arthritis and scleroderma [26]. Infectious reasons were detected in all of our 17 cases who were admitted to our clinic with signs of axillary lymphadenopathy. In the etiology of lymphadenopathy, some diseases, such as Castleman's disease and Melkerssons-Rosenthal syndrome, which are rarely seen and not considered among preliminary diagnoses, should also be considered. Castleman's disease, also known as giant angiofollicular lymphoid hyperplasia, is a benign self-limiting and systemic disorder involving lymph nodes with unknown etiology. It can be clinically classified as localized (single center) or systemic (multicenter) [27]. Melkerssons-Rosenthal syndrome is a clinical entity identified by the presence of the triad of recurrent facial paralysis, recurrent often permanent (labial) oedema, and to a lesser extent, the placation of the tongue [28]. In our study, we identified a few cases that

were initially diagnosed with histopathological features but which we did not consider in pre-diagnosis. This situation shows how important histopathological diagnosis is in revealing the etiology of lymphadenopathies.

Conclusion

Lymphadenopathy is a clinical condition whose etiology must necessarily be investigated in adult patients; it is important to support histopathology along with a detailed history, a careful physical examination for its definite diagnosis. While the patients with LAP evaluate, endemic infectious diseases should be kept in mind, such as TB and tularemia, which may have recurrent characteristics. Finally, undiagnosed patients should be followed until the final diagnosis, and the institutions should develop policies for this purpose, such as telemedicine applications.

Acknowledgements

The authors warmly thank all laboratory staff working in Molecular Microbiology, Pathology, Biochemistry Departments and the hospital pharmacy responsible for helping us access to daily drug outputs of pharmacy.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

The financial support no have.

Ethical approval

This study was obtained from the Inonu University Non-Interventional Ethics Committee (Approval No: 2018/15-26).

References

- Morland B. Lymphadenopathy. Arch Dis Child. 1995;73:476-9.
- Fijten GH, Blijham GH. Unexplained lymphadenopathy in family practice. An evaluation of the probability of malignant causes and the effectiveness of physicians' workup. J Fam Pract. 1988;27:373-6.
- Gaddey HL, Riegel AM. Unexplained Lymphadenopathy: Evaluation and Differential Diagnosis Am Fam Physician. 2016;1;94:896-903.
- Habermann TM, Steensma DP. Lymphadenopathy. Mayo Clin Proc. 2000;75:723-32.
- Viiiala N, Gibson J [Internet]. An approach to the assessment of lymphadenopathy. [cited 2007 Jan 10]. Available from: <http://www.medicalobserver.com.au/news/an-approach-to-the-assessment-of-lymphadenopathy>.
- Bazemore AW, Smucker DR. Lymphadenopathy and malignancy. Am Fam Physician. 2002;66:2103-10.
- Chau I, Kelleher MT, Cunningham D, et al. Rapid access multidisciplinary lymph node diagnostic clinic: analysis of 550 patients. Br J Cancer. 2003;88:354-61.
- Haynes J, Arnold KR, Oskins CA, et al. Evaluation of neck masses in adults. Am Fam Physician. 2015;91:698-706.
- Richner S, Laifer G. Peripheral lymphadenopathy in immunocompetent adults. Swiss Med Wkly 2010;140:98-104.
- Gul M, Aliosmanoglu I, Turkoglu A, et al. Erişkin çağı periferik lenfadenopatileri. Dicle Tıp Dergisi 2013;40:245-9.
- Bosch X, Coloma E, Donate C, et al. Evaluation of unexplained peripheral lymphadenopathy and suspected malignancy using a distinct quick diagnostic delivery model: prospective study of 372 patients. Medicine (Baltimore). 2014;93:e95.
- Mbata GC, Nweke IG, Egejuru RO, et al. South eastern histologic pattern of lymph node biopsies in a tertiary hospital in Nigeria. J AIDS Clin Res. 2015;6:6:475-8.
- Lee Y, Terry R, Lukes RJ. Lymph node biopsy for diagnosis: a statistical study. J Surg Oncol. 1980;14:53-60.
- Deveci HS, Kule M, Kule ZA, et al. Diagnostic challenges in cervical tuberculous lymphadenitis: A review. North Clin Istanbul. 2016;3:150-5.
- Albayrak N, Celebi B, Kavas S, et al. Investigation of the presence of Mycobacterium tuberculosis in the lymph node aspirates of the suspected tularemia lymphadenitis cases. Mikrobiyol Bul. 2014;48:129-34.
- Rahman A, Biswas MA, Siddika TS, Sikder AM. Histopathological Evaluation of Lymph Node Biopsies: A Hospital Based Study. J Enam Med Col. 2012;2(1):8-14.
- Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis. 2017;7:1-12.
- Mohseni S, Shojafard A, Khorgami Z, et al. Peripheral lymphadenopathy: approach and diagnostic tools. Iran J Med Sci. 2014;39:158-70.
- Ochicha O, Edino ST, Mohammed AZ, et al. Pathology of peripheral lymph node biopsies in Kano, Northern Nigeria. Ann Afr Med. 2007;6:104-8.
- Pangalis GA, Vassilakopoulos TP, Boussiotis VA, et al. Clinical approach to lymphadenopathy. Semin Oncol. 1993;20:570-82.
- Kartal O, Ataş E, Gürsel O. Differentiation of benign from malignant cervical lymphadenopathy by ultrasonography in children. Arch Argent Pediatr. 2020;118:11-7.
- Saraswat A, Rajender A, Purohit K, et al. Lymph node biopsy: Spectrum and clinical significance as diagnostic tool at tertiary care centre. J Evolution of Med Dental Sci. 2015;4:1008-15.
- Penn RL. Francisella tularensis (tularemia). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia, PA: Elsevier Saunders, 2015:2590-602.
- Kılıç UA, Kılıç S, Sencan I, et al. A water borne tularemia outbreak caused by Francisella tularensis subspecies holarctica in Central Anatolia region. Mikrobiyol Bul. 2011;45:234-47.
- Erdem et al. Evaluation of tularemia courses: a multicentre study from Turkey. Clin Microbiol Infect 2014;20:1042-51.
- Clarke P, Valadares CN, Balabram D, Pires DM. Bilateral axillary lymphadenopathy: differential diagnosis and management. Mastology 2020;30:e20200036.
- Medina RP, Guio JI, Correa PL. Localized Castleman's Disease in the Breast in a Young Woman. Case Rep Pathol. 2016;2016:8413987.
- Talabi OA. Melkerssons-Rosenthal syndrome: a case report and review of the literature. Niger J Clin Pract. 2011;14:477-8.