Original Article
Evaluation of peripheral lymphadenopathy with excisional biopsy: six-year experience

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Abstract: Background: Lymphadenopathy (LAP) may be the first symptom of many diseases. We aimed to investigate peripheral LAP results taken by excisional biopsy. Methods: Histopathological examination of 185 lymph node biopsy specimens were evaluated between January 2009 and April 2015 in Istanbul Private Ekin Pathology Laboratory, retrospectively. Results: The average age of patients ranged from 1 to 86 was 41.01 ± 20.62 years. 87 of were female, 98 of male. 62 (33.5%) of excisional biopsy materials were benign lesions and 123 (66.5%) of malignant. Benign lesions were consisted of reactive hyperplasia, cat-scratch disease, toxoplasmosis, necrotizing/non-necrotizing granulomatous. Of these patients, 40 had nodes with reactive hyperplasia (15 female/25 male, mean age: 27.35 y), 14 had necrotizing granulomatous disease (9 female/5 male, mean age: 39.86 y), 2 non-necrotizing granulomatous disease (1 female/1 male mean age: 43 y), 4 had cat-scratch disease (1 female/3 male mean age: 54.25 y), 1 toxoplasmosis (26 y, female), 1 Kikuchi disease (25 y, female). In the evaluation of malign lesions; 38 were Hodgkin lymphoma (HL) (20.5%, 17 female/21 male, mean age: 34.89 y) 77 had non-Hodgkin lymphoma (NHL) (41.6%, 37 female/40 male, mean age: 52.26 y), 8 metastasis (4.3%, 5 female/3 male, mean age: 53.5 y). Reactive LAP observed most common in cervical region, NHL in axillary-abdomen-inguinal-mediastinum and HL in the supraclavicular region. Conclusion: Excisional biopsy can be applied safely with minimal morbidity and mortality and a gold standard diagnostic method for LAP. Although LAP is mostly related with benign lesions, malignancy should be kept in mind in differential diagnosis.

Keywords: Benign, excisional biopsy, lymphadenopathy, malignant

Introduction

Lymphadenopathy (LAP) describes the conditions in which lymph nodes become abnormal in size, consistency, and it may be one of the symptoms of many diseases. The history of the patient should be considered carefully because it may provide clues to the underlying disease. Usually points self-limited infection in younger adults although a malignancy in elderly [1].

No further investigation is required in most cases, as the cause is obvious on the patient's first evaluation (such as infection). The cause of peripheral LAP often cannot be ascertained on clinical grounds alone. Laboratory tests, imaging studies, and tissue biopsy are recommended when there are unexplained conditions. The size and distribution of the node can be identified more accurately with imaging than physical examination. Ultrasound is a non invasive method to assess lymph nodes in superficial regions like the neck [2]. Ultrasound can assess the number, size, site, shape, margins, and pattern of vascularity and the internal structure of a lymph node. Computed tomography (CT) is helpful for LAP in the thorax or abdominopelvic cavity [3, 4]. Although needle biopsy is used as

Table 1. Excisional biopsy results of patients with lympadenopathy

Pathological diagnosis	N (%)
Reactive lympadenopathy	40 (21.5%)
Necrotizing granulomatozis	14 (7.5%)
Non-necrotizing granulomatozis	2 (1%)
Other granulomatous diseases	5 (2.7%)
Cat-scratch disease	4
Toxoplasmosis	1
Malignancy	123 (66.5%)
Hodgkin lymphoma	38
Non-Hodgkin lymphoma	77
Metastasis	8
Kikuchi-Fujimoto disease	1 (0.8%)

the first step in the diagnostic approach to lymphomas, excisional biopsy of enlarged lymph nodes is still gold standard procedure. Excision biopsy of the most accessible peripheral lymph node is with the possibility of early diagnosis and is a vital part of the management [5].

In general, if diameter of the lymph nodes exceeds one cm or more it is considered to be abnormal. Of course, there are exceptions in different regions and lymph nodes have different sizes at different ages. The cervical region is most commonly involved area among peripheral LAP at any age. Generalized LAP is usually an indicative of an underlying disease such as the Epstein-Barr virus, HIV, lymphoma, and autoimmune disorders [1]. It is considered that palpable supraclavicular, iliac, popliteal, epitrochlear nodes greater than 0.5 cm, and inguinal nodes larger than 1.5 cm are abnormal [6].

40 years and over, LAP in multiple region, supraclavicular lymph nodes, nodal diameter greater than 2 cm, firm or hard texture, fixed nodes, lack of tenderness, and abnormal chest X-ray is some factors that referring the physicians for tissue sampling. If there are no predictive risks for malignancy, patients with peripheral LAP can be followed for 3 or 4 weeks before lymph node biopsy [1].

In current study we aimed to evaluate the patients with peripheral LAP with uncertain etiology, retrospectively.

Material and methods

A total of 185 lymph node biopsy specimens were examined, between January 2009 and April 2015 in Istanbul Private Ekin Pathology Laboratory, retrospectively. After taking informed consent from patients, excision biopsy of the most accessible peripheral lymph node was performed as an outpatient procedure in all of.

Fixed tissues with neutral buffered formalin, half of the fresh tissues with again neutral buffered formalin, and the other half were fixed with Hollande solution and routinely processed for light microscopy and stained with hematoxylin-eosin. Selected cases (lymphoma cases) were additionally stained with immunohistochemistry using a panel of antibodies or markers through avidin-biotin peroxidase method.

The statistical analyses were carried out by Statistical Package for Social Sciences (SPSS). Variables were expressed as mean ± SD. Comparisons of variables were performed using unpaired Student t test and p value <0.05 was considered indicate statistical significance.

Results

The excisional lymph node biopsy materials of 185 patients were analyzed according to age, location and gender. 87 of the patients were female, 98 were male. The mean (SD) age of the patients was 41.01 ± 20.62 years (range 1-86 years). The pathological diagnosis of patients is shown in **Table 1**.

In the pathological examination, the most common (n = 123, 66.5%) lesions were malignancies. The frequency of malignancies were; non-Hodgkin lymphoma (NHL) (n = 77; 62.6%), Hodgkin lymphoma (HL) (n = 38; 30.8%) and metastasis (n = 8; 6.5%), respectively. The second most common condition was reactive LAP (n = 40, 21.6%). The average age of patients with malignancy was 46.80 ± 19.64 years (5-86 y), while the average age of patients with benign lesions 29.76 ± 17.68 years (1-70 y) and this difference was statistically significant (P = 0.000).

The excisional biopsy materials demonstrated 62 (33.5%) benign lesions and 123 (66.5%) malignant diagnoses. Benign lesions were a heterogeneous group of disorders including reactive hyperplasia, cat-scratch disease, toxoplasmosis, necrotizing granulomatozis and non-necrotizing granulomatozis. Of these pa-

Table 2. Site distribution and histopathological diagnosis of patients with lymphadenopathy

Site of biopsy	Number of cases	Histological diagnosis								
		NHL	HL	Reactive	Necrotizing	Non-nec-rotizing	Kikuchi	Cat-scratch	Toxoplas-mosis	Metastasis
Cervical	71 (38.3%)	17 (24%)	19 (26.7%)	20 (28.2%)	7 (9.9%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	4 (5.6%)
Axillary	30 (16.2%)	10 (33.3%)	5 (16.7%)	9 (30%)	4 (13.4%)	-	-	2 (6.6%)	-	-
Inguinal	29 (15.6%)	16 (55.1%)	8 (27.5%)	3 (10.4%)	-	-	-	1 (3.5%)	-	1 (3.5%)
Abdominal	12 (6.4%)	10 (83.4%)	-	-	-	-	-	-	-	2(16.6%)
Supraclavicular	9 (4.8%)	3 (33.4%)	4 (44.4%)	1 (11.1%)	1 (11.1%)	-	-	-	-	-
Head	23 (12.4%)	13 (56.6%)	1 (4.3%)	7 (30.5%)	1 (4.3%)	-	-	-	-	1 (4.3%)
Mediasten	11 (5.9%)	7 (63.7%)	1 (9%)	-	2 (18.3%)	1 (9%)	-	-	-	-
Total	185	77 (41.6%)	38 (20.6%)	40 (21.6%)	14 (7.6%)	2 (1.1%)	1 (0.5%)	4 (2.2%)	1 (0.5%)	8 (4.3%)

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma.

tients, 40 had nodes with reactive hyperplasia (15 female, 25 male) (1-70 y, mean age: 27.35 y), 14 had necrotizing granulomatous disease (9 female, 5 male) (16-63 y, mean age: 39.86 y), 2 of non-necrotizing granulomatous disease (1 female, 1 male, mean age: 43 y), 4 of had cat-scratch disease (1 female, 3 male, mean age: 54.25 y), 1 of toxoplasmosis (26 y, female), 1 of Kikuchi disease (25 y, female). Malign lesions included NHL, HL and metastasis; 38 of were HL (20.5%, 17 female, 21 male) (5-81 y, mean age: 34.89 y) (18 nodular sclerozane type, 12 mixed cellular type, 8 lymphocyte predominant), 77 of NHL (41.6%, 37 female, 40 male) (6-84 y, mean age: 52.26 y) (54 diffuse large B-cell, 10 follicular lymphoma, 4 peripheral T-cell, 3 mantle cell, 3 B cell rich T cell lymphoma, 2 small cell lymphocytic lymphoma, 1 marginal zone lymphoma), 8 of metastasis (4.3%, 5 female,3 male) (20-86 y, mean age: 53.5 y).

71 lesions were in cervical region, 30 in axillary, 11 in mediasten, 29 in inguinal, 23 in head-neck, 12 in abdomen, and 9 in supraclavicular regions.

The most frequently encountered in the servical region was reactive LAP while NHL in axiller-inguinal-mediastinal-abdomen and HL in supraclavicular region. Site distribution and histopathological diagnosis of patients with LAP are shown in **Table 2**.

In childhood (ages 1-18 y, mean age: 12:31 ± 4:48 y); 17 reactive LAP, 4 HL, 3 NHL, 1 necrotizing LAP, 3 cat scratch disease was observed.

Discussion

There are 600 lymph nodes in different regions of our body [6]. Spleen, tonsils, adenoids, and Peyer's patches are the parts of the lymphoid tissue and clean antigens from the extracellular fluid. Peripheral lymph nodes locate deep in the subcutaneous tissue and can be palpable when any process causes them to enlarge.

If LAP grows rapidly within 2 weeks, and does not shrink within 4-6 weeks and not completely regressed in 8-12 weeks, biopsy should be planned [7, 8]. Usually less than one cm in diameter is accepted as normal sized lymph node. In general, when the size of lymph node larges more than 2 cm it suggests malignancy or a granulomatous disease [9].

Fine-needle aspiration biopsy may be useful in the differentiation of benign or malignant, but are often faced with failure diagnosis. Also it needs excisional biopsy for the definitive diagnosis of lymphoma. Therefore excisional biopsy in the diagnosis of LAP stated as "gold standard" [10]. An excisional biopsy is a diagnostic method that can be applied safely with minimal morbidity and mortality.

In our cases, in the pathological examination; the most common (n = 123; 66.5%) condition was malignancies. The frequency of diseases were; NHL, HL, and metastasis respectively. This is 30-40% higher than reported in previous studies of Nigerian [11-14] and western series [15, 16]. Lymphoma incidence was reported as 28.8% by Obafunwa et al [11] and 19.1% by Pindig et al [13]. Most of these cases (17.4%) were NHL as similar to our study. Mohan et al [10] in their study; the malignancy rate was 25.8%; and it came after non-specific lymphadenitis and tuberculosis lymphadenitis. Darnal et al [17] reported that malignant cases ranked first in adults with 47% ratio. NHL, male/female

ratio was 1.08, while 1:23 in HL. These rates were lower than the rates of Darnal [17] and Desforges's [18] reported. In this study, non specific reactive LAP constituted 40 (21.6%) cases. Reactive LAP has been documented as a common cause of lymph node enlargement in the tropics and ranged from 15-22% in adults in previous Nigerian and other African series [11-14, 19]. Moore et al [20] reported that, even though the first biopsy results were as reactive hyperplasia in children; after 6 months of follow-up, they reported that 3 of were tuberculosis lymphadenitis and 15 of diagnosed as lymphoma. Therefore, even though peripheral LAP biopsy of patients is benign; the patient should not be removed from the clinical follow-up.

Hussain Gadelkarim Ahmed et al assessed 100 patients biopsy outcomes with fine needle aspiration and benign lesions were reactive lymphoid hyperplasia (n = 64), benign granulomatous disease (n = 26) respectively. 10 of these cases diagnosed with malignancy, 7 (7%) were cases of NHL and the remaining 3 (3%) were HL [21].

Mohan et al evaluated 1724 lymph node biopsy specimens of adult patients and they found that non-specific lymphadenitis were most seen pathology. Tuberculosis lymphadenitis and malignancies were the other common causes [10].

Adesuwa N. Olu-Eddo et al evaluated 427 lymph node biopsy specimens. Cervical LAP was predominate region including 250 (58.5%) cases. Tuberculosis lymphadenitis and metastatic disease were the major causes of lymph node enlargement constituting 114 (26.7%) and 113 (26.5%) cases respectively [22].

In our study, we detected one case of Kikuchi disease. Kikuchi disease also known as Histiocytic necrotizing lymphadenitis (HNL); is a self-limiting, benign disease characterized by fever, cervical LAP and transient leucopenia [23].

The most common malignant disease was NHL in this study (n = 77). Types of NHL, the most common was fastest growing type as diffuse large B-cell lymphoma (54 cases, 70.1%) and the second most common was slow-growing type as follicular lymphoma (10 cases, 12.9%).

NHLs are a heterogeneous group of lymphoproliferative disorders originating from B-, T-, or natural killer (NK) lymphocytes. In the United States, B-cell lymphomas constitute 80% to 85% of all cases, 15-20% of is T-cell lymphomas; but NK lymphomas are very rare [24].

In our study, we observed reactive LAP most frequently in children. This result agrees with Lake AM et al whom evaluated 75 children excisional biopsies; 41 (55%) of were non-diagnostic hyperplasia, 16 (21%) of non-caseating granulomatous lymphadenitis, 5 (7%) of caseating lesion of tuberculosis and 13 (17%) of lymphoreticular neoplasm [25] in children. Mbise RL et al analyzed excisional lymph node biopsy of 257 children and reported tuberculosis lymphadenitis frequency as 67.3% of, non-specific reactive lymphadenitis as 20.6% of, malignancy as 11.3% of and histiocytosis-X as 0.8% and Hodgkin disease was the most common neoplasm (34.5%) [26].

Cervical region is the most common involved regional area when compared to other lymphatic regions, infections are usually exist in the front row and when posterior cervical chain lymph nodes involved, malignancy should be thought. In our study we found that cervical region was the most common area and reactive LAP and HL were the most common causes in this area. Enlarged mediastinal lymph nodes are usually with pathological conditions such as lymphoma, ALL, neurogenic tumors and tuberculosis. In our study, 11 patients (5.9%) had mediastinal LAP and the most common cause was NHL. During the determination of supraclavicular LAP, malignancy should be ruled out at first. Left supraclavicular LAP points usually abdominal malignancies such as neuroblastoma, whereas right supraclavicular LAP intrathoracic diseases. NHL was again the most common causes of supraclavicular LAP of our study. Axillary LAP may be associated with local infections or cat scratch disease or lymphoma. The most common cause of axillary LAP was NHL in this study. Inguinal LAP usually caused by infection. The most common cause of inguinal LAP was again NHL in this study. Popliteal palpable lymph node is always considered to be pathological, but we didn't come across popliteal lymph node [27].

In general practice, less than one percent of patients with LAP suggested having malignant

disease [29]. These LAPs are often due to leukemia in children and Hodgkin disease in adolescents [30]. It has been reported that the prevalence of malignancy is 0.4% in patients under 40 years and increases to 4% over 40 years of age in the primary care setting [3].

The most frequent neoplastic diseases with LAP are leukemia, HL, NHL, solid tumor metastases, neuroblastoma, nasopharynx carcinoma, rhabdomyosarcoma, thyroid cancer, histiocytosis and hemophagocytic syndromes. 70% of acute lymphoblastic leukemia and 30% of acute myeloblastic leukemia patients go along with LAP. Besides neoplastic diseases; Kawasaki disease, Rosai-Dorfman, angiofollicular lymphoid hyperplasia (Castleman's disease), autoimmune diseases, metabolic storage diseases, and some anticonvulsant drug intake can be the causes of regional or generalized LAP [1]. In our study, from lymph node biopsy materials, NHL was the most common malignancy.

HLs are seen rare less than 10 years. The Epstein-Barr virus infection in combination with immune deficiency is a risk factor for HL, especially in less-developed countries and in low socioeconomic conditions. NHL is the fourth common malignancy worldwide in males with a frequency of 6.1% [30].

In conclusion LAP is a common problem and necessitates a careful physical examination and follow-up of the patient. Laboratory and imaging methods should be used in the differential diagnosis when necessary. Excisional biopsy can be applied with minimal morbidity and mortality in a safe manner and is a diagnostic method that is used as the gold standard in the diagnosis of LAP. Although LAP is mostly related with benign lesions, care should be taken in terms of malignancy and malignancy should be eliminated. In this study, malignancies were more common than benign lesions and most common seen in the cervical region.

Disclosure of conflict of interest

None.

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