Association Between Clinical, Laboratory, and Ultrasound Characteristics and Cancer Incidence of Peripheral Lymphadenopathy in Children

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ABSTRACT

Objective: Peripheral lymphadenopathy is very common in childhood. Although they are usually benign, they are often seen in pediatric outpatient clinics because they are a major cause of concern for families. However, physicians cannot afford to overlook the possibility of cancer, which is why many of these patients are referred to pediatric hematology and oncology outpatient clinics. In this study, we calculated the proportion of patients requiring biopsy and the frequency of malignancy, and investigated the characteristics that may be associated with malignancy.

Materials and Methods: The records of children admitted to our pediatric hematology and oncology outpatient clinic between May 2023 and March 2024 were retrospectively reviewed. Demographic characteristics, medical history, lymph node characteristics, laboratory and imaging results were evaluated. Lymphadenopathies larger than 1.5 cm in diameter in the inguinal, axillary, and femoral regions or 3 cm in diameter in the cervical region after 2 weeks of antibiotic treatment, located in the supraclavicular region, and fixed were considered pathologic LAP. B symptoms (presence of fever (at least 38°C), weight loss >10%, night sweats) were questioned.

Results: The study included 430 patients. The median age of the patients was 6 years (1-18 years) and 66% were male. Most patients (96%) had localized lymphadenopathy and the most common site (87%) was the head and neck region.

A history of infection within the past month was present in 72% of patients. Lymphadenopathy was followed for more than one year in 14 patients. The median long axis of the lymph nodes was 1.5 cm (0-5 cm) on physical examination and 2 cm (0.5-5.5 cm) on ultrasonography. Blood count and ultrasound imaging were ordered at an outside center for all patients. All but one patient had normal blood counts at initial presentation; the patient with hyperleukocytosis and generalized LAP was diagnosed with T-cell acute lymphoblastic leukemia (ALL). Another patient was referred for supraclavicular LAP and had a normal blood count obtained three days earlier at an outside center; the control blood count showed hyperleukocytosis and this patient was diagnosed with T-cell ALL. Excisional lymph node biopsy was performed in 9 (2%) of 11 (2.5%) patients who met pathologic lymph node criteria; the diagnoses were reactive hyperplasia (n=4), granulomatous lymphadenitis (n=1), Hodgkin's lymphoma (n=3), and giant cell fibrohistiocytic tumor (benign character) (n=1). Among the patients referred for lymphadenopathy, malignancy was diagnosed in only 5 (1.16%) patients; 4 of these patients had diffuse lymphadenopathy including supraclavicular LAP, lymph nodes were firm and fixed in all patients diagnosed with malignancy; B symptoms were seen in 2 patients.

Conclusion: Although the rate of malignancy is low, it is important to evaluate LAPs in a timely and accurate manner and decide which one should be investigated. However, in most of the patients referred to the pediatric hematology and oncology outpatient clinic for LAP by pediatricians, the development of LAP is due to reactive hyperplasia. In our study, 97.5% of patients did not meet the criteria for pathologic LAP. A detailed history and clinical examination can quickly and accurately differentiate the most common causes of lymphadenopathy in children. In this way, parental anxiety and unnecessary procedures can be avoided.

Keywords: cancer, child, peripheral lymphadenopathy, pathologic lymphadenopathy.

INTRODUCTION

Lymph nodes are oval, encapsulated, secondary lymphoid organs with an average size of 2-10 mm located along the lymphatic system throughout the body (1). Lymphatic tissue increases in volume as the immune response matures due to new and frequent antigen exposure during childhood. Thus, the size and number of lymph nodes, which begin to form in the prenatal period, increase markedly in early childhood. By adolescence, the amount of lymphatic tissue reaches twice that of the adult, and the involution of lymphatic tissue begins from this time (2,3). In addition to the physiologic increase in lymphatic tissue volume during childhood, lymph node size can increase for many reasons, including inflammation, infection, cellular infiltration, and the accumulation of foreign material in histiocytic cells due to their filtering function (1).

The terms lymphadenopathy (LAP) and lymphadenitis are often used interchangeably. The term lymphadenopathy describes a change in the size or structure of the lymph nodes for any reason. Lymphadenitis is lymphadenopathy secondary to infection or inflammation (4,5). Although different sources report different limits, palpation of cervical lymph nodes larger than 3 cm and axillary and inguinal lymph nodes larger than 1.5 cm in children may be considered pathologic. The presence of supraclavicular, epitrochlear, popliteal lymph nodes is always pathological and requires further investigation (6-8). However, the history and the change of the lymph node during follow-up are more valuable in the diagnosis than the size.

Lymph nodes that are soft, independent of the underlying tissue, mobile, well-circumscribed, and do not tend to coalesce are generally benign. If there is adherence to surrounding tissue, there may be an infiltrating malignancy or granulomatous inflammation.

In studies, 52% of children aged 6 months to 2 years and 90% of children aged 4 to 8 years had lymph nodes approximately 1.5 cm in size without any additional complaints or symptoms (9). Although the malignancy rate is low, it is important to

evaluate LAPs in a timely and accurate manner and to decide which ones should be investigated.

Referral of patients with enlarged lymph nodes to pediatric oncology outpatient clinics without investigating and monitoring the etiology may cause panic in patients and families. Therefore, it is important to distinguish clinically between benign and malignant lymphadenopathy. Acute cervical lymphadenitis is the most common manifestation of lymphadenopathy in children and is usually due to viral infections (10-13). Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are the most common viral agents (14), while Group A Streptococcus (GAS) and Staphylococcus aureus are common bacterial agents (13, 15,16). Causes of subacute or chronic localized lymphadenopathy include cat scratch disease, tuberculosis, and infections caused by non-tuberculous atypical mycobacteria (17,18). Children with acute lymphadenopathy due to an apparent viral infection do not require evaluation; the risk of malignancy increases with some features, such as systemic symptoms (fever > 1 week, weight loss > 10%, night sweats), fixed and non-tender lymph nodes, and lymph node size > 3 cm. Lymph node size >3cm in the absence of signs of infection, failure to shrink/enlarge within 2 weeks despite appropriate antibiotherapy, unusual location (supraclavicular, mediastinal), generalized LAP, and unexplained abnormal laboratory findings (bicytopenia/pancytopenia, elevated lactate dehydrogenase levels) (6,11,17,19) require exclusion of malignancy.

Ultrasonography (USG) is not a test that should be performed in every patient. The accuracy of USG in differentiating malignant lymph nodes from reactive lymph nodes is limited (7,20). Ultrasound evaluation of the LAP does not definitively differentiate malignant from benign, but it is useful, especially in cases where organ differentiation is impossible (arteriovenous malformation, hemangioma, cystic hygroma) (21). Although increased size, rounding, loss of cortex-medulla separation and hilar vascularity within the lymph node, and increased vascular resistance index are pathologically defined, none of these findings are 100% sensitive or specific for malignancy and/or specific infections (22).

Ultrasonography is an imaging modality with low sensitivity because it is operator dependent.

The gold standard for the etiologic diagnosis of lymphadenopathy is excisional lymph node biopsy, usually performed after 4-6 weeks for persistent or progressive lymphadenopathy (11,23). The malignancy rate is 13-49% in children undergoing biopsy at pediatric referral centers (17,24,25). Reactive hyperplasia, defined as polyclonal proliferation of one or more cell types, is the most common diagnosis found in lymph node biopsies in children. In our study, we planned to determine the clinical, laboratory, and USG characteristics, biopsy rates, and cancer diagnoses of patients referred to our pediatric oncology outpatient clinics with a diagnosis of LAP. To prevent unnecessary referrals to pediatric oncology outpatient clinics by re-evaluating the malignancy criteria of lymphadenopathy, thus reducing unnecessary workload in these centers in addition to the panic and anxiety of patients referred to oncology centers.

MATERIALS and METHOD

Participants

We performed a cross-sectional study including all children aged 1 month to 18 years who presented to our pediatric hematology and oncology outpatient clinic with enlarged peripheral lymph nodes between May 1, 2023 and April 1, 2024. We included all patients with enlarged peripheral lymph nodes regardless of disease duration.

Epidemiologic and clinical data such as age; sex; location, size, tenderness, mobility, and skin color change of the lymph node; history of infection in the last month; recent close contact with a cat; close contact with a patient with tuberculosis; duration of disease; B symptoms (presence of fever (at least 38 C), weight loss >10%, night sweats); presence of dental caries; antibiotherapy administered (if any); and USG findings (reactive, cortical thickening, conglomeration) were recorded. The proportion of patients requiring biopsy and the

frequency of malignancy were calculated, and features that might be associated with malignancy were examined.

Lymph nodes were considered pathologically enlarged if their long axis (assessed by USG) exceeded 1.5 cm in the inguinal, axillary, and femoral regions and 3 cm in the cervical region. If lymph nodes were palpable in the supraclavicular or epitrochlear region, they were considered pathologic regardless of size.

We excluded children with known diseases that could affect the lymph nodes, such as malignant, autoimmune, or storage diseases, and children with enlarged lymph nodes that were inaccessible by palpation (in the thoracic or abdominal cavity).

Methods

Localized lymphadenopathy was defined as enlarged lymph nodes in a single or 2 contiguous anatomical areas, and generalized lymphadenopathy was defined as the presence of lymphadenopathy in 2 or more non-contiguous anatomical areas (23,26).

Patients underwent complete blood count, lactate dehydrogenase (LDH), and USG at an outside center. Hyperleukocytosis was defined as a total white blood cell count greater than 15,000; a total white blood cell count less than 3,000, a hemoglobin level less than 8 g/dl, and a platelet count less than 50,000 were considered cytopenia. LDH levels were assessed using pediatric reference values (27). LDH levels greater than 400 were considered elevated. Specific immunoglobulin M and G class (IgM and IgG) antibody levels were determined for CMV and EBV. Detection of CMV-specific IgM and EBV viral capsid antigen (VCA) was considered evidence of acute CMV and EBV infection, respectively. (28,29). Laboratory testing for B. hensleae or nontuberculous mycobacteria was rarely performed. The location, number, and characteristics of enlarged lymph nodes on USG and the longitudinal diameter of the largest lymph node were recorded.

In the presence of pathological lymph nodes, excisional lymph node biopsy was performed. Criteria for pathologic lymph nodes were: lymph node long axis >3 cm and no findings compatible with infection; lymph node long axis >3 cm or no

progressive increase or decrease in size despite 2 weeks of appropriate antibiotic therapy; supraclavicular, epitrochlear lymph nodes; lymph nodes that were difficult to palpate and adherent to the skin tended to coalesce; and systemic symptoms such as fever, weight loss, sweating, and hepatosplenomegaly. Bone marrow aspiration and flow cytometry were performed for leukemia in patients with hyperleukocytosis or bicytopenia/pancytopenia detected by complete blood count.

Ethical approval and data availability

This study was approved by the Ethics Committee of Istanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, and was conducted in accordance with the tenets of the Declaration of Helsinki. The legal guardians of all participants signed an informed consent form.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 26.0 software (IBM Inc., Chicago, IL, USA). Descriptive statistical analysis was performed on the data of all enrolled patients. The Kolmogorov-Smirnov test was used to assess the normality of data distributions. The Mann-Whitney U test was used to compare quantitative epidemiological, clinical, laboratory, and US characteristics between the aetiological groups.

RESULTS

A total of 441 children were admitted for peripheral lymphadenopathy during the study period, of whom 430 (97.5%) met the inclusion criteria. Their ages ranged from 1 month to 18 years (median 6 years), and 66% were male (Table1).

A history of infection within the previous month was present in 72% of patients. Dental caries was noted in 11% of the patients. None of the patients had been referred to a dentist prior to oncology referral. Systemic symptoms were present in only 2 (0.46%) patients (Table2).

When the cases were examined according to the lymph node regions involved, 96% were observed in a single region and 4% were systemic. Of the 413 patients with non-generalized lymphadenopathy, 360 (87%), 19 (4.4%), 4 (0.9%), and 7 (1.6%) enlarged lymph nodes in the head-neck, axillary, supraclavicular, and inguinal regions, respectively. Other clinical and laboratory characteristics of the patients are shown in Table 3. Hepatosplenomegaly was noted in two patients, and these patients were later diagnosed with malignancy.

Except for one patient, all patients had normal blood counts at presentation; the patient referred for supraclavicular and occipital lymphadenopathy and hyperleukocytosis was diagnosed with T-cell acute lymphoblastic leukemia (ALL). Another patient was referred for supraclavicular LAP, and the CBC series obtained three days earlier at an outside center was normal; Control blood count revealed hyperleukocytosis and this patient was diagnosed with T-cell ALL. EBV and CMV testing was requested in 111 of the patients; EBV or CMV was seen in 21(4.9%) and 9 (2%) of the patients, respectively. LDH was greater than 450 U/L in 1 of the cases studied. LDH was greater than 450 U/L in 1 of the cases studied (Table2).

The median long axis of the lymph nodes was 1.5 cm (range 0-5 cm) by physical examination and 2 cm (0.5-5.5 cm) by ultrasound. On ultrasound, the long axis of the lymph node was less than 1 cm in 19 case (4%) and between 1-3 cm in 368 case (86%). It was found to be larger than 3 cm in 43 case (10%). The median long axis of the lymph node was determined to be 3 cm (range 2-5cm) in the malignant group and 1.5cm (range 0.5-3.5cm) in the benign group. Information on lymph node size was provided in all USG reports. Findings such as conglomeration, thickening of the cortex, spherical shape, which can be used in differential diagnosis, were present in almost 1/3 of the patients, but the lymph nodes were found to be benign in most of these patients.

Pathologic lymph node criteria were not present in 97.5% of patients. The median follow-up time for lymphadenopathy in enrolled patients was 7 days (range 3 days-5 years) and more than 1 year in 14 patients. Patients with benign features were followed for a median of 5 months (range 1-9 months) and no malignancy was

found in any of them. Fifteen cases that did not reach normal size after one month were followed for a median of 20 days (range 14-6 months), and biopsy was planned in 1 case; malignancy was not considered in the other cases. Excisional lymph node biopsy was performed in 9 (2%) of the 11 (2.5%) patients who met pathologic lymph node criteria; the diagnosed diagnoses were reactive hyperplasia (n=4), granulomatous lymphadenitis (n=1), Hodgkin lymphoma (n=3), and giant cell fibro histiocytic tumor (benign) (n=1). Among patients referred for LAP, only 5 (1.16%) patients were found to have a malignant etiology; diffuse lymphadenopathy, including supraclavicular LAP, was present in 4 of these patients, and the lymph nodes of all patients were found to be positive for malignancy (Table4).

Table1. Characteristics of patients

Quantitative characteristic	Median	Interquartile range
Age (months)	6	1-18
Male	284	66
Duration of lymphadenopathy (days)		
Size of lymph node (clinically-cm)	1.5	0-5
Size of lymph node (USG-cm)	2	0.5-5.5

Table2. Etiology of peripheral lymphadenopathy in children.

Etiology	Frequency (n)	Percentage of Patients (%)
History of upper respiratory tract infection	310	72
Dental caries	47	11
Bacterial lymphadenitis	0	0
Epstein-Barr virus	21	4.9
Cytomegalovirus	9	2
Cat scratch disease	14	3.2
Leukemia	2	0.46
Lymphoma	3	0.7

Table3. Characteristics of the lymph nodes

Characteristics	**n**	**(%)**
Locations		
• Common	17	4
• Regional	413	96
Head-Neck	360	87
Axillary	19	4.4
Inguinal	7	1.6
Supraclavicular	4	0.9
Dimensions (USG), 0.5-5.5 cm (median 2 cm)		
• <1cm	19	4
• 1-2.5 cm	368	86
• > 3 cm	43	10

Table 4. Characteristics of patients with pathological lymphadenopathy (LAP)

Patient	Sex	Age (years)	Duration (days)	Region	Size (cm) USG	Systemic findings	USG findings	Patholog y Result	Flow
1	M	5	60	gn	4	none	conglomerate	**HL**	-
2	F	14	10	gn	3	+	spherical, with thick cortex	**HL**	-
3	F	7	20	gn	3.1	+	spherical, with thick cortex	**HL**	-
4	F	14	35	neck	3.1	none	asymmetric, thick cortical, conglomerate	reactive LAP	-
5	M	5	60	neck	2	none	spherical, with thick cortex	reactive LAP	-
6	M	8	50	neck	1.7	none	conglomerate	reactive LAP	-
7	M	10	30	head	1.8	none	could not be specified	reactive LAP	-
8	F	8	60	inguinal	3.5	none	conglomerate, pathological LAP	GCFT	-
9	M	15	50	inguinal	3.5	none	spherical, with thick cortex	GL	-
10	M	8	15	gn	2.6	none	-	-	**T-ALL**
11	F	8	20	gn	3	+	-	-	**T-ALL**

M:Male; **F**:Female; **gn**:generalized; **HL**:Hodgkin Lymphoma; **GCFT:** giant cell fibrohistiocytic tumor**;**
GL: Granulomatous lymphadenitis **T-ALL**:T cell Acute lymphoblastic leukemia.

DISCUSSION

Lymphadenopathy is a common finding in childhood. In a study of children under the age of five, lymph nodes were found in 44% of healthy children and 64% of children evaluated for disease (30). Various studies in the literature reported that lymphadenopathy was more common in the male gender (31). In a study, the mean age of these patients was reported to be 7.4±4.7 years (31). The findings regarding age and gender in our study are compatible with the literature.

Although features such as location, extent, consistency, palpation findings, and size of lymphadenomegaly are helpful in differentiating benign from malignant disease, there is no sensitive and specific LAP examination finding specific for malignant disease. Lymph nodes less than 2 cm in size usually have benign etiology. Kesik et al. reported that there was no correlation between LAP size and benign and malignant diseases (31). In our study, the long axis of the lymph nodes of the patients diagnosed with cancer was over 3 cm, but LAP over 3 cm alone was not a sufficient finding for the diagnosis of cancer.

The most common cause of benign lymphadenopathy is acute upper respiratory tract infection. Dental caries is another important health problem that is often overlooked. In particular, anaerobic bacteria resulting from dental caries and periodontal disease can enlarge lymph nodes in the cervical region (34). In our study, the majority of patients had evidence of a recent upper respiratory tract infection, and patients with dental caries were referred to pediatric hematology and oncology outpatient clinics without being referred to a dentist. These data suggest that patients were not adequately screened for cancer risk prior to referral to oncology.

It has been reported in the literature that peripheral lymphadenopathy is most commonly located in the head and neck region (32). In our study, LAP was located in the head and neck region in 87% of patients. The malignancy rate of cervical LAPs in childhood has been reported to be 10% (6). Generalized involvement and

supraclavicular location have been shown to be strongly associated with malignancy (34), and in our study, generalized LAP with supraclavicular LAP was found in all patients diagnosed with cancer.

It has been reported in the literature that the presence of hepatomegaly and splenomegaly in patients with lymphadenopathy is more in favor of malignancy (6). In our case series, organomegaly was found in two patients and both of these patients were diagnosed with T-cell ALL.

EBV has been reported to be responsible for 27% of all infectious causes of lymphadenopathy (29). In our study, 111 patients were tested for EBV and 21 of them were found to be positive. It has been shown in the literature that the rate of LDH elevation increases by up to 30% in patients with malignant LAP (6).

The importance of the duration of LAP has been emphasized in the literature, and it has been reported that LAPs that shrink in 4-6 weeks, return to normal dimensions according to age in 8-10 weeks, or do not show progressive growth for more than 12 months are most likely benign. In the malignant group, 60-96% of the symptoms lasted longer than 4 weeks (6). In one study, 98.2% of patients in the acute lymphadenopathy group had benign etiology; patients with malignant etiology mostly presented with chronic lymphadenopathy(6). The results of our study are consistent with the literature.

There is no guideline established by national official organizations for empirical treatment of pediatric neck masses. In one study, antibiotic treatment was not started in 50% of patients with LAP, and spontaneous resolution was reported (35).

Ultrasonography is accepted as the first-line imaging modality in the differential diagnosis and follow-up of LAP because of its availability in almost every healthcare facility, its quick and easy application, the absence of ionizing radiation, and the absence of sedation (36). In terms of lymph node size, USG results were found to be significantly larger than manual measurements. The disappearance,

distortion, or thinning of the echogenic hilus structure in ultrasound evaluation can be detected in malignant LAP. With all these data, USG is not a test that should be performed in every patient because it cannot differentiate between malignant and benign LAPs. It is noteworthy that all our patients had undergone USG of the affected lymph node. In our study, although pathologic findings on ultrasound were present in patients with malignancy, benign LAP was detected in a large number of patients (n=...) in whom pathologic LAP was described on ultrasound.

Most lymph node enlargements are reactive, benign, and usually develop during viral infections. As childhood cancers are also considered in the etiology, these concerns may lead to referral to oncology without adequate evaluation and follow-up. The likelihood of malignancy is low, especially in LAPs that have been present for less than 2-4 weeks or have not increased in size for more than one year. In addition, cancer is less likely to develop in patients with mobile, soft, cervically located LAPs that are less than 3 cm in size and without accompanying serious systemic signs and symptoms (11).
Although malignancy is included in the etiology, studies have reported a 1% probability of malignant findings in LAPs evaluated in primary care settings. This rate is 13-27% in pediatric oncology reference centers (30,37). In one study, contrary to expectations, only one of 98 patients referred to a pediatric oncology center was diagnosed with Hodgkin's lymphoma (7).

Excisional biopsy (complete removal of the lymph node) is the most appropriate method for definitive histopathologic diagnosis in pediatric lymph node pathology (38). In cases where the diagnosis cannot be made based on clinical findings and laboratory tests, lymphadenopathy does not resolve or progresses over 4-6 weeks, and malignancy is suspected, the patient should be referred for tissue sampling (11). In studies, the cancer rate has been reported in a wide range of 1-38% (6, 11, 17, 31, 37) In one study reporting the results of patients who underwent biopsy only, the cancer rate was reported to be up to 40.8% (17).

CONCLUSION

As a result, only 1.1% of our patients were diagnosed with cancer. This rate is quite low for an oncology center. It was observed that patients who could be followed up in primary health care centers were unnecessarily referred to pediatric hematology and oncology outpatient clinics. Better clinical evaluation and follow-up of patients for lymph node location, enlargement, structural changes, and additional systemic signs and symptoms would reduce unnecessary referrals. Most children with acute peripheral lymphadenopathy can be diagnosed quickly and accurately with a comprehensive history and clinical examination, supplemented by a few basic laboratory tests.

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