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Pediatric Patient with Lymphadenopathy: Benign or Malignant?

Lenfadenopatili Çocuk Hasta: Benign mi Malign mi?

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Abstract

Objective: Lymphadenopathy (LAP) is a condition that is common especially in childhood, its etiology is mostly benign, but malignancy must be excluded by careful evaluation and follow-up. In this study, it was aimed to examine the etiological, clinical and laboratory features of cases whose peripheral LAP etiology was investigated.

Material and Methods: Patients referred to Erzurum City Hospital Pediatric Hematology/Oncology and Pediatric Infectious Diseases Polyclinics between October 2018 and June 2020 due to LAP were evaluated retrospectively.

Results: One hundred and seventy patients were evaluated. Eleven of them were non-LAP lesions in the head and neck region, and 159 were patients whose LAP etiology was investigated. While 152 of the patients had benign etiology, seven were diagnosed as malignant/premalignant. Most patients with benign etiology (58.5%, 93 patients) had non-specific LAP, and no causative agent could be isolated. In benign lymph nodes where the causative agent was detected, the most common diagnosis was Ebstein Bar virus in 15 (9.4%), tularemia in 12 (7.5%) and tuberculosis in 8 (5%) cases. Thirty-three patients (20%) underwent biopsy. Five of these patients were diagnosed with Lymphoma and one with autoimmune lymphoproliferative syndrome. Two patients were diagnosed with acute lymphocytic leukemia by bone marrow aspiration without LAP biopsy. In the evaluation of LAP in patients, statistically significant differences were found in the malignant/premalignant group compared to the benign etiology group in terms of pathological features such as generalization, duration of more than two weeks, size >3 cm,

Öz

Giriş: Lenfadenopati (LAP) özellikle çocukluk çağında yaygın görülen, etiyolojisi çoğunlukla iyi huylu olan, ancak mutlaka dikkatli bir değerlendirme ve takip yapılarak malignitenin dışlanması gereken bir durumdur. Bu çalışmada; periferik LAP etyolojisi araştırılan olgularının etiyolojik, klinik ve laboratuvar özelliklerinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Erzurum Şehir Eğitim ve Araştırma Hastanesi Çocuk Hematoloji/Onkoloji ve Çocuk Enfeksiyon Hastalıkları polikliniklerine Ekim 2018 ile Haziran 2020 tarihleri arasında LAP nedeni ile refere edilen olgular retrospektif olarak değerlendirildi.

Bulgular: Bu çalışmada, 170 hasta değerlendirildi. Bunlardan 11 tanesi baş boyun bölgesindeki LAP dışı lezyonlardı, 159 tanesi ise LAP etiyolojisi araştırılan hastalar idi. Hastaların 152'si benign etiyolojiyesine sahipken, yedisi malign/premalign tanısı aldı. Benign etiyoloji saptanan hastaların çoğunluğu (93 hasta, %58.5) non-spesifik LAP idi, herhangi bir etken izole edilemedi. Benign lenf nodu olup etken saptananlarda en sık 15 (%9.4) Ebstein Bar virüsü, 12 (%7.5) tularemi ve 8 (%5) olguda tüberküloz tanısı konuldu. Otuz üç hastaya (%20) biyopsi yapıldı. Bu hastaların beşi lenfoma, biri ise otoimmün lenfoproliferatif sendrom tanısı aldı. İki hastaya ise LAP biyopsisi yapılmadan kemik iliği aspirasyonu yapılarak akut lenfositik lösemi tanısı konuldu. Hastaların LAP değerlendirilmesinde; jeneralize olması, iki haftadan uzun sürmesi, boyutunun >3 cm olması, hepatosplenomegalinin eşlik etmesi, B semptomlarının eşlik etmesi, palpasyonla sert/fikse veya lastik kıvamında olması gibi patolojik özelliklerin eşlik etmesi malign/premalign grupta benign etiyoloji saptanan gruba göre istatistiksel anlamlı fark tespit edildi.

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accompanying hepatosplenomegaly, accompanying B symptoms, hard/fixed or rubbery consistency on palpation.

Conclusion: Lymphadenopathy is a common finding in children during physical examination. Although it is usually reactive, it may be associated with malignant diseases, causing concern for both parents and pediatricians. In a child with LAP, if there is generalized LAP, if there is a history of LAP lasting longer than two weeks, if the LAP size is >3 cm, if it is accompanied by hepatosplenomegaly, if there are B symptoms, and if it is hard/fixed or rubbery on palpation, malignancy should be investigated in these patients.

Keywords: Child, benign, lymphadenopathy, malignant

Sonuç: Lenfadenopati, çocuklarda fizik muayenenin sık görülen bir bulgusudur. Genellikle reaktif olmasına rağmen, altta yatan malignitenin bir işareti olabilir ve hem ebeveynler hem de çocuk doktorları için endişeye neden olur. Lenfadenopati saptanan bir çocukta; jeneralize LAP varsa, iki haftadan uzun süren LAP öyküsü varsa, LAP boyutu >3 cm, hepatosplenomegali eşlik ediyorsa, B semptomları eşlik ediyorsa, palpasyonla sert/fikse veya lastik kıvamında ise bu hastalarda mutlaka malignite araştırılmalıdır.

Anahtar Kelimeler: Çocuk, benign, lenfadenopati, malign

Introduction

Lymphadenopathy (LAP) is a condition commonly seen in childhood, with a mostly benign etiology, but requiring careful evaluation and follow-up to rule out malignancy (1,2). In differential diagnosis, characteristic features such as the location, size, firmness or softness of the lymph node, its adherence to or mobility relative to surrounding tissues, the duration of its presence, and its response to antibiotic therapy are important (3). In the pediatric age group, lymph nodes measuring up to 0.5 cm in the axilla, 1 cm in the cervical region, and 1.5 cm in the inguinal region are generally not considered pathological. Supraclavicular LAP of any size is considered pathological. In children, peripheral LAPs are most commonly found in the head and neck region and are often secondary to infections (4). The cause of LAP may be a simple infection or a sign of an underlying serious disease. It often develops in childhood secondary to viral and bacterial infections, medications, post-vaccination reactions, lipid storage diseases, granulomatous diseases, endocrine and autoimmune diseases, or malignant diseases. In this study, the etiological, clinical, and laboratory characteristics of cases with peripheral LAP investigated in the pediatric hematology and oncology clinic and the pediatric infectious diseases clinic were examined.

Materials and Methods

Cases referred to the pediatric hematology/oncology and pediatric infectious diseases outpatient clinics of Erzurum City Hospital between October 2018 and June 2020 due to LAP were retrospectively reviewed using hospital electronic medical records. Patients were classified into age groups: 0-23 months, 24 months-<12 years, and 12-19 years. Patients with LAP measuring >1 cm in the cervical, submandibular, and submental regions, >1.5 cm in the intra-abdominal and inguinal areas, and >0.5 cm in the axillary region were included in the study. The presence of a single or multiple adjacent lymph node involvement was classified as localized LAP, while involvement of two or more non-adjacent lymph node regions was classified as generalized LAP (5). All patients with LAP detected on physical examination underwent ultrasound and/or computed tomography and/or magnetic resonance imaging studies. The age, gender, lymph node size, location, distribution (localized-generalized), duration of lymph node involvement, presence of B symptoms such as fever, night sweats, and weight loss during physical examination, and the presence of hepatosplenomegaly were recorded for all cases. Patients with lymph node involvement were grouped according to lymph node size as <1 cm, 1-3 cm, and >3 cm (5). Laboratory tests included complete blood count (hemoglobin, leukocyte, neutrophil, lymphocyte, platelet counts), increased erythrocyte sedimentation rate (>20 mm/hour), presence of elevated C-reactive protein, lactate dehydrogenase, and uric acid levels, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and toxoplasma serology, Brucella serology, tularemia serology, and results of acid-fast microorganism testing from fasting stomach fluid were recorded. Lymph node biopsy was indicated if any of the following criteria were present: supraclavicular LAP, immobile/fixed and/or hard/rubbery consistency of LAP, progressive increase in LAP size despite antibiotic treatment, presence of structural symptoms such as unexplained fever, night sweats, or weight loss of more than 10%, presence of organomegaly, presence of cytopenia (5). Laboratory data from patients were evaluated for anemia, leukopenia, leukocytosis, thrombocytopenia, and thrombocytosis according to age groups (6). Chest X-rays were performed in all patients to investigate the presence of mediastinal and hilar LAP. A Purified Protein Derivative (PPD) test was performed in cases of LAP that did not improve with antibiotic therapy. Bone marrow examination was performed in patients with bisitopenia/pansitopenia and/or blast-like cells in peripheral smears. Histopathological examination results of lymph node biopsies performed for diagnostic purposes were recorded.

Ethics Approval

This study was approved by the Erzurum City Hospital non-Interventional Research Ethics Committee (ethical approval no: 2020/04-54) and conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

Data were recorded in SPSS 17.0 and statistical analyses were performed. In descriptive statistics, categorical data were presented as percentage frequencies, and continuous data were presented as mean and standard deviation (mean ±

SD) when they followed a normal distribution, and as median and interquartiles [median (interquartile range 25–75)] when they did not follow a normal distribution. The normality of continuous data was assessed using the Kolmogorov-Smirnov test. For continuous data following a normal distribution, the Student's t-test was used to compare two groups. For two groups not following a normal distribution, the Mann-Whitney U test was used. The chi-square test was used to compare the distributions of categorical data. A p-value less than 0.05 was considered statistically significant.

Results

A total of 170 patients referred to the paediatric haematology/oncology and paediatric infectious diseases outpatient clinics between October 2018 and June 2020 due to LAP were evaluated. Of these, 11 had non-LAP lesions in the head and neck region, while 159 were patients with LAP etiology under investigation (Table 1). The ages of patients with non-LAP lesions in the head and neck region ranged from 2 months to 9 years.

Of the 159 patients with LAP, 115 (72.3%) were male and 44 (27.7%) were female. Mean age of all patients was 7.5 ± 4.6 years (range= 4 months to 18 years). Benign LAP etiology was identified in 152 (95.6%) of all patients, and malignant LAP etiology was identified in 7 (4.4%).

When the causes of LAP were examined, the most common etiology was non-specific in 58.5% (n= 93) of patients, and their LAP resolved with nonspecific antibiotic therapy during follow-up. Among the patients with benign lymph nodes and identified etiological agents, the most common etiologies were EBV (15, 9.4%), tularemia (12, 7.5%), and tuberculosis (8, 5%). The 15 cases with infectious mononucleosis presented with cervical lymphadenopathy and received a serological diagnosis (Table 2). Our hospital is a major center receiving patients from rural areas and endemic regions for tularemia. Tularemia was referred from cases with a history of drinking spring water, contact with wild animals, necrotic LAP, and lack of response to antibiotic treatment. Twelve cases diagnosed with tularemia presented with cervical LAP, and necrosis was detected on ultrasound in four patients, while cystic areas were identified in 1 patient. Aspiration and biopsy were performed from the lymph node for both diagnostic and therapeutic purposes in three patients.

Table 1. Head and neck masses mimicking lymphadenopathy

Diagnosis	Number
Hemangioma	4
Torticollis	2
Lymphangioma	2
Thyroglossal duct cyst	2
Branchial cleft cyst	1

Tuberculosis diagnosis in children was established based on tuberculosis exposure history, PPD positivity, interferon gamma release test positivity, pathology results, ARB, and sputum culture evaluation. Four of the eight patients diagnosed with tuberculosis presented with cough and were referred due to hilar calcification on chest tomography. One case presented with cervical necrotic LAP, and two cases presented with axillary necrotic LAP; their biopsies were caseous granulomatous, and they were diagnosed with tuberculosis. One patient presented with fever and abdominal LAP; pleural fluid was ARB positive, sputum ARB and culture were positive, and the patient was diagnosed with miliary tuberculosis.

Biopsy was performed in 20% of the patients (n= 33) due to the presence of immobile/fixed and/or hard/rubbery LAP, supraclavicular localization of LAP, progressive increase in LAP size despite antibiotic treatment, and the presence of structural symptoms such as fever of unknown origin, night sweats, or weight loss. Five of the patients who underwent biopsy were under two years of age. In the malignant patient group, five

Table 2. Diagnostic distribution of the etiologies of lymphadenopathy in patients

Diagnosis		
Malignant	**n**	**%**
T-ALL	2	1.3
Hodgkin's Lymphoma	4	2.5
Burkitt Lymphoma	1	0.6
Total malignant	7	4.4
Benign		
Non-spesific	93	58.5
CMV	5	3.1
EBV	15	9.4
Tularemia	12	7.5
Tuberculosis	8	5
BCG lymphadenitis	4	2.5
Abscess	6	3.8
Kimura disease	1	0.6
Activation of germinal centers	1	0.6
ALPS	1	0.6
Necrotizing granulomatous lymphadenitis	1	0.6
Lymphadenitis secondary to fungal abscess	1	0.6
HIV	1	0.6
Lymphadenitis secondary to panniculitis	1	0.6
Brucella	1	0.6
Lymphadenitis secondary to sialadenitis	1	0.6
Total benign	152	95.6

CMV: Cytomegalovirus, EBV: Epstein-Barr virus, BCG: Bacillus Calmette-Guérin, ALPS: Autoimmune lymphoproliferative syndrome, HIV: Human immunodeficiency virus.

Table 3. Histopathological diagnoses of the patients undergoing biopsy according to age groups

Biopsy diagnoses	0-2 years	2-12 years	13-18 years	Total
Benign				
Non-specific	0	3	0	3
Abscess	2	3	0	5
Necrotizing granulomatous LAP	0	0	1	1
Panniculitis and reactive LAP nearby	0	1	0	1
Tuberculous lymphadenitis	0	1	6	7
BCG lymphadenitis	3	0	0	3
Sialedenitis and reactive LAP nearby	0	0	1	1
Kimura disease	0	0	1	1
Tularemia	0	0	3	3
Faomicaps and reactive LAP nearby	0	0	1	1
ALPS	0	0	1	1
Progressive transformation of germinal centers	0	1	0	1
Malignant				
Burkitt lymphoma	0	1	0	1
Hodgkin's lymphoma	0	3	1	4

LAP: Lymphomapathy, BCG: Bacillus Calmette-Guérin, ALPS: Autoimmune lymphoproliferative syndrome.

children were diagnosed with lymphoma, while two patients were evaluated with bone marrow aspiration and biopsy for T-ALL diagnosis. One patient with pancytopenia, chronic LAP, and hepatosplenomegaly underwent LAP biopsy and was diagnosed with autoimmune lymphoproliferative syndrome (ALPS); no blast cells were detected in the patient's bone marrow aspiration. The histopathological diagnosis distribution according to age groups is shown in Table 3.

When comparing patients with benign etiology and those with malignant etiology, no statistically significant differences were found in terms of gender, age groups, or whether LAP was unilateral or bilateral. Patients were evaluated based on the presence of generalized LAP, a history of LAP lasting more than two weeks, a size >3 cm, the presence of hepatosplenomegaly, the presence of B symptoms, and pathological features such as LAP being hard/fixed or rubbery on palpation. Statistically significant differences were found in the group with malignant etiology compared to the group with benign etiology ($p< 0.05$) (Table 4).

When comparing patients with benign etiology to those with malignant etiology, statistically significant differences were found in the presence of neutropenia, anemia, and thrombocytopenia in the group with malignant etiology ($p< 0.05$) (Table 5).

Table 4. Clinical features in benign and malignant lymphadenopathy groups

Clinical features		Benign		Malignant		p
		n	%	n	%	
Sex	Female	41	25.8	3	1.9	0.397
	Male	111	69.8	4	2.5	
Age groups (year)	0-2 year	12	7.5	0	0	0.563
	2-12 year	103	64.8	6	3.8	
	12-18 ear	37	23.3	1	0.6	
	Total	152	95.6	7	4.4	
Localization upon presentation	Neck-head	136	86.1	3	1.9	
	Axilarry	8	5.1	0	0	
	Inguinal	5	3.2	0	0	
	Supraclavicular	0	0	4	2.5	
	Abdominal	2	1.3	0	0	

Table 4. Clinical features in benign and malignant lymphadenopathy groups (continue)

Clinical features		Benign		Malignant		p
		n	%	n	%	
Distribution	Generalized	54	34.0	7	4.4	0.001
	Localized	98	61.6	0	0	
Laterality	Unilateral	26	16.4	0	0	0.6
	Bilateral	126	79.2	7	4.4	
Duration	<2 weeks	102	64.2	0	0	0.001
	2-4 weeks	27	17	3	1.9	
	>4 weeks	23	14.5	4	2.5	
Size	<1cm	5	3.1	0	0	<0.001
	1-3 cm	103	64.8	0	0	
	>3cm	44	27.7	7	4.4	
Hepatosplenomegaly	Present	19	11.9	7	4.4	<0.001
	Absent	133	83.6	0	0	
B symptoms	Present	7	4.4	7	4.4	<0.001
	Absent	145	91.2	0	0	
Hard/fixed or rubbery consistency and/or malignant features (pathological features) on ultrasound	Present	31	19.5	7	4.4	<0.001
	Absent	121	76.1	0	0	
Biopsy	Performed	28	17.6	5	3.1	0.005
	Not performed	124	78	2	1.3	

Table 5. Laboratory characteristics in lymphadenopathy groups with benign and malignant etiology

Characteristic		Benign		Malignant		p
		n	%	n	%	
Sex	Female	41	27	3	42.8	0.397
	Male	111	73	4	57.2	
Age groups	0-2 years	12	7.9	0		0.563
	2-12 years	103	67.8	6	85.7	
	12-18 years	37	24.3	1	14.3	
Leukocytosis	Present	29	18.2	2	1.3	0.623
	Absent	123	77.4	5	3.1	
Leucopenia	Present	1	6.6	0	0	1.00
	Absent	151	95	7	4.4	
Neutropenia	Present	5	3.1	2	1.3	0.032
	Absent	147	92.5	5	3.1	
Lymphopenia	Present	7	4.4	1	0.6	0.308
	Absent	145	91.2	6	3.8	
Anemia	Present	9	5.7	4	2.5	0.001
	Absent	143	89.9	3	1.9	
Thrombocytosis	Present	15	9.4	0	0	0.99
	Absent	137	86.2	7	4.4	

Table 5. Laboratory characteristics in lymphadenopathy groups with benign and malignant etiology (continue)

Characteristic		Benign		Malignant		p
		n	%	n	%	
Thrombocytopenia	Present	2	1.3	2	1.3	0.01
	Absent	150	94.3	5	3.1	
C-reactive protein	Elevated	60	37.7	4	2.5	0.441
	Within normal range	92	57.9	3	1.9	
Sedimentation	Elevated	45	28.3	4	2.5	0.203
	Within normal range	107	67.3	3	1.9	

Discussion

Palpable LAP is a common finding in children because their immune systems are constantly stimulated by environmental antigens and microorganisms. LAP was detected in 44% of healthy children under the age of 5 during systemic examination, and in 64% of children evaluated for any reason (7). In some cases, conditions mimicking peripheral LAP may occur. Yaris and colleagues reported that among 126 patients referred to their clinic with a preliminary diagnosis of peripheral LAP over a three-year period, 28 cases were found to have conditions mimicking LAP, such as lymphangioma, branchial cyst, thyroglossal cyst, and hemangioma (8). In our study, we identified hemangioma, hematoma secondary to torticollis, lymphangioma, thyroglossal duct cyst, and branchial cleft cyst in 11 of 170 patients.

Peripheral LAPs in children are usually self-limiting and benign. Although the etiology of peripheral LAP can be largely determined after a thorough history and physical examination, LAPs are also a cause of concern for parents, general practitioners, and pediatric specialists because they may be a result of malignant diseases (7,9). In the literature, it is reported that biopsy is required in only 3-15% of patients with LAP (8,10,11). Among the children presenting with peripheral LAP who underwent biopsy, malignant disease was diagnosed in only 1.1-7.7% of cases (4,9,12-15). In our study, biopsy was performed in 33 of 159 patients (20.7%), malignancy/premalignancy was diagnosed in five patients, and bone marrow aspiration was performed in two patients with LAP, resulting in a diagnosis of leukemia. In our study, malignant disease was found in 4.4% of the cases, consistent with the literature. It was found that all patients diagnosed with lymphoma and T-ALL had LAPs for at least two weeks and an increase in size despite antibiotic treatment.

Among the infectious causes of lymphadenitis, the most common include pyogenic bacterial infections, polymicrobial or monomicrobial anaerobic infections associated with dental or periodontal diseases, zoonotic agents such as *Bartonella henselae*, parasitic infections such as toxoplasma, as well as viral infections like EBV and CMV (16).

In our study, similar to the literature, a benign etiology was identified in 95.6% of cases (4,5,14). In 93 of the 152 patients with benign etiology (58.2%), no etiological cause was identified, and the condition improved within 26 weeks with 10-14 days of non-specific antibiotic treatment. Non-specific acute-onset LAP is typically caused by *Staphylococcus aureus* and Group A beta-hemolytic *Streptococcus*, and therefore responds to antibiotic treatment (17,18). Among benign etiological causes, the most commonly identified was EBV in 15 patients (9.4%), tularemia in 12 patients (7.5%), tuberculosis in 8 patients (5%), reactive hyperplasia secondary to abscess in 6 patients (3.8%), and CMV in 5 patients (3.1%). In the literature, the prevalence of EBV in children presenting with peripheral LAP ranges from 4% to 15%, tuberculosis from 0.8% to 6.2%, and CMV from 1% to 2.1, and tularemia 3-6% , which are consistent with the frequencies reported in our study (2,5,8,10,15,19-21).

Bacillus Calmette-Guérin (BCG) lymphadenitis is one of the most common complications of BCG vaccination, and its incidence varies worldwide depending on factors such as host characteristics, vaccine strain type, and vaccination technique. In our study, four cases presented with BCG lymphadenitis (22).

Kimura disease, which is a benign disease but causes chronic LAP and has been reported to increase the risk of malignancy (lymphoma) in follow-up, progressive transformation of germinal centers, and ALPS were detected in one patient (23). No malignancy was observed in the one-year follow-up of the patients.

The limitations of our study are that it was conducted at a single center and included a small number of patients.

Conclusion

LAP is a common finding on physical examination in children. Although it is usually reactive, it can be associated with malignant diseases, causing concern for both parents and pediatricians. The aim of this study was to emphasize that the most common causes of LAP are benign, to highlight which diseases should be considered in the differential diagnosis of LAP, and to determine when enlarged lymph nodes pose a risk for malignancy. If a child has a history of LAP lasting lon-

ger than two weeks, is generalized on physical examination, is >3 cm in size, is accompanied by hepatosplenomegaly, is accompanied by B symptoms, or is hard/fixed or rubbery on palpation, malignancy should always be investigated in these patients. If none of these characteristics are present, LAP has acute onset, and is accompanied by signs of infection, non-specific antibiotic treatment should be started and the patient should be closely monitored.

Ethics Committe Approval: This study has been approved by the Ethics Committee of Erzurum Regional Training and Research Hospital, Health Sciences University (Decision no: 2020/04-54, Date: 17.02.2020).

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