ORIGINAL ARTICLE

A retrospective evaluation of lymphadenopathy in children in a single center's experience

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Abstract

Objective: To determine the causes of lymphadenopathies in children living in our region, and detect the frequency of malignant disease.

Methods: Our study evaluated demographic characteristics, lymph node involvement sites, tests, and viral serologies performed to search for the presence of infection, and ultrasonographic, and histologic findings of 1700 children who were referred to the outpatient clinics of the Paediatric Diseases and Paediatric Surgery between January 2012, and January 2015.

Results: Our study population consisted of 1003 (59 %) boys, and 697 (41 %) girls aged less than 18 years. Definitive diagnosis of 43 (8.68 %) patients with unilateral, and 452 (91.9 %) cases with bilateral lymphadenopathies was established. These cases had benign (n=455) , and malignant (n=40) etiologies. Two hundred and four (12 %) of them underwent biopsies. On histological evaluation TB (n=6), Kawasaki syndrome (n=3), catscratch syndrome (n=4), toxoplasmosis (n=17), sarcoidosis (n=22), non-Hodgkin lymphoma (n=23), Hodgkin lymphoma (n=15), and Langerhans cell histiocytosis (n=2) were detected. Histological examination of the biopsy specimens of 110 cases revealed nonspecific histological changes.

A total of 1205 (70.88%) patients without definitive diagnosis had undergone ultrasonographic assessments, and clinical evaluations performed before or within 4 weeks after antibiotic therapy and revealed regression of the lesions.

Conclusion: The most widely encountered cause of lymphadenopathy is infection. Most of them are secondary to nonspecific viral, and bacterial infections. Most frequently diagnosed viral infections are caused by cytomegalovirus (CMV), and Ebstein-Barr virus (EBV).

The most important issue in patients presenting with complaints of lymphadenopathy is the detection of the underlying malignant disease (if any), with the most frequent being non-Hodgkin lymphoma. Excisional biopsy is still the gold standard diagnostic method. Although our hospital was not an oncology center, our malignancy rate was higher than seen in some series. This might be possibly due to referral of monitored patients to our regional hospital for biopsy.

Keywords: Lymphadenopathy, Etiology, Malignant disease. (JPMA 66: 654; 2016)

Introduction

Lymphadenopathy is defined as an abnormality in size, number, and consistency of one or more than one lymph nodes.[1] Lymphadenopathies involving a single or two neighbouring lymph nodes are termed local lymphadenopathies, when more than two lymph nodes are involved then this condition is called generalized lymphadenopathy which is categorized in two forms. Generalized form is the most prevalent clinical condition.[2] Lymphadenopathy can be caused by various clinical conditions including acute bacterial lymphadenitis, reactive hyperplasia, viral, and bacterial infections, autoimmune, and malignant diseases.[2,3] In the paediatric age group lymph nodes measuring up to 0.5 cm in the axillary, 1 cm in the cervical, and 1.5 cm in the inguinal regions are not generally considered as pathological lesions.[4]

The aim of this study was to determine the etiology of paediatric lympahadenopathy, and frequency of malignant diseases.

Patients and Methods

In this retrospective and cross-sectional study, files of a total of 1700 patients younger than 18 years of age with cervical, axillary, inguinal, mesenteric, and supraclavicular lymphadenopathies who were referred to Clinics of Paediatric Diseases, and Paediatric Surgery of Gaziantep Children's Hospital between January 2012, and January 2015 were retrospectively evaluated.

Information of the patients was accessed through electronic medical recording system, and patients'files.

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Age, gender, white blood cell counts, sedimentation rates, duration of lymphadenopathy, size, site, laterality and consistency of lymph nodes were investigated, and recorded. Since most of the patients did not have contact information their approvals could not be obtained. The patients were assigned consecutive numbers, and their names were kept confidential. Being a retrospective study, ethics committee's approval was not required.

According to the duration of lymphadenopathy, the patients were categorized in 2 groups as having acute (lymphadenopathy regressed within less than 4 weeks), or persistent or chronic (lymphadenopathies persisted for more than 4 weeks) disease.

All patients (n=1700) underwent whole blood cell counts, and erythrocyte sedimentation rate. Six hundred and forty-six cases with chronic lymphadenopathy and some cases with acute lymphadenopathy were evaluated using tuberculin skin test, and serologic tests for cytomegalovirus (CMV), and Ebstein-Barr virus (EBV),rubella and toxoplasma and ultrasonographic examinations which were decided to be appropriate based on the medical history, and clinical symptoms of these patients.

Consistency, and mobility of lymph nodes were evaluated retrospectively. Based on their US findings, lymph nodes measuring up to 0.5 cm in the axillary, 1 cm in the cervical, and 1.5 cm in the inguinal regions, and supraclavicular lymph nodes of any size were evaluated as lymphadenopathies. The hardest, and sonographically detected largest persistent lymph nodes in patients with solid, and rapidly enlarging lymph nodes fixed to the surrounding tissues, and persisting for longer than 4 weeks despite antibiotic therapy or in cases with supraclavicular lymph nodes associated with hepatosplenomegaly or those with mediastinal, and hilar lymphadenopathies were surgically excised for histopathological assessment. Excised lymph nodes were sent to the department of pathology for histological examination.

Results

Among 1700 children, 1003 (59%) patients were male, and 697 (41%) of them were female. In 29.11 % (n=495) of them a specific etiology was detected. The most frequently encountered diagnostic factors among patients with benign lymphadenopathy were. EBV, and CMV infections, and acute lymphadenitis. In 250 (14.7%) patients unilateral, and in 1450 (85.29%) patients bilateral lymphadenopathies were detected. Specific etiology was detected in patients with unilateral (n=43;8.68%), and bilateral (n=452; 91.31%) lymphadenopathies Lymphadenitis, and abscesses were mostly unilateral mobile mass lesions with a soft consistency, and those transformed into abscesses were palpated as fluctuating masses. In systemic viral infections caused by EBV, and CMV, the lesions were detected as soft mobile masses where cortical, and medullary contours of the lymph nodes could be discernible on ultrasonograms. However, malignancies generally manifested as bilateral, solid, immobile lesions with ultrasonographically undetectable cortical, and medullary contours. Kawasaki disease was diagnosed based on the detection of 4 of 5 criteria in addition to fever lasting for 5 days. Diagnosis of tuberculosis was based on histopathological evidence. These patients were then referred to the department of infectious diseases where other forms of tuberculosis

Table-1: Distribution of lymphadenopathies based on their duration, and some laboratory parameters.

	Patients, n	%
Duration <4 weeks	1054	62
Duration ≥ 4 weeks	646	38
Leucocytosis ($>10x10^3$)	493	29
Sedimentation rate <20mm/h	323	19
>20mm/h	1377	81
Toxoplasma antibody (IgM+)	24	1.41
Cytomegalovirus antibody (IgM+)	89	5.23
Ebstein-Barr virus antibody (IgM +)	162	9.52
Rubella antibody (IgM+)	46	2.70

Table-2: Distribution of patients with definitive diagnosis.

Diagnoses	Patients (n)	%
Unilateral lymphadenopathy	43	8.68%
Lymphadenitis (abscess)	24	4,85
Tuberculosis	6	1.21
Kawasaki	9	1.82
Catscratch disease	4	0.80
Bilateral lymphadenopathy	452	91.31%
EBV	162	32.73
CMV	89	17.98
Beta- haemolytic streptococci	57	11.51
Rubella	46	9.30
Toxoplasmosis	24	4.85
SLE	22	4.45
Sarcoidosis	10	2.02
Dermatomyositis	2	0.40
Langerhans cell histiocytosis	2	0.40
Non- Hodgkin lymphoma	23	4.65
Hodgkin lymphoma	15	3.03
Total	495	100

EBV: Epstein Barr Virus. CMV: Cytomegalovirus. SLE: Systemic Lupus Erythematosus.

Table-3: Distribution of patients with Hodgkin, and non-Hodgkin disease.

Age	M	F	Hodgkin	non-Hodgkin	Total n
<6	10	3	4	9	13
7-13	8	7	7	8	15
>13	6	4	4	6	10
Total n	24	14	15	23	38

were investigated, and their treatments were performed. Duration of lymphadenopathies , and some relevant laboratory parameters are summarized in Table-1.

Nonspecific 1205 (70.88%) and 495 (29.11%) specific lymphadenopathies were detected. Benign (n=455), and malignant (n=40) etiologies were detected among patients with specific lymphadenopathies. Causes of lymphadenopathy are summarized in Table-2. Histopathological analyses were performed on patients whose disease persisted longer than four weeks which could not be diagnosed using biochemical tests, viral, and microbiological tests, and diagnosed cases whose disease progressed with atypical manifestations suggesting suspected malignancies. As a result of all these tests, definite diagnosis was established for 495 cases. Definitive diagnosis of 110 cases with chronic lymphadenopathy could not be made, and affected lymph nodes of these cases were soft, and mobile, and during follow-up their sizes diminished which obviated the need for urgent indication for biopsy. Since these lymph nodes returned to their normal size within a period of six weeks, they were considered as sequelae of a nonspecific infection. In other words they were included in the undiagnosed patient group of 1205 (1700-495=205) cases. Besides, 11 EBV, and 8 CMV patients in a group of 110 patients with solid, bulky, and fixed chronic lymphadenopathies which demonstrated nonspecific histopathologic changes, underwent biopsies whose reports indicated nonspecific histological changes.

In our study most of the lymphadenopathies (92%) were localized in the cervical region. As etiological factors of these lympadenopathies, upper respiratory tract, EBV, and CMV infections, tuberculosis (TB), lymphoma, Kawasaki disease, and rubella were detected. In 1% of the patients supracalvicular lymphadenopathy caused by TB, Hodgkin, and non-Hodgkin lymphomas was observed. Axillary lymphadenopathies due to catscratch disease, lymphoma, TB, toxoplasmosis, and EBV infection were encountered in 2% of our patients Inguinal lymphadenopathy with an incidence of 3% stemmed from local infections, diaper dermatitis, insect bites, Hodgkin, and non-Hodgkin lymphomas. Mesenteric lymphadenopathies were seen in 4% of the patients with especially gastroenteritis, invagination, appendicitis, lymphoma, typhoid fever, and toxoplasmosis.

Excisional biopsy was performed on 204 (12%) patients. These biopsied patients had malignant (n=40; 19.60%), and benign (n=164; 80.39%) conditions. Malignant diseases consisted of lymphomas (n=38), and Langerhans cell histiocytosis (n=2). Distribution of the patients with lymphoma is shown in Table-3.

In our study, etiological factors for generalized lymphadenopathy included CMV, and EBV infections, Langerhans cell histiocytosis, tuberculosis, rubella, toxoplasmosis, typhoid fever, systemic lupus erythematosus (SLE), dermatomyositis, Hodgkin disease , and non-Hodgkin lymphoma.

Discussion

In the presented study, a definite diagnoses was made on 495 (29.11%) patients with lymphadenopathy. This was based on histopathological analysis of biopsy specimens (n=205), laboratory findings, and clinical manifestations (n=290). Solid lymphadenopathies greater than 2cm in diameter, present for more than 4 weeks were excised, and evaluated histopathologically. In 40 out of all biopsized patients, malignancy was detected which included non-Hodgkin lymphoma (n=23), Hodgkin lymphoma (n=15), and Langerhans cell histiocytosis (n=2). A total of 1205 (70.88%) patients, without a definite diagnosis, underwent ultrasonographic assessments, and clinical evaluations before or within 4 weeks after antibiotic therapy and which caused regression of the lesions. Consequently these cases were considered to have lymph node hyperplasia (s) secondary to nonspecific infection which was the most frequently seen form of lymphadenopathy.[5]

Lymphadenopathy is an extremely widespread but rarely malignant condition encountered in the paediatric age group.[6,7] It is most frequently seen in the cervical region.The most common cause of cervical lymphadenopathy in children, is infection, with the frequent ones, viral infections of the upper respiratory tract, infectious mononucleosis (IMN), group A beta-haemolytic streptococcal pharyngitis, acute bacterial lymphadenitis (staphylococcus aureus).[8] Lymphoma is the most frequently encountered cause of malignant lymphadenopathy.

In our series, lymphadenopathy of the cervical region was most frequently encountered with the most common cause being infection. Lymphoma was the leading cause of malignancy. These results are similar to the literature findings.

Malignancy was dected in 40 (19.60%) of 204 biopsied children. Only one study in literature has reported a malignancy rate of 23.4 percent which was attributed to the patients being selected from specific oncology centers.[9] Simialr results were reported by Çelenk et al.[10] who established malignant lymphoma as the leading cause of cervical chronic lymphadenopathy (36.7%).

Mycobacterial infections (TB etc.) and catscratch disease are the commonest cause of chronic lymphadenopathy.[1,11] Our study had 6 patients with tuberculosis, and 4 with catscratch disease. The acute lesions had a viral cause with infectious mononucleosis (IMN) (n=162), being the commonest. This has been reported by other studies too.[12]

Our experience shows that lymphadenopathy in children regresses spontaneously in most cases. Others have recommended that in chronic cases, malignancy should be excluded.[13] Excisional biopsy is still the gold standard for diagnosis of enlarged lymph glands, which should be done by excising the entire hard capsule. It is recommended that if the nodes do not resolve in four weeks despite antibiotic therapy, a biopsy should be undertaken.[14]

It is important to exclude malignancy in non-responding cases. The frequency reported by haematology and oncology centres in Turkey are 25-30%[15] whereas a large scale epidemiological study had results showing 1.1% malignancy in children with lympadenopathy.[16]

If progressive regression in US measurements of lymph nodes is detected without any clinical evidence of an inflammatory disease, this signifies reactive hyperplasia which is the most frequent encountered etiological factor of cervical lymphadenopathies.[5] Laboratory, and radiological tests performed in most of the cases fail to determine the specific cause of lymphadenopathy. Similar to another study, the single manifestation in most of our cases (70.88 %) was lymphadenopathy of unknown etiology.[17]

Conclusion

Lymphadenopathy should be investigated for the accurate diagnosis.

Excisional biopsy is still the gold standard. Despite infections being a common etiological agents of lymphadenopathy, in our series incidence of malignancy could not be disregarded. The reason was that patients with lymphadenopathy coming from the neighbouring district Çadirkent near the Syrian border, and surrounding towns and who had been followed up by the best -equipped Gaziantep Paediatric Hospital were sent to our hospital for biopsy when their lymphadenopathies did not regress in the follow-up period. This may be the reason for the higher rate of malignancy in our series.

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