

Usefulness of second lymph node biopsy with a prior report of reactive lymphoid hyperplasia in pediatric patients

Norberto Sotelo-Cruz,* Andrés Cordero-Olivares,**
Guillermo López-Cervantes,*** and Juan Alfonso Romero-Esquer****

Abstract

Background: Physicians in daily practice frequently attend children who present an increase in lymph node size. Care should be taken to determine which children require biopsy. Our objective was to analyze the usefulness of the peripheral lymph node biopsy in pediatric diagnosis.

Methods: We reviewed histological reports of 364 lymph node biopsies. Variables were age, sex, lymphadenopathy evolution time, laboratory and imaging studies, and histopathology diagnoses. Parametric and nonparametric tests were used.

Results: There were 211 males (57.9%) and 153 females (42.0%), the 1- to 6-year age group included 50.8% of cases. Average disease-evolution time was 5 months, and the predominant anatomic site was the cervical region. Histological report was reactive lymphoid hyperplasia (RLH) in 46.9%, followed by neoplasms in (24%), and granulomas (14.5%). Other diagnoses and normal lymph nodes represented 14.6%. Of the 95 patients with high-risk lymphadenopathy, 29 cases had oncological diagnoses. Spearman coefficient was $R^2 = 0.3485$. To obtain a specific diagnosis indicates the probability of disease in lymph nodes of risk areas. However, the majority of the diagnoses were obtained from lymph nodes in different areas (Fisher's test, $p < 0.001$). In 25 children with RLH, the binominal probability of diagnosis in the second biopsy was $p = 0.0493$. There was a >75% chance for detecting disease.

Conclusions: Peripheral lymph nodes in high-risk regions indicate probability relationship for determining disease. In persistent lymphadenopathy with an initial report of RLH, it is important to consider a second biopsy with high probability for obtaining a specific diagnosis.

Key words: lymph node biopsy in children, reactive lymphoid hyperplasia, lymphoma, tuberculosis, coccidioidomycosis.

Introduction

In daily practice, the physician often treats children with enlarged lymph nodes. Care must be exercised in determining whether an acute or chronic condition is causing this growth and what are the limitations and characteristics for making the decision on performing excisional biopsy. From the etiological point of view,

the different diseases that may cause lymph node enlargement are divided into five categories: 1) immune response to infectious agents (bacteria, viruses, fungi), 2) inflammatory cells involving lymph node infection, 3) infiltration by neoplastic cells carried to the lymph circulation (metastasis), 4) localized neoplastic cells with proliferation of lymphocytes or macrophages (leukemia, lymphomas), or 5) infiltration of macrophages saturated with metabolic deposits (hoarding disease).¹ From the physiological point of view, growth of the lymph node will follow the initial cause of the reactive process of the node; physiologically there will be an increase in the number of lymphocytes and macrophages. Lymph nodes grow larger in bacterial, fungal and viral infections, but this also occurs in cases of metastasis.²

Taking into consideration that the patient should be studied due to lymph node enlargement, it is important to remember that there are a number of nodes ranging from 600-1000. Lymph node chains of special clinical interest are the superficial and deep nodes of the neck, followed by sternocleidomastoid nodes, preauricular, submandibular, supraclavicular, axillary, epitrochlear, inguinal and popliteal nodes, as these often relate to other malignancies, particularly if the node persistently remains enlarged.¹⁻³ Clinical history, age of the child, criteria of normality in size in different

* Servicio de Medicina Interna

** Servicio de Cirugía

*** Servicio de Patología

**** Pediatría

Hospital Infantil del Estado de Sonora, Hermosillo, Sonora, México

Correspondence and reprint requests to:

Norberto Sotelo-Cruz
Servicio de Medicina Interna
Hospital Infantil del Estado de Sonora
Reforma 355 Norte, Col. Ley 57
83100 Hermosillo, Sonora, México
Tel: (662) 289 0600, ext. 288
E-mail: norbertosotelo5@hotmail.com

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anatomical regions, place of origin (by endemic diseases), time of evolution, growth rate, formation of characteristic clusters, topographic skin changes adjacent to the node, adherence to deep planes, pain, and compressional phenomena should all be taken into consideration. At present there are mapping techniques to identify sentinel lymph nodes and the choice of biopsy by lymphoscintigraphy.⁴ Attempts have been made to minimize the invasiveness of the procedures for the study of lymph nodes by obtaining samples through needle aspiration. This has been partially effective as a diagnostic method in some diseases.^{5,6}

However, even with these advances, excisional biopsy has not yet been replaced as it offers the pathologist the best study sample. Here we report on the results obtained during 29 years of using lymph node biopsy as a diagnostic procedure in pediatric patients.⁵⁻⁸

Materials and Methods

We retrospectively reviewed the clinical files of 364 patients with adenomegaly who underwent biopsy, obtaining superficial lymph nodes through excision. These procedures were performed between January 1, 1978-August 31, 2006. Variables considered were place of origin, age (ages were stratified according to development of lymphoid tissue from low to high ratio), gender, time of growth evolution of the lymph node, anatomical region of the lymph node, diagnosis at the time of admission, selection criteria of the patient for the study, and laboratory and imaging tests prior to the biopsy. To study the patient with adenomegaly the following criteria and procedures were considered:

- 1) Growth of the lymph node >6 weeks or less than this time if located in an anatomical area of concern
- 2) Criteria for normality in size for different ages were considered before subjecting the patient to a study^{1-3,5}
 - a) newborn, 0.3-1.2 cm in inguinal, occipital, cervical and axillary regions
 - b) children 1-2 years old, occipital chain 0.7 cm
 - c) preschool and school age, cervical and submandibular lymph nodes from 1.5-2.0 cm
 - d) inguinal nodes 1-1.5 cm
 - e) supraclavicular, epitrochlear and popliteal <0.5 cm
 - f) axillary nodes <2.0 cm
- 3) Progressive growth of the lymph node, slow or very explosive in the neck or submandibular region
- 4) Small nodes formed in small clusters
- 5) Lymph nodes in areas of concern, submandibular, supraclavicular epitrochlear and popliteal >0.5 cm
- 6) Inguinal nodes >1.5 and axillary nodes >2 cm
- 7) As well as the above criteria, if no diagnosis was established using laboratory and imaging studies prior to the procedure

Laboratory studies performed were as follows: blood count, erythrocyte sedimentation rate (ESR), peripheral blood smears,

general urine examination, blood chemistry antistreptolysin-O, C-reactive protein, PPD and coccidioidin skin test, monostest, throat cultures, hemocult, febrile reactions. Anti-DNA cells, HIV tests since 1986, blood smear, PA chest, skull and sinus x-rays were also carried out. In a group of patients the following were performed according to initial clinical guidance: ultrasound, computed tomography and lymphography. Histological diagnosis was established from the tissue obtained. Once processed in paraffin and stained with hematoxylin and eosin, tissue was analyzed with a light microscope. A second retrospective review of the histological material was done in order to eliminate error factors in the interpretation of the tissue studied.

We used parametric and nonparametric statistical tests (nominal measurements, proportions, Fisher's test, Spearman's coefficient of determination, and χ^2 binominal probability distribution test.^{9,10} This was done to determine the specificity in terms of diagnosis and the relationship between pathological processes and lymph nodes in areas of concern. Also, the probability of diagnosis in a second biopsy obtained from children who had an earlier report of reactive lymphoid hyperplasia (RLH) was studied.

The review protocol was submitted and approved by the Ethics and Research Committees.

Results

Regarding place of origin, 194 patients (53%) were residents of the city of Hermosillo, 37 (10%) were from the desert area (endemic for coccidioidomycosis) and 35 (9.6%) were from southern Sonora, an area with a high prevalence of pulmonary tuberculosis, 98 patients came from various areas of Sonora and northwestern Mexico. There were 211 males (57.9%) and 153 females (42.0%). Ages ranged from 4 months to 18 years. In 31 cases, 8.5% were <1 year of age. The 1- to 6-years-old group included 50.8% of patients and those subjects between 7 and 18 years of age comprised 40.5% (Table 1).

Time of evolution of lymph node growth varied from 1 month to 1 year (average 5 months). In 40% of the cases it was 6 weeks. Size of the node was considered abnormal if >2 cm in the cervical region and >1.5 cm in the inguinal area. In 64 patients (17.5%), sizes ranged from 5-7 cm.

Diagnoses on admission were adenopathy in 248 cases (68.1%), probable neoplastic process in 56 (15.3%), granulomatous processes and infections with 56 (15.3%) and various diseases in 4 patients (1.0%).

Site of the adenomegaly was most localized in the neck in 66.3% of the cases, and in 15.7% corresponded to enlarged lymph nodes in areas of concern (Table 2). Histopathological study results of lymph nodes obtained in 46.9% of cases were reported as nonspecific lymphoreticular hyperplasia or RLH, followed by neoplasms and granulomatous processes (Table 3).

Table 1. Age groups of patients with lymph node biopsy (n = 364)

Age	# patients	%
4-11 months	31	8.5
1-3 years	94	25.8
4-6 years	91	25.0
7-9 years	61	16.7
10-13 years	41	11.2
14-18 years	46	12.6

In 95 patients with enlarged lymph nodes in regions considered as sites of “alarm,” analyzed by criteria of convenience, 29 had mainly oncological diagnoses established, and in 11 patients RLH was reported (Table 4). Fisher’s exact test was performed in order to demonstrate the sensitivity to establish the diagnosis on removing an abnormally enlarged lymph node in the regions identified. It was found that the largest proportion of diagnoses was made in lymph nodes of diverse regions ($p < 0.0001$). Coefficient of determination was $R^2 = 0.3485$.

In a group of 25 children with adenomegaly who, on initial biopsy had a histological report of RLH and who continued with enlargement of the lymph node for a period that ranged from 6-16 weeks, it was decided to perform re-excisional biopsy. This second procedure is the one in which definitive diagnosis was established. To ascertain the validity of the decision for the new biopsy, a statistical test was used for binomial probability distribution, which had a value of $p = 0.0493$ and χ^2 with p value = 0.0512 (Table 5).

Of the group with diagnosed hematological/oncological diseases, Hodgkin’s lymphoma predominated with 56 cases (15.3%), non-Hodgkin’s lymphoma, 18 (4.9%), histiocytosis X with six cases (1.7%) and the remainder were diverse: two cases of rhabdomyosarcoma, one case of metastatic neuroblastoma, one case of malignant schwannoma (metastatic) and one case of Burkitt’s lymphoma. In 22 of these patients, ultrasound and computed tomography were initially performed without evidence of lymphadenopathy. In three patients lymphography was performed and demonstrated Hodgkin’s lymphoma.

Table 3. Results of histopathological review of lymph nodes according to groups of patients (n = 364)

Histological report	# cases	%
RLH	171	46.9
Neoplasms	87	24.0
Granulomatous processes	53	14.5
Infections	10	2.7
Various	11	3.2
Normal node	32	8.7

RLH, reactive lymphoid hyperplasia.

Table 2. Site of adenomegaly (n = 364)

Site	# cases	%
Right neck*	117	32.1
Left neck*	105	28.8
Bilateral neck	20	5.4
Submaxillary	38	10.4
Axillary	27	7.4
Inguinal	37	10.1
Supraclavicular	18	4.9
Popliteal	1	0.2
Epitrochlear	1	0.2

*Forty three patients presented increase in nodes in other regions.

Regarding granulomatous diseases diagnosed from the overall total, there were 53 cases (14.4%); for TB there were 31 cases (8.5%); coccidioidomycosis 17 (4.7%); reaction to BCG vaccine for TB in four cases 1.0% and actinomycosis in one patient. HIV tests were performed regularly after consent by the family from 1986 when the institution had this test. In this case series of children with enlarged lymph nodes, that test resulted negative.

Discussion

In daily clinical practice it is common to find patients with lymph node enlargement, particularly in the pediatric ages of greater lymphoid tissue development between 3 and 10 years of age. Because of this, the physician should be very careful in considering the normal limits for each age^{1-3,5} and should take a

Table 4. Diagnoses established following the “site of alarm” of growth of lymph node (n = 95)*

Anatomic site	Diagnosis	# cases
Supraclavicular	Hodgkin's lymphoma	6
	Tuberculosis	5
Submaxillary	Hodgkin's lymphoma	3
	Non-Hodgkin's lymphoma	1
Epitrochlear	RLH	3
Inguinal	Tuberculosis	5
	Rhabdomyosarcoma	1
	RLH	8
	Dermopathic lymphadenopathy	4
	Tuberculosis	1
	Hodgkin's lymphoma	3
	Total	40

*With report of reactive lymphoid hyperplasia (RLH) and other diagnoses.

complete medical history and perform necessary laboratory and imaging studies. Some studies, such as lymphography, were used in three patients with results of Hodgkin's lymphoma. Ultrasound and computed tomography have been useful in patients with suspected oncological processes and are also useful for identifying glandular enlargements. In the particular case of children <1 year with generalized and significant lymph node enlargement and who also present risk factors, it is prudent to always request from the family authorization to perform HIV testing. In this respect, this test is requested routinely. It is worth mentioning that in our institution after 31 years of activity, only 28 patients have been diagnosed with acquired immunodeficiency syndrome: six had lymphadenopathy and hepatosplenomegaly and did not meet criteria for biopsy.^{11,12}

If, after considering the assessments already stated, it is not possible to clarify the origin of the adenomegaly, one could choose between a fine needle aspiration biopsy or excisional biopsy.^{2,4,7}

In the authors' experience, a reduced number of aspiration biopsies were performed in the 1980s, but this was abandoned because there were mixed results that eventually compelled that excisional biopsy be performed. However, recent series have reported very large series of about 900 pediatric patients⁷ with various oncological processes in which this procedure was successful. It has been noted that the sensitivity and specificity for diagnosis is up to 90%; however, in many hospitals it is not accepted as an elective procedure for the study of lymphadenopathy in children because it requires specially trained pathology personnel. Also, hematologists/oncologists frequently request other studies to be performed on the lymph node to be removed such as electron microscopy, scanning microscopy, and cytochemical studies.^{1,6,7,11,13}

In our institution, patients studied had frankly abnormal growth of the lymph nodes, and the procedure of choice was excisional biopsy. The report we are presenting is from the results of histopathological analysis using light microscopy.

With respect to the choice of lymph node to biopsy, it is decided between the clinician in conjunction with the surgeon, coinciding with the node of greatest growth, frequently corresponding to lymph nodes of the cervical area, the same as with other reported series. The lymph nodes that are extracted most frequently are those of the cervical region.^{1,3,7,8,13-15}

It is well known by physicians that the length of time for lymph node growth is important for deciding the biopsy procedure. In general, it is accepted that among preschool and school ages, it is more common that there would be rapid growth of lymph nodes in the cervical region accompanied by pain due to an acute pharyngeal or tonsil infection. In these cases the lymph node reduces its size in a few days but, occasionally, the lymph node is persistently reactive due to repeated upper respiratory tract infections and infection of the nasal sinuses, which can also be associated with allergic processes. This favors the persistence of lymph node growth and it is possible that laboratory and imaging

Table 5. Diagnoses established in the second biopsy after a lapse of 6-16 weeks ($n = 25$)

Diagnosis	# cases
Hodgkin's lymphoma	2
Coccidioidomycosis	3
Non-Hodgkin's lymphoma	2
Histiocytosis X	3
Tuberculosis	2
Rhabdomyosarcoma	1
Schwannoma	1
Hemophagocytic syndrome	1
Reactive lymphoid hyperplasia	10
Total	25

procedures do not show the etiology and a group of patients will be subjected to biopsy procedures, reporting RLH in the great majority. This occurred in 10 patients.^{2,7,11}

It is worth mentioning that in children with neoplasms, tuberculosis and coccidioidomycosis, lymph node growth had an evolution of <8 weeks and, in some cases of tuberculosis, >12 weeks. Also in these cases lymph nodes were found with sizes up to 5 cm.^{11,15}

Regarding the likelihood of reaching a diagnosis on removing an enlarged lymph node in the superficial chains considered to be of concern, it was found that a great proportion of the diagnoses were obtained in diverse regions ($p < 0.0001$), but the Spearman coefficient of determination was $R^2 = 0.3485$, indicating that there is a real relationship between the probability of having a disease diagnosis in the nodes located at these areas of concern.

It is recommended that in those children who, after an initial biopsy report of RLH there is continued growth of the lymph nodes, a second biopsy is performed during a period that can vary from 6 weeks or more as there is the possibility of detecting an oncological or granulomatous disease.

This occurred in 25 patients. Binomial probability test ($p = 0.0493$) shows that in a second biopsy there is a >75 % probability for detecting conditions such as cancer, tuberculosis, coccidioidomycosis and others. In the same manner, χ^2 test was $p = 0.0512$, a limit to confirm. The foregoing leads us to believe that an initial histological report of RLH, supposedly benign, should be taken with caution until there is complete certainty that adenopathy is not persistent.^{3,5,14-17}

In the total of reported diagnoses, we have no case with histological features suggestive of Kikuchi-Fujimoto disease, a condition that typically presents with lymphadenitis and fever and whose origin cannot usually be confirmed and may be confused with lymphomas and lupus erythematosus. The histological pattern is of diffuse necrosis, proliferation of large lymphoid cells, macrophages and foamy histiocytes as well as fragments of nuclear karyorrhexis.^{5,18,19}

In conclusion, growth of superficial lymph nodes in areas of concern in children should always be considered for study, regardless of age. Patients who had excisional biopsy performed with an initial report of RLH but who continue to present adenomegaly should be considered for performing a second biopsy.

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