Role of biopsy in pediatric lymphadenopathy

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ABSTRACT

الأهداف: تحديد دور خزعة العقد اللمفاوية في تشخيص اعتلال العقد اللمفاوية، ورؤية نموذج مختلف الأمراض ذات الصلة بالعمر، نوع الجنس وموضع العقد اللمفاوية المصابة.

الطريقة: أجريت دراسة إستعادية بقسم أمراض الأنسجة – مستشفى الأطفال ومركز أبحاث الطفل – لاهور – باكستان، خلال الفترة مابين يناير 1999م وحتى ديسمبر 2007م. تم جمع عينات النسيج من 898 طفلاً حضروا إلى الدراسة وهم يعانون من اعتلال لمفاوي وتم تأكيد التشخيص بواسطة علم الأنسجة، وبوسائل الاختبارات المحددة المختلفة. تم الحصول على البيانات السريرية للمرضى من سجلاتهم المحفوظة في الحاسب الآلي.

النتائج: من بين إجمالي عدد 898 عينة عقدة لمفاوية، كان علم الأمراض المواجه فرط التنسج المتفاعل لدى 356 طفلاً (39.6%)، عقبه الدرن لدى 262 طفل (29.1%)، ورم ليمفاوي خبيث لدى 132 طفل (14.6%). أما بالنسبة لبقية الآفات فشملت: 72 حالة من الأورام الحُبيبية في العقد للمفاوية (8.0%)، كثرة المنسجات إكس (X) لدى 13 طفلاً (1.4%)، الأورام المنتشرة لدى 44 طفل (4.9%)، الالتهاب المزمن لدى 16 طفل (1.8%) وثلاث حالات من مرض كيكوتشي (0.3%). تبين أن وجود حالة الاعتلال اللمفاوي مرتبطة بشكل ملحوظ مع العمر ونوع الجنس وموضع العقد اللمفاوية المصابة.

خاتمة: نختتم بأن حالة الاعتلال اللمفاوي حالة شائعة نسبياً لدى مجموعة من الأطفال. على الرغم من أن (39.6%) من الأطفال قد تعرضوا لفرط التنسج المتفاعل لسبب مرضى غير معروف، و(60.3%) من الأطفال حضروا مع تشخيص محدد.

Objectives: To determine the role of lymph node biopsy in the diagnosis of lymphadenopathy and to find out the pattern of different diseases in relation to age, gender, and the site of lymph nodes involved.

Methods: This retrospective study was carried out at the Histopathology Department of the Children's Hospital and The Institute of Child Health, Lahore, Pakistan, over a period of 9 years, from January 1999 to December 2007. Tissue samples were collected from 898 children presenting with lymphadenopathy, and the diagnosis was confirmed on histology and through various specific tests. The clinical data of the patients were collected from computerized hospital records.

Results: Among the total 898 consecutive lymph node biopsies, the most common pathology encountered was reactive hyperplasia in 356 children (39.6%), followed by tuberculosis in 262 (29.1%) and malignant lymphomas in 132 children (14.6%). The rest of the lesions include; 72 cases of granulomatous lymphadenitis (8%), 13 of histiocytosis X (1.4%), 44 (4.9%) of metastatic tumors, 16 of chronic inflammation (1.8%), and 3 cases of Kikuchi's disease (0.3%). The cause of lymphadenopathy was found to be significantly associated with age, gender, and site of the lymph nodes involved.

Conclusion: Lymphadenopathy is a relatively common condition in the pediatric age group. Although 39.6% of children had reactive hyperplasia of unknown etiology, 60.3% children presented with a specific diagnosis.

Saudi Med J 2009; Vol. 30 (6): 798-802

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Received 14th December 2008. Accepted 3rd March 2009.

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Lymph nodes are normal structures and certain lymph nodes may be palpable in a healthy patient, particularly in a child. Mostly, "lymphadenopathy" in children may be due to a serious underlying

systemic disease. However, the differential diagnosis of lymphadenopathy can be broad.[1] The challenge for the general pediatrician is to learn how to distinguish a pathologic from non-pathologic lymph node, and to develop a rational approach to the evaluation of lymphadenopathy.[1] To identify the infrequent but serious causes of lymphadenopathy, physical examination should be regionally directed by the knowledge of the lymphatic drainage patterns, and should include a complete lymphatic examination searching for generalized lymphadenopathy along with a thorough history including key factors such as age, location, duration, and patient exposure is essential.[2] Unexplained lymphadenopathy without signs or symptoms of serious disease or malignancy can be observed for one month, after which specific tests or biopsy should be performed. While modern hematopathologic technologies have improved the diagnostic yields of fine-needle aspiration (FNAC), excisional biopsy remains the initial diagnostic procedure of choice.[3] Lymphadenopathy is defined as enlargement of lymph nodes beyond its normal state, for example, more than 1 cm in greatest diameter, but certain nodes should be considered enlarged at different sizes as in the inguinal regions up to 1.5 cm in size, and in the epitrochlear region up to 0.5 cm in size.[1-3] Palpable supraclavicular, iliac, or popliteal nodes of any size are considered abnormal.[4] The size limits differ somewhat by age, and generally are less stringent in young children than in adolescents and adults, presumably due to the frequent antigenic exposure in early childhood to common childhood illnesses, and the gradual acquisition of antibodies and immunity.[1] Lymphadenopathy that lasts less than 2 weeks, or more than one year with no progressive size increase has a very low likelihood of being neoplastic.[2,5] The following findings should alert the pediatrician to a malignant disorder like, lymphadenopathy of >3 cm in size, of >4 weeks in duration, with supraclavicular involvement, and with abnormal laboratory and radiological findings.[6,7] Most children with lymphadenopathy will prove to have a benign disorder, however, it is important that the pediatrician also has an appreciation of the malignant diseases that may present with lymphadenopathy, so that in such cases the diagnosis of a serious or life-threatening disease is made in a timely manner.[8] Lymphadenopathy can be either localized or generalized. Generalized lymphadenopathy is defined as lymphadenopathy found in 2 or more distinct anatomic regions, and is more likely than localized adenopathy to result from serious infections, autoimmune diseases, and disseminated malignancy.[1] It usually merits specific testing. Common benign causes include adenoviral illness in children, infectious agents, and tuberculosis, whereas the malignancies causing generalized lymphadenopathy include leukemia, lymphoma, or advanced disseminated metastatic tumor.[1,2] Localized lymphadenopathy is characterized to a single area. It is a more common presenting finding in a primary care practice than generalized lymphadenopathy, with the cervical lymph nodes being involved most commonly, followed by inguinal lymph nodes.[1,2] Lymph nodes should be biopsied if they are >2 cm, not responding to antibiotic therapy in 4-6 weeks, non-resolution in 8 weeks, history of rapid increase in size, further significant increase in size on treatment, supraclavicular lymph nodes, hard or matted lymph nodes (especially in posterior triangle of neck, fixation to surrounding structures, development of new signs and symptoms (weight loss, fever of unknown origin, night sweats), and abscess formation.[9] More than 25% of malignant tumors in children occur in the head and neck area, and the cervical lymph nodes are most commonly involved.[10] The aim of this study is to evaluate children with lymphadenopathy, including an analysis of the causes of lymphadenopathy in relation to age, gender, and site of lymph nodes involved.

Methods. Ethical approval for this work was obtained from the ethical committee of the Children's Hospital and the Institute of Child Health. Written informed consent was obtained from all the patients. A retrospective study was conducted in the Department of Histopathology, Institute of Child Health and Children's Hospital (which is a tertiary care hospital and receives specimens from Lahore, Pakistan, and its periphery) over a period of 9 years (1999-2007). The method includes a review of the clinical features and routine laboratory investigations of all the children from the computerized hospital record. All children up to 16 years of age with excision of the enlarged lymph nodes were included in this study. Particular note was carried out of the anatomic site of the nodes and clinical features on presentation. In addition, the pathologic diagnosis and outcome were recorded. A large number of these children received antibiotics by their treating physicians, prior to their referral for lymph node biopsy. A lymph node biopsy was performed when a significantly enlarged lymph node persisted or increased in size after taking an antibiotic course, and those lymph node biopsies were studied when the diagnosis was unclear on FNAC. These lymph nodes were immediately fixed in 10% formalin. A complete gross examination of the specimens was carried out, and important clinical features were noted. After processing, each block was cut into 3 microns thick sections. Routine Hematoxylin and Eosin stains were used. However, special stains were applied whenever required. Indirect immunoflourescence assay and enzyme-linked immunosorbent assay (ELISA) was applied to exclude the diagnosis of cat-scratch disease. A new working formulation was used for reporting

lymphomas. Immunomarkers were applied whenever indicated including; Tdt, CD19, CD 20, and CD 30 (for the classification of non-Hodgkins lymphoma). After the microscopic examination, a diagnosis was carried out, and the data was compared with the information available from centers in other parts of the country, as well as outside the country. The data was entered for statistical analysis in software using the Statistical Package for Social Sciences version 11.0 (SPSS Inc., Chicago, IL., USA). Chi-square test was applied to compare various diagnosis in relation to the age groups. A p-value of <0.05 was considered statistically significant.

Results. Lymph node biopsy of 898 children, including 490 males and 408 females (with a male to female ratio of 1.9:1.5), was carried out as part of the diagnostic evaluation in this study. The age of the patients included in this study ranged from 1 day - 16 years. The number of patients in the age-stratified samples is shown in **Table 1**. The largest number was found between the ages 5-10 years, closely followed by the age group 1->5 years (**Table 1**). The most common causes of lymphadenopathy is shown in **Figure 1**. The age distribution of lymphadenopathy due to specific causes is shown in **Table 2**. The most common specific cause of lymphadenopathy in children of all age groups was reactive hyperplasia. Tuberculous lymphadenitis was confirmed in 262 children. Mycobacterium tuberculosis was cultured in 181 (54.5%) of these children, and acid fast bacilli were proved on Ziehl-Neelson stain in the remaining 81 children. One hundred and thirty-two cases of lymphoma were diagnosed, and most of the patients presented between 5-10 years of age. Males were affected more than females. The distribution of the different histological types of Hodgkin's lymphoma was; nodular sclerosis (19 [20.8%]), mixed cellularity (47 [51.6%]), lymphocytic predominance (25 [27.4%]), and for non-Hodgkin's lymphoma was; lymphoblastic lymphoma (68 [74.7%]), Burkett's lymphoma (18 [19.7%]), and large cell anaplastic lymphoma (5 [5.4%]). As for the site distribution, the greatest number of cases presented with cervical lymphadenopathy, followed by mesenteric, axillary, inguinal, submandibular,

Table 1 - Age and gender distribution of lymphadenopathy.

Age	Male	Female	Total
		n (%)	
0 - <1 years	46 (9.4)	27 (6.6)	**73 (8.1)**
1 - <5 years	114 (23.3)	146 (35.9)	**260 (28.9)**
5 - <10 years	178 (36.3)	151 (37)	**329 (36.6)**
10 - <16 years	152 (31)	84 (20.6)	**236 (26.3)**
Total	**490 (54.6)**	**408 (45.4)**	**898 (100)**

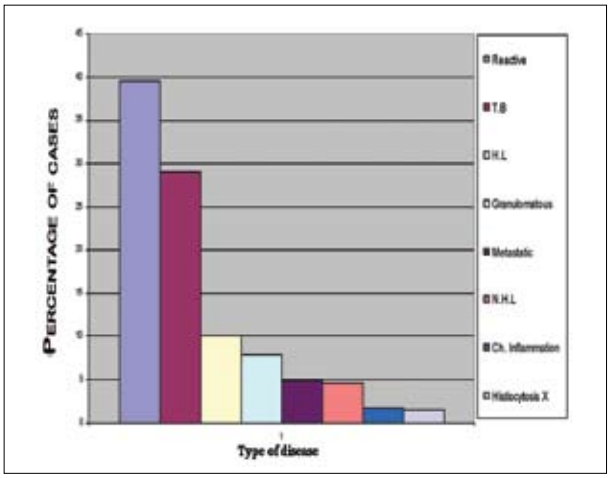

Figure 1 - Different causes of lymphadenopathy.

Table 2 - Age and gender distribution of lymphadenopathy due to specific causes.

Diagnosis	0-<1 year	1-<5 years	5-<10 years	10-16 years	Males	Females	Total n (%)
Reactive hyperplasia	26	148	132	50	216	140	**356 (39.6)**
Tuberculosis	11	54	83	114	120	142	**262 (29.1)**
Lymphomas	1	18	72	41	106	26	**132 (14.6)**
Hodgkin's lymphoma	0	10	56	25	71	20	**91 (10.1)**
Non-Hodgkin's lymphoma	1	8	16	16	35	6	**41 (4.6)**
Granulomatous	25	13	20	14	30	42	**72 (8.0)**
Metastatic	4	8	18	14	26	18	**44 (4.9)**
Chronic inflammation	2	8	4	2	11	5	**16 (1.8)**
Histiocytosis X	4	9	0	0	5	8	**13 (1.45)**
Kikuchi's disease	0	2	0	1	1	2	**3 (0.33)**
Total	**73**	**260**	**329**	**236**	**515**	**383**	**898**

supraclavicular, and hilar lymphadenopathy. Out of the 475 cases of cervical lymphadenopathy, 55.8% had a specific diagnosis, while the remaining 44.2% presented with reactive hyperplasia. The least frequently involved lymph nodes were of the hilar region. The distribution of lymph nodes according to site and number with specific diagnosis is shown in **Table 3**. One hundred and forty patients had axillary lymphadenopathy of which 90 (64.2%) had a specific diagnosis of tuberculosis. Twenty cases (40%) of inguinal lymphadenopathy had a specific diagnosis of non-Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, and histiocytosis X. Children having enlarged submandibular lymph nodes (54%) had a specific diagnosis of tuberculosis, Kikuchi's disease, and metastasis from rhabdomyosarcoma, and nasopharyngeal carcinoma. The sizes of lymph nodes were obtained from the gross examination mentioned in the histopathology reports, which had precise measurements of excision. The size of lymph nodes in patients with a specific diagnosis ranged from 0.8-5 cm (mean 2.5 cm), while in patients with non-specific diagnosis ranged from 0.5-4 cm (mean 1.6 cm). None of our patients who were previously diagnosed as having reactive hyperplasia (39.6%) were subsequently proved to have some specific cause.

Discussion. The evaluation of a child with lymphadenopathy is a common clinical scenario for the pediatrician. Unexplained lymphadenopathy without signs or symptoms of serious disease or malignancy can be observed for one month, after which specific testing or biopsy should be performed.[11] While modern hematopathologic technologies have improved the diagnostic yields of FNAC, excisional biopsy remains the initial diagnostic procedure of choice.[8] Most of the cases resulted from a benign, self-limited disease, and resolve without any sequelae within a limited period. Since it can be a manifestation of a serious systemic disease or malignancy, it is crucial to understand the differential diagnosis in directing an appropriate and timely evaluation.[7,8] During the first 6 years of life, neuroblastoma and leukemia, whereas after 6 years Hodgkin's lymphoma, non-Hodgkin's lymphoma and rhabdomyosarcoma are the most common tumors associated with cervical lymphadenopathy.[12] In our study, the most common cause of cervical lymphadenopathy is reactive hyperplasia resulting from an infectious process. Bacterial cervical lymphadenitis is usually caused by *group A β-hemolytic streptococci* or *Staphylococcus aureus*. Tuberculosis due to both typical and atypical mycobacterium and cat scratch disease are the causes of sub-acute or chronic cervical lymphadenopathy.[13] Oguz et al[7] found a specific cause in 53.8% of the children, whereas Knight et al[14] found a specific cause in only 41% of the children. The enlargement of peripheral lymph nodes is most commonly caused by a local inflammatory process with viral upper respiratory tract infection, or streptococcal pharyngitis as the common causes.[15] Non specific reactive lymphadenopathy constituted 39.6% cases in our study, which has been documented as a common cause of lymph node enlargement, and rates ranging from 7-38% have been observed in previous reported series.[16-17]

In this series, the cervical lymph nodes were most commonly affected by reactive hyperplasia, followed by mesenteric, axillary, and inguinal lymph nodes. Lymphadenopathy due to a specific etiology was found in 60.3% of the children included in our study (**Table 3**). The specific causes of lymphadenopathy in our study included tuberculosis, lymphomas, granulomatous inflammation (other than tuberculosis), metastasis from a primary tumor, chronic inflammation, histiocytosis X, and Kikuchi's disease.

In the developing countries, tuberculosis is still one of the leading health problems, and tuberculous lymphadenitis is the most common presentation of extra pulmonary tuberculosis, accounting for 30-40% of cases in reported series.[18,19] Patients presented with chronic cervical lymphadenopathy with firm, enlarged, painless lymph nodes, which are matted together. Systemic symptoms such as fever, weight loss and malaise, may or may not be present at an early stage.[19] Tuberculosis has been reported by several researchers as the predominant cause of lymph node enlargement in both children and adults.[13,14,19] This was also observed in this study, with tuberculous lymphadenitis constituting 26.1% of the cases. This is lower than 36-77% reported in previous Pakistani studies.[20,21] Due to low socio-economic status and the poor standard of living in the Third World countries, the incidence of tuberculosis has increased.[22] In addition, it has shown resurgence in developed countries due to high incidence of HIV.[23] It has been observed that females are more likely to suffer from the disease,[15] consistent with the findings of this study, with a male to female ratio of 1:1.02.

Table 3 - Site distribution of lymphadenopathy.

Site of lymph nodes	Reactive hyperplasia	Specific diagnosis	Total
		n (%)	
Cervical	210 (44.2)	265 (55.7)	**475 (52.9)**
Mesenteric	41 (26.6)	113 (73.3)	**154 (17.1)**
Axillary	50 (35.8)	90 (64.2)	**140 (15.5)**
Inguinal	30 (60)	20 (40)	**50 (5.6)**
Submandibular	18 (46.1)	21 (54)	**39 (4.3)**
Supraclavicular	4 (12.5)	28 (87.5)	**32 (3.5)**
Hilar	3 (37.5)	5 (62.5)	**8 (1.3)**
Total	**356 (39.6)**	**542 (60.3)**	**898**

The overall percentage of malignant neoplasms causing lymphadenopathy was 24.3% in this study. Moore et al[9] observed 48% reactive lymph nodes, and 11.6% neoplasms in their study, whereas Knight et al[14] observed 11% malignant neoplasms causing lymphadenopathy. Lymphoma was the third most common specific cause of lymphadenopathy constituting 14.6% cases.[24] This is in contrast to the study conducted by Rathi et al,[25] who observed it as the second most common cause of lymphadenopathy. Also, the incidence is lower than 18.5% as reported by Hussain et al.[21] Among the diagnosed cases of lymphoma, most of these cases were of Hodgkin's lymphoma (10.1%), and showed marked predilection for the cervical group of lymph nodes of male children. These findings are in contrast to previous reports in which non-Hodgkin's lymphoma was more commonly encountered than Hodgkin's lymphoma.[26-28] Based on our data, most of the patients had generalized lymphadenopathy, whereas localized lymphadenopathy was relatively uncommon. Malignancies and tuberculosis usually presented as generalized lymphadenopathy, and the most common sites involved were cervical and supraclavicular.

Lymph node biopsy is a time-tested diagnostic procedure practiced world wide, and is the main stay of treatment in many centers in the tropics, and yields of 65-100% have been reported in various Pakistani studies.[20,21,24] The yield in this center was 100%, but despite these encouraging results, FNAC, which is cheaper and less invasive is presently advocated as a first line diagnostic procedure.

The limitation of our study is that it was based only in patients that were referred by other centers and physicians to the Children's Hospital, which is a tertiary care hospital.

In conclusion, lymphadenopathy is a relatively common condition in the pediatric age group, and excision biopsy is the gold standard to evaluate the causes of lymphadenopathy in relation to age, gender, and site of lymph nodes involved.

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