CLINICAL PROFILE AND HISTOPATHOLOGIC DIAGNOSES OF CHILDHOOD PERIPHERAL LYMPHADENOPATHY: AN MMC EXPERIENCE

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ABSTRACT

Peripheral lymphadenopathy is a common clinical problem wherein surgery is performed, especially, when malignancy cannot be eliminated as a differential diagnosis. In the Philippine setting, there is a paucity of data on the incidence of lymphadenopathy in children.

Objectives: This descriptive study aims to describe the clinical profile and histopathologic diagnoses of peripheral lymphadenopathy requiring biopsy in children aged one-to-eighteen years seen at the Makati Medical Center (MMC) from 1998 to 2008.

Methods: Patients' charts were reviewed and 22 patients were included in the study; 17 were male and 5 were female. All patients underwent excision biopsy, except for one who had fine needle aspiration biopsy.

Results: The most common sites of peripheral lymphadenopathy were cervical (78%) and inguinal (14%). The most common histopathologic diagnoses were benign etiology (46%), tuberculous (TB) adenitis (32%), and malignancy (23%). Of the malignant cases, three were Hodgkin's lymphoma and two were non-Hodgkin's lymphoma. Clinical profile included the findings that patients with benign etiology were younger, presented more frequently with fever; and males were more commonly affected; whereas children with malignant etiology were older, had a shorter duration of lymphadenopathy, which were of a larger size, and with accompanying weight loss.

Conclusion: The following occurred more often in patients with malignancy: children more than 12 years old, cervical location of lymph nodes, shorter duration of lymph node enlargement, the lack of response to initial antibiotic treatment, and the presence of certain signs and symptoms such as fever and weight loss. Excision biopsy was the predominant surgical procedure used despite extensive invasiveness and the requirement of general anesthesia.

INTRODUCTION

Lymph node enlargement is a common problem that affects both children and adults. There is no available local data on the incidence of lymphadenopathy in children. However, based on US statistics, estimates of palpable lymphadenopathy in children vary from 38% to 45%.[1]

Significant lymphadenopathy is defined as a lymph node with a diameter exceeding one cm for cervical and axillary nodes and 1.5 cm for inguinal nodes.[2] The broad etiologic categories of lymph node enlargement include: (i) an immune response to infective agents (e.g. bacteria, virus, fungus); (ii) inflammatory cells in infections involving the lymph node; (iii) infiltration of neoplastic cells carried to the node by lymphatic or blood circulation (i.e. metastasis); (iv) localized neoplastic proliferation of lymphocytes or macrophages (e.g. leukemia, lymphoma); and (v) infiltration of macrophages filled with metabolic deposits (e.g. storage disorders).[3]Several reports have shown TB and other infections to be the major causes of lymphadenopathy in tropical countries,[4-7] while malignancies have been the predominant etiology in developed countries.[8,9] Incidence of TB, however, has been increasing in developed countries due to human immunodeficiency virus (HIV) infection.[10,11]

The pattern of lymph node enlargement varies in different age groups. In children, the most common site is cervical (54%), followed by mesenteric (22%), axillary (13%), and inguinal (10%).[12]The site, size, character and growth rate of lymphadenopathy often provides direction for the diagnostic process. For example, supraclavicular lymphadenopathy is often malignant and should always be investigated. As to size, Karadeniz et al. [13] found a majority of patients with peripheral lymphadenopathy who had a maximum lymph node diameter of less than two cm to have a benign etiology. However, they also noted that supraclavicular nodes of less than two cm in diameter were still found to be malignant. On the other hand, inguinal nodes are the least likely to be malignant while cervical nodes are most frequently infectious in nature.

Information from the clinical history is invaluable in the etiologic work-up of lymphadenopathy and is frequently accurate; it foregoes the need for extensive diagnostic testing. The cause is often evident, particularly for the great majority of bacterial and viral infections. In a minority of cases, the diagnosis is less clear and may be diagnostic dilemmas to physicians, especially, when they do not respond to antimicrobials (i.e., unexplained lymphadenopathy). In general, the absence of clinical improvement within 10 to 14 days of treatment may deserve further evaluation.[14]In such cases, if the etiology is still questionable, further investigations such as laboratory tests, 5 TU purified protein derivative (PPD) skin testing and radiography are warranted. When a neoplasm is suspected or cannot be ruled out, a definitive biopsy is considered.

Lymph node excision or fine needle biopsy as a therapeutic and diagnostic measure to determine the etiology of the underlying illness has long been a practice. Due to the high frequency of non-specific, benign, self-limited lymphadenopathy, the number of patients requiring a diagnostic or therapeutic surgical biopsy is correspondingly low.[15]

Fine needle aspiration biopsy (FNAB), a simple and precise diagnostic procedure, used to differentiate between benign and malignant peripheral lymphadenopathy, is performed less often in children than in adults despite evidence stating several advantages over a surgical biopsy; FNAB has been shown to be more rapidly performed, minimally invasive, cost effective, and reliable as a diagnostic tool.[15] Furthermore, it does not require general anesthesia and has low morbidity. However, as children are not likely to acquiesce to such a procedure without sedation, excision biopsy under general anaesthesia is more commonly employed.

This aim of this study was to determine the clinical profile and histopathologic diagnoses of

peripheral lymphadenopathy requiring biopsy in children.

MATERIALS AND METHODS

The Makati Medical Center Medical Records section database was reviewed to identify all children aged one-to-eighteen years old who underwent any form of lymph node biopsy from January 1, 1998 to December 31, 2008 with confidentiality maintained. The study cases obtained were admitted under the services of the Departments of Pediatrics, Surgery and Otolaryngology.

Cases with known malignant illness were not included in the study. Histopathologic diagnoses were divided using the three categories: tuberculous adenitis, benign disease (benign tumors and reactive cases) and malignant disease, based on previous studies which used similar segregation.

The following data were retrieved from the charts: age, sex, chief complaint, location of the lymph node, duration of the lymph node enlargement, size of the lymphadenopathy, type of biopsy done, final diagnosis, and management of the patient. Statistical analysis used measures of central tendency, variance and standard deviation determined through the Epi Info program.

RESULTS

As tabulated in Table 1, there were 22 patients (17 male and 5 female) who fulfilled the inclusion criteria of the study. Overall, the mean age was nine years (range 1 to 17 years), with the oldest mean age being those with malignant etiology (12.4 ± 4.2 years), and youngest mean age being those with benign etiology (6.5 ± 3.8 years). All malignant cases were aged six and above and were male.

Duration of lymphadenopathy was shortest in malignancy (4.5 ± 2.5 months), followed by tuberculous adenitis (11.4 ± 17.2 months) and benign etiology (12 ± 23.7months). Mean size of lymphadenopathy was greatest in tuberculous adenitis (3.4 ± 1.4 centimeters), closely followed by malignant etiology (3.2 ± 1.3 centimeters) and benign etiology (2.7 ± 1.9 centimeters). The number of lymph node enlargement sites involved in all three categories showed no apparent differences, with 16 out of the 22 cases (73%) having single lymphadenopathy.

From the time lymphadenopathy was noted until the time prior to lymph node biopsy, half of the patients received broad-spectrum antibiotics (co-amoxiclav, cefuroxime, etc.).However, the effect of these medications on the size of the lymph node was not recorded quantitatively and was simply described to either have no decrease in size or showed progressive increase in size. Such progression in size was also not quantified on record. Those given antibiotics immediately prior to the biopsy continued to receive antimicrobials while waiting for the results. The other half of the sample population received broad-spectrum antibiotics after the biopsy. These antibiotics were completed despite negative results on all cultures done. Tuberculous adenitis cases were treated with an anti-tuberculosis regimen based on clinical and histopathologic results. Only one case of TB adenitis had a PPD skin testing done, the result of which was negative. All cases of TB adenitis with sputum AFB smear and chest radiography were also negative. All malignant cases were treated with chemotherapy after results were reviewed.

As shown in Table 2, the presence of a mass was the predominant clinical presentation in 82% of the cases. Fever was seen most commonly in benign etiology (30%), while weight loss was seen more often in the malignant etiology compared to benign etiology.

All patients had excision biopsy done, except for one who had fine needle aspiration biopsy (benign etiology). The most common histopathologic diagnoses as shown on Table 3 were benign histopathology of unknown etiology (45%), followed by tuberculous adenitis (32%), and malignancy (23%).

Table 1. Demographic and Clinical Findings of Childhood Lymphadenopathy according to category of Histopathologic Diagnosis (N=22)

Variables	Histopathologic Diagnosis (Mean Value with SD)			Total
	Benign Etiology	TB Adenitis	Malignant Etiology	
***Gender: N(%)**				
Male	8 (36.4)	4 (18.2)	5 (22.7)	17 (77)
Female	2 (9.1)	3 (13.6)	0	5 (23)
Age± SD	6.5 ± 3.8	10 ± 5.2	12.4 ± 4.2	9
Duration of LN enlargement (in months)± SD	12 ± 23.7	11.4 ± 17.2	4.5 ± 2.5	9.3
No. of LN enlargement sites	1.2	1.3	1.8	1.4
Size of LN enlargement± SD (in centimetres)	2.7 ± 1.9	3.4 ± 1.4	3.2 ± 1.3	3.1
***Trial antibiotic treatment prior to biopsy (%)**				
Yes	5 (23)	4 (18)	2 (9)	11 (50)
No	5 (23)	3 (13.5)	3 (13.5)	11 (50)
Total no of patients (%)	10 (45)	7 (32)	5 (23)	22

Table2. Clinical Presentation of Children with Peripheral Lymphadenopathy according to Category of Histopathologic Diagnosis (N=22)

	Histopathologic Diagnosis			Total
	TB Adenitis (N= 7)	**Malignant Etiology (N= 5)**	**Benign Etiology (N= 10)**	(n= 22)
Mass	6 (86)	4 (80)	8 (80)	18 (82)
Fever	1 (14)	1 (20)	3 (30)	5 (23)
Weight loss	1 (14)	2 (40)	0	3 (14)
Colds	0	0	1 (10)	1 (5)
Abdominal Pain	1 (14)	0	0	1 (5)
Difficulty swallowing	1 (14)	1 (20)	0	2 (9)

Table 3.Histopathologic Findings according to Site of Lymphadenopathy (N=22)

Location (%)	Benign	TB Adenitis	Malignant	Total
Cervical	7 (70)	6 (86)	4 (80)	17 (78)
Supraclavicular	0	0	1 (20)	1 (4)
Axillary	1 (10)	0	0	1(4)
Inguinal	2 (20)	1 (14)	0	3 (14)
Total patients (%)	10 (45)	7 (32)	5 (23)	22

All patients with benign etiology (n=10) were found to have reactive hyperplasia (unknown etiology as noted from culture results), except, for one who had a lymphangioma. Histopathology report of benign lymphadenopathy usually showed findings of reactive hyperplasia with aggregates of lymphoid follicles, some, with granulation tissue and fibrosis. The lymph nodes were described as soft, movable, well-defined, and non-tender on palpation.

Tuberculous adenitis (n=7) was described on histopathology as having granulomas composed of epithelial cells, histiocytes and

fibroblast with accompanying Langhan's type of multinucleated giant cells; some had areas of caseating necrosis. The palpated lymph nodes were soft, movable, or fixed and were often tender.

Cases found to be malignant were Non-Hodgkin's lymphoma (n=2) and Hodgkin's lymphoma (n=3). Histopathology reports described Hodgkin's lymphoma with Reed-Sternberg cells and prominent eosinophilic nucleoli; one case has mixed cellularity with lymphocytes and neutrophils. Non-Hodgkin's lymphoma was described as neoplastic cells with predominantly small or large lymphocytes. On examination, the lymph nodes were predominantly matted, fixed, and non-tender.

The distribution of biopsy sites according to etiology was also shown in Table 3. Majority were cervical (78%), followed by inguinal (14%). Only one of the cases with malignant etiology presented as a supraclavicular mass.

DISCUSSION

In this study, the clinical profile included the findings that males were more commonly affected, patients with benign etiology were younger whereas those with malignant etiology were older, majority of the cases have localized lymphadenopathy and the more frequent presentation was a palpable mass and fever. Results also showed benign hyperplasia as the most common cause for lymphadenopathy followed by TB adenitis with cervical area as most common site. Majority of the patients received antibiotics pre and post biopsy and despite the invasiveness of the procedure, excision lymph node biopsy was the predominant procedure utilized.

The demographics of the study showed a male preponderance (77%). A similar study on the clinico-pathological profile of lymphadenopathy done in India also showed male predominance (male-to-female ratio of 1.67:1), although, it further stated that there is no predilection for lymphadenopathy with regards to gender.[12] A study by Adeluso et al. found lymphomas to be more common in males, which was also evident in this study. This suggests that though gender is not a risk factor for lymphadenopathy, certain etiology for significant lymphadenopathy is more prevalent in one gender over the other.

The age and duration of lymph node enlargement are two other risk factors reported in malignant disease;[14]Soldes, et al. reported increasing age, while Bazemore, et al. found older age and duration of greater than two weeks to be associated with increased risk for malignancy. In this study, the duration of lymphadenopathy was shortest in malignant etiology but generally presented longer than eight weeks. The patients' ages varied according to the different etiologies with a tendency towards younger (mean 6.5 years ± 3.8 years) ages in those with benign etiology, and older (mean 12.4 years ± 4.2 years) ages in those with malignant etiology.

The number of lymph node sites involved may be a factor related to etiology. This study had a majority of the cases to have localized lymphadenopathy, with malignant etiology having the most number of lymph node sites involved. However, its mean values were not as varied (benign 1.2 sites; TB adenitis 1.3 sites; and malignant 1.8 sites) as the other clinical factors discussed, which implies that there is no significance in localized versus generalized lymphadenopathy. Generalized and progressive lymphadenopathy often indicates the presence of a significant disease which would entail the need for biopsy in the absence of an apparent etiology. Karadeniz, et al. reported that pyogenic infections more frequently manifested with localized lymphadenopathy while cytomegalovirus infection, infectious mononucleosis, rubella, acute leukemia and non-Hodgkin's lymphoma frequently manifested with limited or generalized lymphadenopathy.

The most common clinical findings were the presence of a palpable mass and fever. In the study by Soldes et al, they found no significant differences in the presence of fever

between patients with benign and malignant lymphadenopathy. Other than fever, malignancy is often associated with constitutional signs, such as weight loss, which was noted in 40% of the malignant cases in this study.

The predominant cause of peripheral lymphadenopathy in the study was reactive hyperplasia of unknown etiology while the most predominant site involved was the cervical area. Several studies done in third world countries also found the cervical area as the most common site, with TB adenitis as the most common cause.[17, 24-29] These studies also found lymph node site to be predictive of certain etiologies. Cervical lymphadenopathy was commonly found to be infectious in nature while supraclavicular nodes were more likely to be malignant.[14]

Majority of the benign cases in this study presented with cervical lymphadenopathy. Cervical adenitis typically results from an upper respiratory tract infection and one case in the study had rhinorrhea as the only symptom other than a mass. However, bacterial cultures of biopsy samples showed no growth in all the benign cases. Benign peripheral lymphadenopathy may result from viral, bacterial, and/or fungal diseases of the skin, teeth, gingivae, throat, sinuses and ears. Infectious mononucleosis caused by Epstein Barr virus is a common cause of cervical lymphadenopathy and patients with this illness typically have firm, non-tender lymph nodes and associated systemic somatic complaints consisting of fatigue, fever, and sore throat. In this study, palpable lymphadenopathy of benign etiology was also described as either firm or soft and non-tender. Other viral causes commonly presenting with lymphadenopathy include herpes simplex, cytomegalovirus, adenoviruses, rubella, rubeola and varicella. Bacterial cervical lymphadenitis is usually due to group A B-hemolytic streptococci or Staphylococcus aureus while anaerobic bacteria are usually in association with dental caries and periodontal disease. Subacute or chronic lymphadenopathy with a gradual progression over two or more weeks may be due to cat-scratch disease, toxoplasmosis and atypical mycobacteria. Fever, which is a major manifestation of an infectious pathology, appears to present more frequently in benign etiology in comparison to TB adenitis and malignancy.

This study showed TB adenitis to be a significant and prevalent cause of lymphadenopathy (32%). Lymphadenopathy or lymphadenitis secondary to Mycobacterium species, can be due to *M. tuberculosis*, *M. scrofulaceum*, and *M. avium-intracellularis*; the latter two are commonly termed non-tuberculous mycobacterium (NTM). The most common site for TB lymphadenopathy is the cervical area, [17with] lymph nodes being the second most common organ involved in tuberculous disease after the lungs. The nodes are typically discrete, firm, mobile, and tender, similar to the clinical profile of TB adenitis in this study. NTM cervical lymphadenopathy is primarily a childhood disease and like localized tuberculous lymphadenitis, does not commonly present with constitutional symptoms such as fever.[18] This study found fever to be least frequent in the TB adenitis cases.

The malignant cases presented with an older mean age in comparison to TB adenitis and reactive hyperplasia; in this study, all five malignant cases were six years or older. In children older than six years, Hodgkin disease and non-Hodgkin lymphoma are the predominant malignancies, [1which] was reflected in this study. A study on the predictors of malignancy in childhood peripheral lymphadenopathy found increasing size, number of sites of adenopathy, and age as being associated with increasing risk of malignancy.[14] Such observations were noted in this study, with increasing trend of lymph node size and number of lymph node sites involved in cases with malignant etiology.

Four out of five malignant cases in this study were cervical in location. More than 25% of malignant tumors in children occur in the

head and neck, and the cervical lymph nodes are the most common site.[23] Malignant lymphoma accounts for approximately 50% of head and neck malignancies in children, while metastatic cervical adenopathy unrelated to lymphoma is very uncommon in children.[24]Lymphomatous nodes are frequently larger and more extensive than those of infectious etiology, which were seen in the histopathologic study cases of Hodgkin's and Non-Hodgkin's lymphoma.

Fifty percent of the cases received broad-spectrum antibiotics, with no apparent effect on the size of the lymph node. Van de Schoot et al. cited absence of clinical improvement in significant lymphadenopathy within 10 to 14 days of treatment deserves further evaluation.[16] In general, majority of inflamed lymph nodes are due to infectious etiology and may resolve spontaneously or with antibiotics.

Excision lymph node biopsy, despite its invasive nature and need for general anesthesia, was the predominant procedure utilized at our institution. Thomas, et al. suggested the use of FNAB for peripheral lymphadenopathy as a simple, cost-effective procedure that has proven to be reliable in distinguishing reactive lymphadenopathy, TB, and malignant conditions. Though difficult to do in young children, adolescents may benefit in FNAB as opposed to excision biopsy.

Unexplained lymphadenopathy lasting for more than a month warrants specific investigation or biopsy[14] and the possibility of a malignant etiology for the lymphadenopathy is foremost in the decision to do a biopsy. Although such procedures may be invasive, this study shows that a 23% yield for a malignant diagnosis is a considerable risk that provides justification to do biopsy.

Although this study's sample size was small, the results show the following to be factors useful in determining if surgery is warranted: the age of the patient, the size and site of the lymphadenopathy, the duration of lymph node enlargement, the lack of response to initial antibiotic treatment and the presence or absence of certain signs and symptoms such as fever and weight loss.

The foremost limitation of the study was the sample size, which made it unfeasible to compute for significant differences between the three histopathologic categories. Incomplete data recording on patients' charts also posed a limitation in expanding the factors included in the clinical profile.

CONCLUSIONS AND RECOMMENDATIONS

The histopathologic biopsy results of childhood lymphadenopathy at MMC showed that TB and reactive lymphadenopathy were common problems, comparable to other third world countries. Malignant cases were also noted, and like in infectious causes, these were seen mostly in the cervical area. The small sample size was a limitation in giving significance to the observations noted in the clinical presentation of the patients. These include the findings that patients with benign etiology were younger, presented more frequently with fever; and that males were more commonly affected; whereas malignant etiology presented with older children, had a shorter duration of lymphadenopathy, which was of a larger size and was accompanied by weight loss. Excision biopsy was predominantly the surgical procedure used in children with peripheral lymphadenopathy despite extensive invasiveness and requirement of general anesthesia.

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