

Aetiology of peripheral lymphadenopathy in adults: Analysis of 1724 cases seen at a tertiary care teaching hospital in southern India

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ABSTRACT

Background. In patients presenting with peripheral lymphadenopathy, excision biopsy of the most accessible lymph node provides material to establish an early diagnosis, and is important in the management of these patients.

Methods. A retrospective study was done of 1724 lymph node biopsy specimens obtained from adult patients and submitted for histopathological examination over a 12-year period.

Results. About one-third ($n=614$; 35.6%) of these patients had non-specific lymphadenitis. This included a heterogeneous group of disorders comprising benign follicular hyperplasia, reactive hyperplasia, marked follicular hyperplasia and reactive sinus histiocytosis. Tuberculosis lymphadenitis ($n=540$; 31.3%) and malignancy ($n=447$; 25.9%) were the other common causes. Of the 540 patients with tuberculosis lymphadenitis, the human immunodeficiency virus (HIV) status was tested in 424 (78.5%) patients; of these, 34 patients (8%) were HIV-seropositive. Epithelioid granulomas with caseation necrosis were more frequently seen in HIV-seronegative patients compared with HIV-seropositive ones ($\chi^2=54.66$; $p<0.001$). In HIV-seropositive patients, multiple sites of lymph node involvement ($\chi^2=40.597$; $p<0.001$), suppurative type with adjacent necrosis and panniculitis ($\chi^2=68.128$; $p<0.001$), and non-reactive histological types ($\chi^2=109.234$; $p<0.001$) were more commonly seen compared with HIV-seronegative patients. Kikuchi-Fujimoto disease ($n=36$), Kimura disease ($n=7$), Rosai-Dorfman disease ($n=6$), were rare aetiological causes that have been infrequently reported from India.

Conclusion. Awareness of the characteristic histopathological findings and uncommon aetiological causes of peripheral lymphadenopathy may spare patients from unnecessary evaluation and treatment. In HIV-positive patients, lymph node tuberculosis may be histopathologically unusual and may be suppurative or non-reactive in nearly one-third of patients.

Natl Med J India 2007;20:78-80

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INTRODUCTION

The lymph nodes along with the spleen, tonsils and mucosa-associated lymphoid tissue play a central role in the control of immune response.¹ Peripheral lymphadenopathy found on physical examination is an important clue to the underlying aetiological diagnosis. However, the cause of peripheral lymphadenopathy often cannot be ascertained on clinical grounds alone. Furthermore, the therapeutic and prognostic implications of peripheral lymphadenopathy necessitate an accurate and prompt diagnosis. Excision biopsy of the most accessible peripheral lymph node provides material to establish an early diagnosis and is a vital part of the management.

In recent times, increased longevity, human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) pandemic, and increased accessibility to and use of immunosuppressive drugs have resulted in a changing spectrum of diseases presenting with peripheral lymphadenopathy. Little published evidence is cited while listing the causes of peripheral lymphadenopathy in most undergraduate and postgraduate textbooks published from India. These observations largely appear to be intuitive or anecdotal. Moreover, during the past decade, little has been documented from India regarding the aetiology of peripheral lymphadenopathy. We, therefore, retrospectively analysed the case records of patients presenting with peripheral lymphadenopathy to ascertain the aetiology.

METHODS

We retrospectively analysed the case records of 1735 patients who presented to the Medicine outpatient services and to the clinic for staff members of the Sri Venkateswara Institute of Medical Sciences (SVIMS) hospital, Tirupati, with peripheral lymphadenopathy, and had an excision biopsy done between January 1993 and December 2005. This tertiary care referral centre and teaching hospital caters to the population of the Rayalaseema area comprising Chittoor, Kadapa, Kurnool and Anantapur districts of Andhra Pradesh. Our institution does not have paediatric and otorhinolaryngological services, two areas where a number of such patients could present. Data obtained from 1724 adult patients were included for analysis.

After obtaining informed consent, excision biopsy of the most accessible peripheral lymph node was performed as an outpatient procedure in all patients. Conventional haematoxylin and eosin staining was used to analyse the biopsy specimens and additional special staining was done (e.g. Ziehl-Neelsen stain for acid-fast bacilli [AFB]) where required. Details of patients such as the demographic parameters, clinical presentation, physical examination findings and histopathological diagnosis were noted in a structured proforma. Among patients with tuberculosis lymphadenopathy, serological testing for HIV-1 and -2 was performed after obtaining informed consent on a voluntary basis using enzyme-linked immunosorbent assay (ELISA; Labsystems OY, Helsinki, Finland).

Statistical analysis

In patients with and without HIV and tuberculosis co-infection, the site of lymph node involvement and histopathological findings were compared by the chi-square test using the software package SPSS (version 10.0, SPSS Inc., IL, USA).

RESULTS

The mean (SD) age of the patients was 28.1 (3.2) years (range 18-80 years); there were 858 men. The aetiological diagnosis in these

patients is shown in Table I. The majority ($n=614$; 35.6%) of these patients had non-specific lymphadenitis. This included a heterogeneous group of disorders comprising benign follicular hyperplasia, reactive hyperplasia, marked follicular hyperplasia and reactive sinus histiocytosis. Tuberculosis lymphadenitis ($n=540$; 31.3%, 240 men) was the second most common cause followed by malignancy ($n=447$; 25.9%). In patients with Kikuchi-Fujimoto disease ($n=36$), women outnumbered men (M:F=1:2.6).

In patients with tuberculosis lymphadenitis ($n=540$; 31.3%) the following histopathological findings were observed: epithelioid granulomas with caseation ($n=398$; 74%); epithelioid granulomas without caseation ($n=103$; 19%); non-reactive type ($n=22$; 4%); and suppurative type with adjacent necrosis and panniculitis ($n=17$; 3%). AFB could be demonstrated in 175 of 398 lymph node samples (44%) with epithelioid granulomas and caseation necrosis. AFB were demonstrated in all the lymph node specimens of patients with non-caseating epithelioid granuloma, non-reactive and suppurative types.

Of the 540 patients with tuberculosis lymphadenitis, the HIV status could be tested in 424 (78.5%) patients who consented for voluntary HIV testing after informed consent. Of these, 34 patients (8%) were HIV-seropositive. In HIV-seronegative patients with tuberculosis lymphadenitis, cervical lymph node involvement was the commonest (90%) followed by axillary (37%) and inguinal (10%) lymphadenopathy. In 129 patients (33%), more than one lymph node site was involved (Table II). Epithelioid granulomas with caseation necrosis were seen more frequently in HIV-seronegative patients compared with HIV-seropositive ones ($\chi^2=54.66$; $p<0.001$).

Multiple sites of lymph node involvement ($\chi^2=40.597$; $p<0.001$), suppurative type with adjacent necrosis and panniculitis ($\chi^2=68.128$; $p<0.001$), and a non-reactive type ($\chi^2=109.234$; $p<0.001$) of histology were more commonly seen in HIV-seropositive than in HIV-seronegative patients.

TABLE I. Lymph node pathology in 1724 specimens

Pathological diagnosis	<i>n</i> (%)
Non-specific lymphadenitis	614 (35.6)
Tuberculosis	540 (31.3)
Other granulomatous disorders	26 (1.5)
Sarcoidosis	16
Cat-scratch disease	9
Lymphogranuloma venereum	1
Malignancy	447 (25.8)
Lymphoma	217
Non-Hodgkin lymphoma	159
Hodgkin disease	58
Metastases	230
Kikuchi-Fujimoto disease	36 (2.1)
Others	61 (3.5)
Progressive transformation of germinal centre	15
Dermatopathic lymphadenopathy	11
Angioimmunoblastic lymphadenopathy	10
Filariasis	7
Kimura disease	7
Rosai-Dorfman syndrome	6
Langerhans cell histiocytosis	3
Gaucher disease	1
Histiocytic medullary reticulosis	1
Total	1724

All percentage figures corrected to the first decimal place

In patients with Kikuchi-Fujimoto disease ($n=36$), only the cervical and submandibular lymph nodes were involved. In 7 patients with sarcoidosis, in addition to the lymph node biopsy, biopsy of the skin lesion also revealed non-caseating epithelioid granulomas.

DISCUSSION

Palpable peripheral lymph nodes offer an important diagnostic clue to the aetiology of the underlying condition. Though fine-needle aspiration and cytology (FNAC) is commonly used to establish the aetiological diagnosis, excision biopsy of the lymph node remains the 'gold standard' for diagnosis.²⁻⁴ In all our patients, biopsy was done as an outpatient procedure with minimal morbidity and no mortality, reiterating the fact that it is a simple and effective method for confirmation of the diagnosis.

Non-malignant causes ($n=1288$; 74.2%) were more frequent in the lymph node biopsy specimens compared with malignant ones ($n=354$; 25.8%). Lymph node hyperplasia was the most common cause of peripheral lymphadenopathy in our study. Similar findings have been reported in studies from Zimbabwe² and South Africa.⁴ Lymph node hyperplasia appears to be the culmination of a variety of pathological processes, an important influence being that of HIV infection. The evolution of changes in primary HIV lymphadenopathy has been reported to range from mild follicular hyperplasia through diffuse follicular hyperplasia to the 'burnt-out' node. These observations of lymph node pathology are thought to reflect the high prevalence of HIV infection.² We could not analyse the HIV status in patients with non-specific lymphadenitis because routine HIV testing was not performed in these patients. As the HIV prevalence rates in Andhra Pradesh are among the highest in India (>5% among high-risk groups and >1% among antenatal women),⁵ it is possible that the high prevalence of lymph node hyperplasia may be related to the high prevalence of HIV. In a study from South Africa ($n=1877$),⁴ a second pathology could be identified in 18 of 637 cases (3%) with reactive lymphoid hyperplasia. Three patients developed tuberculosis lymphadenitis and in 15 patients a diagnosis of

TABLE II. Comparison of characteristics in HIV-positive and HIV-negative patients with tuberculosis lymphadenitis*

Variable	HIV-negative patients (<i>n</i> =390)	HIV-positive patients (<i>n</i> =34)
Mean (SD) age (years)	27.8 (2.4)	28.4 (1.8)
Male:female	1:1.3	1:1.3
Site of involvement†		
Cervical	351 (90)	33 (96)
Axillary	144 (37)	23 (82)
Inguinal	39 (10)	21 (71)
Multiple sites	129 (33)	25 (89)‡
Histopathological type		
Epithelioid granulomas		
with caseation necrosis	235 (75)‡	5 (18)
without caseation necrosis	71 (23)	6 (21)
Suppurative variety	3 (1)	8 (29)‡
Non-reactive	3 (1)	9 (32)‡

Values in parentheses are percentages that have been corrected to the nearest round figure.

* Of 543 patients with tuberculosis lymphadenitis, voluntary HIV testing results were available for 424 patients † More than one site of involvement was found in several patients on clinical examination ‡ $p<0.001$

lymphoma was made from other body sites within 6 months of the initial biopsy. This represents a diagnostically difficult subgroup requiring further investigation. These observations suggest that patients with reactive lymphadenopathy should be followed up to observe whether they develop an additional condition. However, this needs further study as such an event occurred in only 3% of patients.⁴

Tuberculosis is a common cause of peripheral lymphadenopathy⁶ and excision biopsy is done to confirm the diagnosis. We found important differences between HIV-seropositive and -seronegative patients with tuberculosis lymphadenitis. In HIV-seropositive patients with tuberculosis lymphadenitis multifocal disease was more often seen ($p < 0.001$) and suppurative ($p < 0.001$) and non-reactive ($p < 0.001$) histological types were more common. These observations are similar to those reported by Bem.⁷

In India, FNAC and excision biopsy are most often used to diagnose lymph node tuberculosis. Mycobacterial culture and sensitivity testing of the excised lymph node is rarely done in routine clinical practice and is used more often in teaching and research institutions.⁶ Non-availability of facilities for such testing could be a reason for its low utilization. Observations in a large number of patients at the Tuberculosis Research Centre, Chennai,⁸ suggest that the use of transport media such as selective Kirchner liquid medium to transport a part of the excised lymph node specimen to a specialized centre for mycobacterial culture and sensitivity testing increased the mycobacterial culture yield to >60%. This medium can be used to transport specimens at ambient temperature over 18–20 hours without any loss in culture positivity. Also, the specimen can be stored in this medium for up to 15 days in a refrigerator without loss of culture positivity. If the logistics are worked out, this investigation has the potential to be used more widely. No single histopathological observation or combination of features can distinguish sarcoidosis from tuberculosis. Though sarcoid granulomas seldom have necrosis, the necrotizing granulomas are reticulin-rich and this can be used to distinguishing sarcoidosis from tuberculosis.^{9,10}

Malignancy constituted one-fourth of all causes of peripheral lymphadenopathy and more than half of these were due to metastases. Metastatic lymph node involvement usually occurs late in the course of the disease. Our observations reiterate the fact that, in India, as in other resource-poor countries, a large majority of patients with cancer are diagnosed at a late stage.¹¹

In conclusion, the varied aetiology of peripheral lymphadenopathy observed at our tertiary care centre, as documented by histopathological evaluation, indicates that there is a need for proper awareness to avoid unnecessary diagnostic intervention. Furthermore, in HIV-positive patients, lymph node tuberculosis may be histopathologically unusual and may be suppurative or non-reactive in nearly one-third of cases.

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