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Aspiration cytology study of lymphadenopathy: Is EPTB a common pathology? A three-year retrospective study in Melmaruvathur teaching hospital

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Abstract

Background: Lymphadenopathy is a common clinical presentation among all age group and the aetiology may varies from inflammatory condition to malignancy. In India, tuberculous lymphadenopathy is quiet common.

Objective: This study was aimed to assess the common pathology in lymphadenopathy by fine needle aspiration cytology study and to observe the spectrum of cytomorphological features in granulomatous lymphadenitis to enhance the aetiological awareness and diagnostic accuracy.

Materials and methods: This retrospective study was conducted in Melmauvathur teaching hospital for a period of three years between 2016-2018. Patients subjected to Fine needle aspiration cytology study for lymphadenopathy were included in this study irrespective of age and sex. All demographic, clinical and cytological findings were collected from laboratory documents and statistically analysed.

Results: A total of 167 cases were studied, of which 100 Cases were female and 67 were male 81 cases were children below 14 years and 86 were adults. 161 nodes were cervical nodes and 91% of node showed inflammatory pathology. Granulomatous adenitis was the common pathology observed in 107 cases (64%) which was statistically significant ($P = < 0.00001$) followed by nonspecific adenitis in 45 cases (27%). The common age group affected with granulomatous adenitis were adult between 15-30 years ($n=37$; 34.5%) followed by children between 5-10 years ($n=24$; 22.4%) with females predominance (65. 4%). Among the cytomorphological features, late granulomatous changes with caseation were seen predominantly in adults and early granulomatous changes were seen commonly in children and the specific morphology of granuloma with neutrophilic infiltration was predominantly seen in female (82.4%).

Conclusion: Granulomatous inflammation was the common pathology affecting cervical nodes predominantly. Among age, increased prevalence occurs in adults between 15-30 years followed by children between 5-10 years with female preponderance.

Keywords: FNAC, node cytology, EPTB, granulomatous adenitis, node TB

Introduction

Fine needle aspiration cytology is a valuable tool for establishing diagnosis in superficial lymphadenopathy. Now Tuberculosis (TB) is a major public health concern worldwide and the World Health Organization (WHO) estimated 10.4 million incident cases of TB and 1.67 million deaths in 2017 ^[1]. Though Pulmonary TB is the common presentation, it can also involve other organs, of which the common extra pulmonary site affected is lymph nodes. The term extra pulmonary tuberculosis (EPTB) is used to describe an isolated occurrence of Tuberculosis at sites other than lung ^[2]. National Tuberculosis control programs are highly focussed on pulmonary Tuberculosis but currently the occurrence of an isolated extra pulmonary Tuberculosis (EPTB) is increasing. The diagnosis is often delayed due to atypical clinical presentation of this EPTB and the need of tissue samples rather than sputum for diagnosis. The emergence of Non tuberculous Mycobacterial (NTM) infection with different clinical and cytomorphological presentation also created confusion in diagnosis. This paper is aimed to assess the common pathology in lymphadenopathy and to observe the spectrum of morphological changes in granulomatous lymphadenitis to increase the aetiological awareness and diagnostic accuracy.

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Materials and methods

This was a retrospective study conducted at Melmaruvathur Medical college hospital for a period of three years between 2016-2018. All the patients irrespective of the age, sex who attended cytology laboratory for fine needle aspiration cytology (FNAC) study of lymph nodes were included for this study. FNAC procedure was carried out under aseptic precautions after getting consent and smears were prepared. Smears were stained with routine Haematoxylin and Eosin stain after fixation with 70% alcohol. All the slides were screened and reported by same pathologist. Demographic details, clinical and cytological findings were taken from laboratory records and statistically analysed.

Results and Observations

A total of 167 cases were studied during the three-year period of which 100 cases were female (60%) and 67 were male (40%). Among the age group, 81 cases were children up to the age of 14 years and 86 were adult with age beyond 14 years. The common age group affected among children were between 5-10 years (n=46; 57%) followed by adult between 15-30 years (n=45; 52%). Out of 100 female patients, 58 were adults and predominantly between the age of 15-30 years (n=31) and 42 were children with predominantly affected the age group between 5-10 years (n=23) (Table-1). Out of 167 cases, 161 nodes affected were anterior and posterior cervical groups and the remaining were two submandibular, two inguinal and two posterior auricular nodes. Cytological reports showed predominantly non neoplastic inflammatory adenitis (91%) and so we broadly categorized the reports into chronic nonspecific inflammation and granulomatous inflammation of lymph node. Among 167 cases, granulomatous lymphadenitis was reported for 107 cases (64%) and 45 cases (27%) were reported as nonspecific inflammation and it was statistically significant with a p value of <0.00001. (Table-2). Age wise distribution among children (n=81) showed 32 cases of nonspecific inflammation (39.5%) and 46 cases of granulomatous inflammation (56.8%). Out of 86 cases of adult, only 13 cases (15.1%) were reported as nonspecific adenitis and 61 cases (70.9%) were diagnosed as granulomatous adenitis. Two paediatric cases were reported as inconclusive due to insufficient cellularity obtained from small nodes in children. 13 cases were categorized as others which included six neoplastic lesion of node, four salivary gland pathology like sialadenitis, pleomorphic adenoma and three were reported as haemorrhagic colloid cyst where lower anterior cervical submandibular, posterior auricular site swelling were misdiagnosed clinically as lymphadenitis. Among the six neoplastic lesion, three were secondary metastatic deposits from papillary carcinoma of thyroid one plasma cell neoplasm, one squamous cell carcinomatous deposits and one primary lymphoma. All granulomatous lymphadenitis was sub categorised into 6 types based on morphology into

1. Reactive adenitis with suspicious granulomatous changes showing occasional transforming epithelioid cells within histiocytic aggregates among polymorphous lymphoid cells. (Figure-1)
2. Early granulomatous changes in reactive background showing polymorphous lymphoid cells along with few aggregates of transforming epithelioid cells. (Figure-2)
3. Granulomatous adenitis with many classic mature

epithelioid cells aggregates

4. Granulomatous adenitis with caseation necrosis
5. Cold abscess with extensive caseation necrosis and degenerated ghost like epithelioid cell aggregates
6. Epithelioid cell aggregates with superadded neutrophilic suppurative changes.

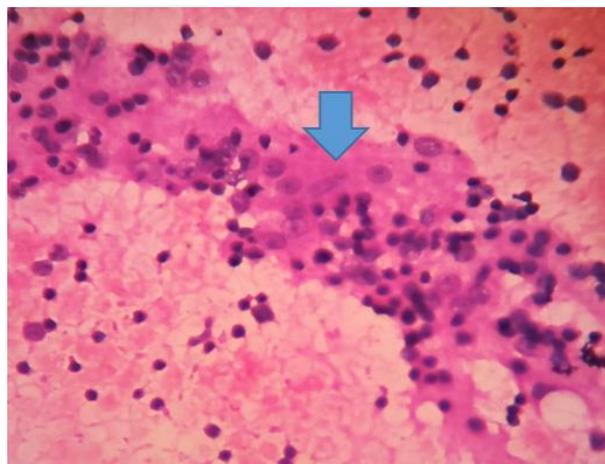


Fig 1: Photomicrograph showing cluster of active histiocytes with suspicious transforming epithelioid cells (Arrow) - categorized as Group-1. Haematoxylin & Eosin x 400

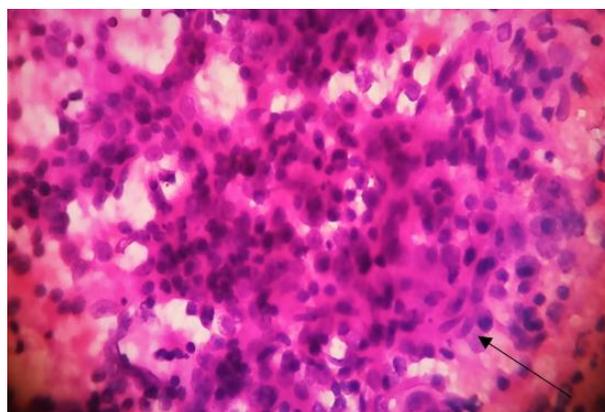


Fig 2: Photomicrograph showing cluster of histiocytes with few transforming epithelioid cells (Arrow)-categorized as Group-2. Haematoxylin & Eosin x 400

Among the 107 cases of granulomatous adenitis, 32 cases (30%) were fallen into third category of granulomatous adenitis followed by fourth category of caseating granulomatous lymphadenitis (n=25; 23%). 17 cases were come under sixth category where pus was aspirated and cytomorphology showed plenty of neutrophils along with lymphocytes and epithelioid cell aggregates. (Table-3) Correlations of these different morphological changes with different age groups were statistically analysed. It showed late changes like granuloma, caseation, and cold abscess were predominantly seen in adult especially between 15-30 years than children. Early changes of transforming epithelioid cells in reactive background were predominantly seen in children than adult. Among sex distribution, females were commonly affected with granulomatous adenitis (n=70; 65%) than male. Morphological sub categorization showed the sixth category of granuloma with suppurative changes was predominantly seen in females (n=14; 82.3%) than male (Table-3).

Table 1: Age and sex distribution

Sex	Age group								
	N ₁ = 81 Children			N ₂ = 86 Adult					Total count
	<5years	5-10 years	11-14 years	15-30 years	31-40 years	41-50 years	>50 years		
Male	12 (48%)	23 (50%)	4 (40%)	14 (31%)	5 (39%)	1 (7%)	8 (61%)	67 (40%)	
Female	13 (52%)	23 (50%)	6 (60%)	31 (69%)	8 (61%)	14 (63%)	5 (39%)	100 (60%)	
Total	25 (31%)	46 (57%)	10 (12%)	45 (52%)	13 (14%)	15 (17%)	13 (14%)	167 (100%)	
	81 (Children)- 49%			86 (Adult) -51%					

Chi-square =4.375 p=0.224

Table 2: Cyto diagnosis among different age groups

Cyto diagnosis	Age group incidence							Total count
	<5years	5-10 years	11-14 years	15-30 years	31-40 years	41-50 years	>50 years	
Inconclusive	1	1	0	0	0	0	0	2
	1%	1%	0%	0%	0%	0%	0%	1%
Non specific Inflammation	7	21	4	6	3	4	0	45
	4%	13%	2%	4%	2%	2%	0%	27%
Granulomatous Inflammation	17	24	5	37	8	8	8	107
	10%	14%	3%	22%	5%	5%	5%	64%
Others	0	0	1	2	2	3	5	13
	0%	0%	1%	1%	1%	2%	3%	8%
Total count	25	46	10	45	13	15	13	167
	15%	28%	6%	27%	8%	9%	8%	100%

Chi-square statistic is 33.326**. The p-value is < 0.00001

Table 3: Distribution of Morphological spectrum of Granulomatous adenitis among age & sex

TB grade	Age group incidence								Sex distribution	
	<5years	5-10 years	11-14 years	15-30 years	31-40 years	41-50 years	>50 years	Total	Male	Female
1-Reactive node with suspicious granuloma	2	2	0	3	1	0	1	9	3	6
	2%	2%	0%	3%	1%	0%	1%	8%	3%	6%
2-Early granuloma in reactive node	8	7	1	2	1	1	0	20	9	11
	7%	7%	1%	2%	1%	1%	0%	19%	8%	10%
3-Granuloma without caseation	4	10	0	12	1	3	2	32	11	21
	4%	9%	0%	11%	1%	3%	2%	30%	10%	20%
4-Granuloma with caseation necrosis	3	2	2	11	4	1	2	25	11	14
	3%	2%	2%	10%	4%	1%	2%	23%	10%	13%
5-Cold abscess	0	0	1	3	0	0	0	4	0	4
	0%	0%	1%	3%	0%	0%	0%	4%	0%	4%
6-Granuloma with suppuration	0	3	1	6	1	3	3	17	3	14
	0%	3%	1%	6%	1%	3%	3%	16%	3%	13%
Total	17	24	5	37	8	8	8	107	37	70
	16%	22%	5%	35%	7%	7%	7%	100%	35%	65%

Chi-square statistic is 25.2863. The p-value is 0.065. Chi-square statistic is 1.316. The p-value is 0.725.

Discussion

Fine needle aspiration cytology is the first line screening diagnostic tool for any superficial mass lesion and nowadays it replaces excision biopsy in majority of cases. Superficial lymphadenopathy is a commonly encountered clinical finding in developing countries like India and increasing trends of EPTB necessitates the morphological confirmation of its diagnosis for appropriate treatment. Though EPTB affect any organs like pleura, bones, joints, meninges, peritoneum, abdominal organs, the commonest site affected is the lymph nodes [3].

In our study the predominant age group affected with lymphadenopathy were between 5-10 years among children (57%) and 15-30 years among adult (52%) whereas study by Srivatsav showed predominance of lymphadenopathy among 21-50 years (49.11%) followed by 0-20 years (36.98%) [4]. Our study showed females preponderance for

lymphadenopathy (60%) especially among adult between 15-30 years of age than male which was supported by other studies where the female predominance observed were 55% and 61% respectively [5, 6]. Similar to other studies, cervical lymphadenopathy was a common presentation in our study. The common pathological lesion we found in our study was Granulomatous lymphadenitis (64%) which was in opposition with the other studies where reactive lymphadenitis was the predominant lesion and the prevalence of granulomatous pathology was less 28.08%, 11.5%, respectively [7, 8]. However, the increased prevalence of reactive lymphadenitis among male children with the age of less than 10 years observed in our study was supported by the study of Mohanty *et al.* Similar to other studies we also appreciated gender predilection for granulomatous adenitis in female (65%) than male [9-11].

The causes for granulomatous inflammatory changes in lymph nodes vary from infective conditions like mycobacterium, fungus, parasite and non-infective causes like foreign body, sarcoidosis, Wegener's granulomatosis, crohns disease and also in association with neoplastic conditions like Hodgkin lymphoma [12]. So correlation of clinical findings, associated cytomorphological features, additional staining procedures and other relevant laboratory investigations are essential for confirming the etiological agent triggering this granulomatous response. We tried an attempt to observe the cytomorphological changes in granulomatous lymphadenitis in order to understand the immune response and the triggering etiological factor for this change.

Cytomorphological spectrum of granulomatous adenitis was categorized by many authors into three or four groups based on the presence of epithelioid cell granuloma, caseous necrosis, giant cells and neurophilic granuloma [13, 14]. But we categorized granulomatous adenitis into six groups by including the earliest transition of histiocytes into epithelioid cells as transforming epithelioid cells. These transforming epithelioid cells have plump ovoid to spindle transitional nuclei with prominent nucleoli entrapped within histiocytic aggregates. We noticed that this early granulomatous changes of first two group with transforming epithelioid cells were predominantly seen among children with small size nodes. The observation of this early transitional change of granulomatous inflammation nicely explained the evolutionary pathogenic mechanism of initial immune response against the persistent pathogen. Probably follow up cytological study may show late changes of mature granulomatous response in these cases and so clinical follow-up can be suggested. The third, fourth, fifth group of granulomatous adenitis showed mature epithelioid cell aggregates, caseous necrosis and cold abscess that obviously explained the tuberculous aetiology. Here the morphology of mature epithelioid cells have spindle boot shaped thin nuclei rather than plump and without nucleoli. However, the etiological triggering factor for the sixth group characterized by suppurative granuloma was confusing. Granuloma with suppurative changes can occur due to variety of infections like fungus, mycetoma, leishmaniasis, bacteria along with atypical mycobacterium mainly *marinum* and *fortuitum* [15, 16]. Cases had been reported with this morphology in non-infective immune conditions like adult onset Still's disease also [17]. The author had an experience of misdiagnosing clinical cold abscess as suppurative abscess since cytomorphology showed neutrophilic necrosis without granuloma. The diagnosis was changed to atypical mycobacterial infection since the cytological material showed positive bacilli for AFB staining. This emphasize the necessity of special staining procedure like AFB, PAS, Grams stain for any lymph nodal pus aspiration in order to avoid misdiagnosis of sixth group cytomorphology.

Our study has limitations that we did not do any special staining procedure especially AFB staining for confirming the granulomatous adenitis as tuberculous lymphadenitis.

In summary we concluded that morphological sub categorization of granulomatous lymphadenitis was useful in cytological study for assessing the immune response of the patient as well as it will give a clue for the aetiological aspect of granulomatous inflammation. Though tuberculosis is the common cause for granulomatous inflammation

superadded suppurative morphology can occur due to many other infections and immune condition. So accurate etiological diagnosis by additional staining techniques are essential in such cases for appropriate treatment so that unnecessary body injury by unwanted medications can be avoided.

Conclusion

Fine needle aspiration cytology study is a useful tool for diagnosing lymphadenopathy. The common age group affected with lymphadenopathy was between 5-10 years among children and 15-30 years among adult with females preponderance. Granulomatous lymphadenitis was a common pathology and increased prevalence of granulomatous lesion among female were noted. Cytomorphological changes of early granulomatous immune response was more among children and mature granulomatous response with caseation necrosis were common among adult. The specific cytomorphological change of suppurative granuloma was common among female.

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