



“DIAGNOSTIC CHALLENGES IN CYTODIAGNOSIS OF HODGKIN LYMPHOMA – AN EXPERIENCE IN RURAL BASED TERTIARY CARE HOSPITALS”

Pathology

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ABSTRACT

Introduction Fine Needle Aspiration (FNA) is an important diagnostic tool in any enlarged lymph node and has significant utility in diagnosing Hodgkin Lymphoma (HL). To evaluate the diagnostic challenges in the cytodiagnosis of Hodgkins Lymphoma and to identify the ways to minimize the false negative diagnosis.

Materials and Methods: A prospective study on 30 FNAC with biopsy proven cases of Hodgkins Lymphoma along with a review of the preoperative FNAC smears and the diagnostic difficulties analyzed.

Results: Fourteen of the 30 cases were labelled HL, which was diagnosed on the basis of atypical mononuclear cells in preference to classic Reed-Sternberg (RS) cells.

Nine cases were termed lymphoproliferative, which showed the presence of only atypical mononuclear cells with eosinophilic nucleoli.

Three cases had an exuberant granulomatous reaction with scattered large mononuclear and occasional classical RS cells in a background of plenty of eosinophils. One case had plenty of histiocytic reaction and scattered single large cells and was called histiocytic reaction in the lymph node and the biopsy proved to be HL.

Fine needle aspiration cytology can be effectively used in the early diagnosis of Hodgkins Lymphoma when corroborated with the clinical details and the nature of the aspirate.

KEYWORDS

Fine needle aspiration cytology, Hodgkin lymphoma, Reed-Sternberg (RS) cells.

Introduction: Fine needle aspiration cytology (FNAC) of lymph node has become an integral part of initial diagnosis and management of patients with lymphadenopathy because it helps to arrive at an early diagnosis or at least plan beforehand the proper management of patients. It has gained acceptance in many centers as a diagnostic tool, when used along with immunophenotyping and molecular studies¹. FNAC has also been advocated as a useful method in comparison to more expensive surgical excision biopsies with limited financial and healthcare resources in developing countries.

Most cases of Non-Hodgkins Lymphoma can be easily diagnosed and classified based on cytology and immunophenotypic findings^{2,3}. However the diagnostic probability for Hodgkin's Lymphoma varies. Prasad et. al.⁴ reported that only 30% of HL were correctly diagnosed by FNAC whereas Jogai et.al⁵ reported that 91.3% of HL were correctly diagnosed.

Objective : To evaluate the diagnostic challenges in the cytodiagnosis of Hodgkins Lymphoma and to identify ways to minimise the false-negative diagnoses.

Materials and Methods

This was a retrospective study done on 30 selected patients (19 males and 11 females) in the study institutions between 2014 to 2017, table 1 represent age and sex ratio, We selected all the cases in which a subsequent biopsy of a previously aspirated lymph node was diagnosed as Hodgkins Lymphoma. The age of the patients ranged from 11 to 76 years (median age - 33years).Two observers independently reviewed both the FNA smears and biopsies of all the cases. The features assessed on review, in cytology smears included cellularity of the smear, presence of classic Reed-Sternberg (RS) cells and atypical mononuclear/Hodgkin cells, granulomas, and the composition of the background infiltrate including eosinophils.

Table 1. Age and sex ratio

Age/years	male	female	total	Percentage
10-19 years	4	0	4	13.33%
20-29 years	3	3	6	20%
30-39 years	6	3	9	30%

40-49 years	1	2	3	10%
50-59years	4	2	6	20%
60-69 years	0	1	1	3.33%
70-79years	1	0	1	3.33%
Total	19	11	30	

Results:

All the cases including site of the lymph node, cytodiagnosis offered on FNAC with the corresponding histopathological diagnosis and IHC report (wherever available). Cervical lymphnodes were the most common site of aspirate similar to that recorded by Khan et al⁶ table 2 represent anatomical lymph node

Table 2. Anatomical LN involved

SNO	Anatomical site	R side	L side	Bilateral	Total
1	Cervical Node	9 (64.28%)	9(75%)	3(75%)	21(70%)
2	Submandibular	-	2(16.66%)	-	2(6.66%)
3	Supraclavicular	2(14.28%)	1(8.33%)	1(25%)	4(13.33%)
4	Axillary	1(7.14%)	-	-	1(3.33%)
5	Generalized	2(14.28%)	-	-	2(6.66%)
6	Total	14	12	4	30

Fourteen cases which were called HL on cytology had classic RS cells and mononuclear RS cells in an appropriate milieu. Among these, 10 cases on excision biopsy were diagnosed as HL, classic type. (Fig 1a,b,c,d)

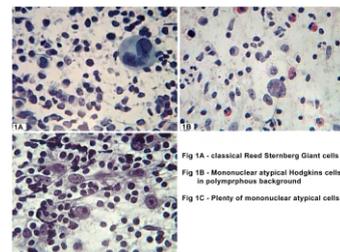


Fig 1A - classical Reed Sternberg Giant cells

Fig 1B - Mononuclear atypical Hodgkin cells in polymorphous background

Fig 1C - Plenty of mononuclear atypical cells

Nine cases were reported as lymphoproliferative disease, as they predominantly contained atypical mononuclear cells and eosinophils. On subsequent biopsy and Immunohistochemistry (IHC), four of them were found to be Classic HL and 1/6 was viral induced lymphadenitis with atypical immunoblasts. (Fig2a,b)

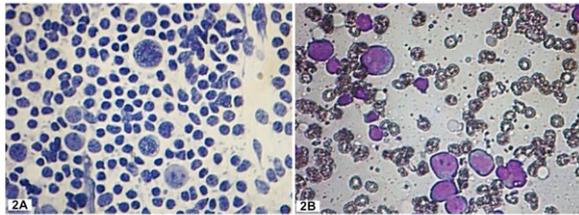


Fig 2a,b- Viral induced lymphadenopathy with immunoblasts resembling mononuclear Hodgkins cells

Three cases had an exuberant granulomatous reaction and two of it was twice treated outside as tuberculosis and received Anti Tubercular Therapy, which did not respond clinically. Repeat FNAC in our institute showed scattered large mononuclear and occasional classical RS cells in a background of plenty of eosinophils, the same has been seen in the whole node biopsy and patient responded well to the Lymphoma chemotherapy. One case was diagnosed as tuberculosis and was treated with ATT and had defaulted therapy twice, later developed pleural effusion and cardiac tamponade. This patient was treated with steroid for effusion, FNAC done in our centre showed large pleomorphic RS cells which on biopsy proved to be HL-LD type. (Fig 3)

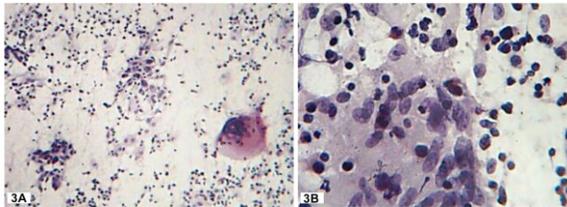


Fig 3a,b -Exuberant granulomatous reaction with scattered atypical cells

In one case the aspirate was hypocellular and non-diagnostic. But the size of the node was too large to neglect, so we asked for excision biopsy. It turned out to be HL, nodular sclerosis type with abundant fibrosis.

Three cases were missed on FNAC. One case was reported as reactive hyperplasia with plenty of immunoblasts suggesting viral etiology. However the LN did not resolve with empirical therapy, which on excision was found to be HL, lymphocyte predominant type. The second case had an exuberant histiocytic response which masked the underlying pathology. (Fig 4) The third case had pleomorphic RS cells and reported as anaplastic carcinoma/NHL, which on tissue biopsy and IHC was proved to be HL, lymphocyte depleted type. (Fig 5a, b) table 3 and table 4, represent cytodiagnosis and corresponding biopsy report

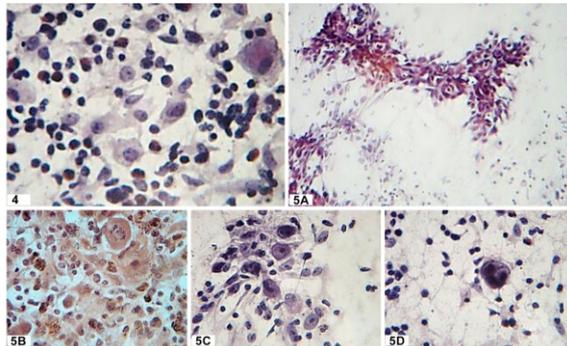


Fig 4- prominent histiocytic reaction with eosinophils
Fig 5a,b,c - Pleomorphic RS cells in clusters resembling like carcinoma

Table 3. FNAC report

S.No	Cytological diagnosis	Number of cases
1.	Hodgkins lymphoma	14(46.66%)
2	Granulomatous reaction with many RS cells	4(13.33%)
3	Viral Lymphadenitis	1(3.33%)

4	LPD suggested excision	9(30%)
5	Anaplastic carcinoma	1(3.33%)
6	Inadequate/scanty material suggested excision	1(3.33%)

Table 4. HPE Report

S.NO	HPE Report	Total	%
1	Nodular sclerosis	10	33.3%
2	Mixed Cellularity	14	46.6%
3	Lymphocyte rich	4	13.33%
4	Lymphocyte depleted	2	6.66%
	Total	30	

Discussion :

The use of FNAC as a diagnostic tool in lymph node enlargement has historically been controversial¹. This dates back to the era when recognition and classification of Malignant Lymphomas was difficult even in the histological material². However, in recent times, it is often used as the first line of investigation for screening cases with lymphadenopathy since it is easy to perform as well as being rapid and inexpensive. FNAC also has a role in staging of Lymphoma and in the assessment of residual and/or recurrent disease and may obviate the need for surgical biopsy in cases of Lymphoma located in the non-accessible sites³.

The diagnostic clue of HL in FNAC smears is the presence of classic RS cells in an appropriate milieu. However classic RS cells are not always abundant. Instead, the presence of atypical mononuclear cells along with eosinophils and florid non-caseating granulomas together should raise a high index of suspicion for HL¹⁰.

Furthermore the RS cells have to be differentiated from atypical immunoblasts seen in patients with reactive hyperplasia associated with infectious mononucleosis, post-vaccinial lymphadenitis and hypersensitivity to phenytoin 11. But these immunoblasts have coarser chromatin, smaller nucleoli and may have a plasmacytoid appearance.

Even though reactive lymphadenopathy can be included in the differential diagnosis of NLPHL, smears of the former entity should demonstrate lymphocytes in various stages of transformation with a range of cell sizes. There should be scattered immunoblasts, tingible body macrophages and follicular center cells. In contrast, NLPHL will be dominated by a monotonous background of small lymphocytes and lack the degree of polymorphism that would be expected in a large reactive node¹².

Another confounding factor is the presence of exuberant granulomatous response associated with Hodgkins Lymphoma which may distract the observer from the underlying pathology. We had 2 cases that had plenty of granulomas. A meticulous search for atypical mononuclear cells in cases with non-caseating granulomas and a clinical suspicion after the lack of response to ATT may help to avoid the false-negative diagnosis in such cases. In our study.

Despite its limitations and pitfalls, FNAC can be effectively used in the early diagnosis of Hodgkins Lymphoma when corroborated with clinical details and the nature of the aspirate. The pathologist should have a high index of suspicion of HL when a patient presents with chronic, unexplained lymphadenopathy and large atypical cells are seen in a polymorphous inflammatory background on aspiration smears and if they encounter a fibrotic node with scanty aspirate, for the size of the node. Also, any chronic lymphadenopathy diagnosed as granulomatous lymphadenitis, when not responding to an Anti-Tubercular Treatment within 2 months, then FNAC smears have to be reviewed for the presence of large RS cells and eosinophils and the lymph node has to be submitted for histopathological examination which will help to avoid unnecessary delay in treating lymphomas.

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