Journal Of Medical Science And Clinical Research
IGM Publication   An Official Publication Of IGM Publication

Original Research Article

Fine Needle Aspiration Cytology (FNAC) Is the Excellent Diagnostic Modalities for Non-Hodgkin's Lymphoma (NHL) in Tertiary Care Hospital at Muzaffarpur, Bihar

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Abstract
Objective: *Fine needle aspiration cytology (FNAC) is popular among clinicians worldwide, as a first line of investigation in all patients with lymphadenopathy and is preferred over biopsy because of its minimally invasive nature and cost effectiveness. Aim of present study was to diagnosing and grading of NHLs on morphological parameters by FNAC. The cytological grading accuracy is compared with the histological grades assigned according to the International Working Formulation (IWF) system which relies solely on morphological features, most important of which is cell size.*

Materials and Methods: *A total of 76 patients present with lymphadenopathy were sending to our department for FNAC from different OPD and IPD were included in the study. These were cases where a cytological diagnosis of NHL or suspicious of NHL was made and corresponding histological sections available and cases where a diagnosis of NHL was made in histology and corresponding FNAC smears were available irrespective of the cytological diagnosis. Cases were also graded on FNAC smears using a three tier grading system based upon cell size into low, intermediate and high grades. Cytological assigned grades were correlated with the corresponding histological grades (IWF) to determine grading accuracy.*

Result: *Out of 76 patients an accurate diagnosis of NHL was possible in 54 (71.05%) patients. Overall accurate grading was seen in 52 (68.42%) patients using cytological criteria. Out of which Accurate cytological grading was possible in 31 patients (59.61%) as low grade, 15 patients (28.84%) as intermediate and 6 patients (11.54%) as high grade Non-Hodgkin's lymphomas.*

Conclusion: *The diagnostic accuracy of FNAC for NHLs was determined using histology as the gold standard. This study highlights the utility of FNAC as a morphological tool for diagnosing and grading NHLs in a significant number of cases. This modality may assist clinicians in management of cases of NHLs, especially in centers working within the constraints of limited availability or non availability of ancillary techniques.*

Keywords: *Fine needle aspiration cytology, Non-Hodgkin's lymphomas, Diagnostic accuracy, Histology.*

Introduction

Primary diagnosis and sub classification of NHL is conventionally done on histological sections. The role of FNAC in the diagnosis and sub typing of lymphomas remains controversial, although success rates ranging from 60-90% have been reported in the published literature. The REAL and WHO classifications lay emphasis on clinical features, immunophenotyping and cytogenetics in addition to the morphological parameters. These ancillary techniques are still beyond reach of most laboratories in the developing countries. The treatment protocols even in certain well established centers are being laid down based upon the NHL grade determined by the International Working Formulation (IWF). The IWF sub typing or grading of NHLs is based upon morphological features, most important of which is the cell size. It is thus more suitable for application to FNAC smears.

Although Non-Hodgkin's lymphomas (NHL) are conventionally diagnosed and graded on biopsy specimens, it may be useful to be able to not only diagnose but also grade these cases on FNAC smears. The WHO and REAL classifications forming the basis of treatment in some centers rely on clinical features, immunocytochemistry and cytogenetics, which are beyond reach of most centers in the developing countries.

FNAC remains the investigation of choice in the initial evaluation of any patient with lymphadenopathy. In cases of lymphomas it has been of proven efficacy in cases of recurrences, in patients with multiple sites of involvement, at locations or in situations where an excisional biopsy is not feasible and in assessment of transformation to a higher grade and in a known case of Non-Hodgkin's lymphoma. It may also be worthwhile to attempt to assign a clinically relevant grade to all cases of Non-Hodgkin's lymphomas diagnosed on FNAC, to assist in planning further management of the patient.

The low and intermediate high grades of Non-Hodgkin's lymphomas correspond to indolent and aggressive lymphomas respectively as far as their clinical outcome is concerned.

This study was therefore carried out in an attempt to grade Non-Hodgkin's lymphomas into low, intermediate and high grades based upon cell size and to compare it with the IWF grade on corresponding histological section.

Materials and Method

Present study was conducted in the Department of Pathology, Sri Krishna Medical College, Muzaffarpur, Bihar, with the help of Department of ENT, Surgery, Pediatrics and Medicine during the period of June 2015 to December 2016.

A total of 76 patients present with lymphadenopathy were sending to our department for FNAC from different OPD and IPD were included in the study. FNACs were performed in all cases using 23G needles along with a 10 cc syringe and a Cameco holder. Papanicolaou (PAP) and May Grunwald Giemsa (MGG) stained smears were available in most cases.

These were cases where a cytological diagnosis of NHL or suspicious of NHL was made and corresponding histological sections available and cases where a diagnosis of NHL was made in histology and corresponding FNAC smears were available irrespective of the cytological diagnosis. Cases were also graded on FNAC smears using a three tier grading system based upon cell size into low, intermediate and high grades. Cytological assigned grades were correlated with the corresponding histological grades (IWF) to determine grading accuracy.

Using this system a case was assigned as low grade, when it would comprise of a monotonous population of small lymphoid cells (equal to or less than one and half times the size of a small lymphocytes). Large cells (size greater than twice that of small lymphocytes) if present comprised of less population. An intermediate grade NHL would comprise of an admixture of small and atypical large lymphoid cells, with the large cells approximately between 20-50% of the cell population. A case was designated as high grade

when approximately more than 50% of the cell population comprised of immature large lymphoid cells with or without one or more nucleoli. Cases of NHL were graded on histological sections using the IWF classification into low, intermediate and high grades. Cytologically assigned grades were correlated with the corresponding histological grades to determine grading accuracy.

Result

Out of 76 patients an accurate diagnosis of NHL was possible in 54 (71.05%) patients. Overall accurate grading was seen in 52 (68.42%) patients using cytological criteria. Out of which Accurate cytological grading was possible in 31 patients (59.61%) as low grade, 15 patients (28.84%) as intermediate and 6 patients (11.54%) as high grade Non-Hodgkin's lymphomas.

Discussion

In this study using cytomorphological features alone 54 (71.05%) cases could be accurately diagnosed as NHLs. None of the cases of low grade NHLs were completely missed and a biopsy was recommended in all cases. Two cases where a low grade NHL could not be ruled out on cytology proved to be reactive lymph nodes on histology. A definitive diagnosis of low grade NHLs is one of the most challenging problems faced in FNA diagnosis of lymphomas. Among the 31 cases of low grade NHLs a definitive diagnosis on FNAC was possible in only 15 cases.

A suspicion of Hodgkin's lymphoma (HL) was raised in 7 cases owing to the presence of a polymorphous cell population comprising of plasma cells, eosinophils and mononuclear cells with prominent nucleoli. These were cases of PTCL, not otherwise specified, which are known to closely mimic cases of HL even on histology Among the 5 cases where a diagnosis of a poorly differentiated malignant tumor was rendered on cytology, they turned out to be T-cell NHL (1 case), anaplastic large cell lymphoma (1 case) and diffuse large B cell lymphoma (3 cases).

One of the most important predictors of behavior in NHLs is the cell size. Although flow cytometry and morphometric evaluation of cell size are more accurate they have their own limitations. Morphometry is a time consuming procedure and cannot be used as a routine method of assessing cell size for grading.

Large cells frequently have a low viability and a significant number of large cell lymphomas may be missed on flow cytometric analysis. Young et al in their series of 58 FNAC specimens used the transformed lymphocyte count to determine the number of large cells. They found that the low grade NHLs comprise of less than 10% transformed cells, while the high grade NHLs had 20% or more transformed cells. An accuracy of 76.7% was achieved by Meda et al in diagnosing NHLs using a combined cytomorphologic and flow cytometric approach. Dong et al could successfully classify 74% of their cases using flow cytometry alone, which improved to 82% on combining morphology with flow cytometry. Gong et al utilized cell size determined by cytomorphology and flow cytometry to subclassify NHLs. They found that using a threshold value of 40% large cells for diffuse large B cell lymphomas (DLBCL), and less than 20% large cells for low grade NFILs, the sensitivity for diagnosing small cell NHLs and large cell lymphoma approached 100%. In this study the grading was attempted on cytomorphological evaluation of cell size by comparing with the size of a small lymphocyte as this cell is always found in smears of all grades of NHLs and is fairly consistent in its nuclear size.

Nuclei of histiocytes, endothelial cells, and red blood cells are also used for morphological assessment of cell size. Cell size and cytomorphological details are better appreciated on FNAC smears as the artifacts of formalin fixation and the problems encountered because of improperly fixed biopsy specimens are eliminated. There was high grading accuracy in low grade NHLs (59.62%) with only one case being erroneously graded. This reflects the relative ease

and consistency with which a small lymphocyte can be delineated from intermediate or large sized lymphoid cells, even on routine morphological evaluation. In sharp contrast, a much lower grading accuracy was achieved for cases of intermediate (28.84%) and high grades (11.54%), when cases were separated using a three tier grading system. This is possibly because is not possible to separate accurately an intermediate sized lymphoid cell from a large cell. This would probably require morphometric manual methods or digital image analysis software, which again would have utility only as research tools and cannot be applied for routine diagnostic purpose. It may also not be possible to reliably delineate borderline cases of intermediate and large cell NHLs using a cut off value of 50% large cells.

When we used a two-tier grading system and classified our NHLs into low and high grade (encompassing intermediate grade), the grading accuracy of high grade NHLs improved to 96.25%.

As far as treatment is concerned the low grade NHLs has an indolent behavior and is managed with more conservative chemotherapy while the higher Cytologic grading of non Hodgkin's lymphomas grades of NHLs are treated with aggressive combination chemotherapeutic protocols.

Conclusion

FNAC will continue to be used worldwide as the most important initial diagnostic tool in all patients with lymphadenopathy. The utility of FNAC for not only diagnosing but also performing grading will be instrumental in imparting a cutting edge to this diagnostic modality in planning management of non-Hodgkin's lymphoma patients. Thus it is important to be able to at least triage cases of NHLs into a low or high grade on FNAC smears in all cases in order to plan management strategies.

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