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IMMUNO-ARCHITECTURAL PATTERN ANALYSIS IN NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA – A RETROSPECTIVE ANALYSIS OF 14 CASES

Oncopathology

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ABSTRACT

Background: Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) is an uncommon subtype of Hodgkin Lymphoma associated with an indolent course. NLPHL has distinct clinical features, histological, immunohistochemical and gene expression profile when compared to Classic Hodgkin Lymphoma, and the recent World Health Organization - Hematolymphoid tumors V edition, suggests a nomenclature change to Nodular Lymphocyte Predominant B Cell Lymphoma as it appears more related to the mature B cell Non-Hodgkin Lymphoma. Various Immunoarchitectural patterns (A to F) have been described of which patterns C to F are called as variant patterns and these patterns are associated with disease recurrence and progression. **Materials And Methods:** This study is a retrospective and descriptive analysis of 16 lymph node biopsies from 14 patients of NLPHL diagnosed over a period of five years. Haematoxylin and Eosin-stained sections, along with CD3 and CD20 immunohistochemistry, amongst others, were used to assess the immuno-architectural patterns. **Results:** Pattern A was seen in five, followed by pattern C and E in four patients each. The remaining patient had pattern B. During the period of study, two patients had recurrence. The recurrent cases had pattern C and pattern E respectively at diagnosis and during recurrence both showed pattern E. **Conclusion:** This study reaffirms the importance of recognizing the immuno-architectural patterns in NLPHL, with variant patterns being associated with disease recurrence. Hence, it is necessary that the hematopathologist reporting on a case of NLPHL should be aware of the patterns and report on the immuno-architectural pattern accordingly.

KEYWORDS

NLPHL, Immunoarchitectural patterns, recurrence, variant patterns

INTRODUCTION:

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a B cell neoplasm of germinal center origin and constitutes approximately 5-10% of all diagnosed Hodgkin lymphomas(1). NLPHL has a distinct clinical features, immunohistochemical findings and gene expression profile when compared to the Hodgkin Lymphoma, and recent World Health Organization V edition suggests a nomenclature change into Nodular Lymphocyte Predominant B Cell Lymphoma.(1) Though it has an indolent clinical course, 3-6% patients can have recurrences and transform into higher grade lymphomas (2)(3). A seminal study by Fan et al described six immuno-architectural patterns in NLPHL and reported that some of the immuno-architectural patterns are associated with a higher stage of disease and poorer prognosis(4). In this study we aimed to evaluate the immuno- architectural patterns in NLPHL cases diagnosed in our hospital and to find, whether there was any correlation between the architectural patterns and disease biology.

MATERIALS AND METHODS:

This was a retrospective study conducted in the Department of Pathology, in a tertiary care center in southern India and a regional cancer center over a period of five years. As it was a retrospective, record-based study and involved observation of architectural patterns in the already diagnosed NLPHL patients, and did not involve any modification in treatment of the patient, the consent of the patients was waived. The study followed the declaration of Helsinki and its revisions. Fourteen patients were diagnosed as NLPHL during the study period. Hematoxylin and Eosin (H&E) stained sections and Immunohistochemistry (IHC) slides were retrieved from the departmental archives. CD3, CD20, CD45, CD15, CD30, EMA, ALK-1 and EBV-LMP as and when indicated were used. H&E and IHC slides were analyzed for the immuno- architectural patterns, especially with CD 20 and CD 3. The necessary clinical details were retrieved from archives of the departmental and medical records department.

The classical histomorphology of NLPHL shows nodular or nodular and diffuse proliferation of small mature lymphocytes with admixed singly scattered neoplastic lymphocyte predominant (LP) cells.(5) These large cells have multilobated oval nucleus, fine nuclear membrane, and fine granular chromatin with visible nucleoli. (Figure 1). The nodules and the small lymphocytes are generally composed of CD 20 positive B-cells and the large cells are also CD 20 positive and negative for CD3, CD 30, CD 15 which differentiates them from Classical HL. (4-6)

Immuno-architectural patterns were designated to individual cases as per the study by Fan et al.(4) Pattern A is defined as presence of non-neoplastic B cell nodules with scattered LP cells, whereas pattern B by interconnected serpiginous nodules with scattered LP cells. In Pattern A and pattern B neoplastic L-P cells are present only within the nodules. Pattern C is characterized by presence of L-P cells outside the B cell nodules. Pattern D, by presence of LP cells within T cell nodules. Here the mature lymphocytes are more of T cells than B cells. Pattern E and F are characterized by diffuse architecture, with pattern E having diffuse T areas, also known as T cell rich B cell like areas. Pattern F has a diffuse B cell area. Pattern “A” and “B” are recognized as classical histology patterns and whereas Patterns “C” to “F” is recognized as variant histology patterns. Variant histologic patterns lack the reactive B cell nodules and they show presence of LP cells outside the reactive nodules.(4)

RESULTS:

In our study, fourteen biopsies at the initial diagnosis and two biopsies at the follow-up from 14 patients were analyzed, making a total of sixteen lymph node biopsies studied. There was a striking male preponderance with a M: F ratio of 13: 1. The ages of the patients ranged from 12 to 66 years. Eleven (78.5%) patients had cervical lymphadenopathy as their initial presentation. Among the remaining three patients, two had inguinal and one had axillary lymphadenopathy.

On analyzing the immuno-architectural patterns at diagnosis, we found that, Pattern A was seen in five patients followed by pattern C and E in four patients each. Only one patient had pattern B. Pattern D and F were not observed in our study.

Two patients had recurrence of disease during the five-year period of study. One patient who had pattern C at diagnosis, recurred within three years. At the time of recurrence, lymph node biopsy showed a change of pattern C to Pattern E. This patient was the only one in the series to have bone marrow involvement and B symptoms during recurrence. The other patient who had recurrence had pattern “E” during the initial presentation and similar pattern in the repeat biopsy. This patient did not show evidence of bone marrow involvement

during relapse. None of the patients have Diffuse Large B cell lymphomatous transformation in our study.

DISCUSSION:

Hodgkin lymphoma (HL) is broadly classified into classic (HL) and NLPHL. The only similarity between the two subtypes includes the presence of a few numbers of neoplastic cells (Reed Sternberg cell in Classic HL and LP cells in NLPHL) in a reactive inflammatory cell background. Both of them differ in their clinical course, histomorphology, immunohistochemical profiles, clinical features and prognosis (7)(8). Usually, NLPHL presents with a superficial peripheral lymphadenopathy with an indolent course, whereas Classic Hodgkin Lymphoma presents with a more generalized disease. Akin to Non-Hodkin Lymphoma (NHL), NLPHL tends to spread by non-contiguous mode. The recent Vth edition of the WHO classification of Haematolymphoid tumours, suggest a change of nomenclature of NLPHL into Nodular Lymphocyte Predominant B cell Lymphoma as the pathogenesis, histology, immunohistochemical and prognostic features resembles more in line with a B cell NHL, However this change has not been made mandatory due to ongoing clinical trials. (1)

In this study we analysed the immuno-architectural patterns of fourteen patients of NLPHL at the time of initial diagnosis and at in two patients. We observed a striking male preponderance of 13:1 and a varied age of presentation from 12 to 66 years. Eight out of fourteen patients (57%) had variant immuno-architectural histology in our study. Among these eight patients with variant histology, two developed recurrences and one amongst them had a pattern change to "E".

Fan et al., first documented the presence of various architectural patterns in NLPHL(4). In their study, they found that pattern "C" and "E" were associated with disease progression and evolution into higher stage of the disease. Also, they found out the diffuse pattern was associated with recurrent disease. Pattern "A" and "B" is characterized by the presence of neoplastic LP cells within the reactive B cell nodule, whereas the variant patterns "C" to "F" show the LP cells outside the nodules. The reactive B cell nodules appear to act like a boundary or a mantle and prevents the escape of the neoplastic LP cells outside the lymph node. Hence the patients with pattern A and B have a relatively indolent clinical course and usually do not have bone marrow involvement. (4)

Studies by Nogova et al., Hartmann et al., Kalashmikov et al. and Nikita et al have evaluated the importance of immuno-architectural patterns in the NLPHL (9-12). Hartmann et al assessed the importance of the variant histologic patterns of NLPHL. In their study, amongst 423 cases of NLPHL, 105 had variant histology. Those with variant histologic patterns had advanced stage of the disease (10). To quantify variant patterns, Shet et al devised a three-tier scoring in NLPHL based on five histological parameters. (13). The five parameters analyzed were (a) percentage of nodularity scored from 100 % to less than 75%, (b) T cell rich areas (less than 20% to more than 50%), (c) nodule type, (d) intact or broken dendritic network, and (e) extra-nodular presence of lymphocyte predominant cells (less than 15% to more than 50%), with final scores from 0 to 10. They divided 72 patients into two groups, with a score of less than or equal to 6 and more than 6. The patients with a higher score had a bad prognosis than those with lower. The 5-year disease-free survival in patients with scores less than 6 was 92% versus 20% in those with scores more than 6. The 5-year overall survival was 100% in patients with scores less than or equal to 6 and 87% in those with scores more than 6. (13) Our study results are concordant with these published studies on immuno-architectural pattern in NLPHL and showed that variant histology was associated with the disease recurrence and higher stage. The patient who changed from pattern "C" to "E" had bone marrow involvement.

There is generally a difference in opinion on how NLPHL needs to be treated. (14) Many believe that early stage NLPHL is curative by complete surgical excision and refrain from providing radiation and chemotherapy. In this context, it needs to be emphasized that the variant immuno-architectural patterns must be reported, as early stage NLPHL with variant patterns may need to be treated aggressively and followed up more stringently. (14)

NLHPL is a rare lymphoma, as exemplified by only 14 cases in five years and although the number of cases is small, the results are in line with the published studies on NLPHL. The follow up of these patients ranged from three months to four years. During this period, two patients recurred both of whom had variant patterns at presentation. In one patient, the pattern "C" progressed to "E" and also had bone marrow involvement. Amongst the fourteen cases, this was the only one with marrow involvement. None of the patients with pattern "A" and "B" had recurrences with the available follow up of four years

Our study underlines the fact that presence of variant histology and immuno-architectural pattern (pattern 'C" to "F") is associated with recurrences, disease progression and the patterns represent biological continuum of the disease.

CONCLUSION:

The main limitation of our study is a low sample size and a short follow up period. However, even with this limitation, we found out that the cases with recurrences and bone marrow spread had a variant immuno-architectural feature. We recommend that while signing out a diagnosis of NLPHL, the pathologist must add a comment about the immuno-architectural pattern in the final report. This would give valuable insight to the treating physician, to keep the patient on a closer follow up and plan for a more aggressive treatment if warranted.

Figure 1: a) Low power view x100 showing LP cell in a background of small lymphocytes, highlighted by arrow b)High power view x400 demonstrating LP cells, highlighted by arrow C) CD3 immunostaining reveals CD3 forming rosettes around LP cells, highlighted by arrow D) CD20 immunostain highlighting LP cell along with the nodule of reactive B cells.

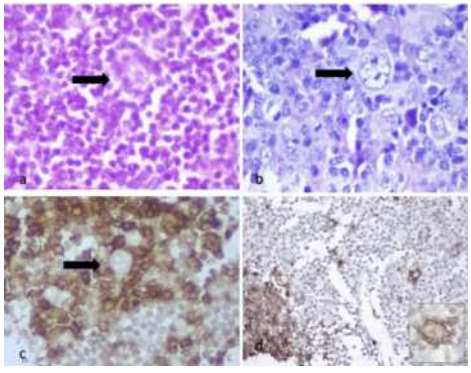
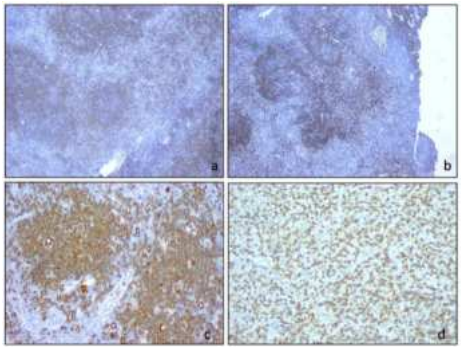


Figure 2: Immunoarchitectural patterns in our cases with CD 20 IHC stain a) Pattern A demonstrating B cell nodules B) Pattern B demonstrating serpigenous B cell nodules c) Pattern C demonstrating presence of LP cells outside B cell nodules d) CD3 Immunostaining demonstrating numerous T cells in the background admixed with LP cells in Pattern E.



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