ORIGINAL ARTICLE

Morphological Study of Reactive Follicular Hyperplasia Lymph Node

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ABSTRACT

Aim: To establish standard for diagnosis of reactive follicular hyperplasia of lymph node.
Methods: This study was conducted at the Department of Pathology, Benazir Bhutto Shaheed College Mirpur, Govt of AJK. 50 cases of reactive follicular hyperplasia were included in the study. Five micron thick, paraffin embedded sections were stained with H & E and reticulin stain.
Results: The median number of follicles per low power field (4x objective x 10 eye piece) was 19. The mantle zone was present in 94% of cases. Fifty percent cases showed polarity of the follicles. Monomorphism was absent in all cases. The median number of mitotic figures per 5 follicles was 17 under high power magnification. The median number of tingible body macrophages was 35/5 follicles.
Conclusion: The study distinguished the morphological features of reactive follicular hyperplasia which can be helpful to distinguish from follicular lymphoma. By studying the various histopathological features and employing morphological standards for the differentiation of reactive follicular hyperplasia from follicular lymphoma, an accurate diagnosis can be made in most of the cases. The preserved architecture; presence of tingible body macrophages, the mantle zone of mature lymphocytes and absence of monomorphism favour the diagnosis of follicular hyperplasia.
Keywords: Lymph node, follicular hyperplasia, reactive hyperplasia

INTRODUCTION

Reactive hyperplasia is a benign proliferative disorder of cells of one or more of the different anatomical and immunological compartments of lymphoid tissue. It may involve any or all of follicles which are the B-cell regions, the T-cell (interfollicular) or the sinusoidal cells[1]. A variety of unusual reactive conditions may be seen in lymph nodes in any age particularly in paediatric age group. These may be autoimmune lymph proliferative syndrome, reflect underlying abnormalities of the immune system and cellular control processes, viral infections or are of unknown cause. Many of these conditions can mimic malignant neoplasms, so it is important that pathologists recognize these unusual reactive patterns[2]. Reactive follicular hyperplasia (RFH) in lymph nodes is characterized by an increased number and size of lymphoid follicles. Lymphoid follicles are the functional units of the B-cell immune response and, as a result, inflammatory and immune reactions that trigger a humoral response and cause activation of B-cells leading to reactive follicular hyperplasia. In broad terms, diseases that cause Reactive Follicular Hyperplasia include bacterial and viral infections, as well as autoimmune diseases. In some patients, the etiology of reactive follicular hyperplasia cannot be ascertained. Follicular hyperplasia is commonly accompanied by hyperplasia of other compartments in the lymph node. Morphologically, reactive follicular hyperplasia is characterized by an increase in the number and size of lymphoid follicles[3]. Many enlarged lymphoid follicles also assume or coalesce into irregular shapes. Despite these changes, follicles in reactive follicular hyperplasia maintain discernible mantle and marginal zones. The germinal centre is frequently expanded, with preservation of the light and dark zones. Scattered within these reactive germinal centres are many tingible-body macrophages, a process that imparts a starry-sky pattern. In pure RFH, the paracortical area is diminished. Sinuses generally remain patent, even if they frequently contain increased numbers of sinus cells (or littoral cells). It is not uncommon for reactive lymphocytes to involve the nodal capsule, but reactive follicles rarely extend into adjacent perinodal soft tissue[4]. Reactive follicular hyperplasia must be distinguished from a neoplastic lymphoid proliferation with a nodular growth pattern, primarily follicular lymphoma (FL). On morphologic grounds, FL generally exhibits numerous follicles that are evenly distributed (back-to-back) and similar in size compared to RFH. Tingible-body macrophages are generally less numerous in FL, and the mantle zones are frequently ill-defined[5,6].

MATERIAL AND METHODS

This study was conducted at the Department of Pathology, Benazir Bhutto Shaheed College Mirpur, Govt of AJK. After taking written consent from the patients and approval from the ethical committee, 50 cases of reactive follicular hyperplasia were included

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in the study. Five micron thick, paraffin embedded sections was stained with H & E and reticulin stain. The morphological study of 50 cases of reactive hyperplasia lymph node was carried out. At the same time the morphological features of 10 cases of follicular lymphoma were also studied for the comparison with reactive follicular hyperplasia. The patients of all age groups and all sexes were included. The following cellular parameters were evaluated.

- Monomorphism**:** A case was recorded as exhibiting monomorphism, when 90% or more of the cells within most follicles had a similar size and nuclear chromatin.
- All slides were screened for evaluation of mitotic activity and tangible body macrophages. The numbers of mitotic figures were counted per five follicles showing maximum activity.
- The presence or absence of plasma cells inside and outside the follicle was also noted.
- The presence or absence of follicle centre cells outside the follicles was recorded as well.

All the specimens of palpable lymph nodes where no clear diagnosis was made on clinical examination were included in the study. Patients who refused to give consent or clear diagnosis was present were excluded from the study.

RESULTS

The maximum (36%) cases of reactive follicular hyperplasia lymph node were seen in the first decade of life. The eldest patient in the series was 67 years of age and the youngest was 2 years old. Thirty four (68%) out of 50 cases were male and 16 (32%) were female. The male to female ratio was 2.1:1. In the majority of cases (42%) lymph node biopsy was taken from cervical region followed by mesenteric nodes (16%) and axillary (14%). Rest of the biopsied were from mediastinal, para aortic, para oesophageal and para ampulary nodes.

Table1. Area of enlargement of lymph node.

Area	**n**	**%age**
Cervical		42
Mesenteric		16
Axillary		14
Rest of the body		28

On the basis of microscopic examination of the lymph node sections, the diagnosis of reactive follicular hyperplasia was made in all the cases. The following morphological features were noted. The architecture was found preserved in all cases of this study. Forty percent cases showed no variation in the shape of follicles. Twenty percent cases showed moderate and 8% marked variation in shape while 32% cases showed only slight variation in the shape like dumbbell shaped follicles (Fig. 1).

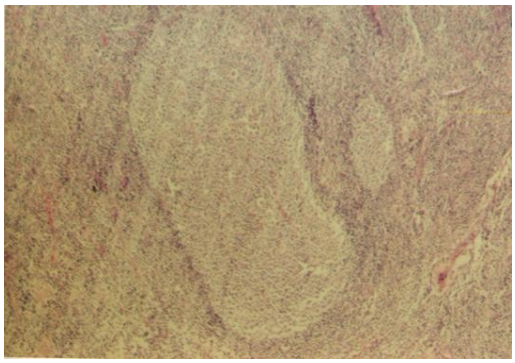

Fig. 1: Photomicrograph of lymph node section showing a dumbbell shaped follicle (H&Ex 100)

Fifty six percent cases showed moderate variation in the size of the follicles. Thirty six percent cases showed slight variation in the size of follicles and only 8% cases showed marked variation in size. (Fig. 2).

Table 2: Variation in the shape of follicles.

Variation	**n**	**%age**
No variation	20	40
Slight variation	16	32
Moderate variation	10	20
Marked variation	4	8

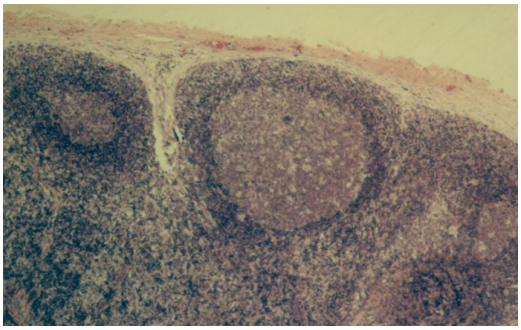

Fig. 2: Photomicrograph of lymph node section showing variation in size of follicles (H&Ex 100)

In all the cases, the distribution of follicles was uneven and more number of follicles were seen in cortical area of lymph node. On counting follicles per unit area in low magnification (4 objective x 10 eye piece), the median number of follicles was 19 per unit area. In 56% cases, the number of follicles ranged from 1-15 per unit area, whereas 16-30 follicles per unit area were seen in 38% cases and 6% cases showed 31-45 follicles per unit area. In 80% cases follicles were sharply demarcated while 20% cases showed vague demarcation of the follicles. The Parallel row of lymphocytes was present in 78% of

cases whereas 22% of cases showed absence of parallel row of lymphocyte (Fig. 3). Polarity of follicles can be defined as the presence of both light and dark staining cells in the follicles. In this study 50% cases showed polarity of follicles (Fig. 4). The mitotic figures were counted in five follicles under high magnification (40 objectivex10 eye piece). The median number of mitotic figures per five follicles was 17. In 20(40%) cases, the number of mitotic figures ranged from 1-10 per 5 follicles under high magnification, 13(26%) cases had 11-20 mitotic figures per 5 follicles, 9(18%) cases had 21-30 mitotic figures per 5 follicles, 4(8%) cases exhibited 31-40 mitotic figures per 5 follicles, 3(6%) cases had 41-50 mitotic figures per 5 follicles whereas 1(2%) case showed 51-60 mitotic figures per 5 follicles. The tingible body microphages were counted per five follicles under high magnification (40 objectivex10 eye piece). The median number was 35/5 follicles.

Table3. Number of mitotic figures.

Mitotic figure per five follicles	n	%age
1-10	20	40
11-20	13	26
21-30	9	18
31-40	4	8
41-50	3	6
51-60	1	2

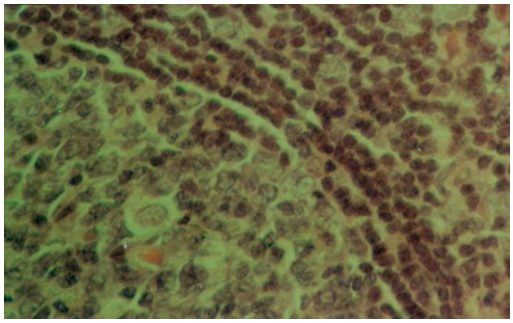

Fig 3: Photomicrograph showing parallel row of lymphocytes around the germinal centre (H&Ex 100)

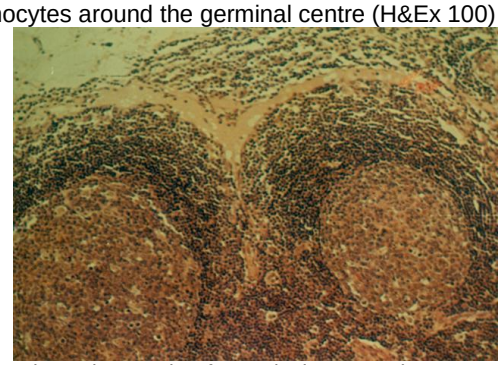

Fig. 4: Photomicrograph of germinal centre demonstrating the polarization of the lymphoid cells. The upper portion of both the germinal centre contains smaller lymphoid cells with scanty cytoplasm and no tingible body macrophages. The lower portion of the germinal centre contains relatively large lymphoid cells with multiple tingible body macrophages (H&E x200)

For comparison, ten cases of follicular lymphoma were also studied. Architecture was found effaced in all cases of follicular lymphoma (FL). The median number of follicles per unit area (4x objective and WF10 x eye piece) were counted and were found to be 22 follicles/ unit area. The follicles were evenly distributed in cortex and medulla, showing a back to back arrangement throughout the lymph node in all the cases. The polarity of the follicles was absent in all FL cases and monomorphism was seen in all the cases.

DISCUSSION

The reactive hyperplasia often poses a diagnostic problem. The distinction of reactive from neoplastic lymph node requires application of general histological criteria including cellular polymorphism or monomorphism and presence or absence of cytological atypia. Although cytological criteria remains valid but still diagnostic ambiguity exists. Although several criteria were helpful in distinguishing FRFH from FL, the single most valuable criterion was the type of pattern encountered. Follicles of variable size and shape lying adjacent to each other throughout the lymph node without or with very little intervening tissue are diagnostic of FL. This pattern was evident in 85% of the FL cases, but was not observed in any of the cases of FRFH[7].

In this study, we have re-evaluated the morphological criteria employed for reactive follicular hyperplasia lymph node. This analysis enabled us to identify the morphological criteria which had diagnostic significance for the differentiation of reactive follicular hyperplasia from neoplastic lesions of lymph mode. Florid reactive follicular hyperplasia (FRFH) of the enlarged lymph node in middle-aged or elderly patients requiring biopsy is a relatively uncommon phenomenon as compared with that in younger age groups[9].

The distinction between reactive and neoplastic lymphoid infiltrates is a common problem in clinical practice and can be problematic. The clinical implications for both the patient and the treating clinician are profound. The common entities that can present as atypical lymphoid hyperplasia and thus can mimic malignant lymphomas, with emphasis on morphologic features, immunophenotypic findings, and molecular correlates that help distinguish these disorders from neoplastic conditions are reactive follicular hyperplasia versus follicular lymphoma[8].

Sometime pseudolymphoma in liver may impose diagnostic problem with follicular hyperplasia.[9] Rarely metastatic gastrointestinal cancers to the liver may mimic hyperplastic lymphoid follicles.[10] Age is an

important factor to consider because of the progressive quantitative reduction in and diminished reactivity of lymphatic tissue which occurs during the aging process. On biopsy specimens, 17% of the lymphadenomegaly in subjects under 30 years old show a picture of aspecific reactive hyperplasia or complete normality, while these findings occur in only 2% of the lymphadenomegaly biopsied after age 30. Moreover, lymphadenomegaly with an inflammatory etiology are much more frequent during infancy, whereas those with a neoplastic cause predominate in people over 40 years old[11].

It should be remembered that in general no single criteria is sufficient. One must analyse each case for all the morphological parameters and then weigh the results to arrive at the correct diagnosis. It cannot be over emphasized that technically good histologic preparations are imperative when one is faced with the problem of distinguishing between reactive follicular hyperplasia and follicular lymphoma[12]. In reactive follicular hyperplasia there is tendency toward architectural preservation, with open sinuses. In the study of Nathwani et al, complete effacement of architecture was observed in 15% cases of florid reactive follicular hyperplasia. In this study no effacement of architecture was seen. Our results are in accordance with that reported by other workers[13.14]. Previously observer had stressed that variation in the size and shape of the follicles within a lymph node was more common in reactive follicular hyperplasia. One may often see germinal centres that have irregular or dumb bell-shaped forms.[15] In cases of florid reactive follicular hyperplasia moderate to marked variation in the shape of follicles has been reported in 30% cases of reactive follicular hyperplasia lymph node. Variation in size and shape of follicles has been reported and in present study only 8% of cases of reactive follicular hyperplasia showed marked variation and moderate variation was observed in 56%cases. The variation in the shape of the follicle was studied in cases of follicular lymphoma and it was found in 50% of cases. This fact was quite evident both in this study and that of Nathwani et al who however, reported that variation in size and shape of follicles was not a reliable criterion for distinguishing between reactive follicular hyperplasia and follicular lymphoma[16].

The number of follicles per unit area and the pattern of distribution of follicles within a lymph node are perhaps the two most important features that one should evaluate at low power magnification[13]. In the present study also low power magnification was used to evaluate the number and distribution of follicles, and was found valuable.

In our study the distribution of follicles in the cases of reactive follicular hyperplasia was not even. The follicles were more prominent in the cortex of lymph node of all cases, while in cases of follicular lymphoma, the follicles were evenly distributed throughout the medulla and cortex of lymph node. Similar finding have been reported by previous study[15].

Reactive germinal centres have sharply demarcated margins and are usually surrounded by a cuff of small mature lymphocytes referred to as the mantle zone or lymphoid cuff. In reactive follicular hyperplasia the mantle zone is often quite broad, it usually surrounds the germinal centre completely and it may show some concentration of lymphocytes at one pole forming a cap.[16] The observations made in this study are almost the same. In contrast, the follicles and margins in follicular lymphoma are often ill defined and usually lack a lymphoid cuff. In a small number of cases in which a lymphoid cuff is present, it is usually thinner than observed in cases of reactive follicular hyperplasia, it rarely completely encircles the follicles and it usually is not observed around all the follicles[12]. In our study, the demarcation of follicles was vague in all the case of follicular lymphoma. The mantle zone of lymphocytes was also absent in all cases. Two cytological features that are extremely valuable are mitotic activity and presence or absence of phagocytes histiocytes within follicles[12]. In the study of Nathwani et al, the mitotic figures were observed in follicles in cases of reactive follicular hyperplasia as well as follicular lymphoma. However, the median number of mitotic figures per five follicles in reactive follicular hyperplasia cases was 50 and was significantly higher than the median number 25, observed in cases of follicular lymphoma. In this study the median number of mitotic figures per five follicles in reactive follicular hyperplasia cases was 17, which was quite high as compared to the median number of 7, observed in follicular lymphoma.

In this study the median number of tingible body macrophages was 35 per five follicles in reactive follicular hyperplasia whereas no tingible body macrophage was seen in any case of follicular lymphoma. The median number of such macrophages was 55 per five follicles in cases reactive follicular hyperplasia in the series of previous study[16].

CONCLUSION

The majority of cases of reactive follicular hyperplasia lymph node have been diagnosed on the basis of morphology alone and can be differentiated from follicular lymphoma. The histological pattern is not often specific for the cause or agent and may also vary according to the stage of development at which the biopsy is taken.

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