

Nodular lymphoid hyperplasia: A thin grey zone between hyperplasia and Pathological aggregate

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Abstract

Introduction: The clinical-pathological characteristics of 12 patients with intestinal nodular lymphoid hyperplasia (NLH) are described with the aim to try and delineate between hyperplasia and pathological aggregate of lymphoid tissue in the intestine and its association with other diseases from Indian subcontinent. **Materials and Method:** 12 diagnosed cases of NLH were retrieved out of 2256 intestinal punch biopsy done at our centre and were evaluated as per histological criteria laid down by various authors including their clinical and pathological features. **Results:** Most frequent symptom includes diarrhoea and weight loss and the severity of these symptoms were directly proportional to the number and location of the lymphoid nodules. Prominent lymphoid nodules in mucosa and/or submucosa were documented histologically in all cases. One patient had associated common variable immunodeficiency which on follow up developed intestinal lymphoid malignancy of NHL type (DLBCL) and the other was having hypogammaglobulinemia. All cases showed absence of plasma cells, except one with predominant symptoms of Gastroesophageal reflux disease (GERD) rather than diarrhea. **Conclusion:** NLH runs as a benign course, but these cases should be followed up with histology as well as thorough clinical and biochemical evaluation to detect early lymphoma that can be managed efficiently.

Keyword: Nodular lymphoid hyperplasia, Common variable immunodeficiency, Non Hodgkin lymphoma.

Introduction

Nodular lymphoid hyperplasia (NLH) is an uncommon histological findings in small bowel characterized by markedly hyperplastic mitotically active germinal center with well demarcated lymphocyte mantle zone [1]. The lymphoid nodules can be present in the mucosa and submucosa; and can be seen in any portion of the gastrointestinal tract, more commonly in the small bowel [2,3]. Endoscopically NLH can be seen as raised lesions or may sometime resemble polyp which are commonly seen in patients with common variable immunodeficiency and infection with human immunodeficiency virus [4].

Literature and experience by authors suggests close follow up of cases with NLH as these patients clinically as well as morphologically bears a risk of developing

intestinal and extra-intestinal lymphoma [5]. NLH is usually seen in pediatric age group but adults are not spared. It usually runs a benign and self-limiting course in children whereas in adults the prognosis is uncertain [6].

Materials and Method

12 cases of NLH were retrieved from the archives of Department of Pathology, Kasturba Hospital, Manipal from January 2012 to January 2016. All the paraffin embedded blocks, hematoxylin and eosin (H & E) slides were retrieved and re-evaluated to see if they all follow the histopathology criteria viz. hyperplastic lymphoid follicles, mitotically active germinal centers and well demarcated lymphocyte mantle localized in mucosa and/or submucosa. While performing the histopathological re-evaluation following features were considered viz. number and localization of lymphoid

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follicles, type and severity of inflammation in the lamina propria, and presence of villous atrophy/blunting. All the H & E slides with faint staining or having poor quality were discarded and assessment was done on freshly cut sections from the paraffin embedded blocks.

For clinical and laboratory data, patient's hospital records were searched and following parameters were evaluated – age, duration and type of symptoms, weight loss, hemoglobin, mean corpuscular volume (MCV), total protein, albumin, globulin, human immunodeficiency virus antibody and stool examination report for ova and cysts of parasites.

Result

A total of 2256 small bowel punch biopsies were done since January 2012 till January 2016, of which only 12 cases were diagnosed as NLH. All these cases were males with a median age of 21 years (7 to 43 years). Duration of symptoms ranged from 1 to 16 months. After evaluating the clinical data, we found that the predominant manifestation among these patients were diarrhea and weight loss (Table 1). The data on weight loss was subjective and the same was monitored on follow up of these patients. All patients along with the other symptoms had associated abdominal pain. One patient had presented with gastro-esophageal reflux disease (GERD) with no history of diarrhea or weight loss.

All diagnosed cases of NLH were re-evaluated following the histological criteria using light microscope. In six cases hyperplastic lymphoid follicles were present in the mucosa (Table 2). Only one patient was showing more than two hyperplastic lymphoid follicles.

Table-1: Symptom and sign of patients with NLH.

Signs & symptoms	N (12 cases)
Diarrhea	11
Weight loss	11
Abdominal pain	12
Lymphadenopathy	01
Pallor	10
Chronic cough	01
Arthralgia	01
Neuroptthy	Nil

Table-2: Mucosal biopsies from patient with NLH

Abnormality	N (12 cases)
Localization of lymphoid follicles	
• Mucosa	06
• Submucosa	02
• Mucosa + Submucosa	04
Inflammatory changes seen in lamina propria	
• Lymphocyte-plasma cells	11
• Plasma cells	01
• Lymphocyte	08
• Eosinophils	04
Villous atrophy	
• Partial	11
• Total	NIL
Increased intraepithelial lymphocyte	08
Crypt hyperplasia	04

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It was noted that patient with mixed (mucosa and submucosa) hyperplastic lymphoid follicles have lower hemoglobin concentration as compared to only mucosal or submucosal localization. Only one patient with symptom of GERD had plasma cell infiltration in lamina propria. Predominant inflammatory infiltrate seen was lymphocyte, with four cases where lymphocyte was associated with eosinophil were seen.

Partial villous atrophy was noted in 11 cases and it was well associated with the weight loss and low globulin levels than those without villous atrophy. One case was having near normal mucosal lining.

Among all cases of NLH only one patient was associated with common variable immunodeficiency (CVI). None of the patients showed infestation by any parasites with repeated stool examinations on follow up. One case with common variable immunodeficiency was found to have intestinal lymphoma of NHL type (diffuse large B-cell) DLBCL type with very high Ki67 index (Fig 2, Fig 3, Fig 4) on follow up after 3 years of the diagnosis of NLH. Three cases had been screened for HIV antibody, which yielded negative result.

Discussion

Nodular lymphoid hyperplasia (NLH) is a rare pathological entity which is associated with increased risk for gastrointestinal malignancies, mainly Non Hodgkin lymphoma. Earlier studies have described NLH in immunocompromised as well as immunocompetent patients [1-5]. The rarity of this lesion can be understood by its incidence among large number of small bowel biopsies done at our center. We have followed the histological criteria described by various authors to label these cases as NLH. We also know from the literature that there is a thin grey zone present between normal lymphoid follicles becoming pathological. There is no strict definition or criteria available to delineate normal lymphoid tissue from hyperplastic, or for hyperplasia becoming pathological [7], even though we described NLH based on criteria discussed by various authors [8].

We have reported 10 cases of NLH in ileum and two in duodenum, which were in accordance with many authors which emphasized the frequent location of NLH in jejunum-ileum [1-3]. The pathogenesis of NLH is idiopathic, but it is proposed that due to the maturation defect in the B-cell there is accumulation of plasma cell precursor to compensate dysfunctional intestinal lymphoid tissue [9]. Due to these dysfunctional intestinal lymphoid tissues, patients are more prone for recurrent parasite infection. It was suggested by various studies that *Giardia lamblia* is one of the commonest infection seen in these cases [10]. We were unable to demonstrate any parasite in stool or on microscopy, although we had one case with hypogammaglobinemia and one case with common variable immunodeficiency who presented with NLH. It would have been possible to pick up parasitic infection by *Giardia lamblia* if we had used fecal ELISA technique to detect the parasite. But again for a country like India, where over the counter medicines are readily available as an empirical therapy for chronic diarrhea, the chances to detect these parasites are grim. It was also proposed by many authors about the possible link of *Helicobacter pylori* (H. pylori) infection with NLH [11,12]. Patients on anti H. Pylori therapy do respond positively and show marked regression of the lesions as compared to the patients with persistent H. pylori infection [13].

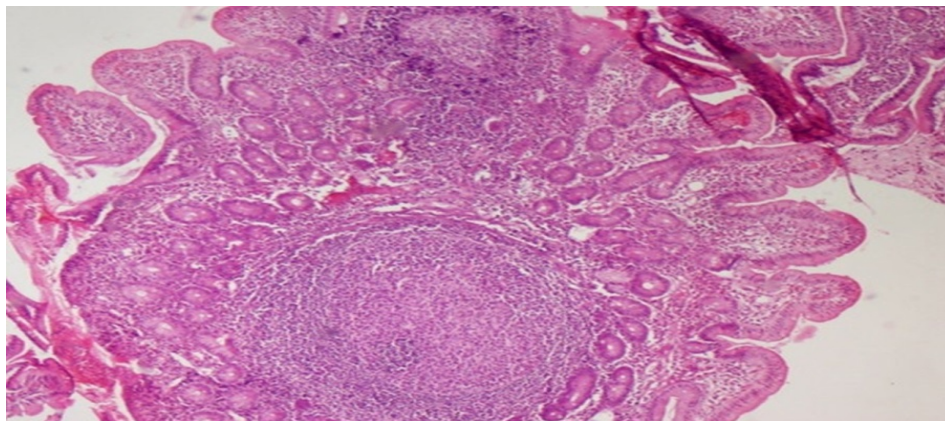


Figure-1: H & E X200 Lymphoid follicles with prominent germinal center

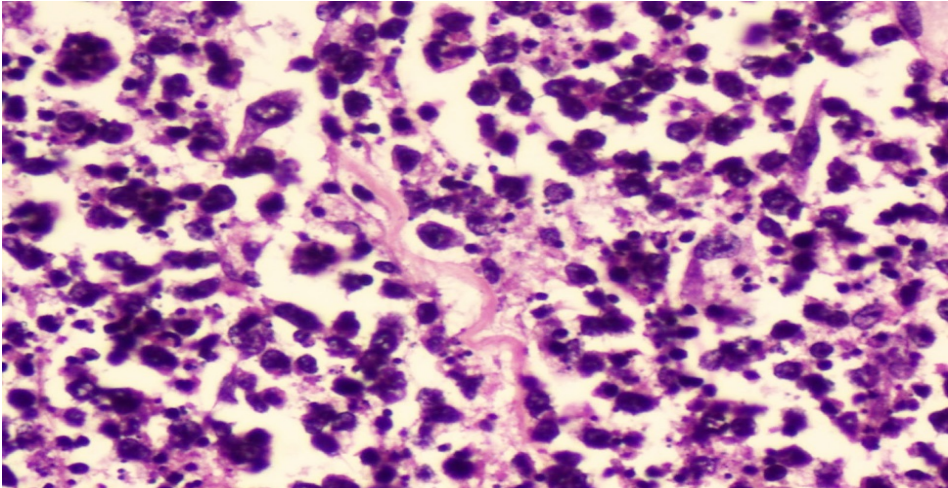


Figure-2: H&E X400 Malignant lymphoid cells with bizzare forms

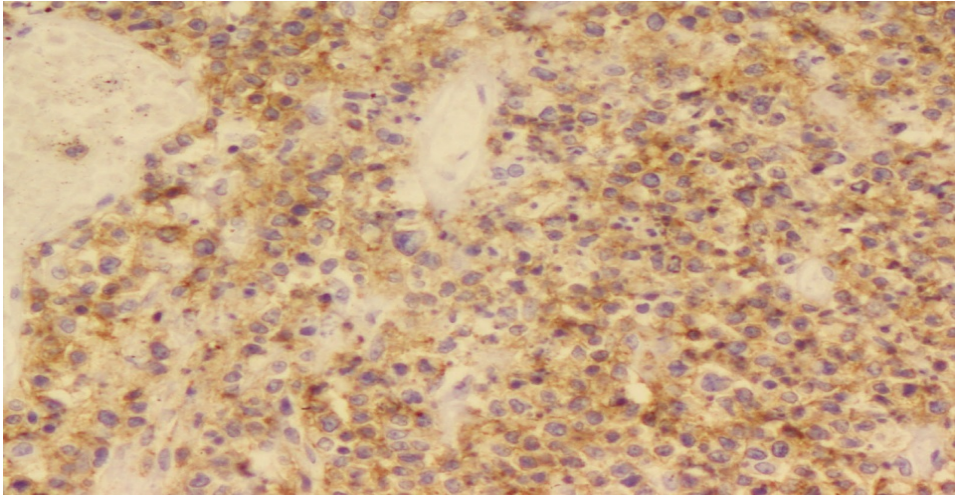


Figure-3:Lymphoid cells positive for leucocyte common antigen, X 200

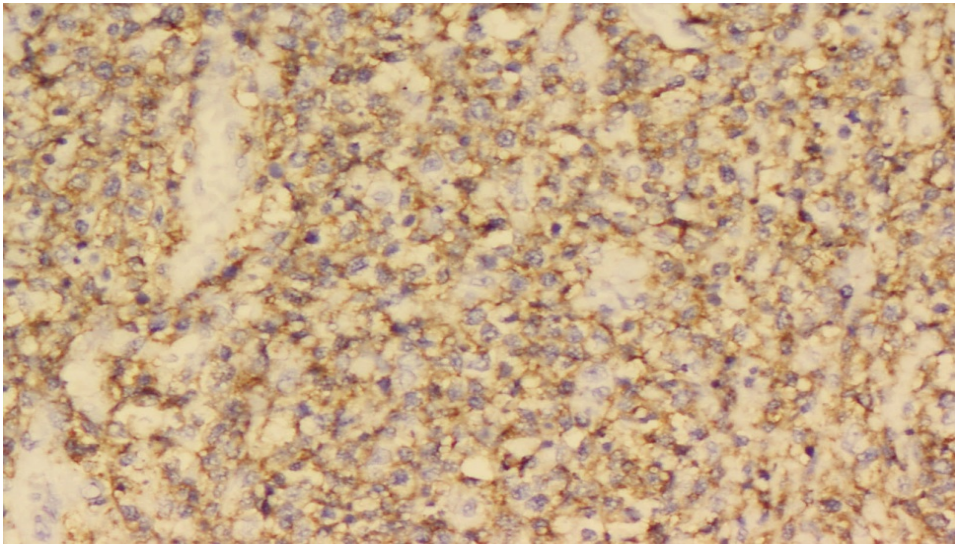


Figure-3: Lymphoid cells positive for CD20, X200

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Histologically, the number of lymphoid follicles with mitotically active germinal centre is not the diagnostic criteria [1,2]. We found majority of the cases presenting with 1-2 hyperplastic lymphoid follicles in the mucosa. Patient who had more number of lymphoid follicles showed more marked weight loss, low hemoglobin and very low MCV as compared to patients who had less number of follicles and located in mucosa and/or submucosa. All these patients presented clinically as chronic diarrhea.

Literature clearly depicts the association of NLH with various organic conditions [10,14,15]. We found only one case with common variable immunodeficiency (CVI) which on follow up presented as diffuse large B cell lymphoma (DLBCL) in the intestine. CVI in itself is a complex of decreased serum immunoglobulin, gastrointestinal dysmotility, sino-pulmonary infection and most of these patients develop malignancies in due course of time. Overall all patients with NLH are at an increased risk of developing lymphoid malignancy in the gastrointestinal tract. It has been suggested by various studies that extra-intestinal site for lymphoid malignancy is not rare. Rubio tapia et al[16] has described Hodgkin's disease in the mediastinum, Jonsson et al[5] has reported extra-intestinal lymphoma with NLH, where hyperplastic lymphoid tissue was completely cured after chemotherapy with remission of lymphoma and then reappeared at relapse. In our study all cases were on close follow up since diagnosis of NLH, and only one case developed lymphoid malignancy.

We have also observed partial villous atrophy, increased intraepithelial lymphocyte and crypt hyperplasia in our study as prominent features seen in association with NLH as described by other authors.

In spite of many theories of various conditions related to NLH, there are various case reports in the literature where no associated conditions have been described, and the diagnosis is made on histo-morphological evaluation alone[17,18,19].

Conclusion

There are several missing links in NLH, such as epidemiological data and non-invasive method to follow up such cases. Although NLH runs a benign course in pediatric as well as adult patients, close follow up with histopathology is warranted in all cases as they bear increased risk of developing lymphoid malignancy. Parasitic infections if detected has to be tackled efficiently in-order to minimize the risk of malabsorption.

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