Nodular Lymphoid Hyperplasia of the Gastrointestinal Tract : a comprehensive review

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Abstract

Nodular lymphoid hyperplasia (NLH) is a rare benign condition that is characterized by diffuse hyperplasia of the lymphoid follicles of the gastrointestinal tract (GIT). During endoscopy, NLH appears as multiple or occasionally innumerable nodules measuring a few millimeters in diameter. NLH occurs mainly in the small intestine, less commonly in the large intestine and rarely involves the stomach. There are multiple associated diseases such as immunoglobulin deficiency syndromes, giardiasis, Helicobacter pylori (H. pylori) infection, HIV and celiac disease. NLH elicits a wide range of symptoms that can range from asymptomatic to chronic diarrhea, weight loss, bleeding from the rectum and, very infrequently, intestinal obstruction. The clinical significance of NLH relies not only on the associated conditions but also on the possible complications. The most important of which are malignant transformation, particularly to gastric carcinoma, and intestinal or extra-intestinal lymphoma. There is no consensus regarding the management and surveillance of NLH. However, surveillance is recommended by most authors, but the intervals and duration have not yet been identified. (Acta gastroenterol. belg., **2017**, 80, **405-410**).

Key words : nodular lymphoid hyperplasia-GIT

Definition

Nodular lymphoid hyperplasia (NLH) is a diffuse hyperplasia of the lymphoid follicles of the gastrointestinal tract (GIT) (1). NLH appears during endoscopy as multiple or occasionally innumerable nodules measuring 2-3 millimeters and usually not exceeding 10 mm in diameter (2) as illustrated in Fig. 1 and 2.

Incidence

NLH is a benign and rare condition (3,4). The exact incidence is unknown, and NLH can occur in any age group but occurs more commonly in children (5,6). NLH primarily involves the small intestine, but it can also involve the colon or both the small intestine and colon. NLH rarely involves the stomach (7). This pattern is believed to be because lymphoid follicles are predominantly found in the small and large intestine (8). These follicles coalesce in the ileum to form Peyer's patches. Moreover, the number of lymphoid structures increases from the caecum to the rectum (9). There are a few case reports and small case series that have been published in the literature, but there are no meta-analyses.

Types

NLH can be classified as the focal type and the diffuse type (10). The diffuse type is the most common type (2,10).

NLH can also be classified as the child and adult type. The child type occurs commonly in people under the age of 10 years and generally spontaneously regresses (11). Many theories have been advanced, but the most famous is related to a delayed type of food hypersensitivity.

The adult type is the less common, and it is usually associated with immunodeficiency syndromes, Giardia Lambila or Helicobacter Pylori infection (3, 13).

Etiology

The exact etiology of NLH is unknown (14). NLH is a lymphoproliferative disease that is characterized by

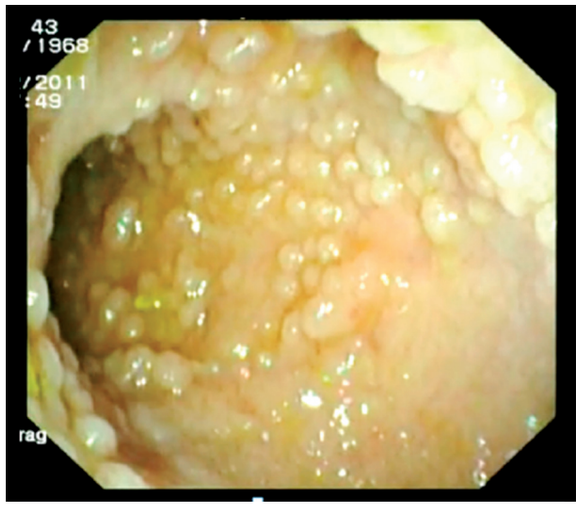

Figure 1. — DNLH in the terminal ileum of a middle aged female who presented with chronic diarrhea.

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Submission date : 11/11/2016
Acceptance date : 03/04/2017

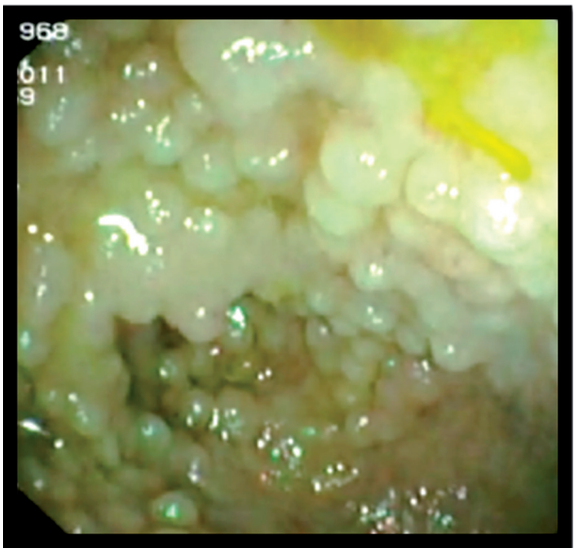

Figure 2. — DNLH in the terminal ileum of a middle-aged female who presented with chronic diarrhea.

the stimulation of the B cell component of the lymphoid follicles, which results in its abnormal proliferation (15). NLH principally occurs in the lymph node cortex without approaching the capsule (15,16).

A generally believed theory is that NLH represents a local immune response to a chronic irritation of the GIT mucosa with certain antigenic stimulators that eventually result in hyperplasia of the lymphoid follicles (17,18). These antigenic stimulators have not yet been identified, but infectious agents may be accused (19).

Another theory is related to immunodeficiency states that lead to maturational defects of the B-lymphocytes that in turn lead to the accumulation of plasma cell precursors within the lymphoid follicles (20,21).

Histology

Histologically, lymphoid nodular hyperplasia appears as enlargements of the mucosal B cell follicles with highly active germinal centers (22). These hyperplastic follicles are confined to the mucosa and the submucosa and are surrounded by a normally appearing mantle zone (1,23). The follicles are cytologically polymorphous, are often polarized and vary in size and shape (22,23).

Associated conditions

1. Common variable immunodeficiency (CVID)

CVID is an immunodeficiency syndrome that is characterized by an impairment of the function of B-cells, T-cells and dendritic cells (24). CVID results in the inability of the B-cells to mature, which disables immunoglobulin secretion. CVID is characterized by the lack or deficiency of IgG and IgA + IgM together with the presence of B cells, a poor response to immunizations and the absence of other immunodeficiency states (25).

CVID usually presents in early adulthood, but it can also present during childhood, which makes its diagnosis challenging (26). Typically, patients with CVID present with repeated infections that are mainly sinopulmonary (27). Moreover, patients may present with autoimmune disease, lymphoid hyperplasia in the form of tonsillar enlargement and hepatosplenomegaly (28). Approximately 20 % of patients with CVID have diffuse nodular lymphoid hyperplasia (29,30). The risk of malignancy increases with CVID; the risk developing gastric carcinoma is increased by 50 %, and the risk of GIT lymphoma is also increased.

2. Selective IgA deficiency syndrome (SIgAD)

SIgAD is the most common primary immunoglobulin deficiency and is defined as an isolated deficiency of serum IgA in the setting of normal serum levels of IgG and IgM in a patient for whom other causes of hypogammaglobulinemia have been excluded (33). Severe deficiency is defined when the serum IgA reaches < 7 mg/dL, which is the lower limit of detection for most assays. Partial deficiency occurs with a serum IgA > 7 mg/dL but below the lower limit of normal (defined as 2 standard deviations below the age-adjusted mean value) (34). Approximately 85-90 % of patients are asymptomatic (35). However, 10-15 % of patients may be symptomatic in the following prominent forms: recurrent respiratory infections, autoimmune disorders, GIT infections, anaphylactic transfusion reactions, food allergies, and respiratory allergies (36,37). There are a few case reports of SIgAD with diffuse nodular lymphoid hyperplasia (7,13,38). Some of these cases have been observed in sarcoid-like syndrome (38), and some exhibit histologies similar to celiac disease, collagenous sprue, and lymphocytic colitis.

Very few published cases have presented with intestinal lymphoma (13,45), which accords with the above-mentioned finding that immunoglobulin deficiencies increase the risk of GIT malignancies such as colonic and gastric adenocarcinomas (39,40).

3. Giardia lamblia infection

Giardia lamblia infection has been reported to be associated with NLH, and it was thought that Giardia lamblia could be one of the antigenic stimulators (41). In contrast to this belief, Giardia lamblia is strongly associated with immunodeficiency syndromes (42). However, case series have reported Giardia lamblia with NLH with or without immunoglobulin deficiency (43).

4. Helicobacter pylori infection

In a single report with a large number of patients, Khuro *et al*. performed a cohort study from 2005 until

2010 on 40 patients with duodenal NLH who were also infected with *H. pylori*. After total eradication of *H. pylori* infection, significant reduction in the duodenal nodular lesions was observed in 26 patients. However, 14 patients who exhibited resistance to *H. pylori* treatment exhibited no improvement. Hence, there could be an etiological correlation between *H. Pylori* and NLH (3,45).

5. Food hypersensitivity

Studies have demonstrated a significant association between NLH and food hypersensitivity in children, especially regarding the focal type that is mainly found in the bulb (12). This hypersensitivity is believed to be an exaggerated humoral immune response to certain types of food, the best known of which is cow's milk, and this condition has been found to be closely associated with high levels of IgA and IgG antibodies to whole cow's milk or a specific fraction thereof (5,12).

6. GIT malignancy

The risk of GIT malignancy increases with NLH, and this risk increases greatly when combined with immunoglobulin deficiency (39,40). CVID increases the risks of gastric and colonic adenocarcinomas by up to 50 times (31, 32). The risks of lymphoma, whether intestinal or extra-intestinal, is also increased (13,45). The risk of lymphoma increases by up to 30-fold in the presence of Epstein Bar virus infection (46).

7. Others

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant condition that is characterized by the formation of hundreds of polyps in the colon (47). Patients inevitably develop carcinomas (47). A variant of FAP called Gardener syndrome is characterized by the additional formation of skin epidermoid cysts, pigmented retinal epithelium, thyroid carcinomas, and skull and mandibular osteomas (48). Both of these conditions have been mentioned in the literature to be associated with NLH that primarily affects the terminal part of the ileum (49,50,51).

NLH has been reported to be one of the changes that occur in the GITs of human immune-deficiency virus (HIV)-infected patients, and this condition is primarily related to immune deficiency states (2,52).

Garg *et al*. reported a single case of a patient with NLH associated with an IgG2 subclass deficiency, autoimmune thyroiditis, and autoimmune hemolytic anemia (10).

Clinical presentation

In most reports, diffuse nodular hyperplasia is asymptomatic and discovered accidently during routine endoscopy. However, diffuse nodular hyperplasia can have a wide range of symptoms that include the following (53):

– Vague non-specific symptoms in the form of abdominal pain and flatulence (53)
– Chronic diarrhea or even malabsorption syndrome (54,55)
– Repeated attacks of gastroenteritis, especially if associated with immunodeficiency syndrome (55)
– Rarely, presentation with GIT bleeding (56) or intestinal obstruction (57).

Differential Diagnosis and Work Up

Although the picture of diffuse innumerable nodules appears classic for the diagnosis of NLH, there are important differential diagnoses that need to kept in mind, especially if the NLH involves less common sites, such as the colon or more rarely the stomach.

NLH should be differentiated from other polyposis conditions, such as familial adenomatous polyposis (when this condition involves the colon, the clinical picture can be very similar), multiple lymphomatous polyposis, juvenile polyposis, hamartomatous polyposis, Peutz-Jeghers syndrome or malignant lymphoma.

Confirmation of the diagnosis of NLH depends upon the classic endoscopic picture and the histological criteria mentioned above. The recommended work up is centralized around the diagnosis of the associated conditions and the exclusion of complications, particularly malignancy. The recommended diagnostic work up includes the following:

– Giardia Lambila diagnosis via stool examination for cysts or trophozites (58), Giardia antigen detection by enzyme-linked immune assay (ELISA) of the stools (59) or even the identification of Giardia trophozites in an endoscopic biopsy (60).
– *Helicobacter pylori* diagnosis via the detection of *H. pylori* antigen in the stools, carbon-13 urea breath test or *H. pylori* serology (61).
– Immunoglobulin electrophoresis or serum immunoglobulin examination for the detection of associated CVID, SIgAD, or any associated hypogammaglobulinemia (32).
– Serology or PCR for HIV due to the mentioned associations as part of the immune deficiency condition (52) and EBV due to the increased risk of transformation into lymphoma (46).
– Screening for celiac sprue with tissue transglutaminase (TTG-IgA) antibodies, anti-endomysial antibodies together with serum IgA levels (62). IgG-based tests, such as tests for IgG deamidated gliadin peptides (DGPs) and IgG-TTG, may be used in cases of associated IgA deficiency syndrome (63).
– The following imaging modalities can be used to screen for small intestinal malignancies following the endoscopic diagnosis of NLH or can be used to illustrate a suggestive picture of NLH when the medical condition of the patient leads to the suspicion of a small intestinal disease prior to endoscopy.

– Barium meal follow through can reveal multiple micronodules located in all of the segments of the small intestine (41).
– C.T. enterography can reveal diffuse mural thickening of the small intestinal wall (13).
– Capsule endoscopy is one of the best modalities for the visualization of the NLH, but it does not allow for biopsies from the lesions (3).
– Double-balloon enteroscopy is diagnostic for NLH. This procedure enables the collection of biopsies from the lesions, and it can also aid in surveillance for the detection of early malignancies [13, 64]. Fig. 3 and 4 represent a patient with NLH who presented with chronic diarrhea and was diagnosed via double-balloon enteroscopy.

Treatment options

There is no definitive treatment for NLH; thus, treatment is mainly directed toward the management of the associated conditions (2), such as giardiasia, *H. pylori*, celiac disease, etc.

However, a very limited number of reviews have suggested that repeated courses of antibiotics, such as amoxicillin, quinolones and metronidazole, might help in terms of improvements of the symptoms, particularly in cases of immunodeficiency syndromes (13,29). NLH in cases with no complications usually requires no special treatment; however, the patients should undergo prophylactic examinations.

These issues cause controversy when selecting treatment options. Following patients without any treatment may lead to malignant progression, but surgical treatment may result in unnecessary radical resections because of the obscurity of the diagnosis.

Surveillance

There is currently no consensus regarding the surveillance of NLH. However, from the authors' perspective, surveillance is highly recommended due to the increased incidence of malignant transformation. Regarding the method of surveillance, imaging examinations, such as barium meal and C.T. enterography, could help, but these modalities are limited in their abilities to detect early lesions. Capsule endoscopy and double-balloon enteroscopy can provide excellent options for the surveillance of NLH, but the necessary facilities are not always available, and these techniques are expensive and require specific experience. Additionally, the duration and intervals of such surveillance are not yet identified.

Conclusion

NLH is a benign condition that is usually disregarded as being insignificant in clinical practice. The presence of NLH signifies an underlying cause, and its management primarily involves the treatment of the underlying cause. Clear guidelines for the follow-up and surveillance of patients with NLH are needed due to the risk of malignant transformation. In conclusion, NLH is a very interesting topic that needs greater awareness in terms of management and follow-up.

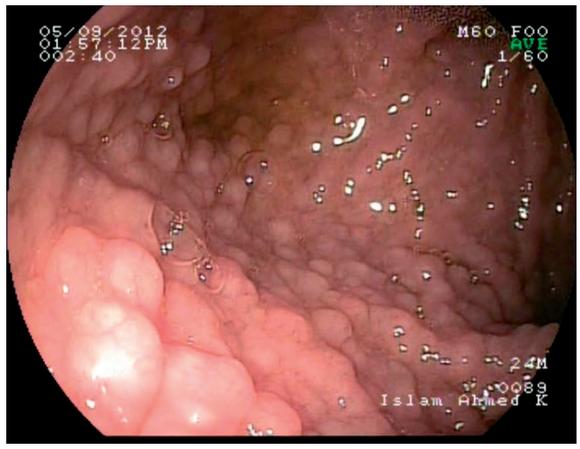

Figure 3. — DNLH in the small intestine of a young male patient visualized with double balloon enteroscopy.

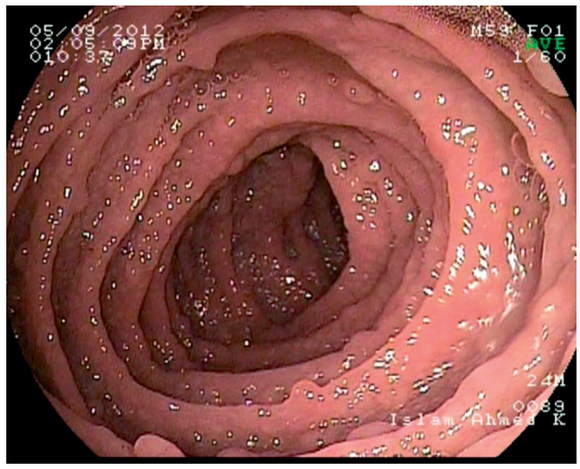

Figure 4. — DNLH in the small intestine of a young male patient visualized with double balloon enteroscopy.

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