Diffuse Nodular Lymphoid Hyperplasia of Intestine in Selective IgG 2 Subclass Deficiency, Autoimmune Thyroiditis, and Autoimmune Hemolytic Anemia: Case Report and Literature Review

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Abstract

Diffuse Nodular Lymphoid Hyperplasia (DNLH) of the intestine is a rare lymphoproliferative disorder of uncertain etiology, which is characterized by the presence of multiple nodular lesions. It can present as an asymptomatic disease or manifest with gastrointestinal symptoms like abdominal pain, chronic diarrhea, occult bleeding or rarely intestinal obstruction. DNLH has been seen in association with common variable immunodeficiency (CVID) where it poses a risk of malignant transformation. We present a case of diffuse lymphoid nodular lymphoid hyperplasia in a patient who was presented with abdominal pain and diarrhea, and was later found to have IgG2 subclass immunodeficieny, autoimmune hemolytic anemia and Hashimoto's (autoimmune) thyroiditis. Through this report, we wish to review current literature as well as share our clinical experience in managing this rare entity.

Key words

Diffuse nodular lymphoid hyperplasia – autoimmune thyroiditis – autoimmune hemolytic anemia – IgG2 subclass immune deficiency – prostate cancer.

Introduction

Diffuse Nodular Lymphoid Hyperplasia (DNLH) of the intestine is a rare lymphoproliferative disorder of uncertain etiology, which is characterized by presence of multiple nodular lesions. It can present as an asymptomatic disease or manifest with gastrointestinal symptoms like abdominal pain, chronic diarrhea, occult bleeding, or rarely intestinal obstruction. DNLH has been seen in association with common variable immunodeficiency (CVID) where it poses a risk of malignant transformation. We present a case of DNLH in a patient who presented with abdominal pain and diarrhea, and was subsequently found to have autoimmune hemolytic anemia, Hashimoto's (autoimmune) thyroiditis, and IgG2 deficiency. In our review of literature, there were no reports of DNLH in a patient with preexisting autoimmune hemolytic anemia, autoimmune thyroiditis, and selective IgG2 subclass deficiency.

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Case presentation

A 60 year-old Turkish male presented to the gastroenterology clinic with complaints of diarrhea and diffuse abdominal pain. The patient reported 4-5 episodes of loose watery diarrhea for 1 month. He described the abdominal pain as crampy and intermittent, and denied any associated nausea or vomiting. He also reported constitutional symptoms of fatigue, episodic sweating with subjective fever, and a 15 pound weight loss over last month. He denied any recent travel or sick contacts. He recently completed a one week course of ciprofloxacin and metronidazole for suspected bacterial gastroenteritis, and experienced mild improvement in diarrhea. The past medical history was significant only for prostate cancer (stage 1) treated 6 years ago with surgery and radiation therapy. He was on hormonal therapy with leuprolide. Family history was unremarkable. Social history was negative for alcohol, smoking, or recreational drugs. Physical examination was remarkable for marked pallor, splenomegaly and mild tenderness of the left upper and lower abdominal quadrants on deep palpation.

Complete blood count showed significant anemia (hemoglobin- 7.2 g/dl, normal-13.5-18.0) and macrocytosis (MCV- 105.2, normal 80.0 – 96.0). Vitamin B12, folate, and the iron panel were all within normal limits, but ferritin was low, 20 (30-400 ng/mL). Peripheral smear showed

anisocytosis and poikilocytosis. Reticulocyte count was elevated at 16.0% (normal 0.8 – 2.1%), total bilirubin was 1.6 (normal 0.0-1.0 mg/dl), haptoglobin <20 (normal 30-200 mg/dL), lactate dehydrogenase 453 (normal 94-250 U/l), and direct Coombs test was positive with warm auto antibody. Computed tomography showed extensive mesenteric, portocaval, periportal, celiac, paracaval, and paraaortic adenopathy. TSH was 12.6 (normal 0.27 – 4.20 uIU/mL), thyroglobulin antibody > 3000 (normal <20 IU/mL) and thyroid peroxidase antibody was 115 (normal < 35 IU/ml). The tissue anti-gliadin, anti-tissue transglutaminase antibodies, intrinsic factor antibodies, were all found to be negative. Three stool specimens were negative for ova or parasites. Esophagogastroduodenoscopy (EGD) showed atrophic gastric mucosa and mucosal nodularity in the duodenal bulb (Fig. 1). The biopsy report showed normal gastric mucosa, while the duodenal biopsy showed mucosal lymph node aggregates. The colonoscopy was significant for diffuse mucosal nodularity in the rectosigmoid area. Multiple biopsies were taken that revealed large lymphoid aggregates in the Peyer's patch in the terminal ileum (Fig. 2) and sigmoid colon. There were no features of cryptitis, lymphocytic colitis, abnormal crypt architecture, or dysplasia. Small bowel series showed multiple filling defects in the small intestine (Fig. 3).

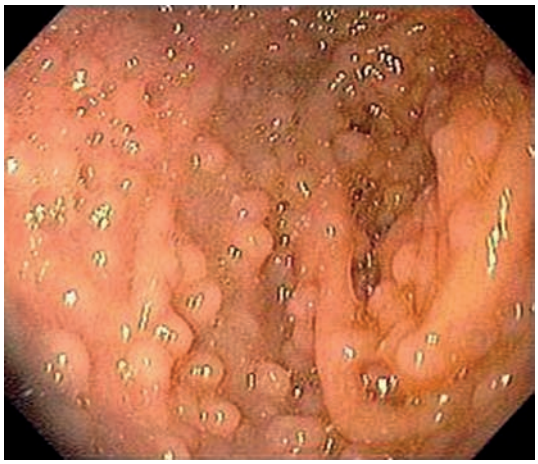

Fig 1. Gross nodularity found in the duodenal bulb on EGD.

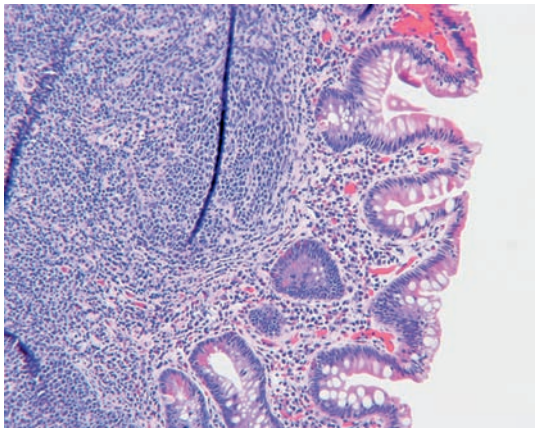

Fig 2. Enlarged lymphoid follicle, preserved crypts (H&E, x200)

Capsule endoscopy showed diffuse nodular mucosa throughout the small intestines (Fig. 4). Immunoglobulin tests showed low IgA 54.8 (normal 70.0 – 400.0 mg/dL), IgM 34.6 (normal 40.0-230.0 mg/dL), and IgG 630.7 (normal 700.0-1600 mg/dL). IgG subclass levels showed IgG1 455 (normal 382-929 mg/dl), IgG2 125 (normal 241-700 mg/dl), IgG3 61(normal 22-178 mg/dl), IgG4 0.2 (normal 4-86 mg/dl). Bone marrow biopsy was performed which showed reactive lymphoid aggregates (Fig. 5), and gallium scan did not reveal enhanced radiotracer uptake. Abdominal lymph node excisional biopsy was performed which showed reactive lymphadenopathy, negative for malignancy. The diagnosis was given of diffuse nodular hyperplasia with autoimmune hemolytic anemia, autoimmune thyroiditis, and IgG2 subclass deficiency.

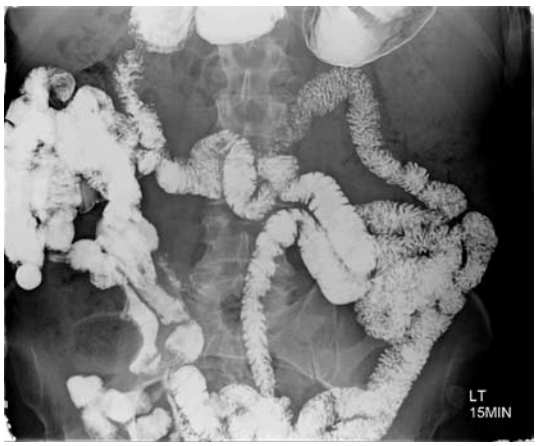

Fig 3. Nodular filling defects in the small bowel.

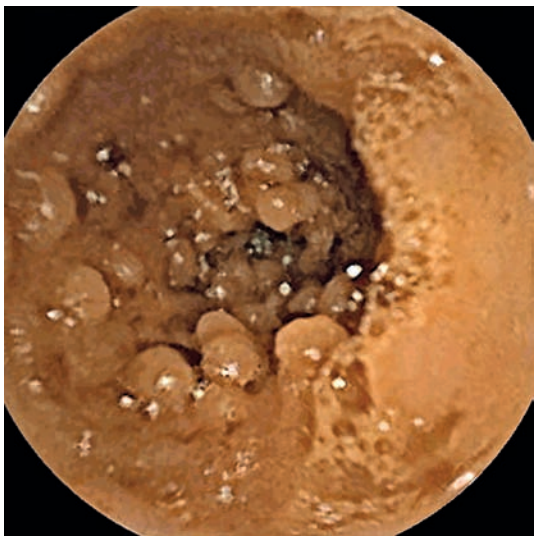

Fig 4. Capsule endoscopy showing diffuse nodular mucosa in the ileum.

Discussion

Diffuse nodular lymphoid hyperplasia is a rare lymphoproliferative disorder which can be seen in immunodeficient, as well as immunocompetent individuals [1]. Patients can often present with chronic diarrhea and abdominal pain. Patients could be asymptomatic and

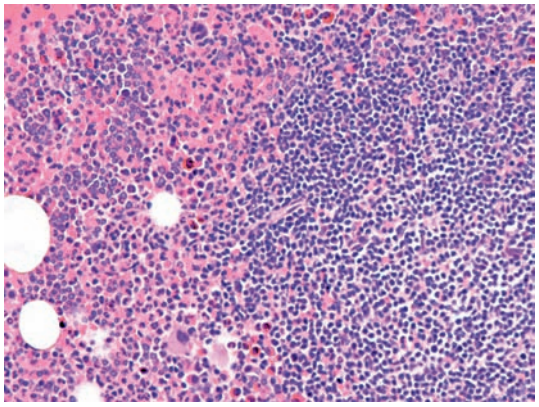

Fig 5. Bone biopsy: focal reactive lymphoid aggregates, without evidence of lymphoma (H&E, x200)

rarely the nodules could be large enough to cause intestinal obstruction and massive bleeding [1]. Diffuse nodular lymphoid hyperplasia had been reported in about 20 % of patients with CVID [1].

Common variable immunodeficiency is the second most common primary immunodeficiency disorder (after IgA deficiency) and is characterized by decreased serum levels of immunoglobulins (IgG, IgA and/or IgM) [2]. Respiratory complaints are most common followed by gastrointestinal [3]. In the majority of cases the biopsy shows paucity of plasma cells and prominent lymphoid aggregates [4]. Symptomatic patients with nodular lymphoid hyperplasia should be evaluated for CVID [5, 6] and parasitic infections should be ruled out, most commonly reported being giardiasis [1, 2, 7-9]. Gastrointestinal manifestations of hypogammaglobulinemia could also mimic atrophic gastritis (10), inflammatory bowel disease and celiac disease [2]. Associated non-gastrointestinal disorders include autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura [11, 12]. A case of acquired immunodeficiency with fatal outcome in metastatic prostate cancer has been reported [13]. Our patient presented with AIHA and although the levels of immunoglobulins were borderline low, he did not meet the diagnostic criteria for CVID which is defined by a decrease in the level of two or three immunoglobulins types (IgA, IgM, or IgG) by more than 2 standard deviations [2]. However, IgG2 subclass deficiency was found. The inheritance, genetic defects or mechanism of selective subclass deficiency is poorly understood. Individuals with IgG2 deficiency are at increased risk of infection with encapsulated bacterial pathogens like *Streptococcus pneumoniae, Haemophilus influenzae* type b (Hib), and *Neisseria meningitides* [14-16]. It has also been associated with primary and secondary immunodeficiency states like chronic mucocutaneous candiasis [17] and human immunodeficiency virus infection [18], respectively. Medical course could vary from spontaneous resolution to progression to CVID [19]. IgG4 deficiency can also be associated with IgG2 subclass deficiency [20].

The exact mechanism of development of DNLH is still unknown. It has been hypothesized that these lymphoid aggregates could be an independent response to antigenic stimuli in the presence of deranged immunoglobulin function such as that seen in selective IgA deficiency [1] or CVID. Cathe et al [4] have hypothesized that DNLH could be a transitional stage in the development of a malignant lesion, or possibly an early lymphomatous lesion. The overall risk of cancer in immunodeficiency states ranges from 2-10% [4]. An increased incidence of intestinal malignancy, mainly gastrointestinal lymphoma [7, 10, 21, 22] has been reported in patients with DNLH and hypogammaglobulinemia [1, 2, 7, 10]. However, the relationship still remains unclear.

Appropriate diagnosis is important in symptomatic patients with DNLH. Nodules could range in size from 2 mm to 10 mm [1], and could be present in stomach, small intestine (terminal ileum –most common) and colon where the diagnosis could be confused with other polyposis syndromes [6, 23, 24]. Immunologic dysfunction should be suspected [5, 6, 23] and infections should be promptly treated [23]. There is paucity of literature on recommendations for rechecking or follow up of immunoglobulin levels. Diagnosis should be based on histopathology and not just on endoscopy alone since misdiagnosis could lead to overtreatment of a benign condition [24, 25]. Bayraktar et al [26] advocate capsule endoscopy in patients proven to have CVID to evaluate for complications and also to gauge extent of disease. Because of the risk of malignant transformation, surveillance capsule endoscopies [23] and small bowel studies [4] are recommended by some authors, however, the duration and intervals of such surveillance are not yet defined [23].

Conclusion

In conclusion, diffuse nodular lymphoid hyperplasia in itself is a rare benign condition of unknown etiology. It can present with varying symptoms, most commonly reported being abdominal pain and diarrhea. In symptomatic patients, workup should be directed towards underlying hypogammaglulinemia, infections and possible malignancy. Eradication of infection could lead to resolution of symptoms. In the absence of CVID it is rarely seen in association with autoimmune hemolytic anemia. Hypogammaglobulinemia is also associated with various autoimmune disorders and an increased risk of malignancy. Patients should undergo prophylactic surveillance endoscopy to rule out complications and to establish extent of disease. However, there are no clear cut guidelines for surveillance.

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