

# Diffuse Nodular Lymphoid Hyperplasia of the Intestine Caused by Common Variable Immunodeficiency and Refractory Giardiasis

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## Abstract

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Diffuse nodular lymphoid hyperplasia of the gastrointestinal tract is a rare disease characterized by numerous small polypoid nodules in the small intestine, large intestine, or both. It is associated with immunodeficiency and infection, such as *Giardia lamblia* and *Helicobacter pylori*. Although diffuse nodular lymphoid hyperplasia associated with common variable immunodeficiency (CVID) and giardiasis is already known, a few studies have reported a regression of the lymphoid nodules after the eradication of infection. We herein describe a case of diffuse nodular lymphoid hyperplasia of the intestine associated with CVID and refractory giardiasis that markedly improved after successfully treating giardiasis.

**Key words:** diffuse lymphoid hyperplasia, common variable immunodeficiency, giardiasis

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## Introduction

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Diffuse nodular lymphoid hyperplasia (DNLH) of the gastrointestinal tract is a rare disease characterized by numerous small polypoid nodules in the small intestine, large intestine, or both (1). The pathogenesis of DNLH is uncertain, but it may be related to the immune status. This condition may arise as compensation for insufficient intestinal lymphoid tissue in immunodeficiency, or it may be related to repeated immune stimulation of intestinal lymphoid tissue, such as infection, in immunocompetent patients (2, 3). It is associated with immunodeficiency, including common variable immunodeficiency (CVID), selective IgA deficiency, and human immunodeficiency virus (HIV) infection, and infections, such as *Giardia lamblia* and *Helicobacter pylori* (3-5). Although several cases of DNLH associated with CVID and giardiasis have been reported (6-8), so far very few studies have reported a regression of the lymphoid nodules after the eradication of infection (6). We herein describe a case of DNLH of the intestine associated with CVID and giardiasis

which markedly improved after successfully treating giardiasis.

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## Case Report

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A 41-year-old woman visited an out-patient clinic for an evaluation of DNLH that had been incidentally detected two years previously. She frequently had colds and suffered cystitis several times. She had been admitted to our hospital for the treatment of acute pyelonephritis one year prior. Although she had received vaccines against hepatitis B, she did not produce antibody against hepatitis B. Her family history was unremarkable.

On physical examination, her vital signs were normal. There was no palpable lymph node or hepatosplenomegaly. She had no signs of fever, weight loss, night sweats, or autoimmune phenomena. Although she had intermittent diarrhea, her abdomen was soft without tenderness.

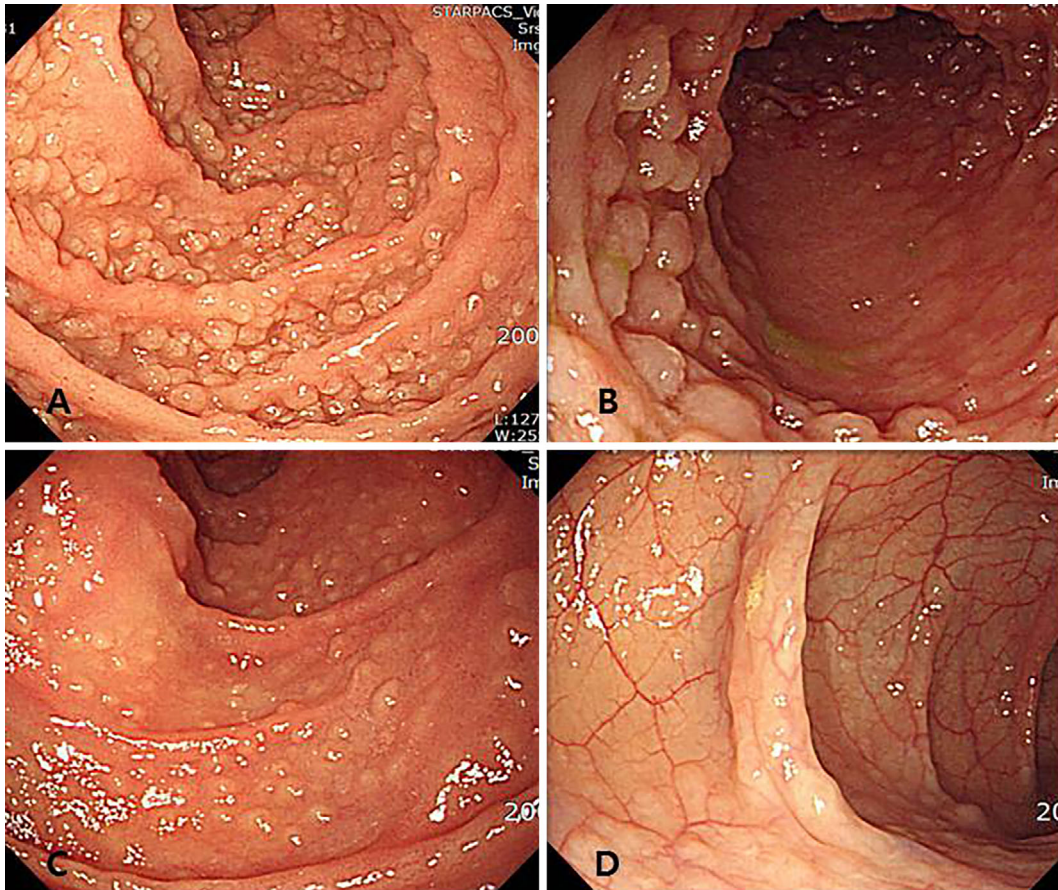
Laboratory tests showed a hemoglobin level of 12.3 g/dL, a white blood cell count of 9,100/μL, a platelet count of 266,000/μL, and normal kidney and liver function tests. Se-

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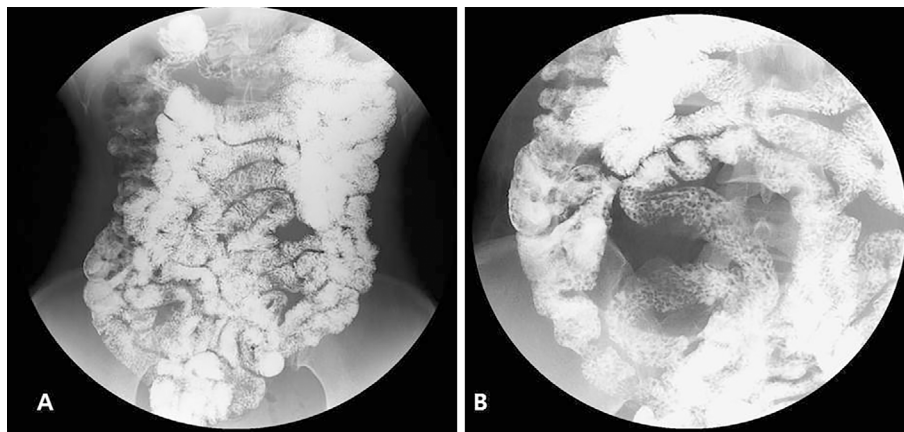
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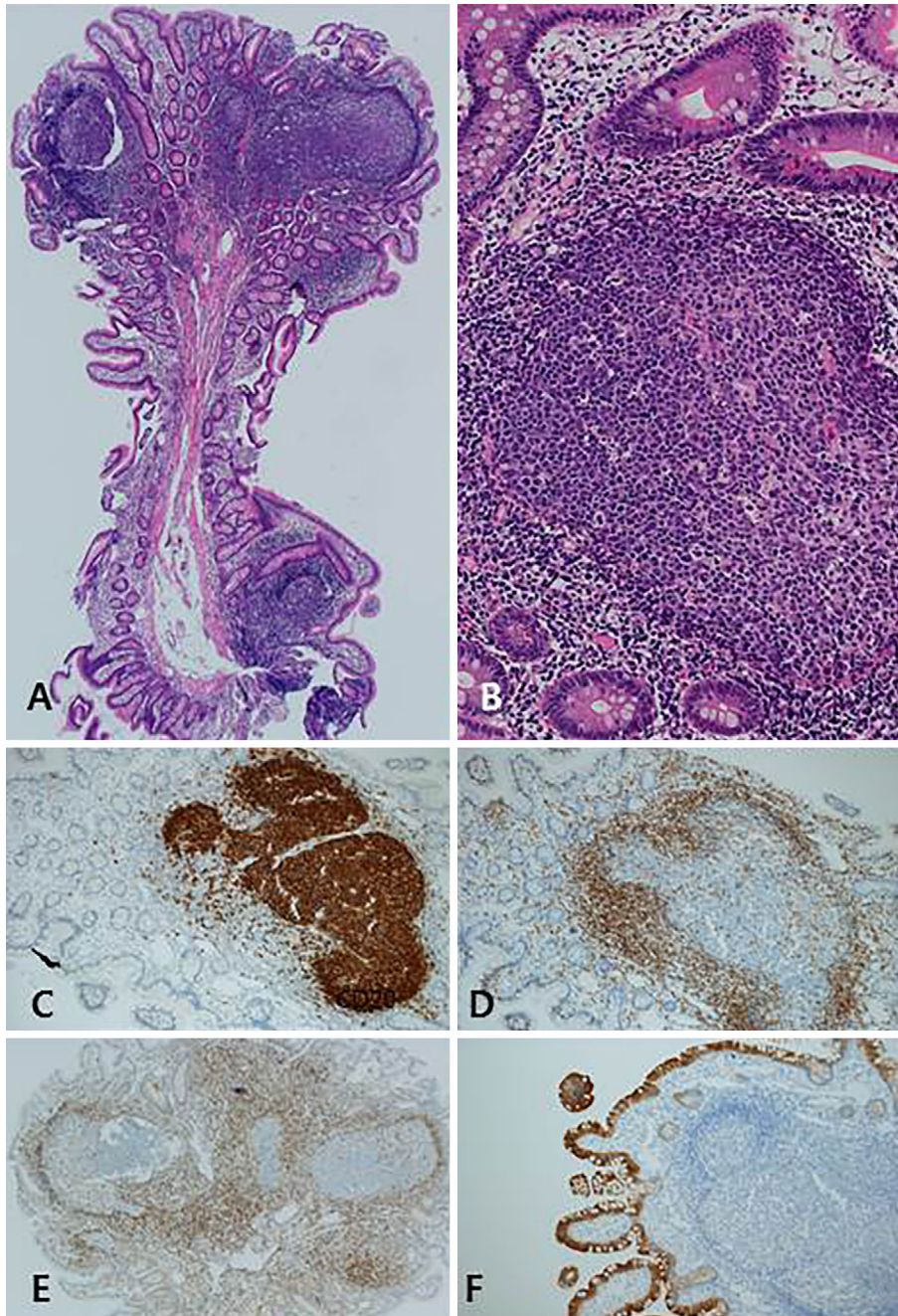
**Figure 1.** Esophagogastroduodenoscopy (EGD) and colonoscopy demonstrated numerous diffuse mucosal nodular lesions in the second portion of the duodenum (A) and colon (B). On follow-up EGD and colonoscopy, the size and number and of mucosal nodular lesions in the duodenum (C) and colon (D) had remarkably decreased compared with the lesions observed 2 years previously.



**Figure 2.** A small bowel series showed numerous small nodular lesions throughout the entire small bowel loop from the duodenum to the terminal ileum.

rologic tests for HIV and hepatitis B and C virus were negative. Antinuclear antibody was skeleton level 2 (1: 80), and C3 and C4 were within the normal range. However, here serum immunoglobulin levels were markedly decreased, with immunoglobulin G (IgG) of 175.0 mg/dL (normal range: 751-1,560 mg/dL), IgA of less than 7.3 mg/dL (82-453), and IgM of 36.6 mg/dL (46-304). A stool examination revealed *Giardia lamblia*. Esophagogastroduodenoscopy

(EGD) showed numerous mucosal nodular lesions in the second portion of the duodenum, and campylobacter-like organism (CLO) tests were negative. Colonoscopy revealed diffuse mucosal nodularity throughout the whole colon and terminal ileum (Fig. 1A, B). There were numerous small nodular lesions in the entire small bowel from the duodenum to the terminal ileum in a small bowel series (Fig. 2). Abdominal computed tomography revealed no abnormal



**Figure 3.** (A) A low power view of the duodenal mucosal tissue showed relatively well-preserved villous epithelial architecture and well-formed lymphoid follicles in the lamina propria [Hematoxylin and Eosin (H&E) staining,  $\times 40$ ]. (B) A high power view showed expansile hyperplastic germinal centers demonstrating well-preserved polarity from the dark to light zone, characteristics of reactive germinal centers, and sharply delineated by a thin layer of mantle zone (H&E staining,  $\times 200$ ). Immunohistochemical staining showed the characteristic features of reactive lymphoid hyperplasia with CD20 (C), CD3 (D), and Bcl-2 (E). (F) No lymphoepithelial lesions were noted on immunohistochemical staining for Cytokeratin ( $\times 100$ ).

findings.

An endoscopic biopsy showed a relatively well preserved mucosal architecture and many hyperplastic lymphoid follicles with expansile reactive germinal centers and sharply delineated bands of mantle zones. No marginal zone hyperplasia was observed. There was no evidence of lymphoepithelial lesions (Fig. 3A, B), and no organisms were detected.

The results of immunohistochemical staining were compatible with reactive lymphoid hyperplasia (Fig. 3C-F). We finally diagnosed DNLH of the intestine in a patient with CVID and giardiasis.

Among the first line therapies for giardiasis, only metronidazole was available at our clinic. Therefore, she received metronidazole [250 mg per os (PO)] three times a day for 5

days, but there was no response. As an alternative treatment, albendazole (400 mg PO once a day for 5 days) was prescribed (9). However, *G. lamblia* persisted in a stool examination. Tinidazole was then selected for the third treatment with a longer duration (2 g PO once a day for 5 days), however, the giardiasis could not be eradicated. Finally, we decided to treat suspected nitroimidazole-resistant *Giardia* with metronidazole (500 mg PO two times a day) in combination with albendazole (400 mg PO once a day). A 4-week course of combination therapy was scheduled. After 2 weeks of treatment, the results of a stool examination showed a negative result for *Giardia* (10).

EGD and colonoscopy were performed 15 months after successfully treating *G. lamblia*. Diffuse nodular lesions still existed from the duodenum to the colon, but they had remarkably decreased in size compared with the lesions that had been observed two years previously (Fig. 1C, D). Her serum immunoglobulin levels were still very low after eradication with IgG of 160.0 mg/dL, IgA of less than 7.3 mg/dL, and IgM of 14.9 mg/dL. Although she refused to undergo immunoglobulin treatment, she was able to return to her normal daily life and physical activities without any complications until now.

## Discussion

CVID, a heterogeneous disease associated with a failure to produce immune globulins and protective antibodies, is diagnosed by low levels of serum IgG, IgA, and/or IgM, impaired antibody production to vaccination, and the exclusion of other causes of failure of immunoglobulin production (11, 12). In our case, the diagnosis of CVID was delayed by 2 years after the incidental detection of DNLH because the patient had no specific symptoms, except for intermittent diarrhea. Since DNLH is associated with immunodeficiency, we performed careful history taking and several tests to determine her immunodeficient status. She had maintained very low serum levels of IgG, IgA, and IgM. She could not produce hepatitis B surface antibody after vaccination, but she had no other immunodeficiency. We finally diagnosed her with CVID based on these findings.

*G. lamblia* is a flagellated protozoan parasite that colonizes the small intestine. It can cause various clinical features from asymptomatic infection to chronic diarrhea and severe malabsorption. *Giardia* infection may be more intense and persistent in an immunodeficient host, such as in this case (13). Although our case showed treatment-resistant giardiasis, we were able to successfully eradicate *G. lamblia* after changing the therapeutic agents four times. The diffuse nodular lesions on the EGD just before successfully treating the giardiasis were very similar compared with the lesions on an initial EGD examination performed two years previously. The patient did not receive any other treatment except for eradication of giardiasis and the diffuse nodular lesions remarkably decreased after successfully treating giardiasis. Therefore, we assumed that the giardia infection played an

essential role in the development of DNLH in this case.

The overall survival of CVID has improved due to replacement of immune globulin and improved microbial therapies. However, immunoglobulin cannot control other important complications, including chronic lung disease, autoimmunity, gastrointestinal disease, and neoplasms, such as non-Hodgkin's lymphoma and gastric cancer (11, 12). While there is no standard follow-up schedule, it is important to keep monitoring the patient's medical history, physical examination, and several tests (12). Although our patient refused immunoglobulin treatment, she was able to lead a normal, active life without severe infection after diagnosis of CVID. She has regularly visited on our clinic and had regular work-ups, including blood tests, chest X-ray, and cancer surveillance.

In summary, we documented a case of DNLH of the intestine due to CVID and giardiasis. Because DNLH is associated with immunodeficiency and parasitic infections, it is essential for patients with DNLH to be evaluated for these diseases. In addition, CVID patients should undergo long-term surveillance for various complications, including the development of malignancy.

**The authors state that they have no Conflict of Interest (COI).**

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