Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8847-21
Intern Med 61: 2593-2599, 2022
http://internmed.jp

【 CASE REPORT 】

Immunoproliferative Small Intestinal Disease Diagnosed by Double-balloon Endoscopy with Biopsy Sampling

Miguel Ricardo Rodríguez Meza[1], Masanao Nakamura[1], Takeshi Yamamura[1], Keiko Maeda[2], Tsunaki Sawada[2], Eri Ishikawa[1], Naomi Kakushima[1], Kazuhiro Furukawa[1], Eizaburo Ohno[1], Takashi Honda[1], Hiroki Kawashima[2] and Masatoshi Ishigami[1]

Abstract:
We herein report an 80-year-old man diagnosed with immunoproliferative small intestine disease (IPSID) via small bowel endoscopy with a biopsy. He developed persistent diarrhea and subsequently presented with hypoproteinemia and moderate anemia. Transanal double-balloon endoscopy showed prominent villous edema in the middle and lower ileum, while a histological examination showed high lymphocyte/plasma cell infiltration in the mucosal layer. Furthermore, an immunostaining analysis showed that Cluster of differentiation (CD)3 and CD20 were partially positive, while CD138 was diffusely positive. Immunoglobulin A positivity was also observed. He was diagnosed with IPSID and received a nutritional agent and minocycline. After three months, the patients' symptoms improved.

Key words: IPSID, αHCD, case report, double-balloon endoscopy, *Campylobacter jejuni*

(Intern Med 61: 2593-2599, 2022)
(DOI: 10.2169/internalmedicine.8847-21)

Introduction

Immunoproliferative small intestinal disease (IPSID) or α heavy chain disease (αHCD) is one of the three types of heavy chain disease (HCD), which presents with small bowel abnormalities (1). IPSID, a variant of extranodal mucosa-associated lymphoid tissue (MALT) lymphoma (2, 3), is prevalent in Middle Eastern and Mediterranean countries (4). Patients diagnosed with IPSID develop intermittent diarrhea, colicky abdominal pain, and malabsorption symptoms (5). These clinical symptoms have been attributed to *Campylobacter jejuni* infections (6).

Double-balloon endoscopy (DBE) is a type of small bowel endoscopy that visualizes the entire small bowel and facilitates biopsy sampling (7). DBE has been established as the gold standard for diagnosing small bowel disease and has the potential to diagnose IPSID. Histologically, IPSID is characterized by intestinal crypts divided by a dense lymphoplasmacytic infiltrate with subsequent villous atrophy. Its immunostaining findings are typically positive for pan B-cell antigens (CD19, CD20, PAX5, and CD79a). While plasma cells do not express CD20, CD138 and CD79a are reportedly positive (1). The treatment strategy depends mainly on the stage of IPSID. For earlier stages, antibiotic treatment is indicated (ampicillin, metronidazole, tetracycline, or a combination) (1, 8). Should initial treatment fail, combination of chemotherapy including doxorubicin, surgery for tumor reduction, radiation therapy, and autologous stem cell transplantation is considered a viable alternative (1, 9).

We herein report a patient with IPSID who presented with positive DBE findings.

Case Report

An 80-year-old man with a history of chronic renal failure was admitted to our hospital for persistent severe diarrhea. Esophagogastroduodenoscopy performed at a previous hospital revealed an ulcer at the stomach angular incisure (Fig. 1). He was thus treated with a proton pump inhibitor.

[1]Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Japan and [2]Department of Endoscopy, Nagoya University Hospital, Japan
Received: October 17, 2021; Accepted: December 21, 2021; Advance Publication by J-STAGE: February 8, 2022
Correspondence to Dr. Masanao Nakamura, makamura@med.nagoya-u.ac.jp

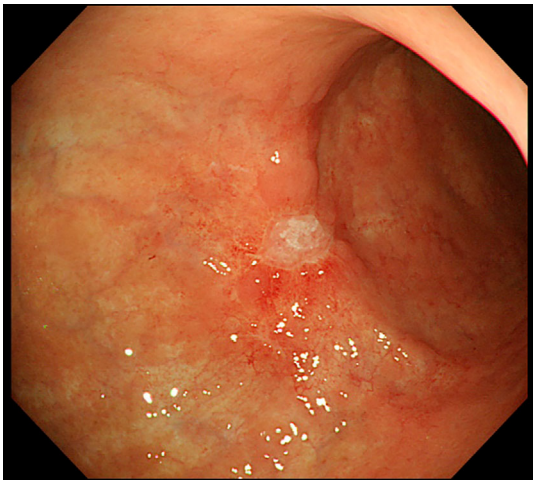


Figure 1. Gastric ulcer in the stomach angular incisure found on esophagogastroduodenoscopy performed during his previous hospitalization.

During his initial consult at our hospital, laboratory studies revealed hypoproteinemia (albumin 2.6 g/dL), moderate anemia (hemoglobin 8.3 g/dL), and an increased inflammatory response (C-reactive protein 1.62 mg/dL). Further testing was negative for *Helicobacter pylori*, T-spot, and cytomegalovirus antigen. Cancer antigen 19-9 and interleukin-2 receptors were slightly elevated (69 U/mL and 978 U/mL respectively) (Table).

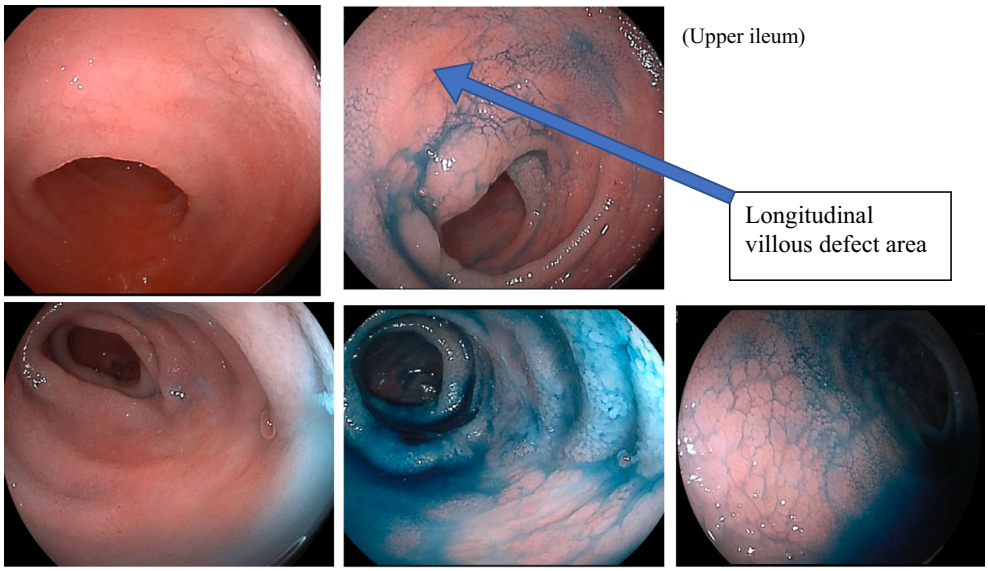
Trans-anal DBE revealed slight villous edema in the upper ileum. The edema became more prominent from the middle to the lower ileum (Fig. 2A). In addition, retrograde gastrografin enterography was performed during trans-anal DBE. Neither rough mucosa, apparent stenosis, nor intestinal dilatation was observed on endoscopy (Fig. 2B). Biopsy specimens were taken from the middle and lower ileum. A pathological examination of the lower ileum specimen revealed no epithelial atypia or lymphocyte/plasma cell infiltration in the mucosa (Fig. 3A, B). A further pathological examination of the lower ileum confirmed that CD3 and CD20 were partially positive, while CD138 was diffusely

Table. Laboratory Findings When the Patient Was Hospitalized.

Parameter	Result	Normal range	Parameter	Result	Normal range
Biochemistry			Plt ($\times10^3/\mu L$)	22.5	15.0-40.0
TP (g/dL)	6.0	6.3-8.3	MCV (fL)	86.2	33-41
Alb (g/dL)	2.6	4.0-5.0	MCH (pg)	27.9	23-33
Glu (mg/dL)	86	70-105	MCHC (g/dL)	32.3	36-41
BUN (mg/dL)	29.7	8.0-15.0	Coagulation/immunity		
Cre (mg/dL)	1.23	0.7-1.5	PT (%)	95.4	85-100
UA (mg/dL)	1.9	2.1-7.1	APTT (%)	178	85-100
Na (mmol/L)	138	138-146	Fib (mg/dL)	495	200-400
K (mmol/L)	5.1	3.6-4.9	IgG (mg/dL)	1,089	870-1,700
Cl (mmol/L)	103	99-109	IgA (mg/dL)	140	110-410
Ca (mg/dL)	8.8	0.3-0.5	IgM (mg/dL)	14	35-220
AST (U/L)	17	15-37	ESR (1h) mm	69	2.0-10.0
ALT (U/L)	15	30-65	*H. pylori* antibody (U/dL)	<3	30.1-39.9
LDH (U/L)	250	140-280	T-spot	Negative	
ALP (U/L)	281	50-136	C7-HRP	Negative	
γGTP (U/L)	25	5-85	ANA	1:40	1:40
TBil (mg/dL)	0.5	0.2-1.0	AntiDNA antibody (IU/mL)	<2	<6
DBil (mg/dL)	0.1	0.0-0.3	Endocrine		
AMY (U/L)	155	38-136	TSH (μIU/dL)	3.42	0.3-3.0
CK (U/L)	22	39-380	Free T3 (pg/mL)	2.2	0.8-2.0
CRP (mg/dL)	1.6	0.0-0.3	Free T4 (ng/mL)	0.9	5,4-11.5
Blood count			Tumor marker		
WBC ($\times10^3/\mu L$)	4.7	3.0-8.0	Gastrin (pg/mL)	55	<200
RBC ($\times10^3/\mu L$)	2.98	6.3-9.0	CEA (ng/mL)	2.9	<5
Hb (g/dL)	8.3	12.4-17.0	CA19-9 (U/mL)	69	<37
Hct (%)	25.7	38.0-54.0	sIL-2R (U/mL)	978	122-496

Alb: albumin, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AMY: amylase, ANA: anti-nuclear antibody, APPT: partial thromboplastin time activated, AST: Aspartate transaminase, BUN: Blood urea nitrogen, CA: calcium, CA19-9: cancer antigen 19-9, CEA: carcinoembryonic antigen, CK: creatinine kinase, Cl: chlorine, CRP: C-reactive protein, Cre: creatinine, C7-HRP: Cytomegalovirus antibody C7-HRP, DBil: Direct bilirubin, ESR: erythrocyte sedimentation rate, Fib: fibrinogen, Free T3: Free triiodothyronine, Free T4: Free thyroxine, γGTP: Gamma-glutamyltransferase, Glu: Glucose, Hb: hemoglobin, Hct: hematocrit, IgA= immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, K: potassium, LDH: L-lactate dehydrogenase, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, Na: sodium; Plt: platelet, PT: Prothrombin time, RBC: red blood cell, sIL-2R: soluble interleukin-2 receptor, T3: triiodothyronine, t4: thyroxine, TBil: Total bilirubin, TP: total protein, TSH: thyroid-stimulating hormone, UA: uric acid, WBC: white blood cell

A



B

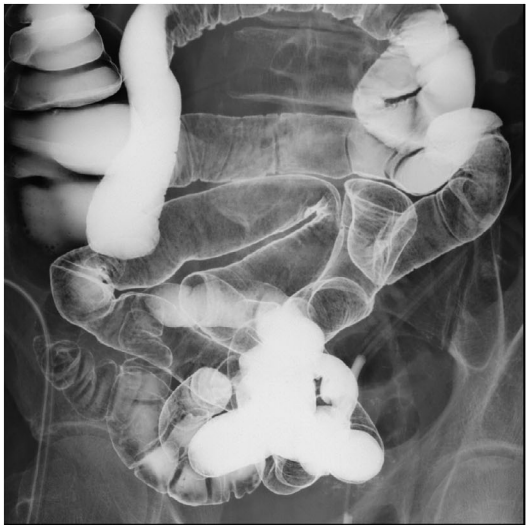


Figure 2. **(A) Transanal double-balloon endoscopy showed discontinuous villous edema and rough mucosa in the middle to lower ileum as well as a longitudinal villous defect area in the lower ileum, indicated by a blue arrow. The biopsy result was positive from that area. (B) Retrograde gastrografin enterography did not show obvious stenosis or intestinal dilatation.**

positive (Fig. 3C-F). In addition, an immunostaining analysis was positive for immunoglobulin A (IgA), while immunoglobulin G (IgG), kappa, and lambda were negative (Fig. 3G). These findings were consistent with IPSID.

Oral DBE was performed 11 days later (Fig. 4). The gastric ulcer detected at the previous hospital was healing (Fig. 5). The villi were slightly swollen, but no clear findings were noted in the lower jejunum. Treatment with Racol® NF was initiated due to persistent diarrhea. The patient's symptoms improved, and bone marrow aspiration revealed no infiltration. The stool culture had normal flora and was negative for *H. pylori* (no *C. jejuni*).

On the 26th day after the onset, the patient orally received 2 tablets of minocycline (minocycline hydrochloride 50 mg) daily. However, the patient relapsed (fever and diarrhea) during the oral administration of treatment. The patient gradually recovered, and his oral tolerance improved. Transanal DBE was performed again on the 74th day. The terminal ileum had an edematous mucosa with multiple submucosal tumor-like ridges (Fig. 6). On the oral side, the mucous membrane was rough, and swollen villi were scattered, as seen previously. On DBE, the endoscopic findings worsened, but the relapsed symptoms were less severe. These were attributed to a therapeutic effect. Due to the advanced

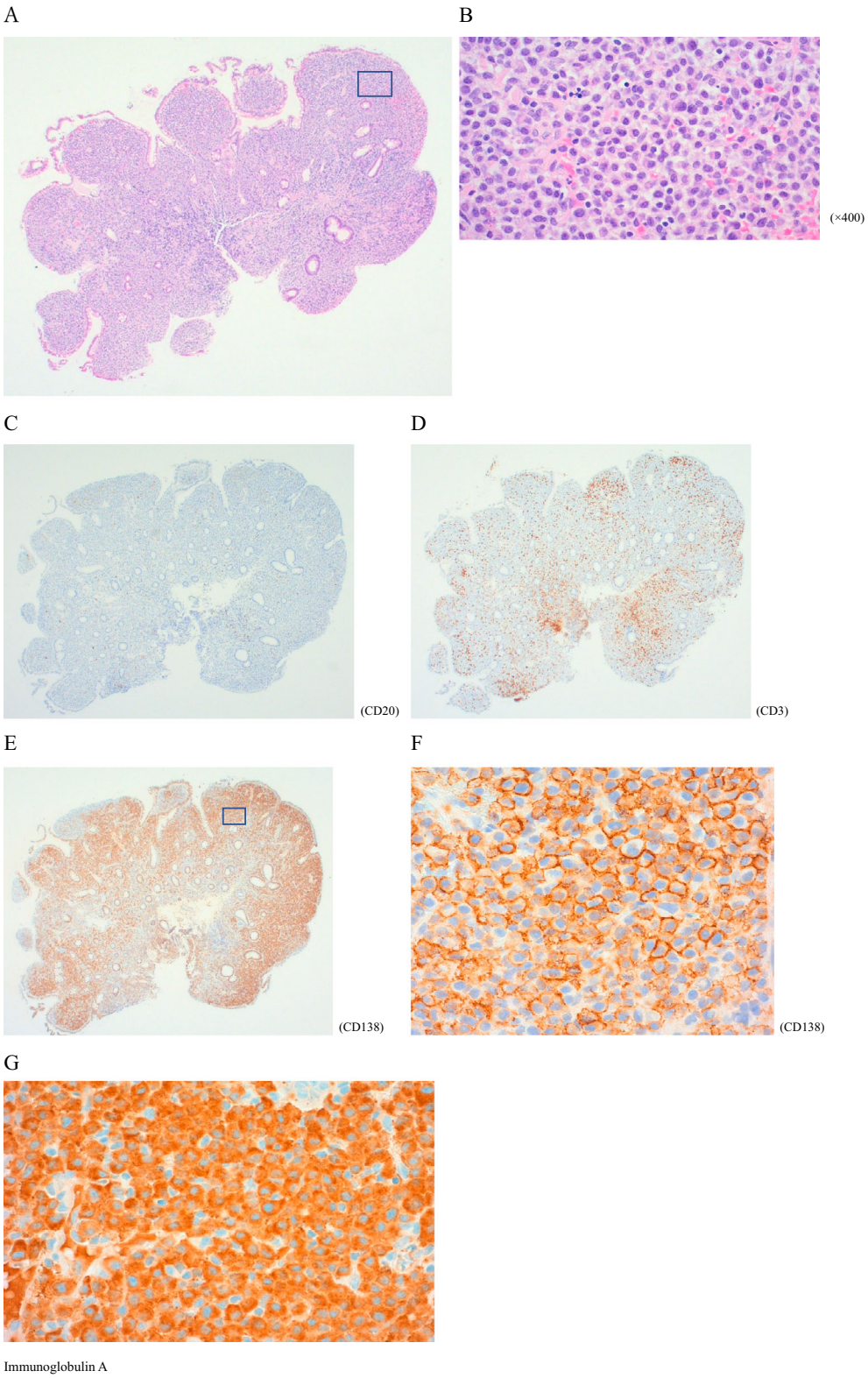


Figure 3. **Histopathological characteristics of immunoproliferative small intestine disease in an 80-year-old man from Japan. (A) Small bowel biopsy specimen showed prominent infiltration of lymphoid plasma cell-like cells into the lamina propria and villous atrophy (Hematoxylin and Eosin staining ×100). (B) Higher magnification from the surrounding area (×400). (C) Immunostaining showed that CD20 (B lymphocytes) was negative (anti-CD20 with hematoxylin counterstain, ×25). (D) CD3 (T lymphocyte) was stained in the background (anti-CD3 with hematoxylin counterstain, ×25). (E) CD138 (plasma cells) was diffusely positive (anti-CD138 with hematoxylin counterstain, ×25). (F) Higher magnification of CD138 immunostaining with an emphasis on the cell membrane (×400). (G) Immunostaining revealed immunoglobulin A positivity.**

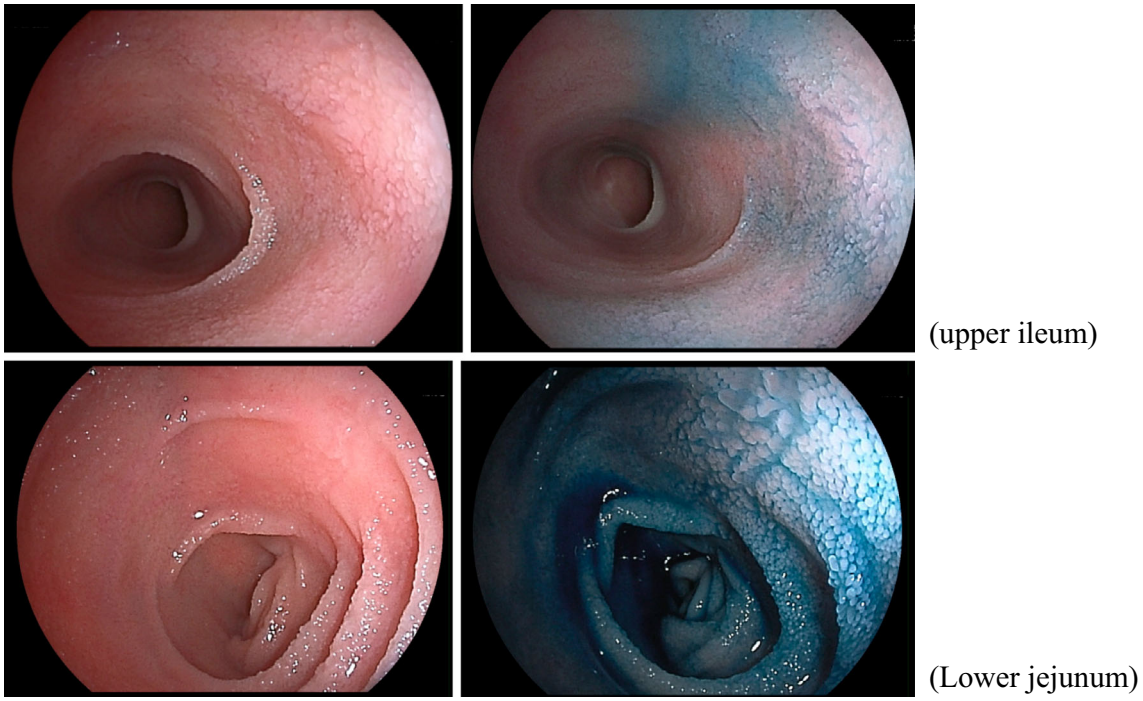


Figure 4. **Oral double-balloon endoscopy was performed after 11 days. Slightly swollen villi were noted, but no clear findings were seen in the lower ileum.**

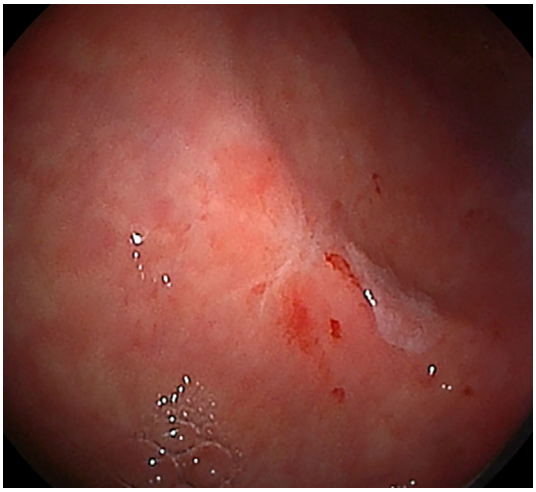


Figure 5. **Oral double-balloon endoscopy showed that gastric ulcer was improving.**

age of the patient, additional chemotherapy was withheld. He was discharged on the 112th day of illness. He returned to his previous health center, where he continued receiving minocycline, but his symptoms did not recur (Fig. 7).

Discussion

HCD refers to various syndromes characterized by the production of monoclonal immunoglobulin heavy chains without an associated light chain (1, 10, 11). Among them, IPSID is mainly associated with the gastrointestinal system (12, 13). In our case, this was mainly reflected in the appearance of persistent severe diarrhea. Although the initial endoscopic finding was the gastric ulcer, it is difficult to determine whether or not this ulcer was an early manifestation of the IPSID. Given that symptomatic treatment improved the gastric ulcer, as shown on posterior endoscopic imaging taken on day 11 (Fig. 5), it is most likely that this gastric ulcer was a finding not associated with the IPSID clinical course. Further changes, such as the rough mucosa found in the ileum on an endoscopic examination, accounted for the patient's symptoms.

The patients' laboratory findings showed hypochromic anemia and hypoalbuminemia, the two main laboratory parameters found in IPSID (14). Other laboratory findings suggestive of IPSID include hypocalcemia, hypokalemia, and hypomagnesemia. Furthermore, IPSID patients are typically deficient in hydrophilic and lipophilic vitamins and minerals. Alkaline phosphatase levels are generally increased in these cases (14). IPSID cases present with narrowing and dilation of the upper gastrointestinal tract. In addition, protuberances and nodules have been observed in two-thirds of cases. Mucosal redness and edema with infiltrative and nodular patterns are characteristic of αHCD (1, 15). A previous report showed that capsule endoscopy presented with rough mucosa in the small bowel (16), and that case demonstrated similar findings in the ileum. However, the specific small bowel findings in IPSID have not been determined.

Histologically, IPSID is characterized by lymphoplasmacytic infiltration, dividing the intestinal crypts and demonstrating villous atrophy (17). In our case, neither *C. jejuni*

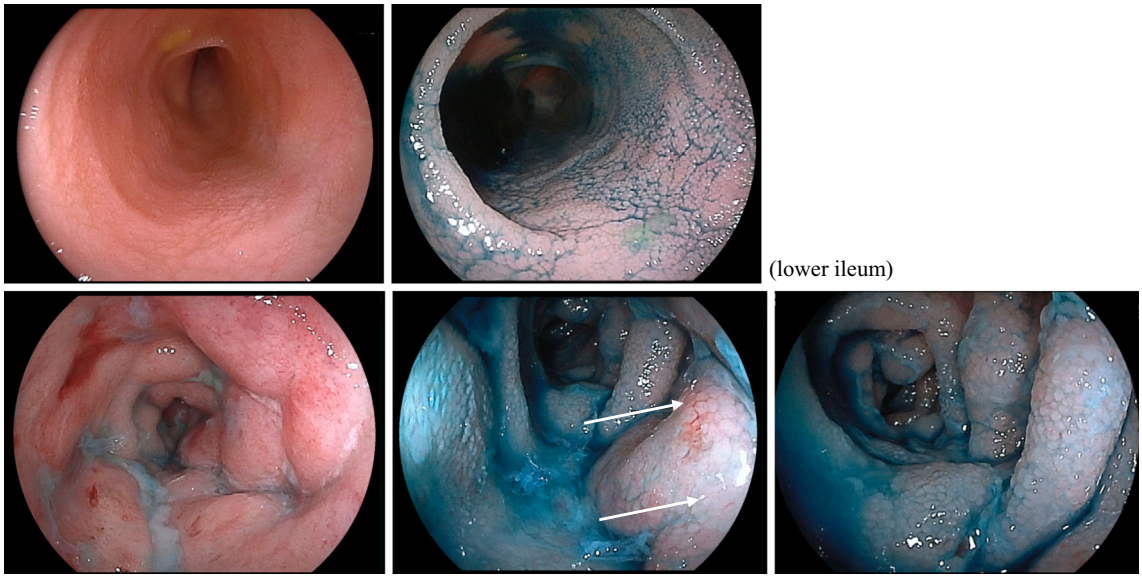


Figure 6. **Transanal double-balloon endoscopy after two months of treatment. Significant mucosal edema and multiple submucosal tumor-like ridges (white arrows) from the edge of the ileum, measuring about 15 cm, were observed in these images. As seen previously, slightly rough and swollen villi were scattered on the oral side.**

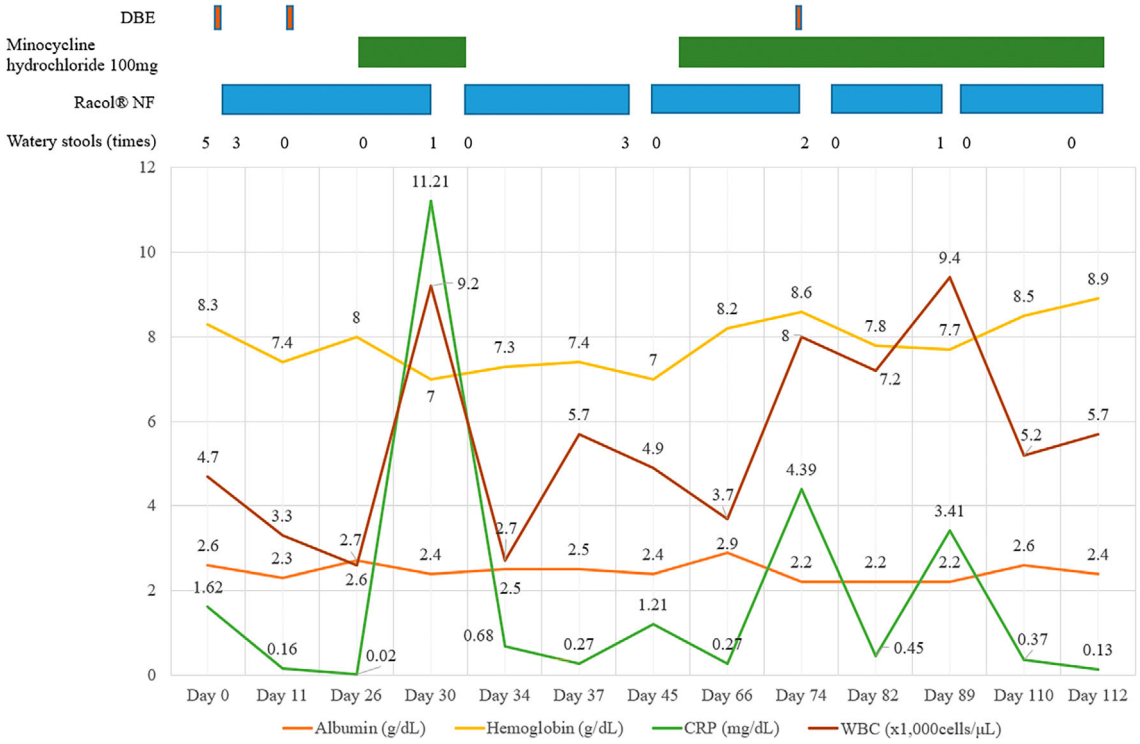


Figure 7. **Clinical course at present. DBE: double-balloon endoscopy**

nor any other microorganisms were isolated from the stool culture, which contradicts previous studies' findings. However, the immunohistochemical analysis showed that the lymphocytes were partially positive for CD3 and CD20 and diffusely positive for CD138. Furthermore, staining for IgA (anti-IgA with hematoxylin counterstain) was positive, while staining for IgG, kappa, and lambda immunoglobulin light chains was negative. These findings established the definitive diagnosis of αHCD (10, 18).

We reported an uncommon IPSID case in an 80-year-old man who had neither Middle East nor Mediterranean ancestry (19, 20) and exhibited no evidence of bacterial infection (negative stool cultures for *C. jejuni*) but was diagnosed based on DBE and histopathological findings.

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

References

1. Bianchi G, Sohani AR. Heavy chain disease of the small bowel. Curr Gastroenterol Rep **20**: 3, 2018.
2. Bennani A, Znati K, Rezzouk S, Bouhadouti H, Maazaz K, Amarti A. An immunoproliferative disease of the small intestine revealed by acute intussusception: report of a case. Pan Afr Med J **17**: 12, 2014.
3. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood **127**: 2082-2092, 2016.
4. Fine KD, Stone MJ. Alpha-heavy chain disease, Mediterranean lymphoma, and immunoproliferative small intestinal disease: a review of clinicopathological features, pathogenesis, and differential diagnosis. Am J Gastroenterol **94**: 1139-1152, 1999.
5. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. Blood **105**: 2274-2280, 2005.
6. Lecuit M, Abachin E, Martin A, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. N Engl J Med **350**: 239-248, 2004.
7. Yamamoto H, Kita H, Sunada K, et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clin Gastroenterol Hepatol **2**: 1010-1016, 2004.
8. Salem PA, Estephan FF. Immunoproliferative small intestinal disease: current concepts. Cancer J Sudbury Mass **11**: 374-382, 2005.
9. Ben-Ayed F, Halphen M, Najjar T, et al. Treatment of alpha chain disease. Results of a prospective study in 21 Tunisian patients by the Tunisian-French Intestinal Lymphoma Study Group. Cancer **63**: 1251-1256, 1989.
10. Witzig TE, Wahner-Roedler DL. Heavy chain disease. Curr Treat Options Oncol **3**: 247-254, 2002.
11. Ria R, Dammacco F, Vacca A. Heavy-chain diseases and myeloma-associated Fanconi syndrome: an update. Mediterr J Hematol Infect Dis **10**: e2018011, 2018.
12. Mrabti H, Raiss G, Raissouni S, et al. Intestinal non-Hodgkin lymphoma: "immunoproliferative small intestinal disease". Presse Med **40**: 995-1000, 2011.
13. Evangelista-Leite D, Madaloso BA, Yamashita BS, et al. Treating chronic diarrhea: a systematic review on immunoproliferative small intestinal disease (IPSID). PLoS One **16**: e0253695, 2021.
14. Bianchi G, Anderson KC, Harris NL, Sohani AR. The heavy chain diseases: clinical and pathologic features. Oncology (Williston Park) **28**: 45-53, 2014.
15. Halphen M, Najjar T, Jaafoura H, Cammoun M, Tufrali G. Diagnostic value of upper intestinal fiber endoscopy in primary small intestinal lymphoma. A prospective study by the Tunisian-French Intestinal Lymphoma Group. Cancer **58**: 2140-2145, 1986.
16. Ersoy O, Akin E, Demirezer A, Atalay R, Buyukasik S. Capsule-endoscopic findings in immunoproliferative small-intestinal disease. Endoscopy **44**: E61-E62, 2012.
17. Isaacson PG, Dogan A, Price SK, Spencer J. Immunoproliferative small-intestinal disease. An immunohistochemical study. Am J Surg Pathol **13**: 1023-1033, 1989.
18. Vaiphei K, Kumari N, Sinha S-K, et al. Roles of syndecan-1, bcl6 and p53 in diagnosis and prognostication of immunoproliferative small intestinal disease. World J Gastroenterol **12**: 3602-3608, 2006.
19. Hibi T, Asakura H, Kobayashi K, et al. Alpha heavy chain disease lacking secretory alpha chain, with cobblestone appearance of the small intestine and duodenal ulcer demonstrated by endoscopy. Gut **23**: 422-427, 1982.
20. Hara T, Tsurumi H, Kato T, et al. Immunoproliferative small intestinal disease with protein loss complicated with duodenal T cell lymphoma during progression. Intern Med **47**: 299-303, 2008.