Gastrointestinal findings in 26 adults with common variable immunodeficiency: The fickle nature of the disease manifests in gastrointestinal biopsies

Burçin Pehlivanoğlu[1*], Ömür Ardeniz[2], Hür Hassoy[3], Murat Sezak[1], Hafize Özdemir[1], Nalan Gülşen Ünal[4], Hüseyin Onay[5], Başak Doğanavşargil[1]

[1]Department of Pathology, Ege University School of Medicine, İzmir, Turkey
[2]Division of Immunology, Department of Internal Medicine, Ege University School of Medicine, İzmir, Turkey
[3]Department of Public Health, Ege University School of Medicine, İzmir, Turkey
[4]Division of Gastroenterology, Department of Internal Medicine, Ege University School of Medicine, İzmir, Turkey
[5]Department of Medical Genetics, Ege University School of Medicine, İzmir, Turkey

Cite this article as: Pehlivanoğlu B, Ardeniz Ö, Hassoy H, et al. Gastrointestinal findings in 26 adults with common variable immunodeficiency: The fickle nature of the disease manifests in gastrointestinal biopsies. Turk J Gastroenterol 2019; 30(9): 789-800.

ABSTRACT

Background/Aims: The aim of the present study was to demonstrate the histopathological findings in gastrointestinal (GI) biopsies in adults with common variable immunodeficiency (CVID).

Materials and Methods: A total of 172 GI biopsies of 26 patients with CVID obtained over a 16-year period were reevaluated. Findings were analyzed using descriptive analyzes and $\chi 2$ test.

Results: Female-to-male ratio was 1.36. The median age at diagnosis was 36±13.94 (16-72) years. Chronic esophagitis was noted in 3 patients. The absence of plasma cells in the stomach, duodenum, and colon was observed in 16, 14, and 9 patients, respectively. Divergent results for the presence of plasma cells in concurrent stomach and duodenum samples were found in 11 (44%) patients. Nodular lymphoid hyperplasia (NLH) was notable in the duodenum (56%). The mean number of eosinophils in one high-power field was significantly higher in duodenal biopsies with NLH (27.21 vs. 14.37, $p=0.002$). Active inflammation was more prominent in the colon (91%) than in the stomach (65%) and duodenum (60%). Helicobacter pylori infection was found in 57.6%, including a case with persistent infection by the coccoid form. Celiac-like villous blunting and increased intraepithelial lymphocytes were seen in 40% and 24%, respectively. In addition, 23% had giardiasis associated with acute duodenitis and duodenal NLH ($p<0.05$).

Conclusion: CVID gastroenteropathy is a challenging entity, and due to the heterogeneity in the presence and distribution of plasma cells throughout the GI tract and diverse disease course, multiple concurrent biopsies may be needed for tissue diagnosis. Duodenal CVID may present with villous alterations and giardiasis, and NLH appears to be an important clue in the duodenum. The association between duodenal NLH and eosinophil infiltration deserves further investigation.

Keywords: Common variable immunodeficiency, gastrointestinal tract, nodular lymphoid hyperplasia, CVID gastroenteropathy, eosinophilic infiltration, Helicobacter pylori

INTRODUCTION

Common variable immunodeficiency (CVID) is a relatively common primary immunodeficiency with a prevalence of 1/25,000-1/50,000 (1,2), comprising a heterogeneous group of disorders of hypogammaglobulinemia (3). Several defects in the genes that are involved in B cell differentiation, such as inducible T-cell co-stimulator (ICOS) and B cell-activating factor receptor (BAFFR), and several pathways, including B and T-cell signaling, have recently been demonstrated to be involved in CVID pathogenesis (4,5). Some patients have been found to have *TACI* mutations (*TACI*: transmembrane activator and calcium-modulator and cyclophilin ligand interactor) that are considered to lead to disease susceptibility polymorphisms rather than being disease-determining mutations since they can also be found in non-immune-deficient family members (6).

Patients with CVID usually present with recurrent respiratory tract infections, but gastrointestinal (GI) manifestations are also common in patients with CVID as they have an increased risk of inflammatory and infectious conditions in the GI tract (7). Moreover, endoscopy is frequently performed in these patients to explore the cause of GI symptoms, as bloating, pain, and diarrhea have been reported to be the most common GI symptoms in patients with CVID in a recent study (8).

*Dr. Pehlivanoglu's current affiliation is Department of Pathology, Adıyaman University Training and Research Hospital, Adıyaman, Turkey
Corresponding Author: **Burçin Pehlivanoğlu; burcinp@yahoo.com**
Received: **October 16, 2018** Accepted: **January 29, 2019**

DOI: **10.5152/tjg.2019.18777**

The most important clue (but not sine qua non) for CVID in a GI biopsy has been considered as paucity of plasma cells. Chronic active gastritis (with or without *Helicobacter pylori*), villous architectural abnormalities, nodular lymphoid hyperplasia (NLH), chronic giardiasis, and colitis are frequently observed in patients with CVID (7,9,10). However, no detailed reports have been published on the number and distribution of other inflammatory cells, and the histopathological evaluation of GI biopsies in patients with CVID suspicion is challenging as it may mimic several other chronic inflammatory entities. The aim of the present study was to evaluate the histopathological features in endoscopic and colonoscopic biopsies of adults with CVID and to investigate whether there are any specific histopathological findings.

MATERIALS AND METHODS

Study design

The study protocol was approved by the institutional ethics committee. A total of 26 patients who were diagnosed with CVID before 2014 based on the European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency diagnostic criteria (1999) (i.e., male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA and fulfills all of the following criteria: onset of immunodeficiency at age >2 years, absent isohemagglutinins and/or poor response to vaccines, and defined causes of hypogammaglobulinemia have been excluded) were included in the study (11).

Histopathological evaluation

Clinicopathological data were obtained from patient files. A total of 172 GI biopsies, including biopsies from the esophagus (5), stomach (83), small intestine (71), and colon (13), obtained in a 16-year period were reevaluated for the presence of plasma cells, acute and/or chronic inflammation including eosinophilic infiltration, atrophy, NLH, increase in intraepithelial lymphocytes (IELs), mucosal architectural distortion, erosion, ulceration, dysplasia, subepithelial collagen deposition, granulomas, microorganisms, and increase in apoptosis. Eosinophilic infiltration was defined as the number of eosinophils per one high-power field (HPF). NLH was defined as reactive lymphoid follicles forming germinal centers in the lamina propria. Mucosal architectural distortion was evaluated mainly based on the presence of atrophy in gastric biopsies, presence of villous blunting and/or crypt hyperplasia in small bowel biopsies, and presence of crypt distortion in colon biopsies. "Increased" apoptosis was defined as ≥1 apoptotic body per gastric or esophageal biopsy and >1 apoptotic body per 10-15 crypts in small bowel and colon biopsies (10). CD138 stained slides, which had been stained according to the manufacturer's protocol, were reevaluated in available cases.

Mutation analysis

TACI, *ICOS*, and *BAFFR* gene mutation analyzes were performed by sequencing of the coding exons and the exon-intron boundaries of the genes after amplification of the regions with polymerase chain reaction (PCR). All PCR products were sequenced by the dye termination method using a DNA sequencing kit (Perkin-Elmer, Foster, CA, USA) and analyzed using the ABI Prism 3100 sequence analyzer (Applied Biosystems, Foster, CA, USA).

Statistical analysis

Statistical analyses (descriptive analyses, χ^2 tests. etc.) were performed using the Statistical Package for Social Sciences software version 20.0 (IBM Corp.; Armonk, NY, USA). Gastric biopsies from antrum and corpus were described as "gastric," duodenum and bulbus samples were described as "duodenal," and colon biopsies from different segments of the colon were described as "colonic"; they were considered as a single biopsy for statistical purposes. The relationship between the variables was determined using χ^2 tests, Mann-Whitney U test, Kruskal Wallis test or T-test. A p value <0.05 was considered significant for all analyzes.

RESULTS

Clinical characteristics

Female-to-male ratio was 1.36. The median age of disease onset was 15±14.88 (between 2 and 72) years, whereas the median age at diagnosis was 36±13.94 (between 16 and 72) years. The majority of the patients had a history of recurrent diarrhea (n=19, 74%), sinusitis (n=20, 77%), and bronchitis (n=23, 88%), whereas more than half of them had a history of otitis (n=15, 58%) and pneumonia (n=16, 61.5%). While one-third (33%) of the endoscopies were repeat procedures, the most common reason of endoscopy was chronic diarrhea (18%), followed by anemia (15%) and abdominal pain (11%). One patient was found to be positive for *TACI* mutation (heterozygous R202H mutation). Clinical characteristics are summarized in Table 1.

Histopathological findings

Esophagus

There were only 5 esophageal biopsies from 4 patients, and chronic esophagitis was noted in 3 patients. No other significant finding was detected.

Table 1. Clinical and demographic characteristics.

Case no.	Sex	Age at the onset of the symptoms	Age at diagnosis	Concentration of IgA**	IgM**	IgG**	Splenomegaly	Lymphadenopathy	Family History	History of recurrent diarrhea	Allergic diseases	Autoimmune diseases	Neoplasm	Granulomatous disease
1	M	2	27	1	64	35	Present			+				
2	F	7	28	<25	<17	152			Parental consanguinity (+)	+	Rhinitis			
3	F	33	37	N/A	N/A	N/A	Present	Retroperitoneal, mesenteric		-				
4	F	18	41	<22	<17	<153	Present			+	Rhinitis, Asthma, Urticaria		Papillary carcinoma of thyroid gland	
5	F	15	33	24	<21	<156	Present	Mesenteric		+				
6	F	3	39	9	24	124	Present			+				Granulomatous lung disease findings on imaging
7	F	15	46	<50	<25	<300		Abdominal, mediastinal		+			MALT* lymphoma	
8	F	7	22	7	11	33		Submandibular		+	Food allergy			
9	F	3	44	N/A	N/A	N/A		Axillary, cervical, abdominal		+	Drug allergy			
10	M	15	16	<25	<17	<145	Present		Parental consanguinity (+)	+				
11	M	13	19	N/A	N/A	N/A	Present			+		Discoid lupus erythematosus		Granulomatous lung disease findings on imaging
12	F	12	40	<24	414	<134	Present			+		Sjogren's syndrome		Granulomatous lung disease findings on imaging
13	F	22	25	24	16	164	History of splenectomy	Axillary, submandibular	Positive for Selective IgA Deficiency and Parental consanguinity (+)	-		Idiopathic trombocytopenic purpura, Autoimmune hemolytic anemia	T-cell/ histiocyte rich large B-cell lymphoma, Adult T-cell leukemia/lymphoma	Granulomatous lung disease findings on imaging
14	M	25	25	<25	<21	<153				+	Drug allergy		Papillary carcinoma of thyroid gland	
15	M	10	47	N/A	N/A	N/A				+			Adult T-cell leukemia/lymphoma,	

Table 1. Clinical and demographic characteristics. (continue)

Case no.	Sex	Age at the onset of the symptoms	Age at diagnosis	Concentration of IgA**	IgM**	IgG**	Splenomegaly	Lymphadenopathy	Family History	History of recurrent diarrhea	Allergic diseases	Autoimmune diseases	Neoplasm	Granulomatous disease
													Colonic adenomas	
16	M	19	25	22	17	153				+	Conjunctivitis			
17	F	10	16	23	17	141	Present	Retroperitoneal		+	Drug allergy	Type 1 Diabetes mellitus		
18	F	35	47	8	15	147	Present	Axillary		+		Celiac disease		
19	M	35	49	47	15	208	Present	Mediastinal		-		Rheumatoid arthritis	Thymoma (B1)	
20	F	7	34	N/A	N/A	N/A	Present			-				
21	F	2	49	<24	20	236				-	Rhinitis, Asthma			
22	M	7	35	<24	<15	279			Parental consanguinity (+)	-				Granulomatous hepatitis
23	M	15	37	N/A	N/A	N/A				+				
24	M	18	28	<25	1416	<320	Present			+				Granulomatous lung disease findings on imaging
25	F	72	72	<25	<17	<140				-			Serous cystadenoma of ovary, Tubular adenoma (colon)	
26	M	28	66	N/A	N/A	N/A				+				

*MALT lymphoma: mucosa associated lymphoid tissue lymphoma; ** Reference range for IgA: 70-400 mg/dL; IgM: 40-230 mg/dL and IgG: 700-1600 mg/dL; N/A: Not available.

Stomach

There were 83 sets of gastric samples from 26 patients (mean: 3.19, range: 1-12 biopsies per patient). There was a lack of plasma cells in the lamina propria in the initial gastric biopsy in 14 (53.8%) patients despite the presence of chronic active gastritis (Figure 1a). The presence of plasma cells was variable in 6 (23%) patients, i.e., plasma cells were not observed in each gastric biopsy sample of these cases.

Seventeen (65%) patients had active inflammation (Figure 1a), 94% of whom was infected with *Helicobacter pylori (H. pylori)* The presence of active gastritis was associated with atrophy (p=0.003). Atrophic gastritis was seen in 14 (53.8%) patients and involved both corpus and antrum in 6 (23%) patients.

NLH was found in 14 (53.8%) patients. The presence of *H. pylori* was found to be associated with the presence of NLH and active gastritis (p<0.001). A coccoid form of *H. pylori* (Figure 1b) in one patient with persistent erosive gastritis was found. No gastric ulcer was found, but erosive gastritis was present in 4 (15.3%) patients.

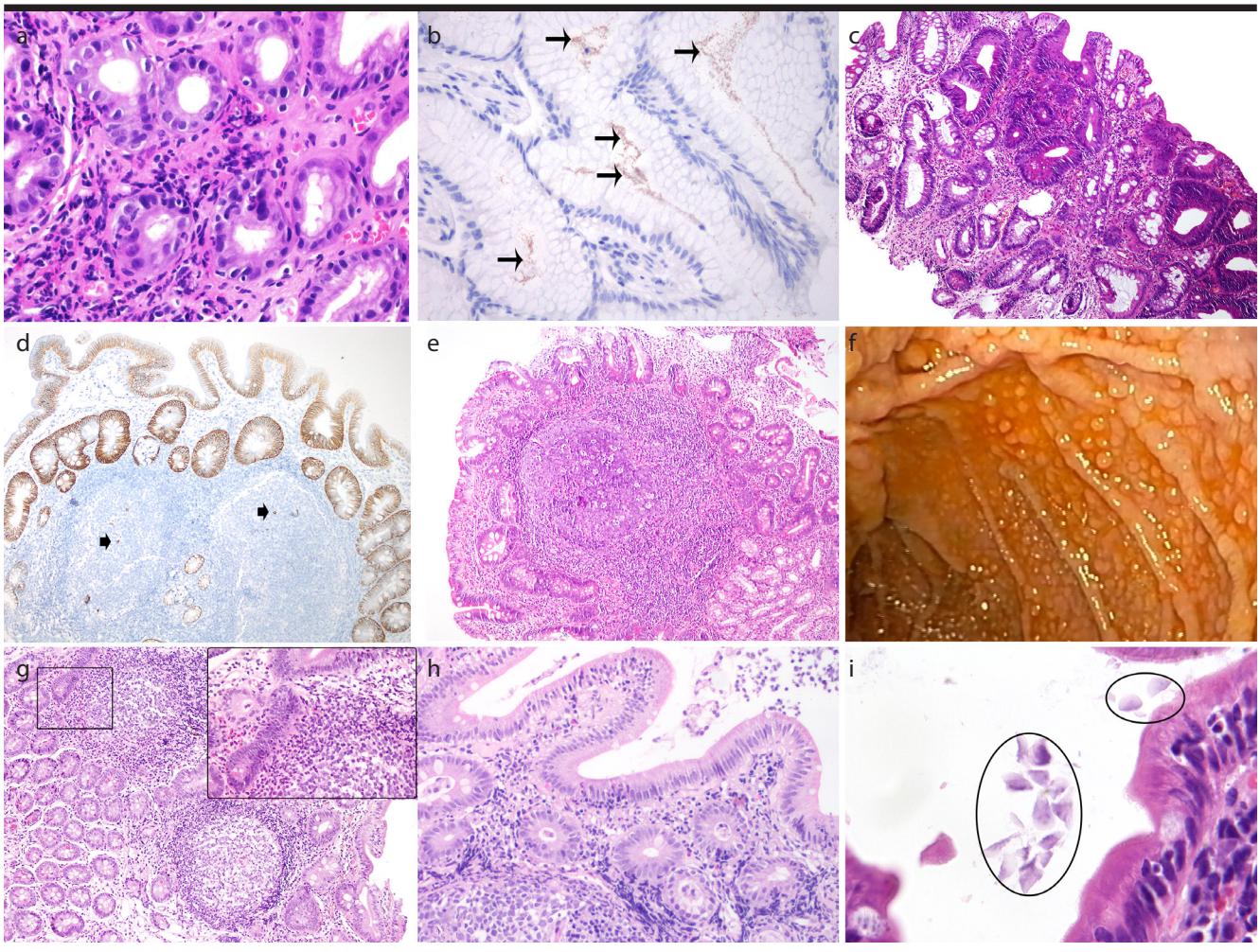

Figure 1. a-i. Gastric and duodenal findings. a) Chronic active gastritis was seen in 65% with *Helicobacter pylori* in 94% of them. Note the regenerative changes and the absence of plasma cells in the stroma, hematoxylin-eosin, x400, b) One patient had recurrent erosive gastritis due to persistent coccoid *Helicobacter pylori* (thin arrows) infection, immunohistochemistry, anti-*Helicobacter pylori* antibody, x400, c) Gastric low-grade dysplasia with atrophy and intestinal metaplasia in the background, hematoxylin-eosin, x100, d) No plasma cells in lamina propria in duodenum, CD138, immunohistochemistry, x200, e) Villous blunting, hematoxylin-eosin, x100, f) Endoscopic appearance of diffuse nodular lymphoid hyperplasia in duodenum, g) Nodular lymphoid hyperplasia, which was detected in more than half of the patients, was found to be associated with eosinophil infiltration (inset), hematoxylin-eosin, x100, h) Acute duodenitis was observed in 60%. Also, note the nodular lymphoid hyperplasia on lower left corner, hematoxylin-eosin, x200, and i) *Giardia intestinalis* trophozoites (circled) next to duodenal surface, hematoxylin-eosin, x400.

An increase in apoptosis was detected in only one biopsy sample of 1 (3.8%) patient. No increase in IELs, granulomas and/or subepithelial collagen deposition were found in gastric biopsy samples.

The number of eosinophils per one HPF ranged between 0 and 62 (mean: 13.64±13.32, median: 12±13.32, range 0-62/HPF). There was no significant association between the number of eosinophils per one HPF and other histopathological parameters. Low-grade dysplasia (LGD) was observed in 2/5 and 1/12 biopsies of 2 (7.6%) patients (Figure 1c). The second case of LGD also had a history of mucosa-associated lymphoid tissue (MALT) lymphoma.

Small intestine

Sixty-five duodenal biopsies from 25 patients were re-evaluated (mean: 2.6, range: 1-8 biopsies per patient). Plasma cells were absent in the initial biopsy in 17 (68%) patients, and no plasma cells were seen in either initial or follow-up biopsies in 9 (36%) patients (Figure 1d), as variable plasma cell status was observed in 6 (24%) patients.

Villous blunting (Figure 1e) was found in 10 (40%) patients with accompanying crypt hyperplasia in 4 (16%) of them.

NLH was found in 14 (56%) patients (Figure 1e-h) and was associated with duodenitis (p=0.02), on the contrary of *H. pylori* status and/or the presence of gastric NLH (p>0.05). Acute duodenitis was detected in 15 (60%) patients (Figure 1h), whereas increased IELs were shown in 6 (24%) patients.

An increase in apoptotic index with intraepithelial lymphocytosis was detected in one patient.

Giardia intestinalis trophozoites (Figure 1i) were detected in duodenal biopsies of 5 patients and in ileum biopsy sample of 1 patient (n=6, 23%). Giardiasis was associated with acute duodenitis (p<0.001) and duodenal NLH (p=0.003).

Table 2. The most frequent histopathologic findings seen in gastric biopsies.

	Percentage of the biopsies showing the feature	Initial biopsy (Number (n) and % of the cases)	Follow-up biopsy* (Number (n) and % of the cases)
Plasma cell status	Absent: 67/83 (81%);	Absent: 21 (80.7%)	Present: 3 (11.5%)
			Absent: 15 (57.6%)
			Variable: 5 (19.3%)
Chronic active gastritis	Present: 51/83 (61%)	Present: 16 (61.5%)	Present: 15 (57.6%)
			Cured: 2 (7.6%)
			New cases: 1 (3.8%)
Helicobacter pylori	Present: 29/83 (35%)	Present: 12 (46%)	Eradication: 8 (30.7%)
			Present (persistent): 7 (27%)
			New cases: 3 (11.5%)
Atrophy	Present: 40/83 (48%)	Present: 10 (38.5%)	Present: 9 (34.6%)
			Absent: 9 (34.6%)
			New cases: 5 (19%)
			Variable: 5 (19.3%)
Intestinal metaplasia	Present: 46/83 (55%)	Present: 10 (38.5%)	Present: 10 (34.6%)
			Absent: 9 (34.6%)
			Variable: 4 (15.3%)
Nodular lymphoid hyperplasia (NLH)	Present: 26/83 (31%)	Present: 9 (34.6%)	Present: 6 (23%)
			Absent: 12 (46%)
			Variable: 5 (19.3%)
			Persistent despite *H. Pylori* eradication: 3 cases

*Three cases did not have follow-up biopsy.

Table 3. The most frequent histopathologic findings seen in duodenal biopsies.

	Percentage of the biopsies showing the feature	Initial biopsy (Number (n) and % of the cases)	Follow-up biopsy* (Number (n) and % of the cases)
Plasma cell status	Absent: 45/65 (69%)	Absent: 17 (68%)	Present: 2 (8%)
			Absent: 11 (44%)
			Variable: 4 (16%)
Active inflammation (duodenitis)	Present: 27/65 (42%)	Present: 12 (48%)	Persistent: 4 (16%)
			Cured: 4 (16%)
			New cases: 3 (12%)
Intraepitelial lymphocytosis	Present: 10/65 (15%)	Present: 4 (15%)	Persistent: 2 (8%)
			New cases: 2 (8%)
			Present in the first biopsy, not seen in follow-up: 1 (4%)
Villous blunting	Present: 20/65 (31%)	Present: 7 (28%)	Persistent: 2 (8%)
			New cases: 3 (12%)
			Improved: 3 (12%)
Giardia intestinalis	Present: 9/65 (14%)	Present: 4 (15%)	Eradicated: 2 (8%)
			New cases: 1 (4%)
			1 recurrent and 1 persistent
Nodular lymphoid hyperplasia (NLH)	Present: 35/65 (54%)	Present: 14 (56%)	Present (persistent): 8 (32%)
			Absent: 7 (28%)
			Variable: 1 (4%)
			Cured: 1 (4%)

*Eight cases did not have follow-up biopsy.

Table 4. The most frequent histopathologic findings seen in colon/rectum biopsies.

	Percentage of the biopsies showing the feature	Number (n) and % of the cases
Plasma cell status	Absent: 11/13 (85%)	Absent: 9 (82%)
	Present: 2/13 (15%)	Present: 2 (18%)
Active colitis	Present: 12/13 (92%)	Present: 10 (91%)
Crypt distortion	Present: 4/13(31%)	Present: 3 (27%)
Nodular lymphoid hyperplasia (NLH)	Present: 5/13 (38%)	Present: 5 (45%)

There were 6 ileum biopsies from 5 patients with a lack of plasma cells. Ileitis and increase in IELs was detected in 3 patients and 1 patient, respectively. Myofibroblastic proliferation accompanied ileitis in one case. Two of the patients with duodenal villous blunting also showed ileal villous blunting (along with crypt hyperplasia in one of them). NLH was a feature in all ileal biopsies.

The number of eosinophils per one HPF ranged between 0 and 72 (mean: 21.21±16.82, median: 18±16.82) and 8 and 62 (mean: 35.20±22.91, median: 26±22.91) for duodenum and terminal ileum, respectively. The mean eosinophil count was found to be higher in duodenal biopsies with NLH (27.21±19.15 vs. 14.37±10.31, p=0.002).

No other finding was recognized in small bowel biopsies.

Upper GI follow-up biopsy findings are summarized in Tables 2 and 3.

Follow-up ileal biopsy was present in only one patient who had persistent ileitis with myofibroblastic proliferation and villous blunting.

Colon

Thirteen sets of colon biopsies from 11 patients were re-evaluated. There was a paucity of plasma cells in 9 patients. Cryptitis (Figure 2a) was seen in 10 (91%) patients, and crypt abscess formation was seen in only 1 (9%) pa-

tient. Ischemia-related changes were noted in 1 (9%) patient (Figure 2b). Crypt distortion and NLH were seen in 3 (27.2%) patients and 5 (45.4%) patients, respectively. The number of eosinophils per one HPF ranged between 2 and 82 (mean: 38.08±25.23, median: 27±25.23). An increase in apoptosis was seen in 2 (18.1%) patients, but only in superficial crypts. No granuloma, subepithelial collagen deposition, increase in IELs, erosion, or microorganisms were detected.

In one patient, plasma cells were observed in a tubular adenoma in the ascending colon biopsy were observed (Figure 2c), without any plasma cells in the adjacent normal mucosa (Figure 2d). In the concurrent sigmoid colon biopsy, nuclear enlargement, prominent nucleoli, and brisk mitotic activity adjacent to an ulcerated area were noted, and the case was evaluated as "high-grade dysplasia" (Figure 2e, f).

Of the 2 cases with follow-up colonic biopsy, the first case had colitis in both without any other abnormalities. The second case also had persistent colitis, with accompanying NLH in the follow-up biopsy. No plasma cells were seen.

Findings in concurrent biopsies

Divergent results for the presence of plasma cells were observed in 11 (44%) out of 25 patients with concurrent biopsies. Plasma cells were absent in gastric biopsies of 9 patients despite the presence of plasma cells in their duodenum samples and vice versa in 2 patients.

Ten patients had synchronous active gastritis and duodenitis. There was no significant association between the presence of gastric and duodenal NLH. The number of eosinophils per one HPF was also higher in the duodenum than in the stomach in concurrent biopsies (p=0.004, mean 21.03±16.90 vs. mean 14.16±14.58).

There were only 3 patients with 4 sets of concurrent colonoscopic biopsies including ileum and colon samples with no plasma cells. In addition, 2 patients had synchronous ileitis and colitis.

DISCUSSION

The absence of plasma cells is a previously reported finding in the GI biopsies of patients with CVID (8,10,12,13). Another aspect that we would like to highlight is the heterogeneity of the plasma cell distribution throughout the entire GI tract. While Daniels et al. (10) reported a similar number of patients showing the absence of plasma cells in the stomach (67%), small intestine (68%), and colon (63%), Jørgensen et al. (8) observed a large difference in the GI tract regarding the absence of plasma cells (stomach 16%, duodenum 42%, rectum 50%, and colon 56% of the patients). In the present study, the absence of plasma cells was found to be 62%, 56%, and 82% in patients with gastric, duodenal, and colorectal biopsies, respectively. Divergent results were also detected for the presence of plasma cells in concurrent stomach and duodenum samples in 44% of the patients.

Another inflammatory cell type evaluated in the present study is the eosinophils. The mean eosinophil count in the duodenum was significantly higher in duodenal biopsies with NLH (27.21 vs. 14.37, p=0.002). Kokkonen and Karttunen have suggested that NLH can be a mucosal immune response to food hypersensitivity or other immunologically active diseases (14). While eosinophils can induce Th2-type immune response, eosinophils have also been demonstrated to promote the generation and maintenance of IgA-expressing plasma cells (15). Therefore, the association between NLH-eosinophil infiltration in duodenal samples in our study may be a result of over-stimulated mucosal immune response to compensate for the lack of plasma cells in CVID. However, further study is needed to elucidate the mechanism.

The number of eosinophils per one HPF was higher in lower segments, and the number of eosinophils per one HPF was also higher in the duodenum than in the stomach in concurrent biopsies. Matsushita et al. (16) compared the number and distribution of eosinophils in the GI tract of healthy Japanese, Japanese-American, and Caucasian individuals, and they found a significant increase in the number of eosinophils from the esophagus to the right colon with a decrease in the left colon in all 3 ethnic groups. Hence, the overall distribution of eosinophils in the GI tract of adults with CVID does not appear to differ from the general population.

NLH was a remarkable finding in our study group, particularly in the duodenum (56%). NLH has been suggested to result from an accumulation of plasma cell precursors due to a maturational defect of B lymphocytes to compensate for functionally inadequate intestinal lymphoid tissue in immunodeficient patients (17,18). There was no significant association between *H. pylori* status and the presence of duodenal NLH, on the contrary of gastric NLH, supporting that duodenal NLH is a feature of CVID. Duodenal NLH was also found to be associated with giardiasis (p=0.0003). The association between NLH and giardiasis has been long known, even in immunocompe-

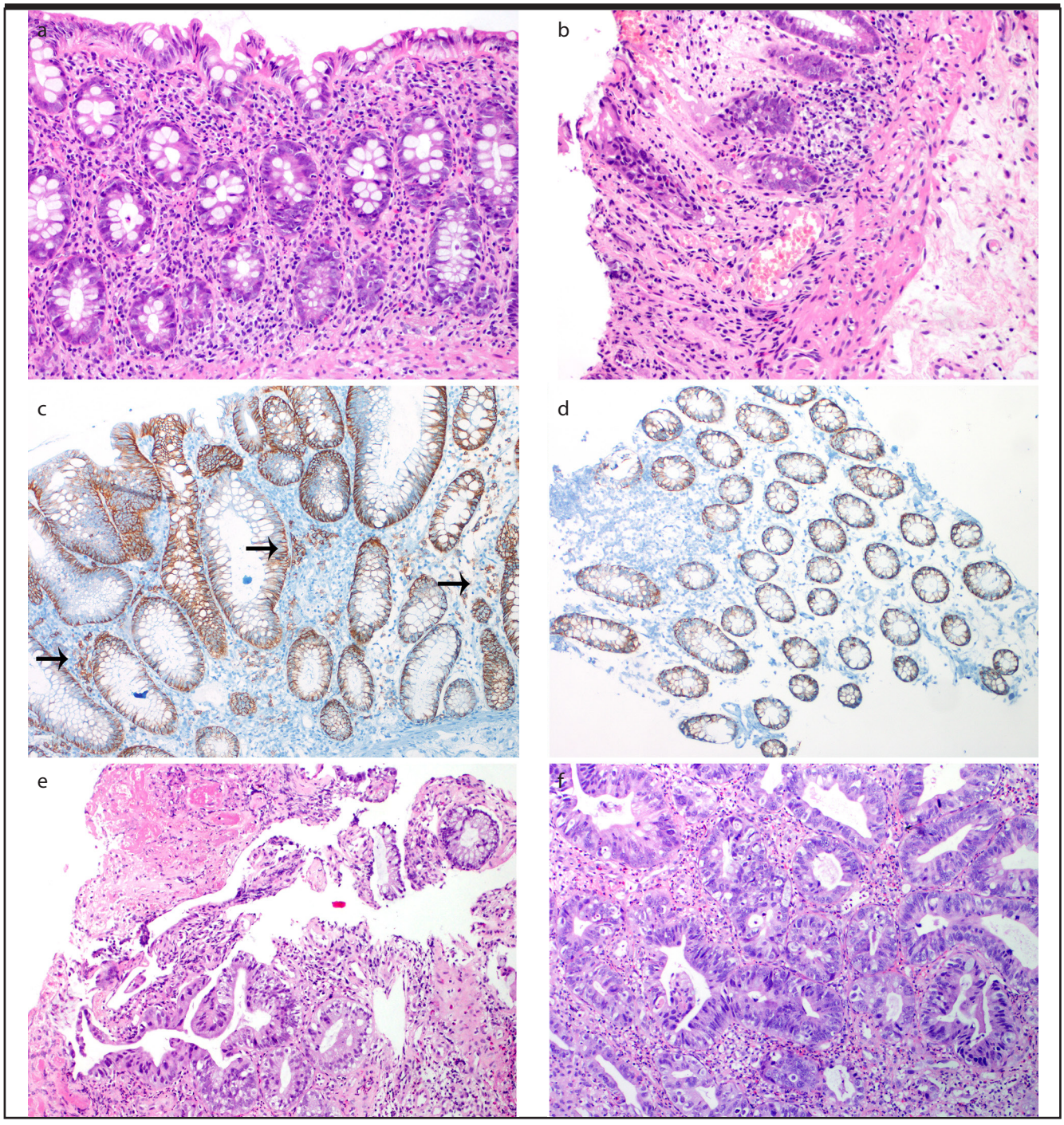

Figure 2. a-f. Histopathologic findings in colon/rectum. a) Cryptitis, hematoxylin-eosin, x200, b) Ischemia related changes (paucity of the crypts and fibrosis), hematoxylin-eosin, x100, c-d) Case 25, ascending colon biopsy; Heterogeneity in plasma cell distribution. Scarce and scattered plasma cells (thin arrows) are seen in stroma of the adenoma, hematoxylin-eosin, CD138, immunohistochemistry, x200 (c) and a normal mucosa sample showing nodular lymphoid hyperplasia embedded in the same tissue block without plasma cells in lamina propria (d), CD138, immunohistochemistry, x100, e) Case 25, sigmoid colon biopsy. An ulceration was seen with related glandular cytological and architectural changes, hematoxylin-eosin, x200, and f) Several serial sections were examined and a deeper cut showed distorted crypts with enlarged and crowded nuclei, prominent nucleoli and brisk mitotic activity, hematoxylin-eosin, x400. The case was diagnosed as "high-grade dysplasia". Unfortunately, no follow-up information and/or biopsy was available for evaluation of an invasive carcinoma

tent patients (19,20), and the association between NLH, dysgammaglobulinemia, and *G. intestinalis* infection is known as Herman's syndrome (17).

The frequency of giardiasis was 23% (n=6). It is noteworthy to mention 2 (8%) patients with recurrent/persistent giardiasis and 1 (4%) patient with ileal giardiasis. The presence of *G. intestinalis* trophozoites in the ileum may be the only clue for the diagnosis of giardiasis in patients with duodenal samples that are free of trophozoites, as shown in a recent study by Oberhuber et al. (21). Although our case did not have a concurrent duodenum biopsy, no *Giardia* trophozoites were observed in the gastric and/or duodenal biopsy that had been obtained 1 week prior to the ileal biopsy.

There was a significant association between giardiasis and acute duodenitis ($p<0.001$). Giardiasis usually causes slight changes in the duodenal mucosa, or the duodenum may be completely normal (22). However, histopathological features including inflammation, villous atrophy, and increase in IELs can be seen (21,22). Hanevik et al. (23) found a significant association between *Giardia* positivity and duodenal inflammation, and they have reported that normal duodenal biopsies are encountered more often as the illness duration increases. *G. intestinalis* is considered to evade the host immune response using several mechanisms (24-26). However, *Giardia* colonization has been suggested to trigger an influx of commensal bacteria in mice, most likely via impaired epithelial tight junctions, even after *Giardia* eradication in a recent study by Chen et al. (27). Therefore, we think that the susceptibility for bacterial infections and the disruption of the humoral immune response may contribute to this altered *G. intestinalis*-host interaction in patients with CVID, resulting in a neutrophil predominant response.

More than half (57.6%) of the patients had *H. pylori* gastritis, indicating a higher prevalence than the previous studies (7-10,12). However, since the overall incidence of *H. pylori* can be as high as 75% regionally (28), one should not consider *H. pylori* infection as a feature of CVID. Notably, a coccoid form of *H. pylori*, which is considered as the viable but non-culturable state of the bacteria in one patient, was found (29,30).

Chronic active gastritis was also associated with the presence of NLH and atrophy. Gastritis-NLH association is most likely due to *H. pylori* effect. However, available data in the literature regarding atrophic gastritis-*H. pylori* association in CVID are controversial (8,9,12). Malamut et al. (12) have reported that atrophy with intestinal metaplasia persisted after *H. pylori* eradication in 3 patients with CVID in their study group, suggesting an autoimmune mechanism involvement. The fact that an association was observed between active gastritis and atrophy but not between *H. pylori* infection and atrophy and that atrophic gastritis persisted following *H. pylori* eradication in 7 out of 8 patients with successful eradication in our series supports an autoimmune process as well.

Increased IELs were found in ~25%, accompanied by villous blunting and crypt hyperplasia in 12%. Increased IELs with mucosal architectural distortion in a patient with CVID may be challenging for the differential diagnosis of celiac disease. While some authors (31) suggest that there is an association between CVID and celiac disease, the association of CVID and celiac disease remains controversial.

Active colitis was seen in 10 out of 11 patients with crypt distortion in 3 of them. The incidence of inflammatory bowel disease (IBD) and inflammatory GI diseases in patients with CVID has been reported to be varying between 2% and 13%, and it has been suggested that intestinal inflammation in patients with CVID with IBD-like disease may be mediated by abnormal cytokine production through a T-cell receptor-mediated pathway (32).

Esophagus involvement is not common in CVID, but the long-term use of antibiotics may cause drug-induced esophagitis or esophageal candidiasis (7,33). Khodadad et al. (7) have reported mild inflammation and esophageal varices in their CVID series, whereas Daniels et al. (10) have found Candida esophagitis in 4 out of 10 patients. Only 4 patients had esophageal biopsies in our study group, and chronic esophagitis without any specific microorganisms in 3 of them was the only notable finding. However, this data is not sufficient to draw a conclusion about esophageal involvement in CVID due to fewer samples.

Many other histopathological patterns have been reported in the GI tract in patients with CVID mimicking lymphocytic gastroenterocolitis, collagenous sprue, granulomatous disease, graft versus host disease (GVHD) (8,10,12,34). However, lymphocytic gastritis and/or colitis, subepithelial collagen deposition, and granulomas were not observed, and GVHD-like pattern was noted in only one patient in the duodenum. While the difference in the upper GI findings may be attributed to geographic/ethnic variations, the limited number of the lower GI biopsies probably led to the exhibition of a limited spectrum of findings in the lower GI tract.

In conclusion, CVID gastroenteropathy is a diverse entity. Although the absence/paucity of plasma cells is considered the best diagnostic clue in GI biopsies, heterogeneity in the presence and distribution of plasma cells suggests that multiple concurrent biopsies must be evaluated for tissue diagnosis, and that a multidisciplinary approach is of utmost importance. Duodenal NLH appears to be an important feature of GI involvement in CVID. To our knowledge, this is the first study that describes an association between the number of eosinophils in the duodenum and NLH in immunodeficient patients. Further studies are needed to elucidate the association between the formation of NLH and eosinophil infiltration in the duodenum in patients with CVID.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Ege University School of Medicine.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study and clinical and pathologic data of the patients were de-identified and analyzed anonymously.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.P., B.D., M.S.; Design - B.P., B.D., H.H.; Supervision - B.D., Ö.A.; Materials - B.P., B.D., H.Ö., M.S., N.G.Ü., Ö.A.; Data Collection and/or Processing - B.P., H.Ö., Ö.A., N.G.Ü, H.O., H.H., M.S.; Analysis and/or Interpretation - B.P., H.H., B.D., H.O.; Literature Search - B.P., H.Ö.; Writing - B.P., Ö.A., N.G.Ü., H.O., B.D.; Critical Review - B.D., H.H., M.S.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Al-Herz W, Bousfiha A, Casanova JL, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol 2014; 5: 162. [CrossRef]

2. Notarangelo LD, Fischer A, Geha RS, et al. Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol 2009; 124: 1161-78. [CrossRef]

3. Unger S, Seidl M, Schmitt-Graeff A, et al. Ill-defined germinal centers and severely reduced plasma cells are histological hallmarks of lymphadenopathy in patients with common variable immunodeficiency. J Clin Immunol 2014; 34: 615-26. [CrossRef]

4. van Schouwenburg PA, Davenport EE, Kienzler AK, et al. Application of whole genome and RNA sequencing to investigate the genomic landscape of common variable immunodeficiency disorders. Clin Immunol 2015; 160: 301-14. [CrossRef]

5. Baldovino S, Montin D, Martino S, Sciascia S, Menegatti E, Roccatello D. Common variable immunodeficiency: crossroads between infections, inflammation and autoimmunity. Autoimmun Rev 2013; 12: 796-801. [CrossRef]

6. Poodt AE, Driessen GJ, de Klein A, van Dongen JJ, van der Burg M, de Vries E. TACI mutations and disease susceptibility in patients with common variable immunodeficiency. Clin Exp Immunol 2009; 156: 35-9. [CrossRef]

7. Khodadad A, Aghamohammadi A, Parvaneh N, et al. Gastrointestinal manifestations in patients with common variable immunodeficiency. Digest Dis Sci 2007; 52: 2977-83. [CrossRef]

8. Jorgensen SF, Reims HM, Frydenlund D, et al. A Cross-Sectional Study of the Prevalence of Gastrointestinal Symptoms and Pathology in Patients with Common Variable Immunodeficiency. Am J Gastroenterol 2016; 111: 1467-75. [CrossRef]

9. Zullo A, Romiti A, Rinaldi V, et al. Gastric pathology in patients with common variable immunodeficiency. Gut 1999; 45: 77-81. [CrossRef]

10. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007; 31: 1800-12. [CrossRef]

11. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999; 93: 190-7. [CrossRef]

12. Malamut G, Verkarre V, Suarez F, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol 2010; 105: 2262-75. [CrossRef]

13. Biagi F, Bianchi PI, Zilli A, et al. The significance of duodenal mucosal atrophy in patients with common variable immunodeficiency: a clinical and histopathologic study. Am J Clin Pathol 2012; 138: 185-9. [CrossRef]

14. Kokkonen J, Karttunen TJ. Lymphonodular hyperplasia on the mucosa of the lower gastrointestinal tract in children: an indication of enhanced immune response? J Pediatr Gastroenterol and Nutr 2002; 34: 42-6. [CrossRef]

15. Chu VT, Beller A, Rausch S, et al. Eosinophils promote generation and maintenance of immunoglobulin-A-expressing plasma cells and contribute to gut immune homeostasis. Immunity 2014; 40: 582-93. [CrossRef]

16. Matsushita T, Maruyama R, Ishikawa N, et al. The number and distribution of eosinophils in the adult human gastrointestinal tract: a study and comparison of racial and environmental factors. Am J Surg Pathol 2015; 39: 521-7. [CrossRef]

17. Hermans PE, Huizenga KA, Hoffman HN, Brown AL, Jr., Markowitz H. Dysgammaglobulinemia associated with nodular lymphoid hyperplasia of the small intestine. Am J Med 1966; 40: 78-89. [CrossRef]

18. Albuquerque A. Nodular lymphoid hyperplasia in the gastrointestinal tract in adult patients: A review. World J Gastrointest Endosc 2014; 6: 534-40. [CrossRef]

19. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 8-1997. A 65-year-old man with recurrent abdominal pain for five years. New Eng J Med 1997; 336: 786-93. [CrossRef]

20. Baran B, Gulluoglu M, Akyuz F. Nodular lymphoid hyperplasia of duodenum caused by giardiasis. Clin Gastroenterol Hepatol 2013; 11: A22. [CrossRef]

21. Oberhuber G, Mesteri I, Kopf W, Muller H. Demonstration of Trophozoites of G. Lamblia in Ileal Mucosal Biopsy Specimens May Reveal Giardiasis in Patients With Significantly Inflamed Parasite-free Duodenal Mucosa. Am J Surg Pathol 2016; 40: 1280-5. [CrossRef]

22. Oberhuber G, Kastner N, Stolte M. Giardiasis: a histologic analysis of 567 cases. Scand J Gastroenterol 1997; 32: 48-51. [CrossRef]

23. Hanevik K, Hausken T, Morken MH, et al. Persisting symptoms and duodenal inflammation related to Giardia duodenalis infection. J Infect 2007; 55: 524-30. **[CrossRef]**
24. Parenti DM. Characterization of a thiol proteinase in Giardia lamblia. J Infect Dis 1989; 160: 1076-80. **[CrossRef]**
25. Cotton JA, Bhargava A, Ferraz JG, Yates RM, Beck PL, Buret AG. Giardia duodenalis cathepsin B proteases degrade intestinal epithelial interleukin-8 and attenuate interleukin-8-induced neutrophil chemotaxis. Infect Immunity 2014; 82: 2772-87. **[CrossRef]**
26. Cotton JA, Motta JP, Schenck LP, Hirota SA, Beck PL, Buret AG. Giardia duodenalis infection reduces granulocyte infiltration in an in vivo model of bacterial toxin-induced colitis and attenuates inflammation in human intestinal tissue. PloS one 2014; 9: e109087. **[CrossRef]**
27. Chen TL, Chen S, Wu HW, et al. Persistent gut barrier damage and commensal bacterial influx following eradication of Giardia infection in mice. Gut Pathog 2013; 5: 26. **[CrossRef]**
28. Bor S, Kitapcioglu G, Kasap E. Prevalence of gastroesophageal reflux disease in a country with a high occurrence of Helicobacter pylori. World J Gastroenterol 2017; 23: 525-32. **[CrossRef]**
29. Azevedo NF, Almeida C, Cerqueira L, Dias S, Keevil CW, Vieira MJ. Coccoid form of Helicobacter pylori as a morphological manifestation of cell adaptation to the environment. Appl Environ Microbiol 2007; 73: 3423-7. **[CrossRef]**
30. Mazaheri Assadi M, Chamanrokh P, Whitehouse CA, Huq A. Methods for Detecting the Environmental Coccoid Form of Helicobacter pylori. Frontiers in public health 2015; 3: 147. **[CrossRef]**
31. Giorgio F, Principi M, Losurdo G, et al. Seronegative Celiac Disease and Immunoglobulin Deficiency: Where to Look in the Submerged Iceberg? Nutrients 2015; 7: 7486-504. **[CrossRef]**
32. Agarwal S, Smereka P, Harpaz N, Cunningham-Rundles C, Mayer L. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. Inflamm Bowel Dis 2011; 17: 251-9. **[CrossRef]**
33. Kalha I, Sellin JH. Common variable immunodeficiency and the gastrointestinal tract. Curr Gastroenterol Rep 2004; 6: 377-83. **[CrossRef]**
34. Washington K, Stenzel TT, Buckley RH, Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol 1996; 20: 1240-52. **[CrossRef]**