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Primary hypogammaglobulinemia with IBD-like features: An ECCO CONFER Multicenter Case Series

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AA: principal investigator for the study, conceived the study idea, contributed three case and prepared the manuscript. P.E., D.G.R., O.B., N.K.B., G.J.M., E.V.S., G.D., R.W., S.F., M.H.M., L.C., E.T. and R.F. contributed the cases and critically revised the manuscript. UK: case manager for the study, supervised the project, and critiqued the manuscript. All authors approved the final version.

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The data underlying this article are available in the article

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Abstract

BACKGROUND

Hypogammaglobulinemia is a disorder characterized by low serum immunoglobulin levels and had high prevalence of gastrointestinal manifestations. In some cases, clinical and endoscopic features are indistinguishable from those of inflammatory bowel disease (IBD).

METHODS

This was a multicenter case series performed as a part of the European Crohn's and Colitis Organisation (ECCO) Collaborative Network of Exceptionally Rare case reports (CONFER) project.

RESULTS

This report includes 27 patients with primary hypogammaglobulinemia and IBD-like features [20 males and 7 females, median age 45.6 years (Interquartile range (IQR) 35.2-59]. Crohn's disease-like features were noted in 23 patients, four patients had ulcerative colitis-like features. The diagnosis of hypogammaglobulinemia preceded IBD-like features diagnosis in 20 patients (median of 7 years prior, IQR 2.6-20.6 years), and followed IBD-like features appearance in 7 cases (median of one year after, IQR 0.45-5.6 years).

Hypogammaglobulinemia etiologies were common variable immunodeficiency (66.6%), agammaglobulinemia (7.4%), selective IgA-deficiency (11.1%), Goods syndrome (7.4%), IgG subclass deficiency with IgA deficiency (3.7%) and hyper-IgM (3.7%). In addition to antibiotics and intravenous immunoglobulin (IVIG) for hypogammaglobulinemia, 12 patients received IBD-related treatment including 5-ASA (2 patients), corticosteroids (1 patient), thiopurines (3 patients), anti-TNFs (4 patients) and vedolizumab (2 patients). By the end of the follow-up [44.5 months (IQR 18-81)], 21/27 (77%) patients were in clinical remission.

CONCLUSION

This case series describes IBD-like features in patients with hypogammaglobulinemia. The diagnosis of IBD-like features mainly occurred after that of hypogammaglobulinemia, with successful recovery in the majority of cases after appropriate treatment.

Key Words: primary hypogammaglobulinemia, immunodeficiency, inflammatory bowel disease, IBD-like features

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Introduction

Inflammatory bowel disease (IBD), primarily encompassing ulcerative colitis (UC) and Crohn's disease (CD), is an idiopathic disorder of the gastrointestinal (GI) tract that results from a complex interplay of environmental factors, abnormal gut microbiome, and dysregulated immune responses in genetically susceptible individuals (1,2). In some cases, other conditions can mimic IBD and have clinical and endoscopic features that resemble those of IBD.

Hypogammaglobulinemias are heterogeneous diseases of either primary origin (genetic disorders and/or chromosome anomalies) or secondary origin (induced by extrinsic factors: infectious agents, mediators such as corticosteroids, immunosuppressants, chemotherapy, metabolic diseases such as nephrotic syndrome, and nutritional disorders). In adults, the two most common forms of primary hypogammaglobulinemia are common variable immune deficiency (CVID) and selective IgA deficiency (3,4).

Infections causing chronic diarrhea, commonly related to parasitic infection, mainly Giardia lamblia, occur frequently due to absence of immunoglobulins resulting in attachment and proliferation of organisms on the intestinal epithelium (5–7).

Gastrointestinal manifestations resembling CD or UC has been reported in CVID cohorts and other hypogammaglobulinemias with weight loss, chronic diarrhea, rectal bleeding, abdominal pain, and malabsorption (8–10). IBD-like features are typically diagnosed after the diagnosis of hypogammaglobulinemias. Endoscopic features may include longitudinal ulcers and cobblestone appearance. Histologically, it can mimic lymphocytic colitis, collagenous colitis, and colitis-associated with graft-versus-host disease (11,12). In light of these identical features, it is difficult to distinguish between primary IBD and inflammatory features secondary to hypogammaglobulinemias, which can be secondary to infection or immuno-mediated. This cohort required long-term follow-up until they received appropriate therapy.

Immunoglobulin replacement does not ameliorate IBD-like disease (8), and the use of corticosteroids increases infectious susceptibility. Treatment of associated infection includes antibiotics to eliminate bacterial overgrowth, oral budesonide, 5-aminosalicylate agents (5-ASA), mercaptopurine (MP), and azathioprine (AZA) (8,13). Immunoglobulin replacement offers a degree of protection from pathogens. Gut inflammation is often difficult to control and unresponsive to standard IBD therapies. Targeted biological therapies, such as infliximab, adalimumab, vedolizumab, and ustekinumab have been used with some benefit in cases of severe enteropathy; however, patients with significant T-cell defects require monitoring for fungal infections and the duration of treatment is not established (9,14–18).

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In this collaborative case series, we aimed to describe primary hypogammaglobulinemia patients with IBD features and try to elicit the impact of the treatment and outcome.

Materials and Methods

Study design

This European Crohn's and Colitis Organisation [ECCO] observational multicenter study retrospectively collected cases through the CONFER project. The CONFER project was initiated by ECCO in order to specifically identify and report together rare IBD disease associations, which otherwise are seldom reported due to their exceptional rarity. Once a specific topic was selected by the Steering Committee as a CONFER project, ECCO launched a call to identify similar cases encountered by IBD physicians worldwide. The call to physicians was made through announcements at the ECCO annual congress and in national and international IBD meetings across Europe. Furthermore, the call for similar cases was disseminated by direct emails to all ECCO members and affiliated physicians and on the ECCO website and eNews. Physicians were then prompted to report their case to the CONFER database using pre-determined standardized Case Reporting Forms [CRF]. The authors were also reminded to report their case[s] to their national pharmacovigilance authorities. The call for the present case series was entitled 'Primary Hypogammaglobulinemia with IBD-like features'.

Patients and procedures

Adult patients suffering from primary hypogammaglobulinemia with IBD-like features were eligible for inclusion in this project. The CRF was divided into two sections. Section 1 included patient [epidemiological data, past medical history, smoking, family history] and IBD-like features characteristics [date of diagnosis, Montreal classification, extraintestinal manifestations and treatment]. Section 2 included a description of hypogammaglobulinemia: categories of primary humoral immunodeficiency's, symptoms, malignancies, treatment, gastrointestinal inflammatory activity, immunoglobulin levels, IBD targeted therapy, and outcome. Data were collected and analyzed anonymously and handled according to local regulations.

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Statistics

All statistical analyses [descriptive statistics] were performed with SPSS 20.0 software package [IBM SPSS Statistics, Armonk, NJ, USA].

Results

IBD-like characteristics

This report includes 27 patients with primary hypogammaglobulinemia and IBD-like features from 14 different centers; 20 males with a median age of 44 years (IQR 35.5-58.7) and 7 females with a median age of 50 years (IQR 30.4-81.9). Twenty-three patients had CD-like features and 4 patients UC-like features. Two (50%) of the 4 UC-like features patients had pancolitis, while most of the CD-like features showed either ileal (14 patients, 60.8%) or ileocolonic (9 patients, 39.2%) disease localization. The median age at IBD-like features presentation was 45.6 years (IQR 35.2-59). Reported IBD treatments before the hypogammaglobulinemia diagnosis mainly consisted of 5-aminosalicylic acid (5-ASA) (1 patient, 3.7%), azathioprine/mercaptopurine (AZA/MP) (2 patients, 7.4%), and anti-tumor necrosis factor (TNF) therapy (1 patient, 3.7%). One patient (3.7%) underwent prior surgery (small bowel resection).

Extraintestinal manifestations (EIMs) were described in seven patients [4 cases of peripheral arthropathy including one with associated episcleritis and another one axial arthropathy, 1 erythema nodosum, 1 pyoderma gangrenosum, and one with ankylosing spondylitis]. Patients characteristics are described in Table 1.

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Hypogammaglobulinemia characteristics

Primary hypogammaglobulinemia etiologies were as follows: common variable immunodeficiency (18 patients, 66.6%), agammaglobulinemia (2 patients, 7.4%), selective IgA-deficiency (3 patients, 11.1%), Goods syndrome (2 patients, 7.4%), IgG subclass deficiency with IgA deficiency (1 patient, 3.7%) and Hyper IgM (1 patient, 3.7%). The main symptoms were respiratory and gastrointestinal infections (20 patients, 83.3%), other infections include 2 cases of bacterial meningitis and two herpes zoster infection. Five cases of malignancy were described [1 chronic lymphocytic leukemia (CLL), 1 intestinal lymphoma, 2 thymomas (one of them had also renal cell carcinoma), and one gastric cancer]. Only one granulomatous disease was described (Granulomatous lung disease). The main treatment was antibiotics (18 patients, 66.6%) and intravenous immunoglobulin (IVIG) (22 patients, 81.4%), and one patient underwent a bone marrow transplant. All the patients had abnormal immunoglobulin levels: Twenty-one patients (77.7%) had abnormal IgG levels, 19 (70.3%) abnormal IgA levels, and 17 (63%) had abnormal IgM levels. The primary hypogammaglobulinemia characteristics are described in Table 2.

The diagnosis of hypogammaglobulinemia was made before and after the development of IBD-like features in 20 patients (median of 7 years prior, IQR 2.6-20.6 years), and 7 cases (median of one year after, IQR 0.45-5.6 years), respectively.

Twenty-two patients had available data regarding gastrointestinal disease activity during the follow up period: ten patients (45.4%) had clinically and endoscopically active gastrointestinal disease and 12 (54.6%) patients had no active disease. Twelve of 16 patients (75%) with available C-reactive protein (CRP) had an elevated CRP level.

During the follow-up period [median 44.5 months (IQR 18-81.75)], eighteen patients received IBD-targeted therapy. Five patients required a short course of steroids [3 systemic steroids and 2 low bioavailability steroids] and thirteen patients received maintenance therapy, of whom two were on 5-aminosalicylic acid, one on corticosteroids, three on AZA, four on anti-TNF inhibitors (3 adalimumab, 1 infliximab), two on vedolizumab and one on total parenteral nutrition (TPN). By the end of the follow-up, 21 of 27 (77%) patients had no gastrointestinal symptoms, of whom eight were on active IBD-targeted therapy (5- biologicals [4-anti TNF, 1-vedolizumab] ,2- 5-ASA, 1- AZA). The 4 patients who received IBD-targeted therapy before the hypogammaglobulinemia diagnosis continued the same treatment, and 3 of them were in clinical remission and one had active GI disease. Figure 1 described the study cohort, treatment and outcome.

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Thirteen patients had at least one episode of recurrent infections, five of them with multiple pathogens (*Campylobacter jejuni*, *Giardia lamblia*, *Clostridium difficile*, and *Cytomegalovirus*). In addition to antibiotics and IVIG as a treatment for hypogammaglobulinemia, six out of the 13 patients were on IBD-targeted therapy [3 patients on corticosteroids, 1- AZA, 1- vedolizumab, 1 adalimumab, and one patient on TPN].

During the follow-up period, nine patients underwent gastrointestinal surgeries: two patients underwent small bowel resections, 4 -ileocecal resections, 2- had colectomy and one distal gastrectomy for cancer. Six of these nine (66.6%) patients experienced recurrent GI symptoms after the operation, two patients had no recurrent symptoms, and one patient died as a result of septic shock. Four of the nine patients received IBD-targeted therapy (2-AZA, 1-adalimumab, 1-vedolizumab) with persistent GI symptoms after the surgery.

Thirteen patients received maintenance therapy, including six -biological therapies (4-anti-TNF inhibitors, 2 anti-integrin). Thirteen patients had at least one episode of recurrent infection, only two of them were on biologicals (1-adalimumab,1 vedolizumab). Two out of the 9 patient who underwent surgery were treated with biologicals (1-adalimumab,1 vedolizumab), both had recurrent GI symptoms after surgery. Five cases of malignancy were described in this cohort, none of the patients were on biological therapy. One case of chronic lymphocytic leukemia were described in patient who treated with 5-ASA.

All deaths (3/27- 11.1%) were secondary to hypogammaglobulinemia and infection. None of the deceased received IBD-targeted therapy.

Discussion

In adults, the most common form of primary hypogammaglobulinemia is common variable immune deficiency (CVID). The most common gastrointestinal manifestations are chronic diarrhea, weight loss, and malabsorption. In some cases, these features can mimic IBD and it is difficult to distinguish from IBD even on clinical and endoscopic grounds (8,10). A cohort of patients with CVID was shown to have reduced bacterial diversity and increased levels of plasmatic lipopolysaccharide and pro-inflammatory soluble CD25. Interestingly, these findings were most pronounced in the subgroup of CVID patients with immune dysregulation, including IBD (19). Autoimmune phenomena occur with some frequency in patients with hypogammaglobulinemia. Activation of tumor necrosis factor-alpha (TNFα) in patients with CVID may contribute to the onset of inflammatory bowel disease (20). Another explanation for IBD-like symptoms in immunodeficient patients is T-and B-cell function defects, more than 80% of patients having normal B-cell quantities

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lacking the ability to maturate to functional plasmocytes (21). In our series, eighteen of the 27 patients (66.6%) had CVID as etiology of their hypogammaglobulinemia, the most common feature for this group was CD-like feature [10 ileal, 8 ileocolonic involvements].

In addition to infections as a cause of chronic diarrhea, IgA deficiency is associated with various autoimmune and inflammatory disorders of the gut. A 10- to 20- fold increase risk for celiac disease in selective IgA deficiency has been reported. The link between these diseases may be genetic through shared HLA haplotypes (7). IBD, mostly ulcerative colitis, has also been reported in association with selective IgA deficiency (22–24). In this study cohort, we reported 3 cases of selective IgA deficiency (11.1%) with IBD-like features with two of them having UC-like features. In one review about the rare constellation of thymoma and hypogammaglobulinemia (Good syndrome), ulcerative colitis as a cause of diarrhea was described in 2 cases, while immune-mediated colitis as a cause of diarrhea was also suggested in 2 more cases. In the literature, we found also 2 more cases in an association of CD-like manifestations (25–28). In this case series, we described 2 cases of Goods syndrome with CD-like features, too.

The most common infectious manifestations of hypogammaglobulinemias are respiratory and gastrointestinal infection (29–31). Also, hypogammaglobulinemia can be associated with many different autoimmune conditions [most commonly immune thrombocytopenic purpura and hemolytic anemia followed by psoriasis, autoimmune thyroiditis, autoimmune atrophic gastritis, rheumatoid arthritis, and Evans syndrome] (32,33). In our cohort 12 of 27 cases had additional autoimmune conditions [3 Evans, 1 autoimmune hemolytic anemia, 2 rheumatoid arthritis, 2 psoriasis, 1 Sjogren syndrome, 4 celiac-like enteropathy (three of the celiac-like have multiple autoimmune conditions: 1 autoimmune gastritis and amyloidosis, 1 diabetes type 1 and autoimmune gastritis and one associated also with Evans syndrome)].

In general, although an appropriate treatment with IVIG and antibiotics can control disease exacerbation, recurrent infections, and symptoms of primary hypogammaglobulinaemias, concurrent gastrointestinal disease cannot be treated with immunoglobulins because these preparations contain IgG, which cannot reach the lumen of the intact gut. Treatment with oral immunoglobulins has not been successful because IgG is rapidly destroyed before reaching the small intestine (34–36). Currently, treatment for gastrointestinal manifestations in antibody-deficient syndromes is guided by successful therapy used for similar disorders in immunocompetent patients, with additional caution when immunosuppressive agents are administered (35). In our series, 5 patients required a short course of steroid and thirteen patients received persistent IBD-targeted therapy, of whom four anti-TNF, one vedolizumab, and one received multiple biological classes without

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response undergoing total colectomy two years after the diagnosis and still with active GI- symptoms.

Our study has several limitations: as it was a retrospective case report data collection and it relied on voluntary submission of cases by physicians who responded to the ECCO calls it might be subjected to geographical and selection biases. Unfortunately, the data regarding response of the other autoimmune manifestations were not available to us. Due to the low sample size, the correlation between IBD-targeted therapies and outcome is difficult to assess. Also, no risk factors or predictors can be investigated.

In conclusion, the current case series of primary hypogammaglobulinemia with IBD-like features illustrates a strong male and CD-like features predilection. The diagnosis of IBD-like features mainly occurs after that of hypogammaglobulinemia, the majority of the cases successfully recovered after appropriate treatment including immunomodulators, biological therapy, and surgical resection. Adding biological therapy may be safely practiced in some patients. However, until further data are available, a case-by-case decision process following careful weighing of the infectious and immunological state as well as the disease activity in the individuals is required.

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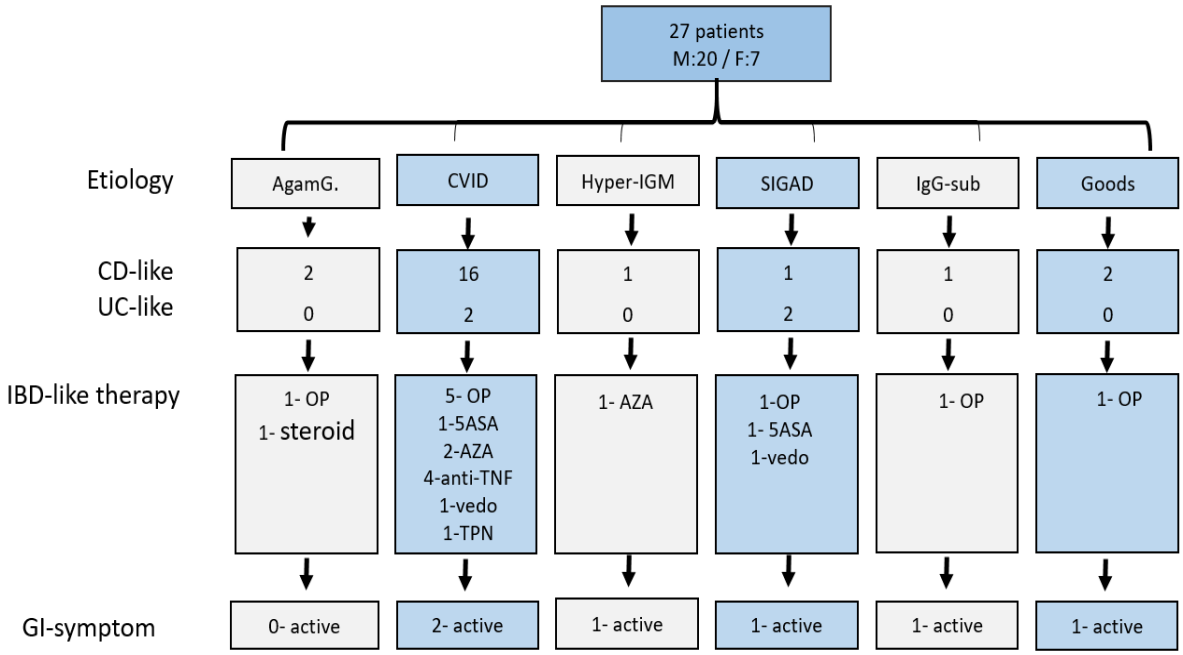
Figure 1:

Flow chart of the study cohort



IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease, GI, gastrointestinal; M, men; F, female; AgamG, agammaglobulinemia; CIVD, Common variable immunodeficiency disease; Hyper-IGM, hyper-Immunoglobulin M; SIGAD, Selective IgA deficiency; IgG-sub, Immunoglobulin G subclass deficiency; Goods, Goods syndrome; Op, operation; 5ASA, 5-aminosalicylic acid; steroid, corticosteroids; AZA, azathioprine; anti-TNF, anti-tumor necrosis factor; vedo, vedolizumab; TPN, total parenteral nutrition.

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Table 1.

Patients demographic and clinical characteristics.

characteristics	**Value (*n* = 27)**
Age (in years)	48 (21-86)
Sex, n(%)	
Female	7(26%)
Male	20 (74%)
Age at IBD-features appearance (years)	45.6 (35.2-59)
Age at hypogammaglobulinemia diagnosis (years)	33.4(2.1-77.7)
Smoking: current/past/never/unknown, n(%)	3 (11.1%) / 3 (11.1%) / 19(70.3%) / 2(7.4%)
Positive family history of IBD, n(%)	3 (11.1%)
IBD-like-features characteristics, n(%)	
Montreal classification—age (<16 /17–40 / >40 years)	3 (11.1%) / 15 (55.5%) / 9 (33.3%)
CD Montreal classification—location (L1 / L3)	14 (60.8%) / 9 (39.2%)
UC Montreal classification—location (E1 / E2 / E3)	1 (25%) / 1 (25%) / 2 (50%)
Perianal disease, n(%)	1 (3.7%)
Race, n(%)	
Caucasian	19(70.3%)
Black	1 (3.7%)
Arab	1 (3.7%)
Geographical spread, n(%)	
Italy	8 (29.6%)
Poland	8 (29.6%)
Israel	4 (14.8%)
Netherland	2 (7.4%)
Belgium	2 (7.4%)
Greece	2 (7.4%)
Switzerland	1 (3.7%)

IBD, inflammatory bowel disease (IBD); UC, ulcerative colitis; CD, Crohn's disease.

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Table 2.

Primary hypogammaglobulinemia characteristics

Age at primary hypogammaglobulinemia diagnosis (years)	33.4(2.1-77.7)
Etiology, n (%)	
Common variable immunodeficiency disease	18 (66.6%)
Selective IgA deficiency	3 (11.1%)
Agammaglobulinemia	2 (7.4%)
Goods syndrome	2 (7.4%)
IgG subclass deficiency with IgA deficiency	1 (3.7%)
Hyper IgM	1 (3.7%)
Hypogammaglobulinemia treatment	
Intravenous immunoglobulin (IVIG)	22 (81.4%)
Antibiotics	18 (66.6%)
Bone marrow transplant	1 (3.7%)
Immunoglobulins level, n (%)	
IgG level (normal / abnormal / unknown)	3 (11.1%) / 21 (77.7%)/ 3 (11.1%)
IgA level (normal / abnormal / unknown)	1 (3.7%) / 19 (70.3) / 7 (26%)
IgM level (normal / abnormal / unknown)	4 (17.8%) / 17 (63%) / 6 (22.2%)
Infections, n (%)	
Isolated respiratory infections	3 (12.5%)
Isolated gastrointestinal infections	3 (12.5%)
Respiratory and gastrointestinal infections	14 (58.3%)
Herpes zoster	2 (8.3%)
Bacterial meningitis	2 (8.3%)
Autoimmune manifestations, n (%)	
Autoimmune hemolytic anemia (AIHA)	4 (20%)
Immune thrombocytopenia (ITP) *	3 (15%)
Rheumatoid arthritis	2 (10%)
Psoriasis	2 (10%)
Celiac-like enteropathy §¥¶	4 (20%)
Autoimmune gastritis (AIG) ¥¶	2 (10%)
Type 1 diabetes (T1D) ¥	1 (5%)
Amyloidosis ¶	1 (5%)
Sjögren's syndrome	1 (5%)

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Granulomatous disease, n (%)	1 (3.7%)
Malignancy, n (%)	
Chronic Lymphocytic Leukemia	1 (16.6%)
Gastric cancer	1 (16.6%)
Thymoma	2 (12.5%)
Intestinal lymphoma	1 (16.6%)
RCC ^{ś}	1 (16.6%)

IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; RCC, Renal cell carcinoma

*, All cases of Immune thrombocytopenia (ITP) were associated also with autoimmune hemolytic anemia (AIHA); §, A combination of several autoimmune conditions: celiac-like enteropathy ,AIHA and ITP; ¥, A combination of several autoimmune conditions: B- Celiac-like enteropathy, type 1 diabetes and autoimmune gastritis; ¶, A combination of autoimmune gastritis and amyloidosis; ś, combined with one case of thymoma.

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