ORIGINAL ARTICLE

Clinical and Immunological Analysis of 23 Adult Patients With Common Variable Immunodeficiency

Ö Ardeniz,[1] ÖK Başoğlu,[2] F Günşar,[3] M Ünsel,[1] S Bayraktaroğlu,[4] N Mete[1] O Gülbahar,[1] A Sin[1]

[1]Ege University Medical Faculty, Department of Internal Medicine Division of Allergy and Clinical Immunology, Izmir, Turkey
[2]Ege University Medical Faculty, Department of Chest Diseases, Izmir, Turkey
[3]Ege University Medical Faculty, Department of Gastroenterology, Izmir, Turkey
[4]Ege University Medical Faculty, Department of Radiology, Izmir, Turkey

Abstract

Background: Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia, defective antibody production, and recurrent upper and lower airway tract infections.
Objectives: To reveal the clinical heterogeneity of this condition, analyze the high frequency of respiratory and gastrointestinal complications despite satisfactory trough immunoglobulin (Ig) G levels, and determine the main difficulties in management and treatment.
Methods: We performed a retrospective analysis of 23 patients (13 male and 10 female) diagnosed with CVID between 2001 and 2008.
Results: The median diagnostic delay for females and males was 15 years (range, 1-32 years) and 8 years (range, 1-31 years), respectively. Restrictive, obstructive, and combined pulmonary function defects were determined in 23%, 27%, and 14% of patients, respectively. The most frequent findings on the thoracic computed tomography scan were bronchiectasis, mediastinal lymphadenopathy, fibrosis, ground-glass patterns, mosaic oligemia, peribronchial cuffing, and parenchymal nodules. Giardiasis and duodenal lymphoid hyperplasia were detected in 52% and 42% of the patients, respectively, and *Helicobacter pylori* in 42%. Vitamin A levels were normal, although ß-carotene and/or vitamin E levels were decreased in patients presenting malabsorption-related symptoms. Malignancy was documented in 3 patients and decreased bone mineral density in 9 patients (3 had osteoporosis and 3 had osteomalacia).
Conclusion: CVID is a multisystemic disease that should be managed by a multidisciplinary team. Intravenous immunoglobulin therapy and antibiotics do not seem to have a suppressive effect on granulomatous or inflammatory manifestations. More comprehensive studies based not only on peripheral blood but also on immunohistological analysis are necessary to shed light on the pathogenesis of these life-threatening complications.

Key words: CVID. Adults. Respiratory manifestations. Gastrointestinal manifestations. Granulomatous disease. IVIG therapy. Antibiotic prophylaxis.

Resumen

Antecedentes: La inmunodeficiencia común variable (IDCV) se caracteriza por hipogammaglobulinemia, una producción deficiente de anticuerpos e infecciones recurrentes de las vías respiratorias altas y bajas.
Objetivos: Revelar la heterogeneidad clínica de esta enfermedad, analizar la alta frecuencia de complicaciones respiratorias y gastrointestinales, a pesar de concentraciones mínimas satisfactorias de inmunoglobulina (Ig) G, y determinar las principales dificultades en el diagnóstico y tratamiento.
Métodos: Se realizó un análisis retrospectivo de 23 pacientes (13 hombres y 10 mujeres) que fueron diagnosticados de IDCV entre los años 2001 y 2008.
Resultados: La mediana de demora del diagnóstico en mujeres y hombres fue de 15 años (intervalo: 1-32 años) y 8 años (intervalo; 1-31 años), respectivamente. Se determinaron los defectos restrictivos, obstructivos y combinados de la función pulmonar en un 23%, un

27% y un 14% de los pacientes, respectivamente. Los hallazgos más frecuentes en la tomografía axial computerizada del tórax fueron bronquiectasia, linfadenopatía mediastínica, fibrosis, núcleos en vidrio esmerilado, oligohemia en mosaico, infiltrado peribronquial y nódulos parenquimatosos. Se detectó giardiosis e hiperplasia linfoide del duodeno en un 52% y un 42% de los pacientes, respectivamente, así como *Helicobacter pylori* en un 42% de estos. Los niveles de vitamina A fueron normales, si bien se observaron niveles reducidos de betacaroteno y/o vitamina E en pacientes con síntomas relacionados con la malabsorción. Se documentó enfermedad neoplásica en 3 pacientes y descenso de la densidad mineral ósea en 9 pacientes (3 presentaban osteoporosis y otros 3 osteomalacia).
Conclusión: La IDCV es una enfermedad multisistémica que debe ser tratada por un equipo multidisciplinario. El tratamiento con inmunoglobulina intravenosa y antibióticos no parece ejercer un efecto supresor en manifestaciones granulomatosas o inflamatorias. Son necesarios estudios más amplios basados no solamente en la sangre periférica, sino también en análisis inmunohistológicos para aclarar la patogénesis de estas complicaciones potencialmente mortales.

Palabras clave: IDCV. Adultos. Manifestaciones respiratorias. Manifestaciones gastrointestinales. Enfermedad granulomatosa. Tratamiento con IGIV. Profilaxis antibiótica.

Introduction

Common variable immunodeficiency (CVID) is characterized by recurrent upper and lower respiratory tract infections, hypogammaglobulinemia, and defective antigen-specific antibody responses [1,2]. Patients with CVID may also present abnormalities in helper T cell function and in dendritic and monocytic compartments [3,4,5]. Expression and function of toll-like receptor (TLR) 9 have also been found to be defective in B cells and plasmacytoid dendritic cells [6]. CVID can present with granulomatous disease mimicking sarcoidosis, interstitial lung disease, autoimmune manifestations (autoimmune cytopenia is the most common), inflammatory bowel disease leading to malabsorption, and lymphoma (usually of B-cell origin), thus making this syndrome difficult to manage [1,7,8].

As the clinical symptoms become overt in early to middle adulthood, most patients with CVID are not usually identified before complications develop. We present the clinical and biochemical features of CVID in 23 patients and analyze methods of dealing with complications.

Methods

Patients

We analyzed the clinical and laboratory data of the 23 (13 male and 10 female) patients who were diagnosed with CVID at Ege University Medical Faculty Internal Medicine Division of Allergy and Clinical Immunology between 2001 and 2008. Diagnosis was based on the following: low serum immunoglobulin (Ig) G, IgA, and IgM levels; low or absent antibody responses to vaccination against pneumococci, *Haemophilus influenzae*, and tetanus; low or absent isohemagglutinin titers; and by ruling out secondary causes of hypogammaglobulinemia [1,9]. Pulmonary function was evaluated using forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), ratio of FEV_1 to FVC, carbon monoxide diffusion capacity (DL_{CO}), and arterial blood gas analysis when necessary. Sputum cultures were obtained. High-resolution computed tomography (HRCT) findings were presented. Lung biopsy and bronchoalveolar lavage were carried out when indicated. In all patients with gastrointestinal complaints, upper gastrointestinal endoscopy and biopsy were performed. The results of abdominal CT, liver biopsy, and fecal culture were recorded. Routine biochemistry, complete blood count, and vitamin (A, D, and E) and ß-carotene analysis were carried out. Fecal fat excretion was measured in patients presenting malabsorption-associated symptoms. We also analyzed different treatment modalities (antibiotic prophylaxis regimens, intravenous immunoglobulin [IVIG] replacement dose and frequency, trough IgG levels) and the main difficulties in management.

Statistical Analysis

The Mann-Whitney test was used to compare the quantitative variables. A *P* value of .05 or less was considered significant. The statistical analysis was performed using SPSS version 17.0.

Immunological Evaluation

Serum Ig levels were measured using nephelometry (Dade Behring, Marburg, Germany), and isohemagglutinin titers were analyzed (Diagnostics Grifols, Barcelona, Spain). The reference range for isohemagglutinin titers in healthy individuals is 1/32 to 1/512; therefore, titers of less than 1/32 were regarded as low. The absolute counts of peripheral blood lymphocyte subsets per mm^3 were analyzed using 4-color flow cytometry (FACSCalibur, BD, San Jose, California, USA). Trough IgG levels were determined. Serum autoantibody analysis (antinuclear antibody, antimitochondrial antibody, anti–smooth muscle antibody, anti–gastric parietal cell antibody, antineutrophil cytoplasmic antibody [ANCA], and anticyclic citrullinated peptide antibody [anti-CCP]) was performed using enzyme-linked immunosorbent assay (ELISA) or immunoblotting in our laboratory.

Results

Demographic Findings and Family History

We evaluated 23 patients (13 male and 10 female) referred to our clinic and diagnosed with CVID between 2001 and 2008. The median (IQR) age at onset of symptoms was 12.5 (7-72) years for females and 15 (7-46) years for males. The median age at the time of diagnosis was 33 (17-73) years for females and 28 (13-49) years for males. The median diagnostic delay was 15 (1-32) years in females and 8 (1-31) years in males. There were no statistically significant differences between female and male CVID patients regarding age at onset of symptoms, age at diagnosis, and diagnostic delay (*P*=.351, *P*=.877, *P*=.112, respectively). No patients had a family member diagnosed with CVID. Consanguinity was reported in 7 (30%) patients, and 2 patients had a family member diagnosed with selective IgA deficiency (Table 1).

Clinical Findings on Admission

Recurrent otitis and sinusitis were observed in all except 2 patients. At least 1 operation to treat sinusitis was reported in 7 patients. Tympanoplasty was reported in 2 patients. At least 1 episode of pneumonia had been reported in 61% of patients. One patient had undergone a lobectomy due to bronchiectasis. Measles encephalitis and pneumococcal meningitis were reported in 2 patients before the diagnosis of CVID. One patient suffered from recurrent herpes simplex infection. One patient was diagnosed with CVID following detailed scrutiny due to constrictive pericarditis. Twelve patients suffered from diarrhea and 2 patients presented with malabsorption-associated symptoms.

Autoimmunity and Comorbid Conditions

Two patients developed autoimmunity during the course of the disease. One patient was diagnosed with autoimmune hemolytic anemia. One patient had been diagnosed with rheumatoid arthritis on the grounds of clinical and radiological findings, while autoantibody titers, including anti-CCP, were negative. This patient was later diagnosed with primary sclerosing cholangitis and ulcerative colitis. One patient had type 1 diabetes mellitus at diagnosis. No patients were autoantibody-positive in our patient group.

During follow-up, 3 patients developed a malignant neoplasm (diffuse B cell lymphoma, pancreatic carcinoma, and papillary thyroid carcinoma). Decreased bone mineral density was observed in 9 patients (3 with osteoporosis and 3 with osteomalacia). Four patients had low vitamin D levels (Table 1). Patient 15 presented significant osteomalacia in the absence of clinical symptoms, and persistently isolated high alkaline phosphatase levels were the only abnormality.

Pulmonary Function, Tomographic Findings, and Sputum Analysis

Eleven (48%) patients were found to have bronchiectasis at the time of diagnosis (Table 2). There were no statistically significant differences in terms of diagnostic delay between patients with bronchiectasis and those who did not have this complication at the time of diagnosis (*P*=.279). Restrictive pulmonary defect was detected in 23% of patients. Spirometry revealed obstructive pulmonary defect in 27% and obstructive and restrictive pulmonary defect in 14% of patients (Table 2). Eleven patients (48%) showed decreased DL_{CO} values. Three patients in whom spirometry revealed an obstructive pattern had low DL_{CO} values. Three patients with normal spirometry results had low DL_{CO} values.

Bronchiectasis was observed on CT in 15 (65%) patients during follow-up. The most frequent findings on the thoracic CT other than bronchiectasis were mediastinal lymphadenopathy, fibrosis, ground-glass patterns, mosaic oligemia, peribronchial cuffing, and parenchymal nodules. In 3 patients with parenchymal lung disease (nodules accompanied by either a mosaic pattern or ground-glass patterns on HRCT) who underwent bronchoscopy, analysis of bronchoalveolar lavage fluid revealed an increased percentage of polymorphonuclear leukocytes (PNL). Respiratory insufficiency developed in 2 patients with hypoxemia on blood gas analysis after 14 and 15 years of follow-up.

In most patients, *H influenzae, Streptococcus pneumoniae,* and *Branhamella catarrhalis* were grown on sputum cultures. In one case (patient 11), sputum and open-lung biopsy cultures yielded *Staphylococcus aureus* and *Staphylococcus haemolyticus*, respectively. In another case (patient 18, pneumonia followed by arthritis), cell culture revealed *Chlamydia pneumoniae* in sputum and synovial fluid. In the same case, *Enterobacter cloacae* was observed in a sputum sample while the patient was taking erythromycin.

Biopsy by video-assisted thoracoscopic surgery (VATS) revealed interstitial septal fibrosis and lymphocytic infiltration comprising follicles in 1 case (patient 11), with multiple nodules and ground-glass patterns on the HRCT image. Corticosteroid therapy was proposed, although the patient declined. HRCT performed due to exertional dyspnea 3 years later revealed more bilateral diffuse parenchymal opacities and nodules, and therapy with corticosteroids was commenced (Figures 1 and 2). The other patient (patient 23) presenting multiple nodules on HRCT declined a lung biopsy.

Gastrointestinal Evaluation

Giardiasis was detected in 12 (52%) patients after fecal examination and/or biopsy obtained by upper gastrointestinal endoscopy. Duodenal lymphoid hyperplasia was detected in 8 out of 19 (42%) patients who underwent upper gastrointestinal endoscopy. Giardia trophozoites were shown to accompany lymphoid hyperplasia in 3 patients (Table 3). *Helicobacter pylori* was detected in the antrum and corpus in 8 (42%) patients by upper gastrointestinal endoscopy. All patients with *H pylori* infection received eradication therapy. In 1 case (patient 20), findings compatible with gluten-sensitive enteropathy were detected (Table 3), but diarrhea did not resolve with a gluten-free diet. As giardiasis was detected, she was started on metronidazole at 750 mg/d for 3 months in conjunction with high-dose IVIG, although no response was observed. The possibility of bacterial overgrowth was considered and prophylaxis with norfloxacin was begun, although, once again, no response was observed. Double-

Table 1. Demographic and Clinical Findings

Patient	Age	Gender	Age at Onset of Symptoms	Age at Diagnosis	Consanguinity	Comorbid Condition
1	36	Male	14	27	No	None
2	29	Female	7	28	Yes	Urticaria, osteopenia
3	53	Female	33	37	No	Vitamin D deficiency, osteomalacia
4	55	Male	36	47	No	Osteoporosis, diffuse B-cell lymphoma and pancreatic carcinoma
5	40	Male	8	20	No	Epilepsy, hypertension, leukopenia
6	42	Female	18	41	No	Hypertension, arrhythmia, asthma, urticaria, angioedema, positive prick test results to pollens
7	35	Female	15	33	Yes	None
8	46	Male	39	43	No	Eosinophilic gastroenteritis, short-bowel syndrome. Died of sepsis
9	46	Female	7	39	No (selective IgA deficiency was diagnosed in her son)	Vitamin D deficiency, osteomalacia
10	30	Male	15	19	Yes	None
11	51	Male	12	43	No	Diffuse parenchymal lung disease, nodule in thyroid
12	29	Female	10	25	Yes (1 sibling diagnosed with selective IgA deficiency)	Diffuse B-cell lymphoma, vitamin D deficiency) pulmonary hypertension, autoimmune hemolytic anemia, multiple nodules in thyroid
13	30	Male	27	28	No	Papillary carcinoma of thyroid
14	58	Male	46	47	No	None
15	26	Female	10	17	No	Type 1 diabetes mellitus, vitamin D deficiency, osteomalacia, sensorimotor polyneuropathy, lobectomy due to bronchiectasis
16	53	Male	41	49	No	Surgery due to thymoma, rheumatoid arthritis, ulcerative colitis, sclerosing cholangitis, osteoporosis
17	37	Male	7	35	Yes	Granulomatous hepatitis, osteopenia, neutropenia, lymphocytosis
18	49	Female	18	33	Yes	Granulomatous hepatitis, portal hypertension, liver cirrhosis, hypersplenism, arthritis due to *Chlamydia* pneumonia
19	78	Female	72	73	No	Hypertension, osteoporosis
20	31	Female	7	22	Yes	Osteopenia
21	26	Male	19	24	No	None
22	24	Male	9	21	No	Pericardiectomy
23	19	Male	13	14	No	Hypersplenism, pancytopenia, congenital nystagmus, perivascular dermatitis

Abbreviations: Ig, immunoglobulin.

Table 2. Pulmonary Function Tests and Computed Tomography Findings

Patient	Diagnostic Delay, y	BAD	FP	FEV_1, %	FVC, %	FEV_1/FVC, %	DL_{CO}, %	PFT/ABGA	Thoracic Computed Tomography	BAL/Biopsy	Treatment
1	13	Yes	Total of 4	58	78	62	94	Obstructive	Cylindrical bronchiectasis, fibrosis	Not performed	$ß_2$-agonist
2	21	Yes	1/y	99	106	81	88	Normal	Bronchiectasis, PBVC, mosaic oligemia	Not performed	Intermittent AB
3	4	No	3/y	36	71	43	52	Obstructive and restrictive hypoxia on ABGA	Reticulation, PBVC, nodules, bronchiectasis, mosaic oligemia, mediastinal LAP, linear branching opacities	BAL: macrophages, 60%; PNLs, 30%; lymphocytes 10%	$ß_2$-agonist inhaled tiotropium, theophylline, prophylactic AB (clarithromycin)
4	11	Yes	Total of 3	78	89	71	71	Obstructive	Consolidation, mediastinal lymphadenopathy, PBVC, bronchiolitis, bronchiectasis reticulation, nodules, ground-glass, abnormality, branching opacities	BAL: PNL, 64%; macrophages 34% Eosinophils 2%	Intermittent AB
5	12	No	None	95	106	74	99	Normal	Reticulation, PBVC, bronchiectasis, linear branching opacities, atelectasis, remarkable atherosclerosis	Not performed	Intermittent AB
6	23	No	Total of 2	94	114	71	82	Normal	Normal	Not performed	Intermittent AB
7	18	Yes	None	79	81	85	65	Mild restrictive	PBVC, bilateral bronchiectasis, mosaic oligemia, bronchiolectasis, atelectasis	Not performed	Intermittent AB, $ß_2$-agonist
8	4	No	3/y	85	70	NA	NA	NA	Multiple mediastinal lymphadenopathies, subpleural nodules	Not performed	None

Continued

Patient	Diagnostic Delay, y	BAD	FP	FEV_1, %	FVC, %	FEV_1/FVC, %	DL_{CO}, %	PFT/ABGA	Thoracic Computed Tomography	BAL/Biopsy	Treatment
9	32	Yes	None	54	85	55	61	Obstructive	PBVC, cylindrical bronchiectasis, nodules, mosaic oligemia, linear branching opacities	Not performed	Inhaled tiotropium $ß_2$-agonist
10	4	Yes	Total of 7	50	77	55	82	Obstructive	PBVC, cylindrical bronchiectasis nodules, mosaic oligemia, linear branching opacities	Not performed	$ß_2$-agonist, inhaled tiotropium, theophylline, intermittent AB
11	31	No	Total of 2	74	76	79	57	Restrictive	PBVC, mediastinal and axillary LAP, bilateral ground-glass abnormality, multiple nodules, reticulation	VATS[a] Interstitial septal fibrosis, lymphocytic infiltration BAL: PNL, 90%; macrophages, 8%; lymphocytes, 1%; eosinophils, 1%	Declined corticosteroid therapy Intermittent AB
12	15	No	None	75	83	78	77	Normal	Mediastinal and axillary LAP, bilateral mosaic oligemia, septal thickening, nodules	Not performed	Intermittent AB
13	1	No	Total of 5	99	101	83	96	Normal	Atelectasis	Not performed	Intermittent AB
14	1	Yes	Total of 2	95	98	78	78	Normal	Mediastinal LAP, ground-glass abnormality, bronchiectasis, bronchiolectasis	Not performed	Intermittent AB
15	7	Yes	Once	73	75	85	73	Restrictive	Bronchial thickening, bronchiectasis,	Not performed	Intermittent AB

Continued

Patient	Diagnostic Delay, y	BAD	FP	FEV_1, %	FVC, %	FEV_1/FVC, %	DL_{CO}, %	PFT/ABGA	Thoracic Computed Tomography	BAL/Biopsy	Treatment
									ground-glass abnormality, nodules, lobectomy findings		
16	8	Yes	None	61	83	59	118	Obstructive	PBVC, apical fibrosis bronchiectasis, ground-glass abnormality, airway trapping, atelectasis	Not performed	Intermittent AB
17	28	Yes	2-3/y	70	77	81	93	Restrictive	PBVC, mediastinal lymphadenopathy, bilateral bronchiectasis bronchiolectasis, fibrosis	Not performed	Prophylactic AB (clarithromycin)
18	15	Yes	None	44	73	52	89	Obstructive and restrictive hypoxia on ABGA	Small airway disease, PBVC, mosaic oligemia, bronchiectasis, air trapping, pleural thickening, linear branching opacities, nodules	Not performed	$ß_2$-agonist Inhaled steroid Inhaled tiotropium Theophylline, Prophylactic AB (moxifloxacin)
19	1	No	Once	43	NA	51	89	Obstructive and restrictive	Nodules, atelectasis	Not pereformed	None
20	15	No	Total of 3	65	87	65	75	Obstructive	Normal	Not performed	Intermittent AB
21	5	No	Twice	91	104	74	84	Normal	PBVC, ground-glass opacities, focal bronchiectasis	Not performed	None
22	12	No	Total of 3	60	60	86	78	Restrictive	Mediastinal and axillary lymphadenopathy, atelectasis, bronchiectasis	Not performed	Intermittent AB
23	1	No	None	81	75	92	60	Restrictive	Multiple nodules and mediastinal lymphadenopathy	BAL; macrophages, 96%; lymphocytes, 3%; PNL, 1%	Prophylactic AB (TMP-SMX)

Abbreviations: AB, antibiotics; ABGA, arterial blood gas analysis; BAD, bronchiectasis at diagnosis; BAL, bronchoalveolar lavage; DL_{co}, carbon monoxide diffusion capacity; FP, frequency of pneumonia; PFT, pulmonary function tests; LAP, lymphadenopathy; NA, not available; PBVC, peribronchovascular cuffing; PNL, polymorphonuclear leukocytes; VATS, video-assisted thoracoscopic surgery.
[a]VATS was performed 3 months after BAL analysis.

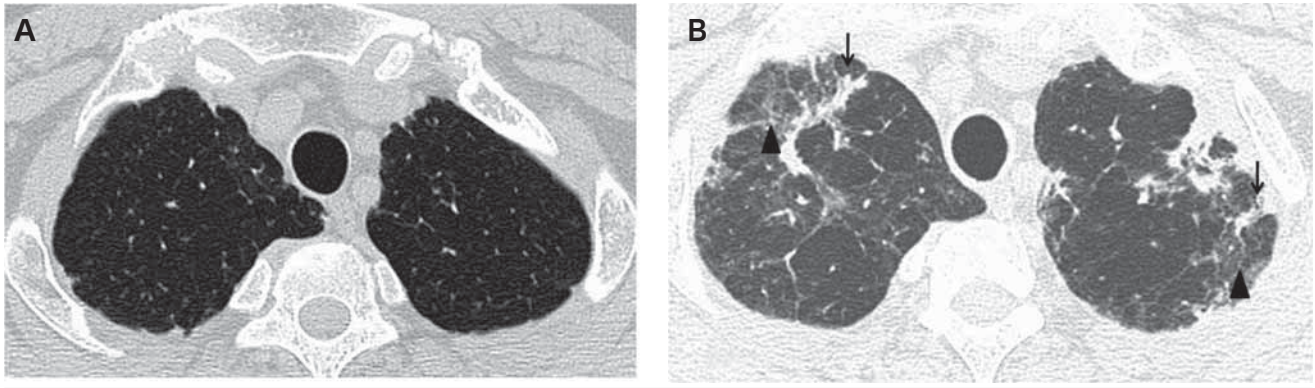

Figure 1. A, HRCT scan at the level of the upper lobes showing the normal lung parenchyma in the year 2005. B, HRCT scan from the same level in the year 2008 showing development of focal areas of fibrosis (arrows) and ground-glass opacities (arrowheads) in the follow-up period. HRCT indicates high-resolution computed tomography.

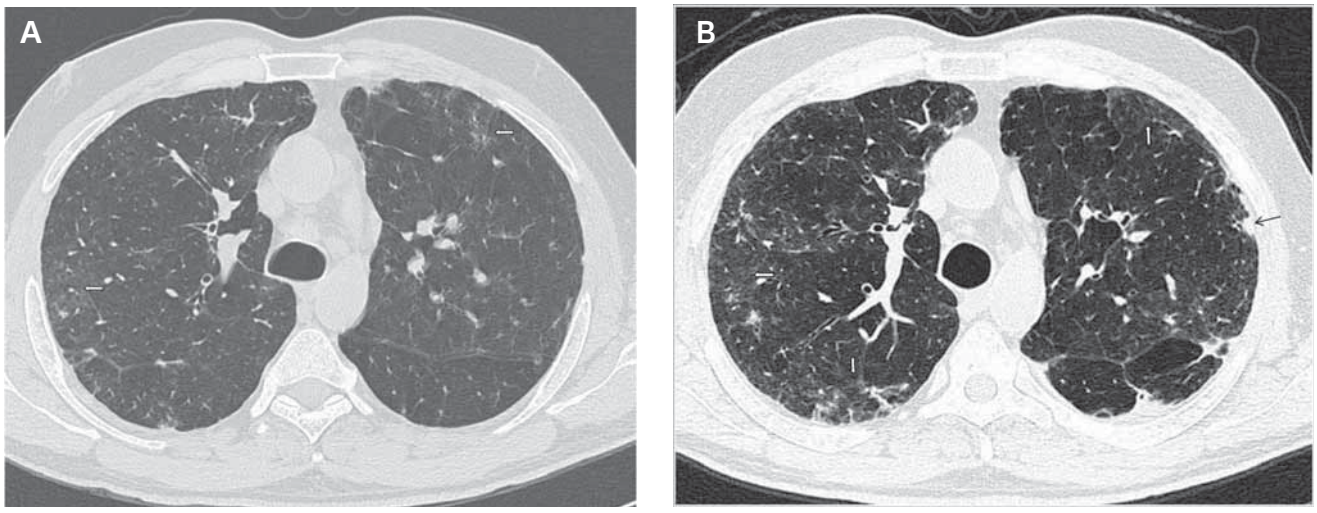

Figure 2. A, HRCT scan of the same patient at a lower level on the upper lobes shows fine reticular opacities and focal peripheral ground-glass areas (thick arrows) in the year 2005. B, Follow-up HRCT scan in the year 2008 showing the development of a subpleural nodule (thin arrow), and progression in areas of ground-glass opacity and reticulation (thick arrows). HRCT indicates high-resolution computed tomography.

balloon endoscopy and colonoscopy were proposed. One patient was diagnosed with eosinophilic gastroenteritis and short-bowel syndrome after wide intestinal resection. This patient died due to massive gastrointestinal bleeding and sepsis while under immunosuppressive treatment.

Twelve patients had chronic or intermittent diarrhea, although no organism was grown on routine cultures. The other gastrointestinal parasites were *Blastocystis hominis* and *Chilomastix mesnili*. Three patients had been suffering from malabsorption-related symptoms. Fecal fat was significantly increased in 2 patients with chronic diarrhea (14 g and 10 g, respectively). Vitamin A levels were normal in all patients, although ß-carotene and/or vitamin E levels were found to be low. Vitamin D (25-hydroxyvitamin D3) levels were lower than normal in 4 cases (patients 3, 9, 12, and 15), although 3 of them did not have clinical symptoms of malabsorption.

Liver biopsy performed due to persistent high alkaline phosphatase levels revealed granuloma in 2 patients, who were started on ursodeoxycholic acid (Ursofalk; Ali Raif, Istanbul, Turkey) at 10-15 mg/kg/d). One patient developed portal hypertension and cirrhosis after 15 years of follow-up. None of these patients had autoantibody titers (antinuclear antibody and antimitochondrial antibody) compatible with primary biliary cirrhosis. One patient with persistent high alkaline phosphatase levels was diagnosed with sclerosing cholangitis after evaluation with magnetic resonance cholangiopancreatography (Table 3). No patient was diagnosed with acute hepatitis after starting IVIG. One patient (patient 15) had been diagnosed with hepatitis C (HCV) and had taken interferon and ribavirin before diagnosis of CVID. Interestingly, serological tests (anti-HCV and HCV-RNA by polymerase chain reaction) were persistently negative during follow-up.

Table 3. Gastrointestinal Findings

Patient	GFE	Endoscopic Biopsy	Vitamin and Mineral Levels	Liver functions/ Liver biopsy	Abdominal CT	Treatment
1	Yes	Duodenitis, increased intraepithelial lymphocytes, *H pylori*	Iron deficiency	Normal	HSM	None
2	No	DLH, *H pylori*	Iron deficiency anemia	Normal	HSM	None
3	No	NA	Iron deficiency Low vitamin D levels	Isolated high ALP	Splenomegaly, multiple mesenteric and retroperitoneal LAP	UDCA
4	Yes	Gastritis, intestinal metaplasia	Iron deficiency, low ß-carotene levels	Normal	HSM, multiple mesenteric LAP	None
5	No	NA	NA	Normal	Splenomegaly, abdominal aortic calcification	None
6	No	Gastritis, intestinal metaplasia, DLH, *H pylori*	Iron deficiency	Normal	Splenomegaly	None
7	Yes	Atrophic pangastritis, giardiasis, DLH	Iron deficiency	Normal	HSM, multiple mesenteric LAP	Iron replacement, metronidazole
8	No	Eosinophilic gastroenteritis	Hypocalcemia, iron deficiency, low ß-carotene and vitamin E levels	Normal	Mesenteric LAP	None
9	Yes	Gastritis, intestinal metaplasia giardiasis, DLH	Iron deficiency, low ß-carotene, vitamin D and vitamin E levels	High ALP and GGT levels	HSM, multiple mesenteric LAP	Long term metronidazole (3 months) or combined therapy (ornidazole + tetracycline)
10	Yes	Gastritis, bulbitis, *H pylori*	NA	Normal	Splenomegaly	Metronidazole
11	Yes	Gastritis	NA	Normal	Splenomegaly left renal atrophy	Metronidazole Intramuscular B_{12} replacement
12	No	DLH	Low vitamin D levels	High ALP and GGT biopsy: sinusoidal $CD3^+$, $CD4^+$, and $CD16^+$ cell infiltration	Multiple mesenteric LAP	None
13	Yes	DLH	Low ß-carotene levels	Normal	Splenomegaly	None
14	No	Duodenitis, focal gastric metaplasia, gastritis intestinal metaplasia *H pylori*	Low B_{12} level, iron deficiency	Normal	Splenomegaly	Iron replacement, intramuscular B_{12} replacement

Continued

Patient	GFE	Endoscopic Biopsy	Vitamin and Mineral Levels	Liver functions/ Liver biopsy	Abdominal CT	Treatment
15	Yes	Giardiasis, intestinal metaplasia, *H pylori*	Low vitamin D Low ß-carotene levels	Normal	Splenomegaly, retroperitoneal LAP	None
16	No	Severe gastritis, *H pylori*, DLH	Low ß-carotene and vitamin E levels	High ALP and GGT levels. MRCP: primary sclerosing cholangitis	HSM	Mesalamine (Salofalk), Salazopyrin, zinc, calcium, vitamin D and vitamin E replacement
17	Yes	Gastritis *H pylori*	NA	High ALP and GGT Biopsy: granulomatous hepatitis	Multiple mesenteric LAP	UDCA
18	No	Gastritis	NA	High ALP and GGT. Biopsy: Granuloma	Liver cirrhosis, splenomegaly, craniocaudal collaterals, portal hypertension. Mesenteric and retroperitoneal LAP	UDCA
19	No	Foveolar hyperplasia in antrum	NA	Normal	Atherosclerosis of the abdominal aorta, iliac and femoral arteries	None
20	Yes	Villous flattening, epithelial PNL infiltration, increased in $CD3^+$ T cells	Hypocalcemia, hypokalemia, iron deficiency	Normal	Splenomegaly steatosis	Long-term metronidazole (3 mo) for giardiasis and prophylactic norfloxacin
21	Yes	Giardiasis, DLH	NA	Normal	Splenomegaly	None
22	Yes	NA	NA	Normal	HSM	None
23	No	NA	NA	High ALP	Splenomegaly	None

Abbreviations: ALP, alkaline phosphatase; DLH, duodenal lymphoid hyperplasia; GFE, giardiasis on fecal examination; GGT, gammaglutamyl transpeptidase; HSM, hepatosplenomegaly; LAP, lymphadenopathy; MRCP, magnetic resonance cholangiopancreatography; NA, not available; UDCA, ursodeoxycholic acid.

Immunoglobulin and Antibiotic Treatment

Most of the patients received IVIG at 500-600 mg/kg every 3 to 4 weeks (Table 4). One patient received 800 mg/kg every 2 weeks due to unsatisfactory trough levels (<400 mg/dL), which were considered to have been caused by diffuse gastrointestinal inflammation (Table 4). One patient was given 1000 mg/kg every 4 weeks due to insufficient trough IgG levels and diffuse parenchymal lung disease. Prophylactic antibiotic treatment was implemented in 5 patients. In 3, this was to treat bronchiectasis and recurrent bronchitis attacks with growth of *S pneumoniae* on sputum culture despite appropriate trough IgG levels. Initially, erythromycin was administered (3 times a week, 500 mg bid). However, all the patients continued to have purulent sputum with bacterial growth; therefore, erythromycin was replaced by clarithromycin (1 wk/mo, 500 mg bid) in 2 patients and moxifloxacin (1 wk/mo, 500 mg/d) in 1 patient. Antibiotics were started 7 days before IVIG. Clarithromycin did not control the respiratory infection in patient 3. One patient (patient 20) received continuous norfloxacin prophylaxis due to chronic diarrhea that did not respond to long-term metronidazole and a celiac diet. One patient (patient 23) was given trimethoprim-sulfamethoxazole.

Laboratory Findings

Serum Ig levels at diagnosis are shown in Table 4. Two patients had normal IgM levels. Isohemagglutinin titers were negative in 10 patients and low in 8 (between 1/2 and 1/8) (Table 5). Absolute lymphocyte levels are shown in Table 5. The $CD19^+$ B lymphocyte count was lower than 1% in 5 patients. Four patients showed increased B lymphocyte counts. Thirteen patients had lymphopenia and 2 had lymphocytosis. $CD4^+$ T lymphocyte counts were decreased in 20 patients, and

Table 4. Ig Levels at Diagnosis, Trough IgG Levels, and IVIG Dosage

Patient	IgG, mg/dL	IgA, mg/dL	IgM, mg/dL	Trough IgG, mg/dL	Dosage of IVIG
1	35	1	65	613	500 mg/kg/4 wk
2	152	<25	<17	921	600 mg/kg/3 wk
3	<194	<31.3	<27	874	600 mg/kg/3 wk
4	141	<22.5	<18.3	956	600 mg/kg/3 wk
5	250	42	32	958	400 mg/kg/4 wk
6	<153	<22	<17	849	400 mg/kg/3 wk
7	<300	<50	<25	779	500 mg/kg/3 wk
8	187	<25	< 17	550	400 mg/kg/4 wk
9	124	9	24	759	600 mg/kg/3 wk
10	<145	<25.4	<16.8	683	600 mg/kg/3 wk
11	125	<50	<50	652	500 mg/kg/4 wk
12	139	6.67	17.2	906	400 mg/kg/4 wk
13	<153	<25	<21	688	500 mg/kg/3 wk
14	117	6	10	658	600 mg/kg/4 wk
15	141	23	17	550	600 mg/kg/4 wk
16	229	42	17	849	600 mg/kg/3 wk
17	271	<24	<15	1110	500 mg/kg/3 wk
18	212	1	23	931	500 mg/kg/3 wk
19	<140	<25	<17	920	400 mg/kg/4 wk
20	33.3	6.67	17	312	800 mg/kg/2 wk
21	<153	<22	<17	New diagnosis	500 mg/kg/3 wk
22	<138	<25	<18	740	500 mg/kg/4 wk
23	<134	<22.1	106	671	1 g/kg/4 wk

Abbreviations: Ig, immunoglobulin; IVIG, intravenous immunoglobulin.

Table 5. Absolute Lymphocyte Counts per Cubic Millimeter in Peripheral Blood and Isohemagglutinin Titers

Patient	$CD3^+$ T	$CD4^+$ T	$CD8^+$ T	$CD19^+$ B	$CD16^+56^+$ (NK Cell)	Blood Group	Isohemagglutinin Titer
1	985	405	485	121	80	A Rh positive	Negative
2	1178	410	683	410	34	AB Rh positive	Not evaluated
3	1315	529	721	64	32	O Rh positive	Anti-A 1/2 positive anti-B negative
4	1685	512	1024	85	256	A Rh positive	Negative
5	1030	399	565	11	33	A Rh positive	Negative
6	868	478	402	130	43	O Rh positive	Anti-A and anti-B 1/4 positive
7	1378	583	654	230	212	B Rh positive	Negative
8	–	–	–	–	–	NA	Not available
9	518	148	362	98	98	A Rh negative	Negative
10	1829	499	977	104	83	A Rh positive	Negative
11	1785	294	1490	20	78	B Rh positive	Negative
12	5200	800	4200	500	200	O Rh positive	Anti-A 1/2,

Continued

							Anti-B 1/4 positive
13	1003	239	718	11	91	O Rh positive	Anti-A 1/4, anti-B 1/2 positive
14	438	46	383	5	18	A Rh positive	Negative
15	1000	540	430	100	20	NA	Not available
16	590	203	346	1	41	B Rh positive	Anti-A 1/2 positive
17	5694	1694	3999	542	271	O Rh positive	Anti-A 1/4, anti-B 1/2 positive
18	263	60	198	124	23	O Rh positive	Anti-A 1/4, anti-B 1/8 positive
19	985	240	687	34	69	O Rh positive	Negative
20	2229	691	1435	179	77	AB Rh positive	Not evaluated
21	972	409	614	712	665	A Rh positive	Anti-B 1/32 positive
22	1127	282	751	282	394	A Rh positive	Anti-B 1/8 positive
23	910	653	203	64	53	A Rh positive	Negative

Abbreviations: NA, not available; NK, natural killer.

6 patients showed increased $CD8^+$ T lymphocyte counts. There were no statistically significant differences for $CD3^+$, $CD4^+$, $CD8^+$ T lymphocyte, or $CD19^+$ B lymphocyte counts between patients with bronchiectasis and those who did not have this complication (P=0.526, P=0.418, P=0.275, P=0.597). Clonality in T cells was detected by T-cell receptor gene rearrangement analysis and a polyclonal B-cell pattern on lymph node biopsy in 1 patient (patient 12) with significant lymphocytosis. However, 2 years later this patient developed B-cell lymphoma. The other patient (patient 17) showed oligoclonality by T-cell receptor repertoire analysis in peripheral blood T cells.

Discussion

We found a median diagnostic delay of 15 (1-32) years for females and 8 (1-31) years for males, thus indicating insufficient recognition of immunodeficiency by primary care physicians. Upper and lower respiratory tract infections were the main reason patients sought medical help in our series.

We could not find a statistically significant association between presence of bronchiectasis at the time of diagnosis and length of diagnostic delay. Four patients developed bronchiectasis while receiving IVIG replacement therapy to treat the disease.

Obstructive and restrictive pulmonary function defects, which sometimes lead to respiratory failure, are the main causes of morbidity and mortality in patients with CVID [10,11]. Occasionally, lymphocytic interstitial pneumonia may develop, leading to progressive fibrosis, restrictive pulmonary insufficiency, and death [12]. Spirometry revealed obstructive, restrictive, and combined respiratory function defects in our series. About 50% of patients had decreased DL_{CO} values. Some patients presenting an obstructive pattern by spirometry showed decreased DL_{CO} values suggestive of a defect in the alveolocapillary membrane.

The most frequent HRCT findings other than bronchiectasis in our series were mediastinal lymphadenopathy, peribronchial cuffing, ground-glass abnormality, bronchiolectasis, mosaic oligemia, fibrosis, and nodules, all of which are compatible with findings in the literature [11,13]. In 3 patients with parenchymal lung disease characterized by nodules accompanied by either ground-glass abnormality or mosaic patterns on HRCT, neutrophils were found to be predominant or increased in bronchoalveolar lavage fluid. Polymorphonuclear leukocytes play an important role in granuloma formation [14]. T_H17 cells and γΔ T cells have been implicated in recruitment of polymorphonuclear leukocytes and granuloma formation through production of IL17 [15]. The role of T_H17 and γΔ T cells in the development of granulomatous disease and interstitial lung disease in CVID requires further analysis.

Granulomatous disease due to dysfunction of the target organ is one of the main causes of morbidity and mortality, and has been reported to occur in 8% to 22% of patients with CVID [16]. Granulomas can be found outside the lungs, for example in lymph nodes, bone marrow, liver, skin, spleen, kidneys, gastrointestinal tract, and even the brain [10,16]. In some cases, granulomatous lesions may accompany lymphocytic interstitial pneumonia. This condition is known as granulomatous lymphocytic interstitial lung disease and has been shown to shorten survival in CVID [17]. In our series, 2 patients were considered to have granulomatous and/or lymphocytic interstitial lung disease on the grounds of HRCT findings. Although the condition was not confirmed by biopsy in 1 of these cases, corticosteroid therapy was implemented. Two patients were found to have liver granuloma on biopsy, and 1 developed cirrhosis and portal hypertension 15 years later. More patients may have had liver granuloma, although this is difficult to determine, as some declined further analysis by biopsy.

About 25% of patients with CVID develop autoimmune diseases [1,2]. The pathogenesis of these conditions remains unclear, although several mechanisms have been proposed, including genetic background, molecular mimicry, decreased and dysfunctional regulatory T-cell compartment, and mannose binding lectin polymorphisms [18,19,20,21]. Granulomatous disease, increased immature B lymphocyte counts, and decreased isotype-switched memory B cell percentages have all been found to be relevant to autoimmunity [22,23]. In our series, 3 patients had autoimmune disease.

Patients with CVID have a tendency to develop both hematological and solid tumors, with non-Hodgkin lymphoma and gastric carcinoma being the most common [1,2]. The risk of lymphoma has been reported to be 30 to 259 times higher in patients with CVID [24,25]. Lymphoma is usually of B-cell origin [1]. In recent years, mucosa-associated lymphoid tissue lymphoma has been reported to occur in CVID [1,26]. Lymphoma has been reported in some cases of CVID with lymphocytic interstitial pneumonia; therefore, biopsy is recommended in order to make a definitive diagnosis [27]. In our series, 3 patients developed a malignant neoplasm, and in 2 of these, the diagnosis was diffuse B-cell lymphoma.

About 20% of patients with CVID present gastrointestinal symptoms [1]. The most reported conditions are giardiasis, nodular lymphoid hyperplasia, *H pylori* infection, enteropathy resembling celiac disease, inflammatory bowel disease, and intestinal granulomatous disease [1,28,29]. Inflammatory bowel disease has been shown to occur in about 6% of patients with CVID [1]. In most patients with diarrhea, routine culture does not usually yield growth [30]. However, specific and complex tests might be necessary to reveal the causal agent. In some patients with CVID, cytomegalovirus has been detected in biopsy specimens [28].

In most patients, giardiasis was demonstrated by fecal examination and/or biopsy. We administered long-term metronidazole (3 months) to patients with nodular lymphoid hyperplasia and clinical findings of malabsorption in the presence of giardiasis; however, most patients experienced recurrences.

In our sample, endoscopy revealed that 42% of patients had duodenal lymphoid hyperplasia, which is a frequent finding in CVID and is considered a risk factor for lymphoma [25]. Biopsy revealed *H pylori* in 42% of patients, and this result is consistent with that of other authors [31]. As *H pylori* has been associated with mucosa-associated lymphoid tissue lymphoma, eradication is suggested [26,30,32]. Given that the risk of gastric carcinoma has been reported to be 50 times higher in patients with CVID than in the general population, endoscopy should be considered part of the routine evaluation, as patients are often asymptomatic [30].

Duodenal villous atrophy is another frequently detected biopsy finding. About 31% of patients with CVID in whom iron deficiency and malnutrition are the main accompanying features have been found to have this abnormality [30]. The absence of hyperplastic crypt epithelia and the paucity of plasma cells in the intestinal lamina propria are the main features that help in the differential diagnosis of villous atrophy mimicking celiac disease in patients with CVID [28,30]. Autoantibody (antigliadin and anti-endomysial) titers are not considered reliable when attempting to establish a diagnosis in patients with CVID [28,32]. The response rate to a gluten-free diet has been reported to be 50% in these cases [30]. In our series, villous atrophy suggestive of celiac disease was detected in 1 patient, who did not respond to a gluten-free diet.

One patient suffering from chronic diarrhea was diagnosed with ulcerative colitis. Lymphocytic colitis, collagenous colitis, and colitis similar to that observed in graft-versus-host disease have all been reported in patients with CVID [28], although pathogenesis remains unclear. Increased IL-12 and IFN-γ production has been observed in the lamina propria mononuclear cells of patients with inflammatory bowel disease and CVID [33]. One patient in our series was diagnosed with eosinophilic gastroenteritis; to our knowledge, this is the first report of such a case.

Higher doses of IVIG have been found to be beneficial in controlling recurrent infections [34]. Therefore, we mainly administered 600 mg/kg of IVIG every 3 weeks in patients with pulmonary complications and observed a decrease in the requirement for antibiotics and hospitalization. This finding is consistent with those reported in the literature. However, we had difficulty in controlling sinusitis in some patients, even when trough IgG levels were satisfactory. One patient underwent surgery for sinusitis due to an unsatisfactory response to long-term antibiotic therapy.

Prophylactic antibiotic therapy has been suggested for CVID patients with bronchiectasis and in whom recurrent infections could not be controlled [10]. However, there are no data on the efficacy of antibiotic prophylaxis in preventing pulmonary damage in patients with CVID. Additionally, the likelihood and frequency of antibiotic resistance have not been addressed in patients with CVID taking antibiotic prophylaxis. Prophylaxis with erythromycin was unable to decrease the frequency of lower respiratory tract infection in any patients; clarithromycin was successful as prophylaxis in 1 patient. Macrolides and quinolones were chosen due to their effectiveness against *Mycoplasma* species, which is one of the main causes of respiratory and urogenital tract infections in patients with CVID.

In conclusion, CVID is a highly heterogeneous disease.

In some patients, the gastrointestinal tract is the most affected system, whereas in others, pulmonary manifestations predominate. Occasionally, both systems may be affected. Genetic background could be responsible for this predilection. We experienced difficulty in controlling upper or lower airway symptoms in some patients, even in those with high trough IgG levels, and continuous antibiotic therapy or surgery for sinusitis was necessary. The other salient finding in this series was the high frequency of decreased bone mineral density and osteomalacia with low vitamin D levels in some cases.

Regular IVIG therapy and antibiotic prophylaxis do not seem to play a protective role in the development of granulomatous and inflammatory complications. More comprehensive studies based on immunohistological analysis are needed in order to understand pathogenesis and tailor treatment. As CVID is a multisystemic disease with many clinical manifestations that limit quality of life, patients should be followed by a multidisciplinary team. In our department, patients with CVID are closely monitored by a pulmonologist, otorhinolaryngologist, gastroenterologist, radiologist, and infectious diseases specialist to reduce the risk of serious complications and mortality.

References

1. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34-48.
2. Park MA, Li JT, Hagan JB, Maddox DE, Abraham RS. Common variable immunodeficiency: a new look at an old disease. Lancet. 2008;372:489-502.
3. Cunningham-Rundles C, Radigan L. Deficient IL-12 and dendritic cell function in common variable immune deficiency. Clin Immunol. 2005;115:147-53.
4. Scott-Taylor TH, Green MR, Eren E, Webster AD. Monocyte derived dendritic cell responses in common variable immunodeficiency. Clin Exp Immunol. 2004;138:484-90.
5. Giovannetti A, Pierdominici M, Mazzetta F, Marziali M, Renzi C, Mileo AM, De Felice M, Mora B, Esposito A, Carello R, Pizzuti A, Paggi MG, Paganelli R, Malorni W, Aiuti F. Unravelling the complexity of T cell abnormalities in common variable immunodeficiency. J Immunol. 2007;178:3932-43.
6. Cunningham-Rundles C, Radigan L, Knight AK, Zhang L, Bauer L, Nakazawa A. TLR9 activation is defective in common variable immune deficiency. J Immunol. 2006;176:1978-87.
7. Fasano MB, Sullivan KE, Sarpong SB, Wood RA, Jones SM, Johns CJ, Lederman HM, Bykowsky MJ, Greene JM, Winkelstein JA. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. Medicine (Baltimore). 1996;5:251-61.
8. Mechanic LJ, Dikman S, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. Ann Intern Med. 1997;127:613-7.
9. Spickett GP. Current perspectives on common variable immunodeficiency (CVID). Clin Exp Allergy. 2001;31:536-42.
10. Busse PJ, Farzan S, Cunningham-Rundles C. Pulmonary complications of common variable immunodeficiency. Ann Allergy Asthma Immunol. 2007;98:1-8.
11. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. QJM. 2002;95:655-62.
12. Davies CW, Juniper MC, Gray W, Gleeson FV, Chapel HM, Davies RJ. Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A. Thorax. 2000;55:88-90.
13. Tanaka N, Kim JS, Bates CA, Brown KK, Cool CD, Newell JD, Lynch DA. Lung diseases in patients with common variable immunodeficiency: chest radiographic, and computed tomographic findings. J Comput Assist Tomogr. 2006;30:828-38.
14. Seiler P, Aichele P, Bandermann S, Hauser AE, Lu B, Gerard NP, Gerard C, Ehlers S, Mollenkoph HJ, Kaufmann SH. Early granuloma formation after aerosol Mycobacterium tuberculosis infection is regulated by neutrophils via CXCR3-signalling chemokines. Eur J Immunol. 2003;33:2676-86.
15. Nembrini C, Marsland BJ, Kopf M. IL-17-producing T cells in lung immunity and inflammation. J Allergy Clin Immunol. 2009;123:986-94.
16. Ardeniz O, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. Clin Immunol. 2009;133:198-207;
17. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol. 2004;114:415-21.
18. Yu GP, Chiang D, Song SJ, Hoyte EG, Huang J, Vanishsarn C, Nadeau KC. Regulatory T cell dysfunction in subjects with common variable immunodeficiency complicated by autoimmune disease. Clin Immunol. 2009;131:240-53.
19. Fevang B, Yndestad A, Sandberg WJ, Holm AM, Müller F, Aukrust P, Froland SS. Low numbers of regulatory T cells in common variable immunodeficiency: association with chronic inflammation in vivo. Clin Exp Immunol. 2007;147:521-5.
20. Brandt D, Gershwin ME. Common variable immune deficiency and autoimmunity. Autoimmune Rev. 2006;5:465-70.
21. Mullighan CG, Marshall SE, Welsh KI. Mannose binding lectin polymorphisms are associated with early age of disease onset and autoimmunity in common variable immunodeficiency. Scand J Immunol. 2000;51:111-22.
22. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99:1544-51.
23. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M, Hernandez M, Detkova D, Bos PR, Poerksen G, von Bernuth H, Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-van der Cruyssen F, Le Garff M, Debre P, Jacobs R, Jones J, Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE, Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M, Oksenhendler E, Peter HH, Warnatz K. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111:77-85.
24. Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothil JF, Thompson RA. Prospective study of cancer in patients with hypogammaglobulinemia. Lancet. 1985;1:263-6.
25. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S,

Lieberman P. Incidence of cancer in 98 patients with common variable immunodeficiency. J Clin Immunol. 1987;7:294-9.
26. Desar IM, Keuter M, Raemaekers JM, Jansen JB, van Krieken JH, van der Meer JW. Extranodal marginal zone (MALT) lymphoma in common variable immunodeficiency. Neth J Med. 2006;64:136-40.
27. Kohler PF, Cook RD, Brown WR, Manguso RL. Common variable hypogammaglobulinemia with T-cell nodular lymphoid interstitial pneumonitis and B cell nodular lymphoid hyperplasia: different lymphocyte populations with a similar response to prednisone therapy. J Allergy Clin Immunol. 1982;70:299-305.
28. 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.
29. Onbası K, Günşar F, Sin A, Ardeniz Ö, Kokuludağ A, Sebik F. Common variable immunodeficiency (CVID) presenting with malabsorption due to giardiasis. Turk J Gastroenterol. 2005;16:111-3.
30. Khodadad A, Aghamohammadi A, Parvaneh N, Rezaei N, Mahjoob F, Bashashati M, Movahedi M, Fazlollahi MR, Zandieh F, Roohi Z, Abdollahzade S, Salavati A, Kouhi A, Talebpour B, Daryani NE. Gastrointestinal manifestations in patients with common variable immunodeficiency. Dig Dis Sci. 2007;52:2977-83.
31. Zullo A, Romiti A, Rinaldi V, Vecchione A, Tomao S, Aiuti F, Frati L, Luzi G. Gastric pathology in patients with common variable immunodeficiency. Gut. 1999;45:77-81.
32. Luzi G, Zullo A, Iebba F, Rinaldi V, Sanchez Mete L, Muscaritoli M, Aiuti F. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. Am J Gastroenterol. 2003;98:118-21.
33. Mannon PJ, Fuss IJ, Dill S, Friend J, Groden C, Hornung R, Yang Z, Yi C, Quezado M, Brown M, Strober W. Excess IL-12 but not IL-23 accompanies the inflammatory bowel disease associated with common variable immunodeficiency. Gastroenterology. 2006;131:748-56.
34. Eijkhout HW, van Der Meer JW, Kallenberg CG, Weening RS, van Dissel JT, Sanders LA, Strengers PF, Nienhuis H, Schellekens PT, Inter-University Working Party for the Study of Immune Deficiencies. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: a randomized, double-blind, multicenter crossover trial. Ann Intern Med. 2001;135:165-74.

Manuscript received July 10, 2009; accepted for publication September 30, 2009.

Ömür Ardeniz, MD

Ege University Medical Faculty
Department of Internal Medicine Division
of Allergy and Clinical Immunology
Bornova, 35 100
İzmir/TÜRKİYE
E-mail: tanmehomu@yahoo.com