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Common variable immunodeficiency from the perspective of rheumatology

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ABSTRACT

Aim: Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by impaired B cell differentiation and immunoglobulin production. In addition to increased susceptibility to infection, patients with CVID have an increased tendency to autoimmune disease. Immune dysregulation in these patients may lead to granulomatous disease, malignancy, allergy and autoimmune manifestations. In this study, it was aimed to increase the awareness of rheumatologists about the main signs and symptoms of CVID.

Material and Method: Adult patients followed in the rheumatology department between January 2015 and September 2021 were included in the study. Demographic and clinical characteristics (infections, pulmonary and extrapulmonary granulomatous involvement, autoimmune manifestations), laboratory and imaging findings and treatments of the patients were analyzed.

Results: Ten adult patients with CVID were included in the study. At least one autoimmune manifestation was observed in 80% of the patients. In the follow-up period, 40% of the patients developed arthritis. Involvement of lower extremity joints such as knee and ankle was more prominent. While all patients were given 0.8 g/kg/3 weeks of intravenous immunoglobulin, 80% required immunosuppressive therapy for autoimmune manifestations.

Conclusion: Autoimmune diseases can be seen in patients with CVID, and sometimes this may be the first presentation of CVID. Heterogeneous clinical findings of the disease may lead to delay in diagnosis. Clinicians should be more careful about the different manifestations of CVID to avoid delay in diagnosis.

Keywords: Common variable immunodeficiency, arthritis, autoimmunity

INTRODUCTION

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency. Its prevalence has been reported as 1/20,000-50,000 (1). However, the prevalence is probably underestimated due to heterogeneous clinical presentations of the disease and low level of clinician awareness. CVID is characterized by low serum immunoglobulin (Ig) levels, decreased specific antibody response to polysaccharide and/or protein antigens, and increased episodes of infection in young adulthood (2). In addition to the increased susceptibility to infection, patients with CVID have a high propensity for autoimmune disease. Immune dysregulation in these patients may lead to granulomatous disease, malignancy, allergies, and autoimmune manifestations (3). Autoimmunity affects more than 30% of patients with CVID (4-6) and the likelihood of autoimmune disease in patients with CVID increases with age. Autoimmune diseases may be the first presentation of CVID (5, 7). Autoimmune disorders can be seen such as rheumatologic (systemic lupus erythematosus, rheumatoid arthritis, sicca syndrome, vasculitis), hematologic (immune thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia), dermatologic (alopecia, psoriasis, vitiligo), endocrinologic (hyperthyroidism, hypothyroidism), ophthalmologic (uveitis, scleritis), pulmonary (lymphocytic interstitial pneumonia) and/or gastrointestinal (inflammatory bowel disease, primary biliary cholangitis, autoimmune hepatitis, pernicious anemia, atrophic gastritis) (8). Patients are followed up in consultation with hematology, rheumatology, ophthalmology, dermatology, endocrinology and/or gastroenterology specialists for autoimmune findings.

The incidence of rheumatic disease in patients with CVID is between 5-13% (9,10). Musculoskeletal findings were observed before the diagnosis of immunodeficiency in 35% of patients with CVID who had rheumatic disease (4). In addition, rheumatological findings appear earlier than other autoimmunities. Therefore, it is critical to

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increase the awareness of rheumatologists about the main signs and symptoms of CVID and reduce the delay in diagnosis and treatment.

MATERIAL AND METHOD

The study was carried out with the permission of Dokuz Eylul University Faculty of Medicine, Non-invasive Clinical Ethics Committee (Decision No: 2022/01-28). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Adult CVID patients followed in the rheumatology-immunology outpatient clinic between January 2015 and September 2021 were included in the study. Patients were classified as CVID according to the new diagnostic criteria defined by Ameratunga et al. (11). Demographic data of the patients such as age, gender, age of symptom onset, age at diagnosis and delay in diagnosis, infections (such as sinopulmonary, gastrointestinal, genitourinary, soft tissue infections), pulmonary and extrapulmonary granulomatous involvement, autoimmune manifestations, and their treatments were investigated. Hemogram, serum Ig levels, acute phase reactants, and autoantibody profiles such as antinuclear antibody (ANA), extractable nuclear antigen antibodies (ENA), rheumatoid factor (RF), anti-cyclic citrulline peptide (anti-CCP), antineutrophil cytoplasmic antibody (ANCA) were evaluated. Low-titer autoantibody positivity due to defect in specific antibody response and hypogammaglobulinemia in patients with CVID was considered significant for the diagnosis of autoimmune disease in the presence of a appropriate clinical presentation (12).

RESULTS

Ten patients who were referred to the rheumatology outpatient clinic and followed up since 2015 were included in the study. The gender distribution of the patients was similar and the median age was 38±10.0 (min 23, max 57) years. The mean time to CVID diagnosis was 123.5±89.3 months. All patients had a history of sinopulmonary infection. A total of 40% of the patients had gastrointestinal tract infection. On the other hand, other infections (genitourinary, soft tissue, etc.) were observed in seven patients. In the examination of the chest X-ray and/or high-resolution computed tomography of the patients for pulmonary involvement, pulmonary nodules in three patients, bronchiectasis in three patients, lymphocytic interstitial pneumonia in one patient, and cavitation in one patient were detected. Half of the patients had extrapulmonary granuloma. In 80% of the patients, at least one autoimmune manifestation was observed. Autoimmune disorders such as lymphocytic interstitial lung disease, autoimmune neutropenia, thyroiditis, atrophic gastritis, scleritis, uveitis, alopecia, chronic ileitis, colitis, sicca syndrome and arthritis were seen in this study. The demographic and clinical characteristics of the patients are summarized in **Table 1**.

Table 1. Autoimmune manifestations of common variable immunodeficiency patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age/Sex	36/F	43/F	40/M	25/M	23/M	36/M	41/M	57/F	35/F	48/F
Symptom duration (years)	12	11	11	4	17	12	11	13	12	7
Diagnosis duration (years)	6	11	8	3	17	10	9	1	11	2
Sinopulmonary infection	+	+	+	+	+	+	+	+	+	+
GI infection	-	+	-	+	-	+	+	-	-	-
Other infections	+	+	-	+	+	-	+	+	-	+
Pulmonary Involvement	lymphocytic ILD	nodule	*bronchiectasis	-	-	bronchiectasis	bronchiectasis cavitation	nodule	nodule	-
Extrapulmonary Granuloma	brain parenchyma, bone marrow, liver, spleen, skin	liver, spleen	-	renal°, liver	-	**bone	-	•lymph node	-	-
Autoimmune manifestations	-	monoarthritis, chronic ileitis	oligoarthritis, atrophic gastritis, chronic ileitis	alopecia, thyroiditis, bilateral anterior uveitis	-	oligoarthritis, autoimmune neutropenia, chronic ileitis, kounis syndrome	oligoarthritis, autoimmune neutropenia	oligoarthritis, thyroiditis, sicca syndrome, recurrent scleritis	colitis	-
Cirrhosis of the liver	+	+	-	-	-	+	-	-	-	-
Lymphadenopathy	+	+	+	+	-	+	+	+	+	+
Splenomegaly	+	+	+	+	-	+	+	-	+	-
Immunosuppressive Treatment	Steroid, AZA, CSA, Adalimumab	Steroid	Steroid, SSZ	Steroid, MMF, CYC	-	Steroid, SSZ, MTX, LEF, CSA	Steroid	Steroid, MTX, AZA, CSA	Steroid, AZA	-

Abbreviations: AZA-azathioprine, CSA-cyclosporine, CYC-cyclophosphamide, F-female, GI-gastrointestinal, ILD-interstitial lung disease, LEF-leflunomide, M-male, MTX-methotrexate, SSZ-sulfasalazine, *right lower lobectomy, ** right foot 5th toe enucleation, •mediastinoscopic lymph node biopsy ° interstitial granulomatous nephritis

Allergic manifestations may also be seen in CVID and one patient had kounis syndrome (allergic angina). Three patients had chronic ileitis, while one patient had colitis. When the abdominal imaging was evaluated, cirrhotic appearance was observed in the liver in three patients. One of the patients who developed cirrhosis was decompensated with ascites. Arthritis (one monoarthritis, three oligoarthritis) was observed in 40% of the patients during the follow-up period (**Figure 1**). In patients with CVID, lower extremity joint involvement such as knee and ankle was more prevalent. Magnetic resonance imaging performed in one patient due to persistent toe pain revealed a 1x4x2 cm multiloculated cystic lesion (**Figure 2**). Granulomatoid reaction was detected in the histopathological examination. In one patient, ANA was positive with a titer of 1/100-1/320 and a speckled pattern, but his clinical presentation was not compatible with connective tissue diseases. Immunological markers such as ANA, ENA, ANCA, RF, and anti-CCP in other patients were negative. Sarcoidosis in one patient and peripheral spondyloarthritis (SpA) in another patient was considered at the first admission to the outpatient clinic; however, it was found to be CVID in the follow-up period. While all patients were given 0.8 g/kg intravenous immunoglobulin for 3-week periods, 80% required immunosuppressive therapy for autoimmune manifestations. A patient with interstitial granulomatous nephritis was undergoing 3/7 hemodialysis. One of the patients died of Pneumocystis Jiroveci pneumonia.

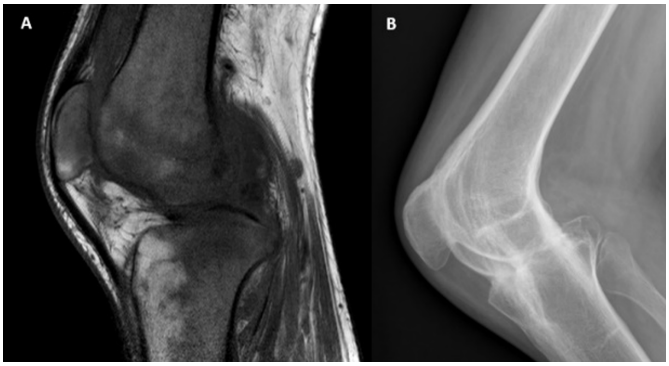

Figure 1. a. Subchondral bone marrow edema is present on the femoral and tibial surfaces adjacent to the joint. There is effusion in the joint space and lymph nodes are seen in the popliteal fossa **b.** The left tibiofemoral and patellofemoral joints are markedly narrowed.

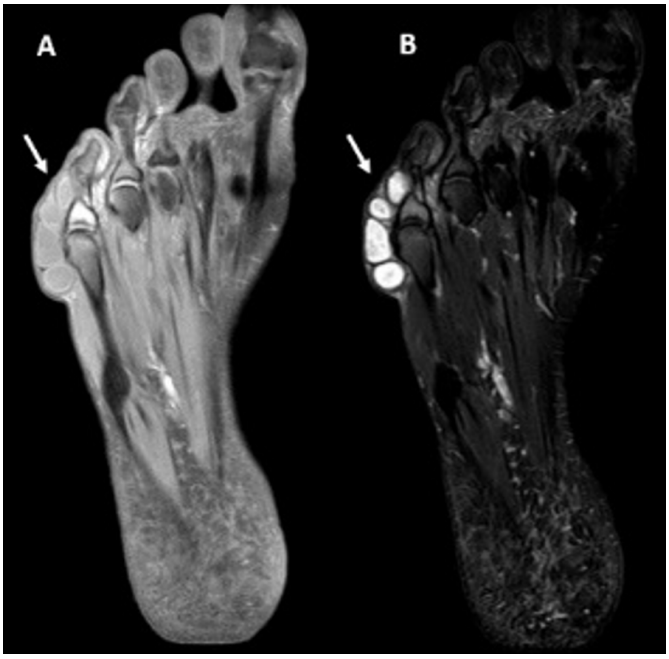

Figure 2. A sharply contoured multiloculated cystic lesion of approximately 1x4x2 cm, starting from the distal 5th tarsal bone and extending to the distal 1st proximal phalanx.

DISCUSSION

CVID is a primary immunodeficiency disease characterized by hypogammaglobulinemia, recurrent infections, and various complications. Due to the heterogeneous clinical manifestations of the disease, a delay of 6-7 years is observed in the diagnosis (13, 14). In this study, the mean time from symptom onset to the diagnosis was 27.6±24.0 months. Although the gender distribution is equal in patients with CVID, the frequency of rheumatic disease is approximately 3 times higher in women (4). In this study, however, there was no relationship between gender and the presence of arthritis.

In our study, autoimmune disorders related to different disciplines such as arthritis, alopecia, cytopenia, atrophic gastritis, ileitis, colitis, lymphocytic ILD, uveitis, scleritis, and thyroiditis were detected. The coexistence of immunodeficiency and autoimmunity seems paradoxical, leading to difficulties in the management of autoimmune complications of patients. Autoimmunity in patients with CVID has been associated with polyclonal lymphocytic infiltrative disorders, increased serum IgM levels, decreased IgE values, and decreased isotype-altered memory B cell counts (15). A wide range of rheumatological presentations can be observed in patients with CVID. Peripheral spondyloarthritis was initially considered in a male patient who presented with arthritis in the large joints of the lower extremities but was diagnosed with CVID during the follow-up period. In a study conducted in Spain, autoimmune/inflammatory manifestations were observed in one-third of 33 patients with CVID, and 6% of the patients were diagnosed with SpA (16). One of our patients was misdiagnosed as sarcoidosis because of non-caseating granuloma of the liver and lung, diffuse adenopathy, and splenomegaly. Differentiating between the granulomatous variant of CVID and sarcoidosis may also be difficult due to their overlapping clinical characteristics (17).

In the literature, it has been reported that patients with CVID are more prone to juvenile idiopathic arthritis (JIA) (18), Sjogren's syndrome (SS) (19), and systemic

lupus erythematosus (SLE) (20). In fact, coexistence of CVID and SLE is rare and the relationship between them is complex. In the case reports in the literature, the diagnosis of CVID was made after the diagnosis of SLE. When hypogammaglobulinemia occurs, some improvement may be observed in SLE presentations of some patients; however, some autoantibodies (such as ANA, anti-DNA and anticardiolipin) may be permanent despite decreased serum Ig. Moreover, it should also be kept in mind that hypogammaglobulinemia may be associated with immunosuppressive agents used in the treatment of SLE. However, hypogammaglobulinemia does not improve when immunosuppressive therapy is discontinued (21). Rheumatoid-like polyarthritis occurs in 1-10% of patients with CVID (22). In this study, polyarthritis was not observed in any of the patients, and oligoarthritis was found in 30% of the patients. In a study evaluating 248 patients with CVID, there were 2% RA, 0.8% SLE, 1.6% JIA, and 1.2% vasculitis cases (23). In the study by Resnick et al. (24) the prevalence of RA was 3.2% (n=15). It was identified that CVID patients with JRA had higher levels of transitional B cells than patients with other autoimmune complications (3). The frequency of this polyreactive transitional B cell increases 3.4 times in patients with active and treatment-naïve RA compared to the control group (25).

The risk of mortality was 11 times higher in CVID patients with non-infectious complications. Presence of chronic lung disease, lymphoma, hepatitis, gastrointestinal inflammatory disease is associated with worse survival (24). In this study, one patient died due to Pneumocystis Jiroveci pneumonia.

Inclusion of the patients referred to the rheumatology outpatient clinic only, small sample size, having a single center are limitations of the study. Further prospective multicenter studies with more patients are needed.

CONCLUSION

Autoimmune diseases can often be seen in patients with CVID, and sometimes this may be the first presentation of CVID. Rheumatological findings usually appear earlier than other autoimmunities, therefore, it is very important to increase the awareness of rheumatologists about this issue for accurate diagnosis and to prevent delay in treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dokuz Eylul University Faculty of Medicine, Noninvasive Clinical Ethics Committee (Decision No: 2022/01-28).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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