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Case Report

Follicular Lymphoma Secondary to Common Variable Immune Deficiency- A Mini Review

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Introduction

Common Variable Immunodeficiency (CVID) is a rare immunodeficiency characterized by low serum immunoglobulin G, A, and/or M levels with loss of antibody production. Common variable immunodeficiency is the most common cause of primary immunodeficiency after selective IgA deficiency in adults. Adults are often diagnosed between the ages of 20-40 [1]. The range of clinical symptoms is wide, including acute and chronic infections, inflammatory and autoimmune diseases, increased incidence of cancer and lymphoma. For all these reasons, the phenotype of the disease is both heterogeneous and complex. The lymphomas seen in CVID are usually extranodal, originating from the B lymphocyte. Unlike lymphomas seen in other congenital immune deficiencies, it occurs in the 4th to 7th decade of life, that is, at a later age [1,2]. The case we reported here, was found to be CVID after the development of lymphoma.

Case

A 47-year-old male patient with sequelae of meningitis and mental retardation and no known comorbidity was admitted to the hospital for the first time with the complaint of a rapidly appearing swelling in the neck. Submandibular and preauricular lymph nodes were palpated. Excisional lymph node biopsy was performed, and he was referred to the Hematology outpatient clinic for further examination and treatment upon the result of high-grade B-cell lymphoma. His vital signs were stable at admission to the service. But he was hypoxic and tachypneic. We started him on nasal O_2 supply. On physical examination, submandibular, periauricular, axillary, cervical and inguinal lymphadenopathies were palpated. On lung auscultation, respiratory sounds were decreased in both lungs, and rales were present in the right lung base. His laboratory findings are shown in Table 1. In neck MRI, cortical thickness increased, conglomerate lymph nodes filling the entire cervico-jugular chain in the neck and reaching 4x3 cm, especially in the supraclavicular area, were detected. In the abdominal and chest CT of the case, mediastinal and bilateral axillary localized multiple lymph nodes, the largest of which tends to cluster about 25 mm in diameter, pleural effusion up to 36 mm wide in the right lung, multiple solid mass lesions in the lung approximately 74 x 47 mm in the right lung and 77 x 56 mm in the left lung. Two lower bronchi were found to be occluded due to lesions. Submassive hepatosplenomegaly and multiple conglomerated lymph nodes of 2-3 cm in diameter under the diaphragm were also detected.

Firstly, we planned to pathological revision of excisional lymph node biopsy. The old lung images of the patient were examined and round pneumonias were seen. When the patient's history was questioned more carefully, it was said that he had frequent lower respiratory tract infections. Immunoglobulin levels were requested for primary immunodeficiency and panhypogammaglobulinemia was detected (Table 1). To exclude secondary causes of hypogammaglobulinemia; RF, C3, C4, serum total kappa and serum total lambda levels, serum and urine immunofixation electrophoresis were requested. No other underlying cause was found. There were findings considered as sequelae in brain imaging and images in paranasal areas that may be compatible with sinusitis. He was diagnosed with CVID. We started IV immunoglobulin to the patient.

WBC	7.91 10^3/µL	**T.PROTEIN**	45 g/L **(L)**
RBC	4.8 10 (6) / µL	**ALBUMIN**	32 g/l **(L)**
HGB	12.5 g/dL **(L)**	**CRP**	82 mg/L **(H)**
HCT	37.4 % (L)	**PROCALCITONIN**	0.14 µg/L
PLT	293 10^3 µL	**ESR**	23 mm/h **(H)**
MCV	77.9 Fl **(L)**	**APTT**	28.6 s
MCH	26 pg	**PT SEC**	16.5 s
INR	1.25	**ANTI-HCV**	NEGATIVE
D-DIMER	1.57 µg/mL FEU	**ANTI-HIV**	NEGATIVE
Ig A	1.44 g/L	**ANTI-HBc IgM**	NEGATIVE
Ig G	5.9 g/L **(L)**	**ANTI-HBc IgG**	NEGATIVE
Ig M	0.13 g/L **(L)**	**HBs Ag**	NEGATIVE
Ig G1	4.73 g/L	**GLUCOSE**	121
Ig G2	1.24 g/L **(L)**	**UREA**	25 mg/dL
Ig G3	0.27 g/L	**FERRITIN**	197.0 µg/L
Ig G4	0.33 g/L	**FOLATE**	7.0 µg/L
VITAMIN B12	494 ng/dL	**ANA**	NEGATIVE
KREATININ	0.67 mg/dL	**FT3**	2.3 ng/dL
BUN	11.68 mg/dL	**FT4**	1.10 ng/dL
AST	21 U/L	**TSH**	2.10 m IU/L
ALT)	9 U/L	**IRON (SERUM)**	23 µg/dL (L)
ALP	152 U/L	**TOTAL IRON BINDING**	320 µg/dL
GGT	20 U/L	**CALCIUM**	8.6 mg/dL
TOTAL BILIRUBIN	0.35 mg/dL	**PHOSPHOR**	4.1 mg/dL
DIRECT BILIRUBIN	0.11 mg/dL	**SODIUM**	138 mmol/L
LDH	416 U/L **(H)**	**POTASSIUM**	4.25 mmol/L

Table 1: Laboratory findings of the patient.

Grade 2 follicular lymphoma was reported after pathological re-examination of the cervical lymph node. The pathologist stated that there was atypical granulomatosis in the lymph node and also suggested that the immunodeficiency be checked for the underlying cause. Bone marrow biopsy and PET-CT imaging were performed to examine the lymphoma. Since pulmonary lesions seem suspicious for lung malignancy, we also performed tru-cut biopsy from the dominant pulmonary nodule. PET-CT was consistent with previous imaging. There were also nodules uptaking FDG in intermuscular and subcutaneous fatty planes. There are foci of FDG uptake in the skeletal system. There was no follicular lymphoma involvement in the bone marrow or any other sign of hematological disease. Pathological examination of pulmonary nodules was also reported as B-cell lymphoma.

The patient was accepted according to Ann Arbor staging as stage 4 follicular lymphoma secondary to CVID. FLIPI score was 4, high. Even if he had indolent lymphoma, he had three Gelf criterias (pleural effusion, compression symptoms of lymph nodes, bulky disease) and high FLIPI score. Thereupon, the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine,

prednisolone) chemotherapy regimen was started. Intermediate PET-CT was seen after 4 cycles of R-CHOP. His response was close to complete remission, and his treatment was completed to 6 R-CHOP cycles. Complete remission was achieved in PET-CT taken at the end of the treatment (Figure 1). During the treatment period, IVIG was continued and the case was not complicated by infection. We planned to give the patient immunotherapy with rituximab every 3 months for 2 years. We also recommended that he receive IVIg supplementation every three weeks.

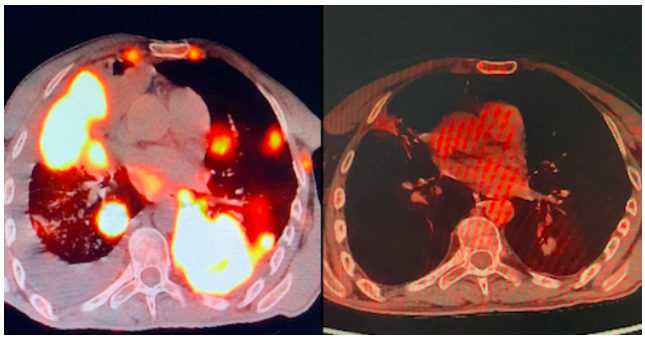

Figure 1: Pre and post-treatment PET-CT findings of the patient.

Discussion

Common variable immunodeficiency is rare disorders with a wide and heterogeneous clinical spectrum. It includes syndromes of hypogammaglobulinemia characterized by marked reductions in two or three major immunoglobulin isotypes (IgG, IgA, and IgM), often associated with insufficient antibody production and defects in cell-mediated immunity [1,2]. While precise definitions vary, consensus groups include CVID as a significant decrease in IgG (≥2 standard deviations below mean for age) with a significant decrease in IgA (usually) or one or both of the IgM isotypes and/or lack of or weak antibody response to vaccines or microbial diseases [3,4]. Antibody responses are commonly examined by determining IgG responses to 2 or more protein vaccines (tetanus or diphtheria toxoids; Haemophilus conjugate; measles, mumps, and rubella vaccines), as well as lack of responses to pneumococcal polysaccharide vaccines. Extensive antibody testing is not recommended at very low immunoglobulin levels (below 200 mg/dl). However, if serum IgG levels are between 450-600 mg/dl or if the serum IgA level is slightly low, the consensus recommends more extensive evaluation [1].

Peripheral blood flow cytometry analysis is very useful for immunophenotyping circulating B lymphocytes. $CD27^+$ memory B cells, but especially IgD-$CD27^+$ isotype-switched memory B cells, are decreased [5]. The diagnosis of CVID obviously requires the exclusion of other causes of hypogammaglobulinemia [6]. In our case, we detected low serum immunoglobulin levels. We checked the other etiological reasons but we detected none of them. We couldn't examine lymphocyte subgroups and counts by flow cytometry. According to severity of CVID, the presentation time of the disease and first clinical presentation of the disease can be variable every individual. Depending on the severity of CVID, the time of onset of the disease may vary from individual to individual. Sanchez L. et al. showed that pediatric-onset CVID patients present with more septic complications, growth retardation, compared to adult-onset cases. Adult patients had more non-infectious manifestations of CVID such as autoimmune phenomenon, lymphoma and other malignancies. Also, there was no remarkable differences for serum Ig levels and lymphocyte counts [7]. Follicular lymphoma was not the patient's first clinical history. However, he did not receive a diagnosis of CVID until he developed lymphoma. We learned from other family members that the patient had frequent infections. One of them was childhood meningitis and there was cognitive loss after meningitis. We thought that he didn't respond to pediatric age vaccines. Because of this, purulent meningitis occurred.

Lymphoproliferative disorders are common in CVID. Gastrointestinal lymphoid hyperplasia and/or splenomegaly are found in at least 20% of the patients with CVID [8]. Sometimes, this feature makes the clinicians confused. Our patient had multiple lymphadenopathy and submassive splenomegaly. Also, he had no B symptoms. His cognitive retardation was another challenge to clarify whether the emerging findings were new or old. Lymph nodes usually have atypical or reactive lymphoid hyperplasia, but granulomatous inflammation may also be present. The absence of plasma cells and the presence of ill-defined germinal centers in lymphoid tissues are expected histopathological findings in CVID [9]. Considering that patients with CVID may have unusual lymphoid structures in which characteristic borders are lost, it is important that biopsies be reviewed by an experienced pathologist. Because the presence of clonal lymphocytes alone is not enough for the diagnosis of lymphoma, these cells can already be found in the lymphoid tissues of patients with CVID showing reactive hyperplasia [9]. A recent study showed that patients with CVID exhibit abnormal clonal expansions of unmutated or naive B cells relative to healthy control individuals, regardless of whether they have been previously diagnosed with a B-cell neoplasm [10]. Sander et al noted that although altered nodal architecture within lymph nodes and florid lymphoid hyperplasia in extra-nodal regions in patients with CVID can mimic lymphoma, the vast majority of cases are benign [11].

To ensure a diagnosis of lymphoma, the same tissues should be examined for B- and T-cell clonality using fluorescent markers, cytogenetic and/or molecular analysis. In lymph nodes with B-cell infiltrates, examination for EBV-encoded RNAs by in situ hybridization should be performed. This issue is further complicated by the fact that studies of B-cell gene rearrangement in patients with CVID can be misleading because these patients are known to generate subtle clonal populations of B- and

T-cells due to chronic infections and impaired antibody response [8,5,12]. Sometimes, neither clonality studies by IHC, ISH, flow cytometric immunophenotyping, nor EBV status by ISH were able to distinguish indolent proliferations from malignant neoplasms. Overinterpretation, with an inappropriate emphasis placed on clonality studies, may lead to the overtreatment of these already-immunocompromised patients with cytotoxic chemotherapy regimens, which would put them at an unnecessary risk for infectious complications, therapy-related myeloid neoplasms, and/or bone marrow failure [12]. The risk of lymphoma in CVID is estimated to be between 1.4% and 7% [13-16]. In a study of 248 consecutive CVID patients followed for 1-25 years, 23 patients were diagnosed with lymphoid malignancy. Non-Hodgkin lypmphoma developed in 19 patients, Hodgkin's lymphoma in 3 patients, and Waldenström macroglobulinemia in 1 patient [17].

At this point, it should be emphasized that (a) NHL rarely occurs in the pediatric population and (b) in most cases it is usually B-cell type, extranodal, EBV-negative, and is more common in females than males [18,19]. In a study conducted on 98 CVID patients followed for 1-13 years, an 8-13-fold increase in cancer and a 438-fold increase in lymphoma in women was observed in general [19]. An earlier report based on a European cohort of 176 patients found three of the four NHL in women [15]. A meta-analysis of 48 studies with a total of 8123 CVID patients showed the overall prevalence of malignancy to be 8.6%. And also, the prevalence of lymphoma, gastric cancer, and breast cancer in those patients were 4.1%, 1.5% and 1.3% respectively [20]. Gottesman et al. described the occurrence of a peripheral extranodal T cell lymphoma arising in the bone marrow, liver and central nervous system of a patient with CVID. And it was not associated with EBV infection of the lymphoma cells [21]. Recently, Jesus et al. reported a case of CVID associated with hepato-splenic T-cell lymphoma mimicking juvenile systemic lupus erythematosus. Lymphoma cells were CD3 positive and CD20 and lysozyme negative [22]. CD8 positive granulomatous cutaneous T-cell lymphoma is a rare condition that appears to be associated with immunodeficiency, as reported in a retrospective review of four cases by Gammon et al. Patients were characterized by an asymptomatic papulo-nodular rash associated with immunodeficiency [23]. Lung failure has been a leading cause of death amongst CVID patients. Bronchiectasis is present in 25% to 79% of cases. The severity of bronchiectasis correlates with the number of previous lower respiratory tract infections [24].

Histopathologically, patterns of interstitial lung disease may have both lymphocytic and granulomatous features [24,25]. Granulomatous disease is relatively common and occurs in 10% to 15% of patients with CVID. Granulomas seen in CVID are not necrotizing, have a variable pathological appearance, and may be either well-circumscribed or poorly shaped [24]. The necessity of tissue diagnosis should always be kept in mind in selected cases to differentiate lung nodules from malignancy. In one case series, the most common pathological features were lung granulomas. Diffuse lymphoid infiltrates and granulomas may be seen simultaneously in some patients. Rarely, pulmonary fibrosis can be seen in CVID patients [26]. Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) is a recently described interstitial process that is uniquely associated with CVID and CVID-like disorders. Clinical findings are often nonspecific and surgical lung biopsy may be required to establish the diagnosi [27,28]. There are pulmonary MALT lymphoma (BALToma) and pulmonary involvement of other systemic lymphomas [24]. Our case had lots of nodules and masses at the lung. Our first work was the histopathological examination of these nodules. We already knew that granulamatous inflamation is very commonly seen in the lungs of CVID patients and as well as pulmonary malignancy.

Extranodal Marginal Zone Lymphomas (ENZMLs) are an important complication of CVID. They can arise insidiously. Stomach, parotid, lung, orbita and cranium are commonly reported as the origin of ENMZLs [29]. There are also a few Burkitt's lymphoma and Hodgkin's lymphoma cases [30-32]. A few cases of lymphocyte-poor Hodgkin lymphomas have been reported in CVID patients [30]. And, as expected, immunodeficiency syndromes show atypical presentations outside of the classic disease presentations. These patients also respond inadequately to neoplastic manifestations due to immune dysregulation or their unique immune response characteristics. In our opinion, this state may also allow cases to progress. The treatment choice is not different from immuncompromised patients [29-33]. Although our case had low-grade follicular lymphoma, it had more than one treatment indication. There are no previously reported cases of follicular lymphoma in CVID patients. Therefore our patient is unique. We didn't do anything different for the staging and the treatment of the patient. But the outcome was excellent. To handle these kinds of patients is difficult for the clinicians and the pathologists.

Conclusion

Common variable immunodeficiency is an important ve relatively common in primary humoral deficiency syndromes. Especially, in adults clinical manifestations are heterogeneous. So it should be kept in mind when we meet atypical presentations and pathological findings.

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