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【 CASE REPORT 】

Pathogenic *TNFRSF13B* Variant in an Adult Japanese Patient with Common Variable Immunodeficiency

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Abstract:
Common variable immunodeficiency (CVID) is a primary B cell immunodeficiency disorder. Symptoms do not develop immediately after birth, and patients are often diagnosed in childhood and adulthood. These patients often develop autoimmune diseases and malignant tumors. We herein report a 50-year-old woman with severe hypogammaglobulinemia and recurrent respiratory tract infections who was diagnosed with CVID. Target sequencing showed a *TNFRSF13B* heterozygous frameshift variant. The patient had many comorbidities, probably caused by a CVID-induced immune imbalance. Physicians who treat adult patients are often unaware of CVID. CVID should be recognized as a differential diagnosis in hypogammaglobulinemia and recurrent infections.

Key words: primary immunodeficiency, common variable immunodeficiency, hypogammaglobulinemia

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Introduction

Common variable immunodeficiency (CVID) is a primary B-cell immunodeficiency disorder characterized by marked hypogammaglobulinemia that is often diagnosed in adulthood (1-4). Recently, genetic mutations associated with the B-cell maturation, function, and differentiation, such as transmembrane activator, calcium-modulator, and cytophilin ligand interactor (*TACI*), a receptor for B-cell activating factor belonging to the tumor necrosis factor family (*BAFF*), and B-cell maturation antigen (*BCMA*), have been reported in patients with CVID (5-10). Patients with CVID have poor humoral immunity and often experience recurrent and chronic infectious diseases (11, 12). In addition, CVID patients often develop autoimmune diseases and malignant tumors (13-16).

However, while the number of reports on CVID is gradually increasing among pediatric immunologists, this disease is still not well known among physicians treating adult patients (17). Physicians who treat adult patients need to consider this disease as a potential differential diagnosis in the setting of hypogammaglobulinemia and recurrent infections.

We herein report an adult Japanese patient with CVID, multiple sclerosis, hypersensitivity pneumonitis, atopic dermatitis, and chronic rhinitis, as well as several food and drug allergies.

Case Report

A 50-year-old woman was referred to the Hematology Department of Shinko Hospital for the evaluation of severe hypogammaglobulinemia. The patient had experienced sinusitis, bronchitis, and pneumonia many times a year from approximately 40 years old. The causative pathogens are both bacteria and viruses. She was diagnosed with multiple sclerosis, symptomatic epilepsy, hypersensitivity pneumonitis, atopic dermatitis, chronic rhinitis, and dyslipidemia in adulthood. She also developed many allergies in adulthood, including food allergies (milk, egg, chicken, pork, nuts, shellfish, avocado, garlic, kiwi, banana, melon, peach, pineapple, mango, grape, acerola, okra, zucchini, soybean, and

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Table 1. Blood Test Data at the Time of the Diagnosis of CVID.

	Patient data	Normal range		Patient data	Normal range		Patient data	Normal range
WBC	4.40 $\times 10^9$/L	3.30-8.60	PT-INR	0.91		CRP	0.08 mg/dL	<0.14
RBC	4.45 $\times 10^{12}$/L	3.86-4.52	APTT	37.2 s	24-39	$VitB_{12}$	244 pg/mL	233-914
Hb	12.5 g/dL	11.6-14.8	Fib	222 mg/dL	200-400	Folic acid	14 ng/mL	3.6-14.4
Ht	36.9 %	35.1-44.4	AST	17 U/L	13-30	ANA	Negative	
Plt	312 $\times 10^9$/L	158-348	ALT	15 U/L	7-23	CH50	55 CH50/mL	30-46
Neut	65.0 %	46.0-70.0	LDH	126 U/L	124-222	C3	122 mg/dL	73-138
Lymph	16.0 %	30.0-40.0	ALP	81 U/L	38-113	C4	31 mg/dL	11-31
Eosino	6.0 %	3.0-6.0	TP	6.7 g/dL	6.6-8.1	CD4	42.7 %	34-54
Baso	1.2 %	0.0-1.5	Alb	4.2 g/dL	4.1-5.1	CD8	32.4 %	22-39
Mono	11.8 %	4.0-8.0	T-Bil	0.3 mg/dL	0.4-1.5	CD4/CD8	1.32	0.6-2.9
IgG	202 mg/dL	861-1,747	Cre	0.51 mg/dL	0.46-0.99	CD3	77.5 %	61-80
IgA	16 mg/dL	93-393	UA	2.7 mg/dL	2.6-5.5	CD20	7.9 %	9-22
IgM	19 mg/dL	50-269	UN	16 mg/dL	8-20	FLC κ	14.2 mg/L	3.3-19.4
IgE	21 mg/dL	<170	Na	139 mEq/L	138-145	λ	11.0 mg/L	5.7-26.3
IgD	2 mg/dL	<9	K	4.1 mEq/L	3.6-4.8	κ/λ	1.29	0.26-1.65
			Cl	103 mEq/L	98-108	HIV ab	Negative	

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, Neut: neutrophils, Lymph: lymphocytes, Eosino: eosinophils, Baso: basophils, Mono: monocytes, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, TP: total protein, Alb: albumin, T-Bil: total bilirubin, Cre: creatinine, UA: uric acid, UN: urea nitrogen, Na: sodium, K: potassium, Cl: chlorine, CRP: C-reactive protein, $VitB_{12}$: vitamin B_{12}, ANA: antinuclear antibody, CH50: 50% hemolytic unit of complement, C3: complement C3, C4: complement C4, FLC: free light chain, HIV ab: human immunodeficiency virus antibody

red bean), drug allergies (valacyclovir, penicillin antibiotics, and first- and second-generation cephem antibiotics), allergies to latex and alcohol, and hay fever. The patient was completely blinded due to congenital cytomegalovirus chorioretinitis. We were unable to obtain a family history because the patient had been estranged from her entire family since elementary school. The patient did not exhibit any facial or skeletal abnormalities.

At the time of presentation, serum IgG, IgA, IgM, IgE, and IgD concentrations were 202, 16, 19, 21, and 2 mg/dL, respectively (Table 1). The differential leukocyte count was normal. A physical examination, blood tests, and whole-body computed tomography were performed to exclude malignant tumors, infections, acquired immunodeficiency syndrome (AIDS), and systemic lupus erythematosus (SLE). We then discontinued or changed all patients' medications, but hypogammaglobulinemia persisted. We excluded drug-induced hypogammaglobulinemia.

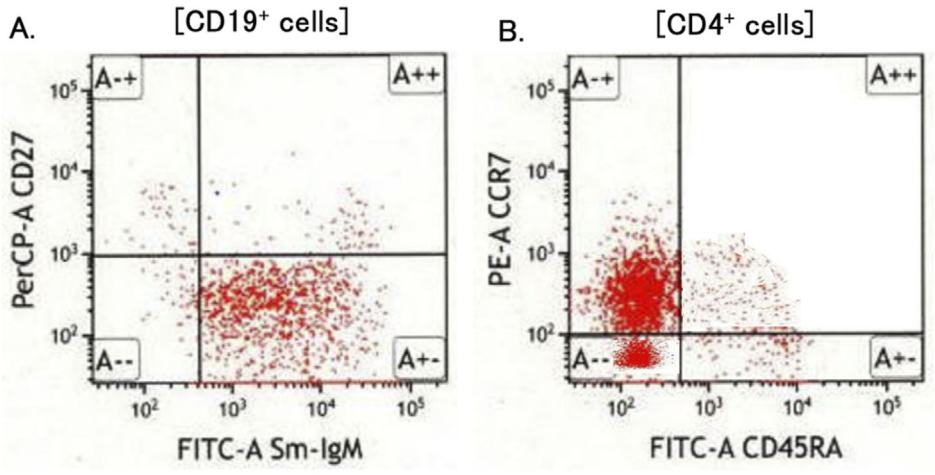
A lymphocyte subset analysis of peripheral blood showed a slight decrease in B lymphocytes and a normal CD4/CD8 ratio (Table 1). A fluorescence-activated cell sorting (FACS) analysis of peripheral blood revealed decreases in class-switched memory B cells ($CD19^+/CD27^+$) and naïve T cells ($CD4^+/CCR7^+/CD45RA^+$) and increases in central memory T cells ($CD4^+/CCR7^+/CD45RA^-$) and effector memory T cells ($CD3^+/CD4^+/CCR7^-/CD45RA^-$; Figure). Proliferation stimulated by phytohemagglutinin (PHA) or concanavalin (ConA) was decreased compared to that of healthy individuals [PHA, stimulation index (SI), 27.2 (normal range, 44-447), ConA, SI, 32.3 (normal range, 45-517)]. According to the cytokine profile, the type 2 helper T cell (Th2)-related cytokine levels were low (Table 2). Targeted capture sequencing of DNA extracted from peripheral blood showed a tumor necrosis factor receptor superfamily 13b (*TNFRSF13B*) heterozygous frameshift variant (p.Asp191GlufsTer46, Supplementary material). Computed tomography (CT) showed no thymoma.

Based on the clinical course and test results, the patient was diagnosed with CVID. She developed anaphylactic shock to subcutaneous immunoglobulin preparations. Therefore, we administered an intravenous immunoglobulin preparation monthly and closely monitored her with regular checkups for the onset of malignant tumors and other autoimmune diseases. Fortunately, the patient developed no additional infections or comorbidities.

Discussion

We herein report an adult Japanese patient with CVID, multiple sclerosis, hypersensitivity pneumonitis, atopic dermatitis, and chronic rhinitis, as well as food and drug allergies.

Evidence-based guidelines are lacking for the diagnosis of CVID (18-20). CVID has heterogeneous clinical and immunological features, which contribute to diagnostic difficulties and delays (21, 22). Severe hypogammaglobulinemia and recurrent infections are key to the diagnosis of CVID (21, 23, 24). However, it is necessary to exclude other diseases, such as malignant tumors, viral infections, AIDS, SLE, and drug-induced hypogammaglobuline-



	Number of plots	% Gated	Age-matched normal range
A − −	57	2.8	1.3–3.6
A + −	1858	92.5	53.5–69.9
A − +	35	1.7	15.8–27.8
A + +	58	2.9	11.4–17.2

	Number of plots	% Gated	Age-matched normal range
A − −	1222	28.5	11.7–18.8
A + −	115	2.7	1.8–4.5
A − +	2597	60.5	29.2–40.2
A + +	357	8.3	41.2–50.0

Figure. A fluorescence activated cell sorter (FACS) analysis in peripheral blood. A: FACS plot of B cells (CD19$^+$) showing that class-switched memory B cells (CD19$^+$/CD27$^+$) decreased (% gated=4.6%, age-matched normal range=30.5-40.2%). B: FACS plot of CD4$^+$ T cells (CD3$^+$/CD4$^+$) showed that naïve T cells (CD4$^+$/CCR7$^+$/CD45RA$^+$) decreased (% gated=8.3%, age-matched normal range=41.2-50.0%), and central memory T cells (CD4$^+$/CCR7$^+$/CD45RA$^-$) and effector memory T cells (CD3$^+$/CD4$^+$/CCR7$^-$/CD45RA$^-$) increased (% gated=60.5% and 28.5%, age-matched normal range=29.2-40.2% and 11.7-18.8%).

Table 2. Cytokine Profile.

	Patient data		Normal range of healthy people	Unit
Th1-related cytokines	IL-1β	1.33	0.63-1.27	pg/mL
	IL-2	19.2	11.5-19.7	pg/mL
	TNF-α	4.5	3.3-4.6	pg/mL
	TNF-β	19.8	12.2-17.7	pg/mL
	IFN-γ	22.2	18.1-22.5	pg/mL
Th2-related cytokines	IL-4	0.8	4.8-7.2	pg/mL
	IL-5	1.0	3.1-4.9	pg/mL
	IL-6	1.1	5.9-8.0	pg/mL
	IL-10	0.7	1.2-2.8	pg/mL

Th1: type 1 helper T cells, Th2: type 2 helper T cells, IL: interleukin, TNF: tumor necrosis factor, IFN: interferon

mia (25). A FACS analysis of peripheral blood helps with the diagnosis. Patients with CVID reportedly often have decreased CD19$^+$/CD27$^+$ and CD3$^+$/CD4$^+$/CCR7$^+$/CD45RA$^+$ cell counts and increased CD3$^+$/CD4$^+$/CCR7$^+$/CD45RA$^-$ and CD3$^+$/CD4$^+$/CCR7$^-$/CD45RA$^-$ cell counts (21, 26-28), and a FACS analysis in the present case yielded similar results. The mechanism responsible for the changes in lymphocyte subsets is yet to be determined (21). Finally, genetic testing, such as chromosomal microarray, Sanger sequencing, and next-generation sequencing, is the most important tool for the diagnosis of CVID (21, 29, 30).

In the present case, targeted capture sequencing of DNA extracted from the peripheral blood showed a *TNFRSF13B* heterozygous frameshift variant (p.Asp191GlufsTer46). This variant is known to be a pathogenic loss-of-function variant and to be associated with CVID (31, 32). *TNFRSF13B* encodes TACI, a receptor for BAFF and a proliferation-inducing ligand (33, 34). TACI is a regulator of humoral immune responses (35, 36), modulates the expression of certain crucial molecules (e.g., inducible T-cell costimulatory ligand and B lymphocyte-induced maturation protein-1) in B cells and plasma cells, and promotes the differentiation and survival of plasma cells (37, 38). Therefore, failures in B-cell differentiation and class-switched antibody production are induced in patients with *TNFRSF13B* variants (32-34).

Our present patient had comorbidities (including multiple sclerosis, hypersensitivity pneumonitis, atopic dermatitis, and chronic rhinitis), many food and drug allergies, and was totally blind because of congenital cytomegalovirus chorioretinitis. Patients with CVID often develop autoimmune diseases owing to humoral immunodeficiency (16). Multiple sclerosis is the most common chronic inflammatory demyelinating disease of the central nervous system and results in various neurological disabilities (39). It is induced by the

production of myelin oligodendrocyte glycoprotein antibody (40). In addition, the local production of lymphoid chemokines and BAFF is responsible for the recruitment and maintenance of B and plasma cells in demyelinating lesions (41). Hypersensitivity pneumonitis, another comorbidity our patient had, is a syndrome caused by sensitization to various environmental antigens that results in a pulmonary immunologic inflammatory process (42). An imbalance between Th1 and Th2 lymphocytes is strongly associated with the onset of hypersensitivity pneumonitis (43). It has been reported that the Th1/Th2 balance shifts towards a Th1-type immune response in patients with CVID (44, 45). We confirmed that the Th2-related cytokine levels were low in our case. A Th1/Th2 imbalance is also known to be associated with atopic dermatitis, chronic rhinitis, and food and drug allergies (46-48). In our case, the patient developed atopic dermatitis, chronic rhinitis, and anaphylactic reactions to several foods and drugs in adulthood and was subsequently diagnosed with CVID. We expect that CVID, multiple sclerosis, hypersensitivity pneumonitis, atopic dermatitis, chronic rhinitis, and many food and drug allergies are closely related. Our patient lost her eyesight due to a congenital cytomegalovirus infection. Immunocompromised patients, especially those with T-cell dysfunction, often develop cytomegalovirus infections (49). Unfortunately, we were unable to obtain her family history, so whether or not her mother had been immunocompromised remains unclear.

Currently, there is no curative treatment strategy for CVID (21). Immunoglobulin replacement therapy, prophylactic oral antibiotics, and vaccination may be effective for infectious risk reduction and consequent hospitalization (50). Hematopoietic stem cell transplantation (HSCT) may be a potentially curative approach; however, the true effect of HSCT is yet to be revealed (21). The only treatment for CVID is prevention of infection with intravenous or subcutaneous immunoglobulin therapy (51). Periodic check-ups for autoimmune disease and malignant tumors are recommended (21, 52). In our case, the patient developed anaphylactic shock due to the subcutaneous immunoglobulin preparations. Therefore, we planned to use an intravenous immunoglobulin preparation monthly. In addition, we closely monitored the patient during regular check-ups for the onset of malignant tumors and other autoimmune diseases.

Conclusion

We encountered a case of an adult Japanese patient with CVID and comorbidities related to autoimmune and allergic diseases. Physicians who treat adult patients tend to be unfamiliar with CVID and should consider this disease as a differential diagnosis in the setting of hypogammaglobulinemia and recurrent infections.

The authors state that they have no Conflict of Interest (COI).

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