〈Case Report〉

Home-based subcutaneous immunoglobulin after switch from intravenous immunoglobulin improved quality of life in pediatric patient with common variable immunodeficiency: A case report

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ABSTRACT Common variable immunodeficiency (CVID) is one of the primary immunodeficiency. Regular immunoglobulin G (IgG) replacement therapy is often performed for patients with CVID.

We experienced a patient who was hospitalized in our hospital for repeated pneumonia and diagnosed CVID at the age of 10 years. He had often been absent from school due to infectious diseases. We were administered intravenous IgG (IVIG) two times and his serum level of IgG became over 1,000 mg/dL. Afterward, he was affected the hand-foot-and-mouth disease one week after discharge. At that time, his IgG level decreased to 751 mg/dL. To maintain stable IgG trough levels, we introduced subcutaneous IgG (SCIG). Since then, his IgG levels remained around 1,000 mg/dL, he has lived without suffering from infectious diseases.

There are some reports that IVIG and SCIG were compared and SCIG was able to obtain a stable IgG trough levels to prevent infection. In addition, because our patient is a mother and child family, it was difficult to visit the outpatient department frequently, so it was desirable to infuse at home.

We experienced a patient who had a stable trough levels with SCIG and improved quality of life, so we report this case with literature reviews.

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Key words：Subcutaneous immunoglobulin, Interavenous immunoglobulin, Common variable immunodeficiency, Quality of life

INTRODUCTION

Common variable immunodeficiency (CVID) is characterized by low levels of immunoglobulins, a lack of B mature lymphocytes especially memory B cells and/or a differentiation into plasma cells that are antibodies producing cells[1]. CVID is one of the primary immunodeficiencies that are easily infectious due to antibodies production deficiency and repeat bacterial infections.

CVID patients require regular immunoglobulin

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G (IgG) replacement therapy to prevent infection for a lifetime[2]. IgG replacement therapy has two routes of administration, intravenous (IVIG) and subcutaneous (SCIG) route. IVIG has problems such as difficulty of venous access, difficulty in obtaining stable IgG lebel and adverse events[3].

We experienced a patient with CVID suffered from hand-foot-mouth disease ,when IgG levels dropped from the peak to the trough after IVIG was introduced. We report that the patient subsequently swiched from IVIG to SCIG for obtaining stable IgG trough level and could prevent infection.

CASE REPORT

A 10-year-old boy was referred to our hospital, because of prolonged fever and cough. He had experienced repeated otitis media, sinusitis and pneumonia since early childhood. Therefore, he had often been absent from school due to infectious diseases. He was never suspected of immunodeficiency because he did not have a family doctor. In addition, since he was a mother-child family and her mother worked, it was difficult to visit clinics frequently. At the age of 10 years, he was repeatedly afflicted with pneumonia and was often hospitalized in other hospital. His serum levels of IgG, IgA, IgM were <100 mg/dl, <6 mg/dl, 12 mg/dl, respectively. Because his immunoglobulin levels are low, he was first suspected of immunodeficiency and was referred to our hospital.

Laboratory data showed low serum antibody titers for specific pathogens despite of each vaccines (Table 1). Regarding T cells, the total number was 1,961/μl, lymphocyte blastoid transformation by phytohemagglutinin was 42,200 cpm (control 302 cpm), and there were no numerical or functional abnormalities. Fluorescence activated cell sorter using peripheral blood revealed CD19+CD20+ mature B cells were normal number (8.9%), and X-linked agammaglobulinemia was denied. IgD-CD27+ swiched memory B cells were markedly decreased (1.7%), and he was diagnosed as CVID (Table 2).

Tazobactam/Piperacillin was administered by intravenous infusion, and IVIG (350 mg/kg) was administered on admission. Fever was reduced on the 2nd hospital day, and pneumoniae could be controlled. IVIG (350 mg/dl) was further administered aiming at IgG 1,000 mg/dl on the 3rd hospital day. His serum level of IgG was 1,269 mg/dl at 4th hospital day (Fig. 1).

After discharge, He was scheduled to received IVIG infusion at 4 weeks interval but suffered from hand-foot-and-mouth disease. The IgG level at that

Table 1. Laboratory data

Peripheral blood		Blood chemistry		Virologic test	
WBC	16,400 /μL	CRP	8.27 mg/dL	CMV IgG (EIA)	3.7
Neut	74.7 %	TP	6.2 g/dL	EBV-EBNA-IgG (EIA)	0.2
Lym	18.2 %	Alb	4.0 g/dL	VZV IgG (EIA)	<2.0
RBC	535×10^4 /μL	T-bil	0.5 mg/dL	Mumps IgG (EIA)	8.7
Hb	13.5 g/dL	AST	17 IU/L	Meales IgG (EIA)	<2.0
Ht	40.2 %	ALT	12 IU/L	Rubella IgG (EIA)	<2.0
Plt	32.4×10^4 /μL	LDH	163 IU/L		
		ALP	880 IU/L	Sputum culture:	
		γ-GTP	15 IU/L	Haemophilus influenzae	
		BUN	7 mg/dL	Urine culture : 48 hour(-)	
		Cr	0.28 mg/dL	Blood culture : 7 days(-)	
		UA	2.8 mg/dL		
		Na	138 mEq/L		
		K	3.9 mEq/L		
		Cl	101 mEq/L		

Table 2. Immunological data

Pheripheral blood		Flow cytometry	
C3	169 mg/dL	Lymph	2,800 / μL
C4	54 mg/dL	CD3+	1,624 / μL
CH50	>58.0 U/mL	CD4+	596 / μL
IgG	<100 mg/dL		
IgA	<6 mg/dL	CD4+CD45RA+	14.1 %
IgM	12 mg/dL	CD4+CD45RO+	7.5 %
IgG2	<20 mg/dL	CD19+	8.9 %
IgE	<1 mg/dL	IgD+CD27-	84.6 %
PHA	42,200 CPM	IgD+CD27+	12.9 %
ConA	41,600 CPM	IgD-CD27+	1.7 %

PHA: lymphocyte blastoid transformation by phytohemagglutinin
ConA: lymphocyte blastoid transformation by ConcanavalinA

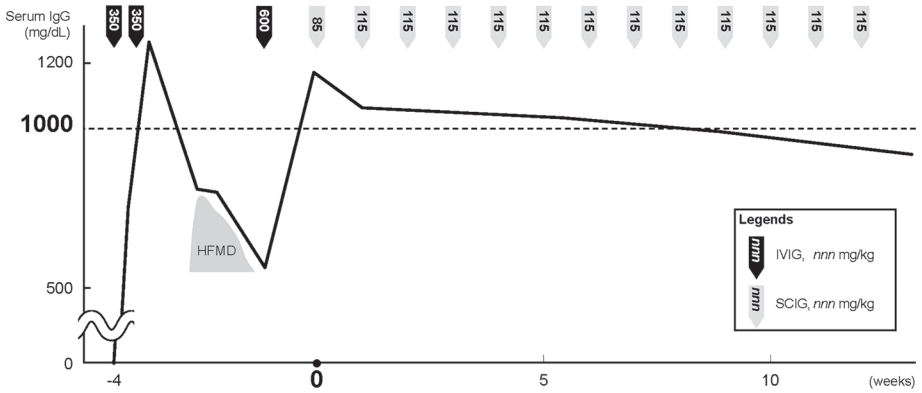

Fig. 1. clinical course : Transition of serum IgG trough levels
IgG: immunoglobulin G, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin

time was 751 mg/dl. He had a prolonged fever for 7 days and generalized vesicles. Stable serum IgG levels were necessary for prevent infection, and he was switched IgG replacement therapy from IVIG to SCIG. He received first SCIG infusion (85 mg/kg) at hospital for safety confirmation followed by home-based SCIG infusion (115 mg/kg) at 1week interval. Since then, the IgG trough level has remained around 1,000 mg/dl, and he has lived without serious infections (Fig. 1).

Genetic analysis using next generation sequencer revealed no causing gene mutations (*ICOS, TNFRSF13B (TACI), TNFRSF13C (BEFF-R)*, CD19, *MS4A1, CR2*(CD21), CD81, IL21, *NFKB1, NFKB2, IKZF1, MSN, PLCG2*) of CVID.

DISCUSSION

CVID is characterized by low levels of immunoglobulins, a lack of B mature lymphocytes especially memory B cells and/or a differentiation into plasma cells that are antibodies producing cells[1]. T cell dysfunction is exhibited in some patient. There were about two hundred patient with CVID reported by nationwide survey of Japan conducted in 2009[4]. Because many patients with CVID develop after age 10 years, CVID occupies an important position as an adult form of immunodeficiency (average age is 20-30 years old). Many patients with CVID have some symptoms by the age of 2-20 years and may be diagnosed in childhood like our patient. Patients with CVID experience recurrent bacterial infections

such as otitis media, sinusitis and pneumonia. Sinopulmonary infection are most commonly reported followed by gastrointentinal infection because of IgA deficiency[5]. One third to a half of patients with CVID develop autoimmune disease or malignancy in their course. The causing genes identified include *ICOS, TNFRSF13B (TACI), TNFRSF13C (BEFF-R)*, CD19, *MS4A1, CR2*(CD21), CD81, IL21, *NFKB1, NFKB2, IKZF1, MSN, PLCG2*. However, monogenic forms count for only 2-10% of patients with CVID[6]. Causing gene was not identified in our patient either.

Patients with CVID require IgG replacement therapy regularly to prevent infections and maintain for their lifetime[2]. IVIG infusions every 3-4weeks are formerly standard practice in Japan, but developing systemic adverse effects of intravenous infusion and difficulty of obtaining venous access had been concerns in pediatric patients. In Japan, SCIG was introduced in 2013 later than other countries. Advantages of SCIG are no need of obtaining venous access, decreased systemic adverse effects and steady stable IgG trough level. Berger M reported that the difference between the peak and trough IgG level was 900 mg/dl for IVIG, 100 mg/dl for SCIG. Adverse effects such as migraine and headache may be associated with rapid change of IgG levels for IVIG[7]. Jolles S et al reported that switching the replacement therapy from IVIG to SCID could improve IgG levels without dose increases and prevented infection[8]. Furthermore, there is a report that switching from IVIG to SCIG raised IgG trough levels and reduce days missed from work/school for infection treatment[2, 9]. In our case, the number of days missed from elementary school has decreased remarkably. Disadvantages of SCIG are frequency of administration weekly and necessity of acquiring skills of subcutaneous infusion by patient's family. Since our patient is a mother-child family, it was difficult to have regular outpatient visits in a short period of time. In our case, home-visit nursing has been introduced as an aid to the family's skill acquisition and assist with administration.

Cunningham-Rundles C reported baseline serum IgG trough level suggested to keep 600-900 mg/dl to prevent infection in CVID[10]. On the other hand, Orange JS reported that patients with primary immunodeficiency required more than 1,000 mg/dl IgG through level to prevent pneumonia[11]. Because our patient had history of pneumonia, we managed to keep 1,000 mg/dl IgG through level.

In conclusion, we experienced a pediatric patient who was diagnosed with CVID at 10 years old and introduced SCIG for prevent infection. Since SCIG is not necessary to obtain venous access and can be administered at home, it was considered useful in children like our case who have difficulty in visiting a clinic in a short period of time due to the home environment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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