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【 CASE REPORT 】

Progressive Massive Splenomegaly in an Adult Patient with Kabuki Syndrome Complicated with Immune Thrombocytopenic Purpura

Toshiki Mushino[1], Takayuki Hiroi[1], Yusuke Yamashita[1], Norihiko Suzaki[2], Hiroyuki Mishima[3], Masaki Ueno[2], Akira Kinoshita[3], Koichi Minami[4], Kohsuke Imai[5], Ko-ichiro Yoshiura[3], Takashi Sonoki[1] and Shinobu Tamura[1]

Abstract:
Kabuki syndrome is characterized by multiple systemic anomalies and intellectual disability. It is complicated with immunodeficiencies and autoimmune disorders. The syndrome is caused by a mutation in the *KMT2D* gene. We herein report a case of a Kabuki syndrome with developing immune thrombocytopenic purpura (ITP) and progressive splenomegaly. Laparoscopic splenectomy was performed and the patients' symptoms quickly disappeared with platelet recovery. After this operation, the patient had no severe complications. A sequence analysis of the *KMT2D* gene identified a pathogenic mutation frequently associated with ITP. Laparoscopic splenectomy is therefore considered to be a good therapeutic option for recurrent ITP and symptomatic splenomegaly with Kabuki syndrome.

Key words: Kabuki syndrome, splenomegaly, immune thrombocytopenic purpura, laparoscopic splenectomy, KMT2D

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Introduction

Kabuki syndrome is a rare congenital disorder that is characterized by intellectual disability and multiple anomalies, including distinctive facial features, skeletal abnormalities, dermatoglyphic abnormalities, and a short stature (1-3). Although first described in Japan, the syndrome has been reported in various ethnic groups. It is an autosomal dominant disorder, in Japan, the incidence is estimated to be one in 32,000 people (4). It occurs sporadically, and its incidence is roughly equal between the sexes (1). A pathogenic mutation of *KMT2D*, which encodes the histone-lysine N-methyltransferase 2D protein, is responsible for most cases with Kabuki syndrome (5, 6). Additionally, genetic mutations of *KDM6A* (lysine-specific demethylase 6A) are found in roughly 5% of all cases (5, 7). These genes, which control histone methylation and epigenetic gene expression, are largely involved in cranial, facial, heart, and brain development. Their functions in the immune system, however, remain unclear (8).

Among the patients with Kabuki syndrome, there is often a dysfunction of adaptive immunity, with the most frequently observed complication being hypogammaglobulinemia (9-12). The clinical features of this disorder resemble common variable immunodeficiency (CVID) with impaired antibody production (9-12). A recent report demonstrated an impairment of terminally differentiated B cells in patients with Kabuki syndrome (10), but the detailed molecular mechanism of this impairment remains unclear. Furthermore, the immune dysregulation occasionally leads to autoimmune hematological disorders, such as immune thrombocytopenic

[1]Department of Hematology/Oncology, Wakayama Medical University, Japan, [2]Second Department of Surgery, Wakayama Medical University, Japan, [3]Department of Human Genetics, Graduate School of Biomedical Sciences, Nagasaki University, Japan, [4]Department of Pediatrics, Wakayama Medical University, Japan and [5]Department of Pediatrics, Tokyo Medical and Dental University, Japan
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Correspondence to Dr. Shinobu Tamura, stamura@wakayama-med.ac.jp

purpura (ITP) or autoimmune hemolytic anemia (AIHA) (9-12). In a recent French patient registry of Kabuki syndrome, the estimated incidences of hypogammaglobulinemia, ITP, and AIHA were reported as 26.0%, 7.3% and 4.0%, respectively (11). Based on the current guidelines, immunosuppression with corticosteroids is the primary treatment for these diseases (13). However, the immune dysregulation associated with Kabuki syndrome can confer difficulties for second-line treatments against these complications, especially surgical procedures such as splenectomy (14, 15). Meanwhile, in CVID patients, when splenectomy was performed for refractory autoimmune cytopenia and suspected lymphoma, overall mortality was reported as 1.6% per patient year (16).

There are a limited number of reports of progressive splenomegaly complicated by Kabuki syndrome with humoral immunodeficiency, and therapeutic splenectomy for these patients remains controversial (15). We herein describe an adult patient with Kabuki syndrome with recurrent ITP and progressive splenomegaly who showed a marked improvement following laparoscopic splenectomy.

Materials and methods

Peripheral blood mononuclear cells (PBMCs) were obtained before splenectomy and were isolated using Ficoll solution (Histopaque-1077; Sigma-Aldrich, St Louis, USA) for each experiment. Soon after PBMC isolation, a multicolor flow cytometry (MFC) analysis was conducted using a BD LSRFortessa (BD Biosciences, San Jose, USA). Genomic DNA was purified from the PBMCs with a NucleoSpin Tissue Kit (Macherey-Nagel, Duren, Germany). Targeted sequencing was conducted using the Illumina MiSeq platform, and the obtained genetic mutations were confirmed by Sanger sequencing (17). The T cell receptor excision circles (TREC) and Kappa-deleting recombination excision circles (KREC) levels in his peripheral blood were measured by real-time PCR (Light Cycler 96 system; Roche, Hague Road, USA) (17, 18). Written informed consent was obtained from the patient and his family. The Institutional Review Board approved the present study (approval number: 57), in accordance with the Declaration of Helsinki.

Case Report

Our patient was born at 36 weeks gestation weighing 4,140 g. At 1 year of age, he was diagnosed with Kabuki syndrome based on distinctive facial appearances. He had mild intellectual disability and additional anomalies, including brachycephaly, large ears, cleft palate, and partial syndactyly. There was no known family history of Kabuki syndrome. At 10 years of age, he underwent pyeloplasty for left hydronephrosis. During adolescents and young adulthood, there were recurring bacterial infections, including otitis media and epidermoid cyst. At 22 years of age, he showed a low serum level of immunoglobulin (Ig) A (15 mg/dL; normal range 110-440 mg/dL). His serum IgG and IgM were within the normal levels at age 22, but they gradually decreased after this period.

At 30 years of age, he presented with bleeding of the oral cavity after dental procedures with profound thrombocytopenia (platelet count of 6.0×10^9/L). Laboratory testing showed hemoglobin levels of 14.1 g/dL, aspartate transaminase (AST) levels of 23 U/L, lactate dehydrogenase (LDH) of 277 U/L, and total bilirubin of 1.7 mg/dL. The serum levels of IgG and IgM were in normal lower limits (819 and 24 mg/dL, respectively), and the serum IgA level remained very low (14 mg/dL). He was clinically diagnosed with ITP and received prednisolone (0.5 mg/kg/day; due to concerns about inefectious complications) and intravenous immunoglobulin (IVIg) therapy for five consecutive days. A bone marrow examination was not performed, because it was considered that prompt treatment initiation was required. Serum anti-Helicobacter pylori IgG antibodies were negative. His symptoms and laboratory data improved soon after these therapies. Prednisolone was discontinued at 9 months after the recovery of the platelet count. Two months after prednisolone discontinuation, laboratory data showed that his platelet count was 124×10^9/L, hemoglobin was 16.9 g/dL, AST was 37 U/L, LDH was 303 U/L, total bilirubin was 1.1 mg/dL, and haptoglobin was below 10 mg/dL. A computed tomography (CT) scan showed a diffusely enlarged spleen (Fig. 1A). He also underwent a positive direct antiglobulin test and a reactive elevation of reticulocyte count of 148×10^9/L. On the basis of there being no symptoms, we took the "watchful waiting" approach. At this time, platelet associated IgG was positive for 95.2% of the platelets according to a flow cytometric analysis.

At 35 years of age, the patient showed hypogammaglobulinemia (serum IgG level was 330 mg/dL; Fig. 2). To prevent opportunistic infections, weekly subcutaneous immunoglobulin (SCIg) therapy was started and his biological IgG level was successfully above 800 mg/dL. To determine the status of adaptive immunity in this patient, before starting SCIg therapy, we used a TREC/KREC assay and a MFC analysis in the peripheral blood (18). The KREC value was 6.0×10^3 copies/μgDNA, which is within the normal range, but the TREC value was very low (<10 copies/μgDNA). Despite normal neogenesis of B cells, a MFC analysis revealed that the proportion of circulating memory B cells had markedly decreased (Fig. 3). Meanwhile, high proportions of both T helper 1 (Th1) and follicular helper T cells (Tfh) were observed, with a normal CD4/CD8 ratio (Fig. 3). These findings suggested that our patient had an impaired terminal differentiation of B cell and a skewing toward Th1 and Tfh cells.

At 36 years of age, he was admitted to our hospital with abdominal pain, appetite loss, and weight loss. A CT scan revealed massive splenomegaly and mild ascites (Fig. 1B), but no significant lymph node enlargement was present throughout the body. Furthermore, thrombocytopenia recurred without bleeding tendency (platelet count was 52×10^9/L). The patient's laboratory data at admission are shown in

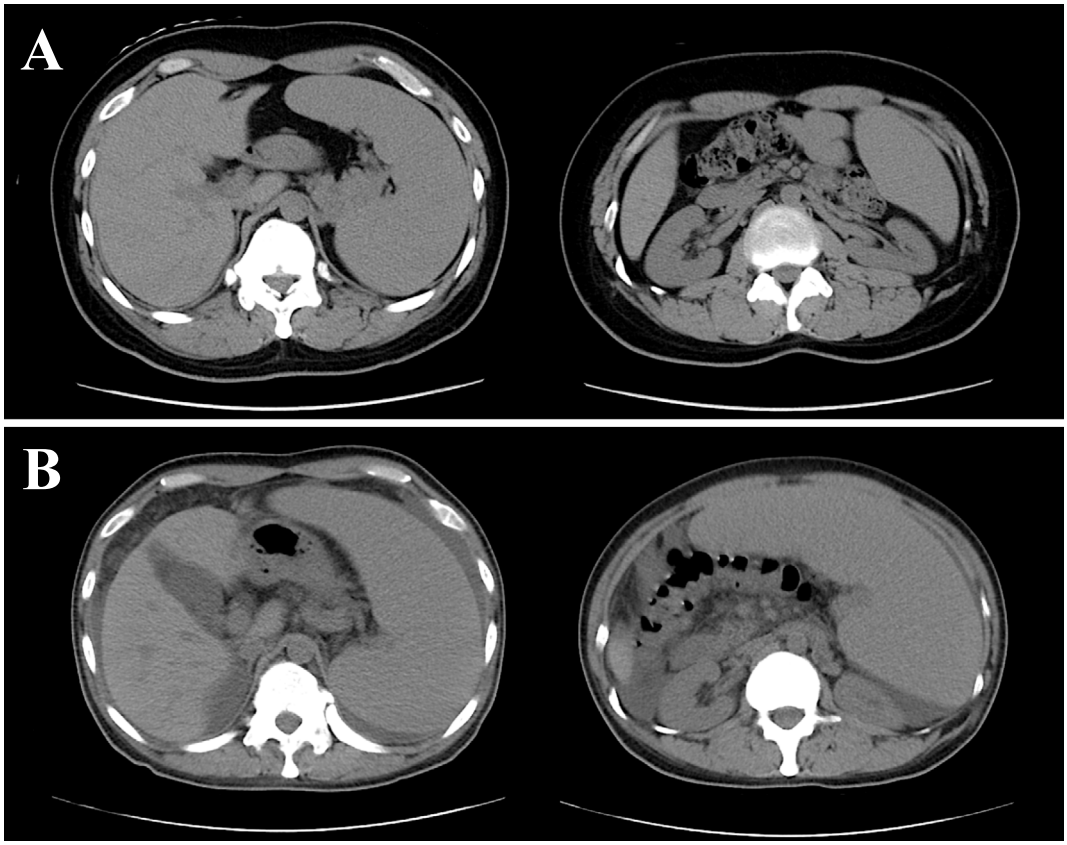

Figure 1. Computed tomography (CT) scan findings (A) three years before splenectomy and (B) just before splenectomy. An abdominal CT scan without contrast material (axial view) just before splenectomy showing marked splenomegaly and mild ascites. There was no mass lesion in the spleen.

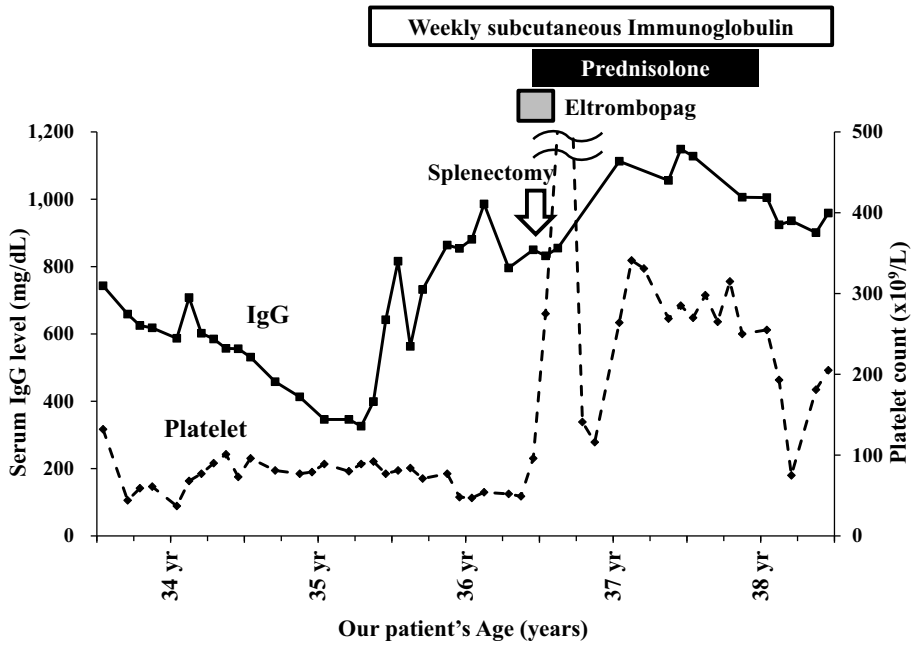

Figure 2. Clinical course. The splenomegaly worsened at 36 years of age accompanied with abdominal pain and appetite loss. Two months after the onset of abdominal symptoms, laparoscopic splenectomy was performed. The platelet count recovered immediately after splenectomy. Eltrombopag was used shortly. PSL was discontinued within one year after initiation. IgG level was slowly decreased, subcutaneous gamma globulin therapy was beginning at 35 years of age. After the initiation of immunoglobulin (Ig) therapy, IgG was increased. Plt: Platelet count, PSL: Prednisolone, EPAG: Eltrombopag

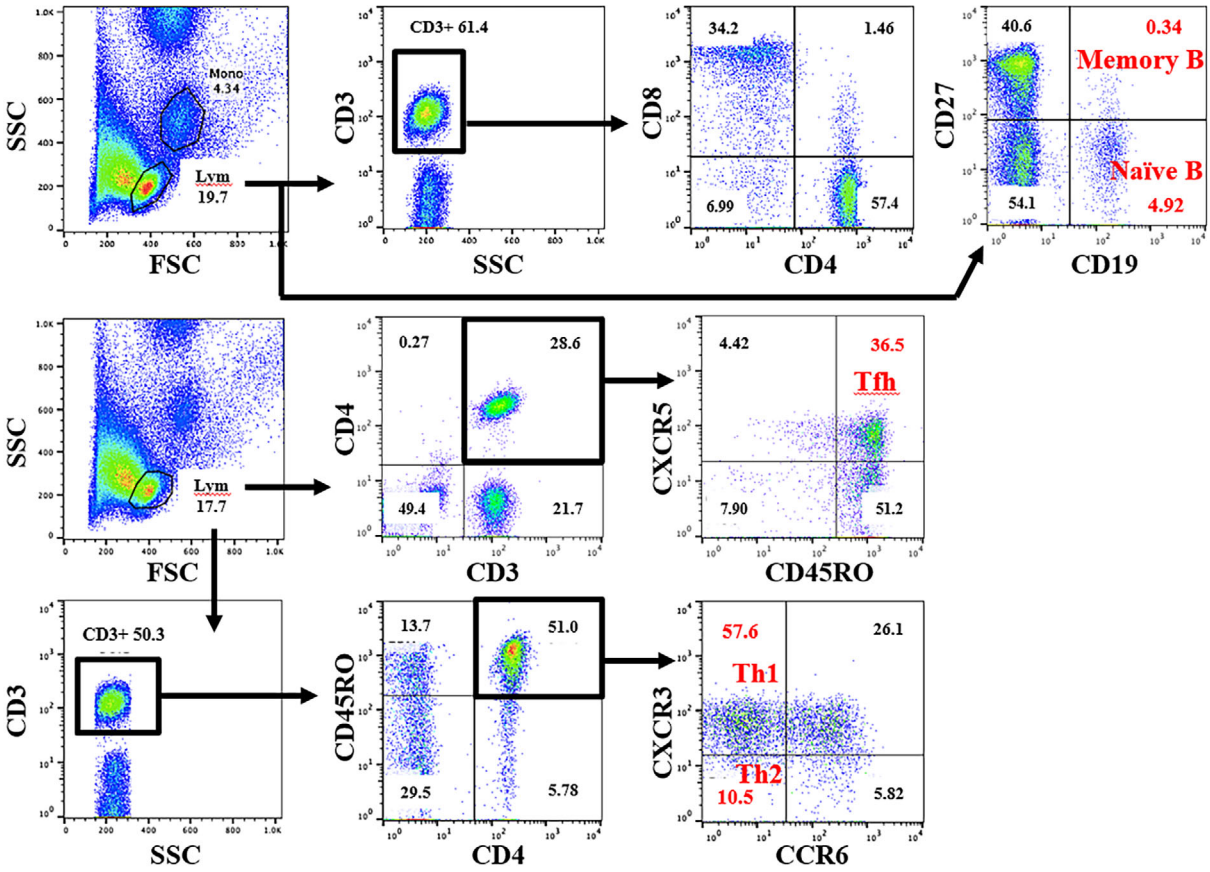

Figure 3. **Multi-color flow cytometry of the characterization of B and T cell-lineage in the peripheral blood mononuclear cells obtained from this patient. T and B cells were identified by gating on $CD3^+$ and $CD19^+$ cells, respectively. Naive and memory B cells were identified based on CD27 expression. Helper T cell (Th) were stained with specific antibody for CD4. Follicular helper T cell (Tfh), Th1, and Th2 were then determined by $CD45RO^+/CXCR5^+$, $CD45RO^+/CXCR3^+/CCR6^-$, and $CD45RO^+/CXCR3^-/CCR6^-$, respectively. Representative gating is depicted. FSC: forward-scatter, SSC: side-scatter**

Table. These data suggested hemolysis and progression to Evans syndrome. The serum soluble interleukin-2 receptor value was 1,430 U/mL. A bone marrow examination showed slight hypercellularity with normal megakaryocytes, consistent with the diagnosis of ITP. Combination therapy with prednisolone (0.5 mg/kg/day) and eltrombopag, a thrombopoietin receptor agonist (TPO-RA), was started with the aim to recover platelets because of the possibility of splenectomy for abdominal symptom relief. Three weeks after the combination therapy, his platelet counts remained at around 50×10^9/L. During this admission, abdominal symptoms associated with massive splenomegaly became very severe, so urgent laparoscopic splenectomy was planned to improve these symptoms and rule out malignant lymphoma. The operation was successful with no postoperative complications. Platelet count was approximately 50×10^9/L before the splenectomy, IVIg therapy was not administered. In addition, platelet transfusion was performed only on the day of the surgery. The 23-valent pneumococcal vaccine was administered 4 weeks before the operation. The pathological findings showed progressive congestion and fibrosis of splenic cords without malignancies such as lymphoma. After laparoscopic splenectomy, his abdominal symptoms disappeared completely, and the platelet count recovered quickly above 100×10^9/L. The administration of eltrombopag could therefore be stopped immediately. The oral administration of prednisolone was discontinued about 1.5 years after initiation, the platelet count and hemoglobin level remained within the normal range. Our patient continues weekly SCIg for hypogammaglobulinemia and has not developed any serious infections after 2 years to date. There has been no development of malignant lymphoma.

Targeted sequencing was later conducted to identify the unique mutations in our patient. We identified a nonsense mutation in exon 48 of the *KMT2D* gene (c.14710 C>T, p. Arg4904X) (Fig. 4), which has been previously reported as a pathogenic mutation (19).

Discussion

Altered immune regulation occurs frequently in patients with Kabuki syndrome and this can lead to recurrent infec-

Table. **Laboratory Data of the Patient at the Second Admission to Our Hospital.**

Complete Blood Count		**Chemistry**		Calcium	8.3 mg/dL
White Blood Cells	2.58 $\times 10^9$/L	Total Protein	5.7 g/dL	Total Bilirubin	1.6 mg/dL
Neutrophil	57.0 %	Albumin	3.7 g/dL	C-reactive Protein	2.00 mg/dL
Eosinophil	0.0 %	Creatine Kinase	87 U/L	IgG	796 mg/dL
Basophil	0.0 %	Aspartate Transaminase	56 U/L	IgA	10 mg/dL
Monocyte	3.0 %	Alanine Transaminase	26 U/L	IgM	14 mg/dL
Lymphocyte	39.0 %	Lactate Dehydrogenase	465 U/L	Haptoglobin	<1 mg/dL
Atypical Lymphocyte	1.0 %	Alkaline Phosphatase	1,042 U/L	sIL-2R	1,430 U/mL
Red Blood Cells	3.39 $\times 10^{12}$/L	γ-Glutamyl Transpeptidase	130 U/L		
Hemoglobin	10.5 g/dL	Cholinesterase	285 U/L	**Coagulation system**	
Hematocrit	32.6 %	Amylase	63 U/L	APTT	33.2 sec
MCV	96.2 fL	Creatinine	0.58 mg/dL	Prothrombin time	12.3 sec
Platelets	52 $\times 10^9$/L	Uric Acid	7.1 mg/dL	Fibrinogen	281 mg/dL
Reticulocytes	7.19 %	Blood Urea Nitrogen	7 mg/dL	D-dimer	0.59 μg/mL
Absolute reticulocyte count	245 $\times 10^9$/L	Sodium	138 mmol/L		
		Potassium	3.7 mmol/L		
		Chloride	103 mmol/L		

Ig: Immunoglobulin, MCV: mean corpuscular volume, sIL-2R: soluble interleukin-2 receptor, APTT: Activated partial thromboplastin time

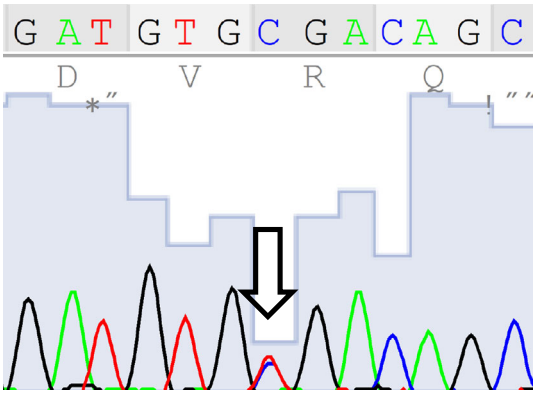

Figure 4. **The Sanger sequencing results for this patient. An electropherogram of exon 48 of *KMT2D* gene in this patient. A heterozygous C>T substitution was confirmed at position c.14710 (arrow), changing an arginine codon (CGA) into a stop codon (TGA) at amino acid position 4904 (p. Arg4904X).**

tion and/or autoimmune disease (10, 11). Consistent with this, our patient presented with an infectious history, including otitis media, and autoimmune hematological disorders. Most patients with the *KMT2D* mutation have IgA deficiency and low levels of other Igs because of impaired terminal differentiation of B cells (10, 11). Furthermore, some patients with Kabuki syndrome exhibit autoimmune hematological disorders, such as ITP and AIHA, typically in childhood and adolescence (9-12). In our patient's serum, a very low level of IgA continued after the first presentation. Meanwhile, the serum levels of IgG and IgM slowly decreased for more than 10 years during adulthood. Notably, ITP recurred, despite of progressive hypogammaglobulinemia. These findings suggest that patients with Kabuki syndrome require close monitoring as they can develop autoimmune hematological diseases throughout their life (10, 11).

Kabuki syndrome has been reported to mimic the clinical phenotype and immune profile associated with CVID, as both are characterized by defective antibody production (9-12). Our patient had autoimmune disease and hypogammaglobulinemia, which were consistent with the clinical features of CVID. Furthermore, the results of the KREC quantification assay and MFC analysis demonstrated that the number of circulating memory B cells in our patient had dramatically decreased, although normal B cell neogenesis was found. A reduction in memory B cells is considered to be a hallmark of CVID (20). An analysis of the T cell phenotype showed increased frequencies of Th1 and Tfh cells, a phenotype that is associated with autoimmune diseases in CVID patients (21, 22). Our patient showed the CVID-like immune dysregulation associated with autoimmune diseases.

Splenomegaly is also common in both Kabuki syndrome and CVID, but most patients are asymptomatic. Accordingly, the development of symptomatic splenomegaly in our patient provided a valuable new clinical insight. There have been cases of lymphoid malignancies in Kabuki syndrome (23), but the increased risk of developing lymphoma in CVID is better known (16, 24). An enlarged spleen in Kabuki syndrome resembling CVID therefore requires the exclusion of lymphoma involvement. Our patient reported weight loss at his second admission, so we kept in mind in the differential diagnosis of malignant lymphoma. He showed exacerbated symptomatic splenomegaly in a short period and exhibited no malignancies from the pathological findings of the spleen. To date, the pathogenesis of the splenomegaly remains unknown. In CVID patients, however, the expansion of $CD21^{low}$ B cells and a reduction of class-switched memory B cells have been associated with splenomegaly (16). We therefore hypothesized that in this patient, B cell immune dysfunction was likely associated with splenomegaly.

The recommended initial treatments for adult patients

with ITP include corticosteroids, TPO-RAs, and high-dose IVIg. Splenectomy has curative effects in many patients with ITP who fail to respond to immunosuppressive drugs, so it is considered to be a second-line therapy. For patients with refractory autoimmune cytopenia, the safety of laparoscopic splenectomy has already been well established. Furthermore, despite existing immunodeficiency, splenectomy has been widely used in CVID patients, mainly for the management of autoimmune cytopenia and the diagnosis of suspected lymphoma, and it does not worsen outcome in these patients (25). However, Torii et al. (15) explained that splenectomy should be avoided for patients with Kabuki syndrome because they are more susceptible to infection throughout life. Furthermore, rituximab is recommended as an alternative option in refractory ITP associated with Kabuki syndrome (14, 15). Nevertheless, we decided to perform laparoscopic splenectomy to improve our patients' abdominal symptoms associated with splenomegaly as well as curative treatment for recurrent ITP and exclusion of splenic malignant lymphoma. The operation was successful, the thrombocytopenia resolved and the patients' abdominal symptoms fully disappeared. Special attention was required, however, to prevent the development of late post-splenectomy infection.

The function of KMT2D mainly depends on conserved C-terminal domains, including a plant homeodomain (PHD), an FY-rich N-terminal (FYRN), an FY-rich C-terminal (FYRC), and a catalytic *Su(var)3-9* enhancer-of-zeste, Trithorax (SET) domain. Kabuki syndrome with ITP has been shown to have pathogenic mutations that affect enzymatic SET domains at its C-terminal cluster (10). Our patient exhibited a missense mutation in exon 48 of the *KMT2D* gene (c.14710 C>T, p. Arg4904X), localized on the PHD of the C-terminus, suggesting potential mutational hotspots. Our findings suggest that it is important to identify pathogenic mutations of the *KMT2D* gene in patients with Kabuki syndrome to predict the potential complications of autoimmune hematological disease such as ITP.

To our knowledge, this is the first detailed description of the management of ITP and splenomegaly in an adult patient with Kabuki syndrome. Laparoscopic splenectomy was conducted safely and successfully for recurrent ITP and symptomatic splenomegaly complicated by Kabuki syndrome.

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

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