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Immunoglobulin-Resistant Kawasaki Disease Associated with Human Parvovirus B19 Infection

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Abstract A 23-month-old female presented with 6 full symptoms of Kawasaki disease (KD) and thrombocytopenic purpura of the lower extremities. Repeated intravenous immunoglobulin normalized the platelet counts, but not improved the activity of intractable KD. Primary infection of human parvovirus B19 (B19V) was determined at the diagnosis of KD based on the hypocomplementemia and the positive tests for anti-B19V IgM antibody. Infliximab therapy led to the complete resolution with no atypical or persistent infection of B19V, or coronary artery lesions. This is the first report of intravenous immunoglobulin-resistant KD associated with the primary infection of B19V. Successful treatment of the B19V-associated KD case suggested a clinical utility of the standard rescue infliximab for the treatment of intravenous immunoglobulin-resistant KD, possibly with concurrent infection.

Abbreviations: B19V: human parvovirus B19, IVIG: intravenous immunoglobulin, KD: Kawasaki disease

Key words: infliximab, Kawasaki disease, parvovirus B19, virus reactivation

Introduction

Human parvovirus B19 (B19V) is a single-stranded DNA virus that preferentially targets the bone marrow erythroblasts. Primary infection of B19V causes erythema infectiosum, arthralgia, and hydrops fetalis. It induces aplastic crisis in patients with congenital hemolytic anemia, and hemolytic crisis with acute hepatic failure in those with Wilson disease.¹ Immunocompromised patients are often affected more severely, and develop prolonged infection or atypical presentation.² B19V might be also involved in the induction and pathogenesis of vasculitis including systemic lupus erythematosus, giant cell arteritis, Henoch-Schönlein purpura, and Kawasaki disease (KD).^{3,4} Immune thrombocytopenic

purpura (ITP) or papular-purpuric gloves and socks syndrome (PPGSS) develops in patients during primary B19V infection, presenting purpuric skin lesions.^{5,6}

KD is an acute, febrile, and systemic vasculitis primarily occurring in infants and young children.⁷ Erythema and edema of hands and feet, which is sometimes painful, are a frequent manifestation of KD at the onset of the disease, and these symptoms last for 1 to 3 days.⁷ The exanthema in KD is polymorphous and nonspecific as skin symptoms. It appears as an erythematous, maculopapular rash, and occasionally a scarlatiniform and micropustular rash.⁷ However, purpura is not common in KD patients. Intravenous immunoglobulin (IVIG) is the first-line therapy for KD, although 15-20% of patients do not

respond to IVIG and are at high risk of developing coronary artery lesions (CAL). There is growing evidence of the efficacy of infliximab (IFX) for the treatment of intractable KD cases.^{8,9} IFX is a chimeric monoclonal antibody against tumor necrosis factor (TNF)- α . This biologic agent is effectively used for the treatment of rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. On the other hand, patients with IFX-therapy have an increased risk of serious infections including viral, fungal and mycobacterial infections because of the attenuating effect of immune responses.¹⁰ Infections and live-attenuated vaccines are a matter of concern in pediatric patients who undergo the biologics therapy.

We first report a 23-month-old girl with B19V-associated IVIG-resistant KD who initially presented purpura in the hip and legs, and successfully underwent IFX therapy. Clinical expression and outcome of the patient with B19V-associated KD are then discussed with respect to the treatment choice of intractable KD.

Case report

A 1-year and 11-month-old female was admitted to our hospital because of antibiotics-resistant high fever for 5 days, erythema of the hands and trunk, conjunctival hyperemia, and redness of the lips under the suspected diagnosis of KD. Purpuric edema in the hip and

legs, and decreased factor XIII activity (46% of normal) initially suggested the diagnosis of allergic vasculitis purpura, despite the low platelet count (86.0×10^9 /L). The patient was previously healthy, and had been born to healthy parents with unremarkable family history.

On admission, physical examination revealed cervical lymphadenopathy, truncal maculopapular rash, and erythema at the site of Bacille de Calmette et Guerin (BCG) inoculation, along with purpuric lesions and edema of the hip and lower extremities (Fig. 1). The constellation of KD symptoms appeared as shown in Fig. 2. These figures were posted with patient's family consent. These fulfilled the diagnostic criteria of complete KD on the 5th day of illness. Complete blood counts showed leukocytes 8.8×10^9 /L, erythrocytes 4.54×10^{12} /L, and platelets 27.0×10^9 /L. Blood chemistries revealed hypoalbuminemia (3.2 g/dL, reference range [rr]: 3.7-4.7), increased levels of aspartate transaminase 44 U/L (rr: 12-34) but not alanine transaminase 21 U/L (rr: 5-43), low levels of sodium (129 mmol/L, rr: 137-147), and increased levels of C-reactive protein (3.45 mg/dL, rr: 0.01-0.14). Coagulation studies revealed normal ranges of prothrombin time (PT%) 80%, activated partial thromboplastin time 35.2 s (rr: 26-41), and increased levels of fibrinogen 410 mg/dL and D-dimer 11.3 mg/mL (rr: <0.5).

IVIG (2 g/kg) and aspirin (30 mg/kg, p.o.)

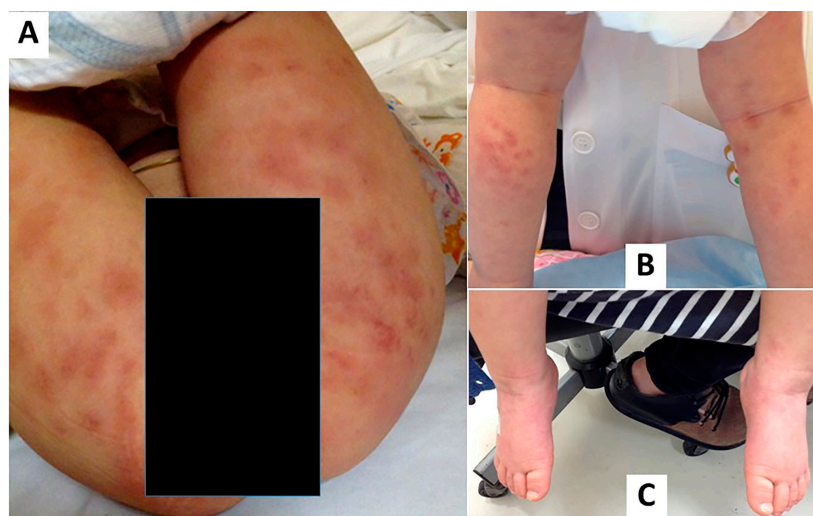


Fig. 1 Purpuric skin lesions and edema in the hip (A), lower legs (B), and feet (C) emerged on the 4th days of illness.

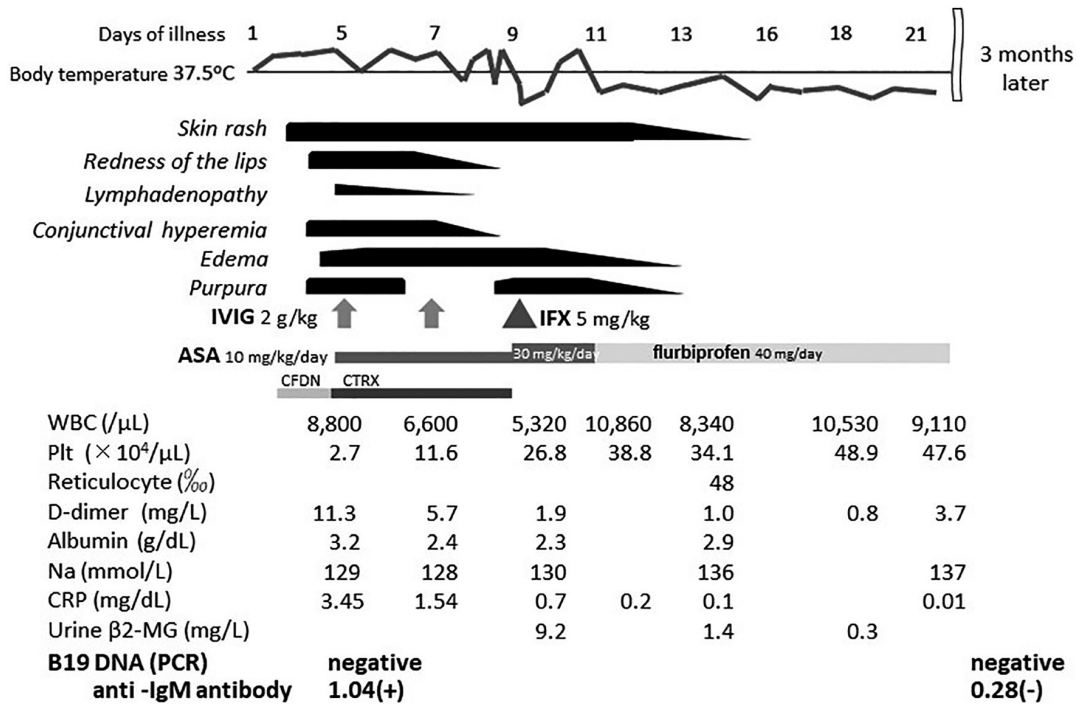


Fig. 2 Clinical course of the patient with refractory Kawasaki disease associated with human parvovirus B19 infection. IVIG: intravenous immunoglobulin, IFX: infliximab, ASA: acetyl salicylic acid, CFDN: cefdinir, CTRX: ceftriaxone

started on the 5th day of KD, led to the increase of platelet counts but not the defervescence. Repeated IVIG on the 7th day of illness normalized the platelet counts. However, high fever continued with the active symptoms of KD. Thrombocytopenia and hypocomplementemia (CH50: <12 U/mL [rr: 30-60], C3 48 mg/dL [rr: 65-135], C4 2 mg/dL [rr: 13-35]) at the onset of illness prompted us to test the B19V infection prior to the initial IVIG therapy. Positive results for anti-B19V IgM antibody but not the virus DNA on the 4th day of illness determined the primary infection (Fig. 2). Later it turned out that antibody value against B19V in immunoglobulin we administered was 7.66 cut off index. Single dose IFX (5mg/kg) was administered as the third line therapy for refractory KD, which led to the complete resolution of KD symptoms. No slapped cheeks or lace-like eruptions in the extremities were observed during the entire course of illness. On the other hand, apparent desquamation of finger tips was found in the patient during the convalescent phase of KD. There was neither recurrence of KD nor reactivation or persistent infection of B19V. We

examined echocardiographic for evaluation of coronary artery, and dilatation of coronary artery was not observed. She is alive and well without CAL one year after the hospital discharge.

Discussion

The etiology of KD remains unknown, but the systemic vasculitis may occur in relation to ubiquitous infectious agents or to unidentified respiratory viruses. Kusuda et al.¹¹ reported that synthetic microbe-associated molecular patterns precipitated the development of KD, in potential association with intestinal microbiota. The genetic susceptibility in Japanese ancestries,¹² together with a triggering infectious agent, could be involved in the KD pathogenesis.¹³ Various microorganisms were reported in association with KD pathogenesis, including *Streptococcus pyogenes*, *Staphylococcus aureus*, Epstein-Barr virus, B19V, influenza virus, and so on.⁷ B19V has long been suggested as a cause of KD because of the vasculitic presentation and immune activation in the affected patients during the convalescent

phase.^{9,10} However, IVIG-resistant KD cases have never been reported in association with B19V infection.

IFX is the effective rescue therapy of IVIG-resistant KD, although the first line treatment of the agent does not warrant the higher utility than IVIG.¹⁴ Adverse events of IFX therapy include infection, demyelinating disease, interstitial pneumoniae, dyshematopoiesis, rhabdomyolysis and infusion reaction. The immunoregulatory effect of TNF-blockers but not IVIG is then a matter of concern in the treatment of KD infants who have comorbid infection or received live-attenuated vaccination. Placental transferred IFX was reported to result in the disseminated infection of BCG in the newborn.¹⁵ Suwannalai et al.¹⁶ reported that the overall infection rates were increased after IFX but not etanercept treatment in patients with rheumatologic diseases. Lee et al.¹⁷ reported that HBV reactivation was found in 8 (1.7%) patients among 468 HBsAg-negative and anti-HBc-positive patients with rheumatic diseases treated with anti-TNF agents. B19V precipitates persistent infection and/or abnormal presentation in children during cancer chemotherapy.^{8,18} There have been a report that IFX was administered as an additional treatment of IVIG to patients of KD who inoculated with live vaccines within 90 days, and they did not cause severe infections.¹⁹ This report refers to the possibility that the antiviral neutralizing antibody contained in IVIG inactivated the vaccine virus and prevented dissemination. There is little information what kinds of primary virus infection expose the IFX-treated infants to the risk of dissemination. Further studies are needed to confirm our observation of a single case with B19V-associated KD with respect to the safety and efficacy of IFX therapy for refractory KD.

Thrombocytopenia, hypocomplementemia and the changing anti-B19V IgM titers determined the primary infection in this patient who fulfilled the diagnostic criteria of complete KD. Purpuric edema in the legs was a unique prodrome of this patient, in the comparison with the reported cases of B19V-associated KD. Distribution and form of the purpuric lesions mimicked those of allergic vasculitis and differed from those of ITP or

PPGSS induced by primary B19V infection.^{5,6} Repeated IVIG improved the platelet counts, but not led to the resolution of KD. It was regrettable that reticulocytes counts were not monitored during the acute febrile phase. On the other hand, B19V DNA was not detected in serum on 4 days of KD. It may raise the possibility that repeated IVIG and low viral load resulted in no reactivation of B19V after IFX therapy. The antibody contained in globulin might have worked to prevent exacerbation of B19V infection. Concurrent infections at the diagnosis of KD make a clinical dilemma on the administration of IFX but not IVIG. Treatment effects of initial IFX therapy did not exceed those of initial IVIG therapy for KD.¹⁴ Antibodies against other bacteria or viruses, such as cytomegalovirus or mumpsvirus, are also included in globulin, so administration of IFX might be safer after administration of immunoglobulin, under the circumstances where infection is considered to be the cause of KD. In this setting, immunomodulation of IFX, cyclosporine-A and high dose corticosteroid may not be recommended as the standard initial therapy for KD, as long as triggering or concurrent infections are not excluded.

Contributions to authorship

Y.I. and S.O. were the principal investigators taking primary responsibility for the paper and wrote the paper. Y.I., K.Y., S.O., Y.S., and R.H. treated the patient. S.O. and S.H. controlled the treatment strategy for refractory KD.

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Conflict of interest

The authors declare no conflict of interest.

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