Case Report

A case of hypocomplementaemic urticarial vasculitis in a child due to coxsackievirus type A9

Mayumi Yamazaki,¹ Kazuko Sugai,¹ Yoshinori Kobayashi,¹
Yoichi Kaburagi,¹ Kazuaki Murashita,² Norimitsu Saito,³ Niino Hitoshi,⁴
Tomoyuki Imagawa,⁵ Hiroyuki Tsukagoshi⁶ and Hirokazu Kimura⁷

Correspondence

Kazuko Sugai
kazgoto@be.mbn.or.jp

¹Department of Pediatrics, National Hospital Organization Yokohama Medical Center, 3-60-2 HarajyukuTotsuka-ku, Yokohama, 245-8575, Japan

²Department of Plastic Surgery, National Hospital Organization Yokohama Medical Center, 3-60-2 HarajyukuTotsuka-ku, Yokohama, 245-8575, Japan

³Department of Dermatology, National Hospital Organization Yokohama Medical Center, 3-60-2 HarajyukuTotsuka-ku, Yokohama, 245-8575, Japan

⁴Department of Pathology, National Hospital Organization Yokohama Medical Center, 3-60-2 HarajyukuTotsuka-ku, Yokohama, 245-8575, Japan

⁵Department of Pediatrics, Yokohama City University School of Medicine, 3-9Fukuura, Yokohama, 236-0004, Japan

⁶Gunma Prefectural Institute of Public Health and Environmental Sciences, 378Kamioiki-choMaebashi, Gunma, 371-0052, Japan

⁷National Institute of Infectious Disease, Infectious Disease Surveillance Center, 4-7-1Gakuen, Musashimurayama, Tokyo 208-0011, Japan

Introduction: We present a rare case of hypocomplementaemic urticarial vasculitis in a 1-year-old girl with a coxsackievirus type A9 (CA9) infection.

Case presentation: At first, we thought that the patient had Kawasaki disease, but a skin biopsy showed overriding evidence of urticarial vasculitis and serum complement levels were severely reduced. Treatment with prednisolone was effective. We isolated and confirmed CA9 from all samples (nasal fluid, serum and stool). We also analysed CA9 genetically.

Conclusion: CA9 may induce systemic small-vessel vasculitis resulting in transient decreases in complements.

Keywords: corticosteroid; coxsackievirus type A 9; enterovirus infection; leukocytoclastic vasculitis.

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Introduction

Urticarial vasculitis is characterized by recurrent episodes of urticaria and by biopsy evidence of leukocytoclastic vasculitis (Wisniewski, 2000). Although urticarial vasculitis is frequently idiopathic, it has been reported to accompany infection, malignancy, connective tissue diseases such as systemic lupus erythematosus, Sjögren's syndrome, viral hepatitis and cryoglobulinaemia, as well as administration of certain drugs (Venzor *et al.*, 2002). Hypocomplementaemic urticarial vasculitis syndrome (HUVS)

is a type III hypersensitivity allergic reaction characterized by urticaria with persistent hypocomplementaemia (McDuffie *et al.*, 1973). HUVS has frequently been described in adults but is very rare in children. We report a case of HUVS diagnosed in a 1-year-old girl in the course of a coxsackievirus type A9 (CA9) infection.

Case report

In August 2012, a 1-year-old girl presented with fever and multiple urticarial rashes and wheals on her face, trunk, back and limbs. Before onset of these symptoms (about 10 days prior to presentation), she had upper respiratory symptoms such as cough, nasal discharge and mild fever, but these disappeared naturally. A skin rash developed and

Abbreviations: CA9, coxsackievirus type A9; CRP, C-reactive protein; C3, complement 3; C4, complement 4; CH₅₀, 50 % complement haemolytic activity; C1q, complement component 1; HUVS, hypocomplementaemic urticarial vasculitis.

was followed by fever. Urticaria was diagnosed by a local doctor, but treatment with an antihistamine was ineffective. She was admitted to the Department of Pediatrics at the National Hospital Organization Yokohama Medical Center for further evaluation.

Essential laboratory data from acute and convalescent phases are shown in Table 1. Her serum complement levels were significantly reduced, although her immune-complex complement component 1 (C1q) level, ($1.5 \mu\text{g ml}^{-1}$) was slightly elevated on admission day. In addition, inflammation markers such as leukocyte counts and C-reactive protein (CRP) levels were significantly elevated. Antinuclear antibody was not detected. Proteinase 3–anti-neutrophil cytoplasmic antibody and myeloperoxidase–anti-neutrophil cytoplasmic antibody were also negative.

Although we started to treat the patient for a bacterial infection using $100 \text{ mg cefazolin kg}^{-1} \text{ day}^{-1}$ and oral $10 \text{ mg clarithromycin kg}^{-1} \text{ day}^{-1}$, urticaria and fever persisted. We had at first regarded her condition as Kawasaki disease, but no symptoms besides fever and rash appeared. When she flexed any of her joints, she complained of pain, indicating that she had arthralgia.

Skin biopsy of her urticarial lesion revealed leukocytoclastic vasculitis with histological changes of early lesions. Permeation of lymphocytes and histocytes with nuclear dusts (the products of the destruction of neutrophil nuclei), eosinophils and neutrophils had occurred around superficial dermal blood vessels and the leakage of the blood cells from capillary vessels was observed (Fig. 1). Because there were no deposits of fibrin in the vascular walls, and because of the large number of nuclear dust particles seen around the small blood vessels, we deduced

Fig. 1. Permeation of lymphocytes and histocytes with nuclear dusts (the products of the destruction of neutrophil nuclei), eosinophils and neutrophils had occurred around superficial dermal blood vessels and the leakage of the blood cells from capillary vessels.

that the lesions were early lesions. No IgG, IgM, complement 3 (C3), complement 4 (C4) or C1q was recognized on immunohistochemical staining. The patient's skin lesions were diagnosed as HUVS. We therefore treated her with $2 \text{ mg prednisolone kg}^{-1} \text{ day}^{-1}$ intravenously, gradually reducing the dose after the urticaria had disappeared. The serum C3, C4 and 50 % complement haemolytic activity (CH_{50}) levels were increased by this treatment (Table 1).

After informed consent was obtained from the patient's parents, we collected specimens by nasopharyngeal swab as well as stool and blood specimens for microbiological examination. We isolated and confirmed CA9 from all samples (nasal fluid, serum, and stool) using human embryo lung fibroblast (MRC-5) cells. Neutralizing antibody against CA9 in the convalescent phase serum was significantly higher than that in the acute phase serum (Table 1). No pathogenic bacteria were detected in the samples using culture or (R)-PCR methods. To genetically analyse the CA9 isolate, we amplified the VP1 coding region (319 nt) of the strain as described elsewhere (Oberste *et al.*, 2000). We performed phylogenetic analysis and evolutionary distances were estimated using Kimura's two-parameter method and phylogenetic trees were constructed using the neighbour-joining method (Kimura, 1980; Saitou & Nei, 1987). The nucleotide identity between the prototype strain of CA9 (GenBank accession no. D00627) and the present strain was 79.6 and 96.2 % at the amino acid level. In the phylogenetic tree, the present strain was located in a cluster with a reference strain (165/Chita/Rus/2010) (Fig. 2). We gradually reduced the quantity of prednisolone to zero. No reappearance of symptoms occurred, and the white blood cell count, CRP and the complement levels were normalized (Table 1).

Table 1. Clinical laboratory data in acute and convalescent phases in the present case

Item	Acute phase (day 1)	Convalescent phase (day 15)
White blood cells (mm^{-3})	21 200	7300
Neutrophils (%)	76	57
Platelet count (mm^{-3})	30.5×10^4	58.5×10^4
Fibrin degradation products (mg ml^{-1})	12.8	2.2
D-Dimer (mg ml^{-1})	9.1	<0.5
Total protein (g dl^{-1})	5.6	7.1
Albumin (g dl^{-1})	2.8	4
C-reactive protein (mg ml^{-1})	13.55	0.02
Complement haemolytic activity (mg dl^{-1})	5.9	31.5
Complement 3 (mg dl^{-1})	16	95
Complement 4 (mg dl^{-1})	1	11
Neutralizing antibody against CA9	<4-fold	32-fold

Fig. 2. Phylogenetic tree among the enteroviruses based on partial VP1 coding region.
*Present case.

Discussion

Urticarial vasculitis resembles urticaria itself, is usually painful, rarely non-pruritic, but occasionally both, and always persists for more than 24 h (Wisniewski, 2000). Urticaria is a type I allergy in which histamine is released by the mast cells. However, urticarial vasculitis is a type III allergy due to malfunction in the immune complex (Jones & Eady, 1984). The immune complex is detected in the blood of 30–75 w/wof urticarial vasculitis patients (Berg *et al.*, 1988). The rashes of urticarial vasculitis occur as a result of sthenia of blood vessel permeability due to activation with C3a and C5a by leukocytoclastic vasculitis in the capillary vessels and not due to histamine (Lotti *et al.*, 1998). These rashes leave an area of pigmentation on the skin after healing because of the vasculitis.

Patients with urticarial vasculitis can be divided into two groups: those with normal complement levels and those with low complement levels (Venzor *et al.*, 2002; Wisniewski, 2000). The latter are suffering from HUVS and are more likely to exhibit systemic manifestations, including constitutional symptoms (fever, malaise and fatigue), arthralgia, arthritis, serositis, glomerulonephritis, interstitial nephritis and Raynaud's phenomenon (Venzor *et al.*, 2002). Some patients suffer inflammation such as conjunctivitis and episcleritis (Wisniewski *et al.*, 1995). There are few reports of urticarial vasculitis in children.

On the other hand, it is very important to exclude Kawasaki disease. A recent study suggested that Kawasaki disease and enterovirus infections may have similar laboratory findings (Lin *et al.*, 2012). The findings in our case were also similar to those of Kawasaki disease.

The criteria for diagnosis of HUVS were established by Schwartz (1982). Major criteria are chronic urticarial exanthema and hypocomplementaemia. Minor criteria are leukocytoclastic vasculitis, arthralgia and arthritis, uveitis or episcleritis, glomerulonephritis, abdominal pain and a

positive reaction for C1q antibody. It was confirmed that the present patient had chronic urticarial exanthema, hypocomplementaemia, vasculitis based on a skin biopsy and arthralgia.

Serum complement levels are decreased in HUVS. Complement with low C1q and C4 levels and variably decreased C3 levels indicate activation of the classical complement pathway. C1q precipitins were identified and later confirmed to be autoantibodies against C1q (anti-C1q autoantibody) (Wisniewski & Naff, 1989). It is thought that an activated degree of complement is one of the factors that controls the serum complement levels. In this patient, when urticarial vasculitis was seen, C3 and C4 levels were extremely decreased. It is thought that various types of exanthema occurred because of the activated degree of the complement.

In most cases, urticarial vasculitis exhibits a majority of the features of fully developed leukocytoclastic vasculitis (Venzor *et al.*, 2002). Direct immunofluorescence of skin biopsy samples from HUVS patients usually shows immunoglobulin and complement deposition in a granular pattern in and around the blood vessels of the upper dermis and basement membrane. The presence of immunoglobulin in the vessel walls is usually accompanied by complement component C3 and activation products of C3, C4, and C5b–9 complement (Kawana, 1996). In this patient, we were not able to perform a direct immunofluorescence technique, and indirect immunofluorescence testing did not show immunoglobulin or complement deposition. We did not examine CD31 and CD3, although these are potentially useful markers for the pathophysiology of HUVS. However, a skin biopsy revealed an early lesion of leukocytoclastic vasculitis. Accordingly, our diagnosis was HUVS.

HUVS has been reported to accompany infection, malignancy, the use of certain drugs and connective tissue diseases such as systemic lupus erythematosus, Sjögren's syndrome, viral hepatitis and cryoglobulinaemia (Venzor

et al., 2002). In this patient, we inferred that, as CA9 was detected, CA9 infection can cause HUVS.

Enteroviruses including coxsackievirus group A may be associated with exanthematous diseases such as herpangina and hand-foot-and-mouth disease (Cherry *et al.*, 2004). Indeed, previous reports have suggested that various enteroviruses may cause exanthematous diseases (Bligard & Millikan, 1986). To date, this includes coxsackieviruses B1 and B5 and echoviruses 4, 5, 9, 11, 16 and 18 and parechovirus 1 (Cherry *et al.*, 2004). In addition, coxsackievirus is a common causative agent of exanthema (Cherry *et al.*, 2004). However, the relationships between these enteroviruses and the pathogenesis of HUVS are not clearly known. In the present case, CA9 was isolated from various samples including serum, and it is therefore strongly suggested that viraemia had occurred. In addition, it can be inferred that small-vessel vasculitis is a leading event in most exanthematous diseases (Cherry *et al.*, 2004). It may induce aberrant consumption of complements including C1q and C4 (Cherry *et al.*, 2004). Together, in the present case, CA9 might induce systemic small-vessel vasculitis resulting in transient decreases in these complements. Furthermore, homology and phylogenetic analysis showed that the significant differences of the VP1 coding region were not seen in the present strain when comparisons were made with other strains (Fig. 2). Thus, in order to diagnose HUVS, histopathological results, laboratory data (hypocomplementemia), and clinical symptoms are all essential.

There is no specific treatment for HUVS, although multiple therapies have been attempted, and no consensus as to an effective therapeutic regimen has been established. Antihistamines may provide temporary relief, but as the disease advanced in this patient, antihistamines were found to be ineffective. Non-steroidal anti-inflammatory agents for symptomatic relief of joint pain may be helpful (Aydogan *et al.*, 2006). Treatment decisions in HUVS must be individualized according to the patient's clinical status. Given the spectrum of disease from urticarial vasculitis to the rare form of HUVS, treatment options are proportionately diverse. Glucocorticoids are the agents most frequently employed to combat the inflammation and immune-complex formation, the dosage depending on the severity of the disease. Dapsone has also been used in the treatment of HUVS. Because of the wide range of disease severity, however, its usage has not been clearly delineated. Serious cases of HUVS, particularly those presenting with glomerulonephritis or other forms of serious organ involvement, may require high doses of glucocorticoids and cytotoxic agents. Cytotoxic agents of choice include cyclophosphamide, cyclosporine A, azathioprine, mycophenolate mofetil and methotrexate, alone or in combination with prednisolone, and will control the disease if used over the long term. Plasmapheresis and intravenous immunoglobulin have been proposed as valuable alternatives to be considered, particularly in those cases with rapid deterioration of

kidney function or crescentic glomerulonephritis (Balsam *et al.*, 2008). In this patient, the skin lesions were quickly eliminated with the steroid treatment.

In conclusion, to reliably distinguish HUVS from other exanthematous diseases, skin lesions should be biopsied. Coxsackievirus may be a causative agent for HUVS. CA9 may induce systemic small-vessel vasculitis resulting in transient decreases in complements.

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