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SHORT COMMUNICATION

Maculopapular rash in the convalescent phase of Kawasaki disease: case series and literature review

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Abstract Intravenous immunoglobulin (IVIG) is currently the standard treatment for Kawasaki disease (KD). Although IVIG therapy is generally well tolerated, several minor adverse reactions have been reported. We report a patient with KD treated with IVIG, who developed a cutaneous reaction in the convalescent phase (approximately 10 days after therapy). We identified seven additional KD cases with a similar presentation, accounting for 9.3 % of KD patients at our hospital. We performed a literature review and found that a maculopapular rash could be observed approximately 10 days after IVIG treatment, in patients with and those without KD. *Conclusion*: Maculopapular rash can occur in nearly 10 % of IVIG-treated children with KD in our cohort, approximately 10 days after treatment. A delayed-onset adverse event of IVIG could be a causative etiology of this unrecognized eruption.

Keywords Adverse reaction of drug · Delayed onset · Intravenous immunoglobulin

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Abbreviations
KD Kawasaki disease
IVIG Intravenous immunoglobulin

Kawasaki disease (KD) is a systemic vasculitis affecting infants and young children [5, 8]. Intravenous immunoglobulin (IVIG) is a promising treatment of KD, resulting in rapid resolution of fever and decreasing the risk of cardiac complications [6, 8].

Although IVIG therapy is well tolerated in KD children [6], minor reactions occur up to 10 % of IVIG-treated patients with various conditions [2]. Among these adverse reactions, skin reactions occur in up to 6 % of treated patients, including pruritus, rash, alopecia, and erythema multiforme [2]. However, few cutaneous reactions due to IVIG have been reported in KD patients.

In this report, we present eight patients with KD complicated by a rash in the convalescent phase. We also discuss the possible etiology of the eruption.

Case report and chart review

An 11-month-old male infant (case 1) was referred to Chigasaki Municipal Hospital because of fever lasting for 4 days. On admission, he also presented with a rash, conjunctival injection, cervical lymphadenitis, inflammation of the lips, and erythema of the hands and feet. Erythema around the BCG scar was also noted. The diagnosis of KD was made and IVIG therapy (2 g/kg) was started on the fourth day of the disease. Within 48 h, his temperature returned to normal and other KD-associated symptoms disappeared. He was in good health thereafter. However, on the 16th day of the KD course, a rash first appeared on both legs and extended to his trunk (Fig. 1). The skin rash was

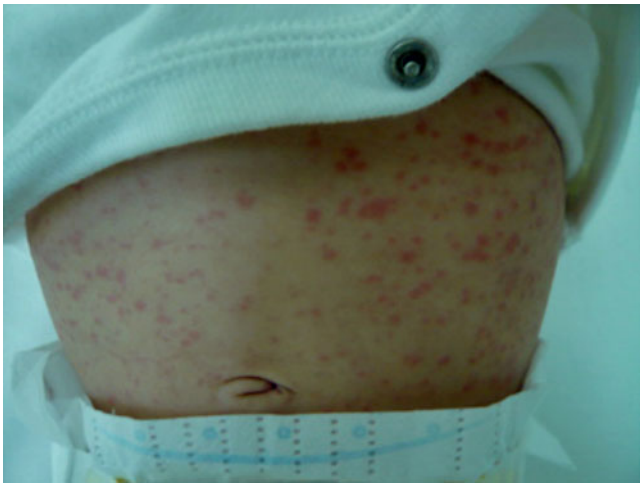

Fig. 1 Maculopapular rash observed in a child with Kawasaki disease at 16 days of illness

maculopapular without itching. Erythema at the site of BCG inoculation was absent at that time. A relapse of KD was suspected. However, the rash was different from that typically observed in KD and no other symptoms suggestive of KD relapse (e.g., fever) were recognized. Laboratory tests were unremarkable, including negative inflammatory markers, such as white blood cell count or C-reactive protein. The rash spontaneously disappeared over the next 3 to 4 days, with mild pigmentation.

We performed a chart review of KD patients admitted to our hospital from 2003 to 2008. During the study period, 86 children were hospitalized for KD and we found seven additional cases with cutaneous symptoms in the convalescent phase (Table 1). Demographic data and clinical features were similar between patients with and those without a rash (data not shown). The rash appeared on 13–18 days of illness, corresponding to 6–12 days after IVIG therapy (mean, 10.1 days). The location of the rash was the limbs in four patients and limb and trunks in another four patients. It was uncertain whether a rash was present on the palms and soles through chart review. Three patients were associated with low-grade fever and mildly elevated liver enzymes; none was diagnosed with a relapse of KD. All eight patients recovered within 5 days without treatment. Two patients were tested for parvovirus B19, although IgM antibodies for the virus were negative. With respect to IVIG preparation, Venoglobulin IH (Mitsubishi Tanabe Pharma Corp, Tokyo, Japan) was used for all 86 patients; however, the lot number was not associated with eruption. Similarly, the rash appeared irrespective of anticoagulant drugs.

Literature review and discussion

A literature search retrieved three Japanese publications, two of which were abstracts, reporting a rash in KD patients

Table 1 The characteristics of patients with Kawasaki disease presenting with a rash in the convalescent phase

No.	Age (years)	Sex	Criteria[a]	Start of IVIG (days of illness)	Appearance of rash (days of illness)	Disappearance of rash (days of illness)	Concomitant drugs[b]	Notes
1	0	Male	6/6	4	16	20	Aspirin	Presented case: negative for parvovirus B19 IgM antibody
2	3	Female	5/6	4	16	21	Aspirin + dipyridamole	Associated with low-grade fever and mild liver dysfunction
3	3	Female	4/6	4	16	20	Aspirin	Associated with low-grade fever and mild liver dysfunction
4	1	Male	5/6	3	13	16	Aspirin	Negative for parvovirus B19 IgM antibody
5	0	Male	5/6	7	18	Not available	Aspirin	
6	1	Female	5/6	8	14	19	Aspirin	
7	1	Male	6/6	5	15	15	Dipyridamole	
8[c]	1	Male	5/6	5, 8	13	19	Aspirin + dipyridamole	Associated with low-grade fever and mild liver dysfunction

IVIG intravenous immunoglobulin

[a] Fever, rash, lymphadenopathy, extremity change, conjunctival injection, and changes in lips and oral cavity

[b] Dipyridamole was used during influenza season

[c] Refractory to first course of IVIG therapy, requiring an additional dose

in the convalescent phase [3, 4, 7]. A total of 11 KD patients with IVIG treatment had cutaneous eruptions in the subacute phase. The eruptions appeared on 8–9 days post-IVIG treatment in two patients. Detailed information were not available in the remaining nine cases. No patients were diagnosed with a relapse of KD.

No English literature has reported a late-onset skin rash in KD patients. However, notably, Vecchietti et al. summarized 29 cases with eczematous rashes, which appeared approximately10days after IVIG treatment [9]. These eruptions usually began on the palms and limbs, followed by extensive generalized rashes. Although the etiology of the skin eruptions was not identified, they suggested that the eruptions were attributed to IVIG, based on the following observations: (1) most patients had neurological disorders in which cutaneous rashes were uncommon, (2) no infectious agents could be detected, and (3) all patients with IVIG reinfusion (nine of nine) had the same skin rash in the earlier phase with the more severe form. Similarly, Aubart et al. reported skin eruption in nine patients treated with IVIG [1], and the onset and location of the rash were similar to those reported by Vecchietti et al. Aubart et al. concluded that eczematous eruption is a side effect of IVIG.

These previously reported cutaneous eruptions shared similar features with those highlighted in our eight cases. We postulate that these previously reported skin rashes were identical to those in our cohort. If our hypothesis is true, skin eruption in the convalescent phase of KD is possibly an adverse event of IVIG therapy. Another possibility is that the rash appeared in the natural course of KD, regardless of IVIG therapy, although we could not find any studies describing a convalescent-phase rash in KD patients before the IVIG era. Further research is required to confirm the association between IVIG therapy and the late-onset cutaneous reaction. However, even if the delayed-onset rash was truly an adverse event of IVIG therapy, the skin reaction was mild, and we thus believe that the benefit of IVIG therapy outweighs the risk of eruption. We consider that a thorough assessment of the child is also required to ensure that no additional features of flare-up are present (e.g., fever and elevated inflammatory markers).

As with any retrospective analysis, specific study data elements were not always recorded contemporaneously at the time of actual patient management. For example, none of our patients had a skin biopsy. This may be a limitation of our report. Another potential imitation is that, although we found that nearly 10 % of patients receiving IVIG had a rash, a single-institution experience may not accurately reflect its true prevalence. Further studies across hospitals are required to evaluate whether this frequency of 10 % is observed in other settings.

In summary, we describe eight patients with KD who had a rash approximately 10 days after IVIG therapy, accounting for 9.3 % of the cases treated with IVIG in our institution. This cutaneous rash could be a late-onset adverse event of IVIG therapy. However, we believe that the benefit of IVIG remains much greater than the potential risk.

Conflict of interest None

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