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Short Communication

Kawasaki disease refractory to standard treatments that responds to a combination of pulsed methylprednisolone and plasma exchange: Cytokine profiling and literature review

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ABSTRACT

We present a case of Kawasaki Disease (KD) that was refractory to plasma exchange (PE), but which finally responded to concurrent intravenous methylprednisolone pulse (IVMP) and PE treatment. To determine direct and indirect evidence for the efficacy of this combination therapy, we analyzed data of patients with refractory KD by review of the literature using medical databases and cytokine profiling. For literature searches, we used the Pubmed™ and Ichushi™ databases. Search terms used included "Kawasaki disease" and "plasma exchange" to extract articles that described KD cases treated with PE. For cytokine profiling, we measured interleukin (IL)-6, soluble tumor necrosis factor-α receptor (sTNF-αR) type 1 and type 2 before and after PE and PE with IVMP. Our search revealed 201 KD patients treated with PE, of which PE treatment was effective in 188 patients (93.5%), but not in 13 cases (6.5%). All 13 cases were treated successfully with additional treatment. Of the 13 cases, only six (2.5%) had recurrence during the PE treatment period. In our case, cytokine profiling showed PE treatment decreased IL6, while sTNF-αR type1 and type2 remained at high levels. PE and IVMP decreased IL-6 and sTNFα-R type 1 and type 2 levels. Conclusion: PE concurrent with additional anti-inflammatory treatment such as IVMP might be a very promising treatment option for PE refractory patients.

1. Introduction

Kawasaki disease (KD), which was initially documented in 1967 [7], is an acute systemic vasculitis in infants and toddlers and occasionally causes coronary artery lesions (CALs). The aims of treatment for KD include controlling its acute inflammatory signs/symptoms and reducing the risk of CALs. Administration of intravenous immunoglobulin (IVIG) for KD is effective, but 10–15% of patients failed to respond in the acute phase [4,8] and the prevalence of CALs is 3–10% [11,13]. Although a significant number of reports have described therapeutic options for refractory KD such as pulsed intravenous steroids [3], infliximab [1], plasma exchange (PE) [5,14], and immunosuppressants, it is hard to recommend a definite second-line treatment for refractory KD because of lack of pivotal clinical trials in this setting. For example, PE is a possible effective treatment option for refractory KD although no clinical trial has confirmed its efficacy. We present a case of refractory KD that failed to respond to IVIG, cyclosporine A (CsA), additional IVIG and PE, but which finally responded to concurrent intravenous methylprednisolone pulse (IVMP) and PE. To identify direct and indirect evidence for efficacy of this combination therapy, we analyzed data from patients with refractory KD by literature review using medical databases.

2. Case report

A 3-year-old girl was diagnosed with atypical KD based on the following symptoms and signs: fever for 2 days, skin rashes, lymphadenopathy of the neck, conjunctival hyperemia and bright-red lips. Laboratory data on admission included white blood cells (WBC) 16,600/μL, C-reactive protein 8.5 mg/dL, aspartate transaminase (AST) 2725 IU/L, and alanine transaminase (ALT) 1,435 IU/L. Treatment with IVIG (2 g/kg) and oral prednisolone (2 mg/kg/day) was promptly started. An anti-inflammatory agent, flurbiprofen (5 mg/kg/day) was concurrently administered as a substitute for aspirin because of hepatic dysfunction. Although a transient improvement in clinical signs was seen on the 3rd day,

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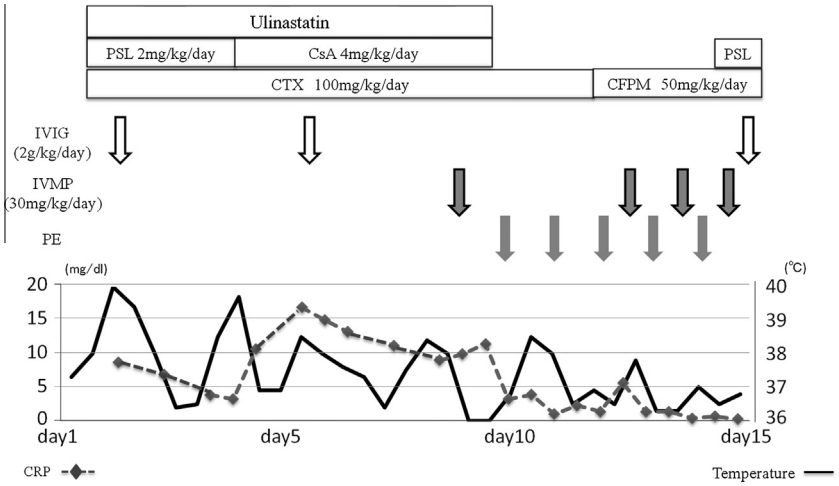

Fig. 1. Clinical course of the case study. Treatment with IVIG (2 g/kg), oral prednisolone (2 mg/kg/day), and ulinastatin was started on the second day of KD. Frequent recurrence of high fever necessitated additional treatments with CsA (4 mg/kg/day) on the 4th day, additional IVIG (2 g/kg) on the 6th day followed by daily PE beginning on the 10th day. Finally, on the 12th day, IVMP (30 mg/kg/day) was added to the PE for 3 days. This combination of IVMP and PE dramatically improved the signs and symptoms of the patient. IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone pulse; CsA, cyclosporine A; CRP, C-reactive protein; PSL, prednisolone, CTX, cefotaxime, CFPM, cefepime; PE, plasma exchange.

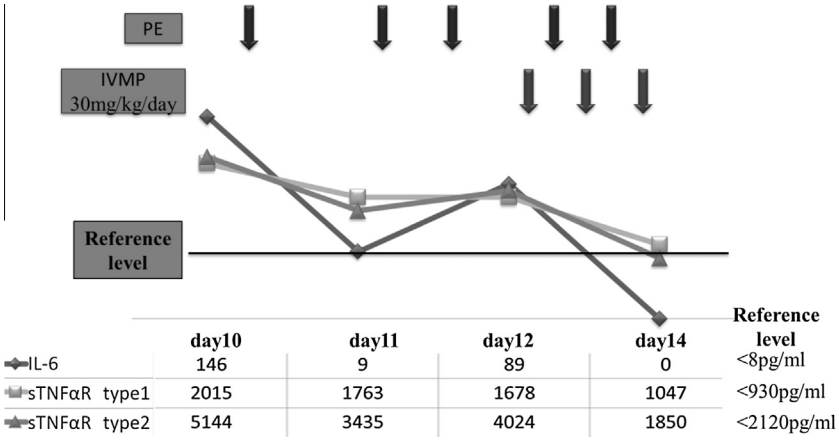

Fig. 2. Changes in serum levels of IL-6, sTNF-αR type 1 and type 2 under PE treatment and PE with IVMP. Before starting PE on day10, serum level of inflammatory cytokines including sTNF-αR type 1, sTNF-αR type 2, and IL-6 were high. After PE treatment on day10, IL-6 decreased, while sTNF-αR type 1 and type 2 remained at the same levels. Although these cytokine levels increased during the treatment with PE alone, addition of IVMP decreased them. IL-6 and sTNF-αR type1 and 2 were normalized. IL, interleukin; sTNF-αR, soluble tumor necrosis factor alpha receptor; IVMP, intravenous methylprednisolone pulse; PE, plasma exchange.

recurrence of symptoms required starting CsA (4 mg/kg/day) and switching from flurbiprofen to aspirin (50 mg/kg/day) on the 4th day. She also received additional IVIG (2 g/kg) on the 6th day when high temperature and inflammatory signs on conjunctiva and lips recurred. Because of the transient effectiveness of IVIG, a single dosage of IVMP (30 mg/kg/dose) was administered on the 9th day, followed by daily PE beginning on the 10th day. Because systemic inflammation recurred on the 12th day, IVMP (30 mg/kg/day) was added to PE for 3 days until the 14th day. The combination of IVMP and PE dramatically improved the signs and symptoms of the patient. Her body temperature normalized on the 13th day and skin desquamation appeared on the 16th day (Fig. 2). Maintenance therapy with oral prednisolone was continued from the 15th day to the 31st day. Aspirin dosage was reduced to the maintenance dosage (5 mg/kg/day) on the 21st day and stopped on the 90th day. She has been free of recurrence and CAL for more than 13 months.

At commencement of PE, inflammatory cytokines were high (soluble tumor necrosis factor α receptor [sTNF-αR] type 1 2015 pg/mL, sTNF-αR type 2 5144 pg/mL, interleukin [IL-6] 146 pg/mL). Fig. 1 showed the trend of inflammation cytokine levels. Cytokine profiling showed PE decreased IL-6, while sTNF-αR type 1 and type 2 remained at the same levels. PE and IVMP decreased IL-6, sTNF-αR type 1 and type 2 levels.

3. Review of literature

3.1. Methods

To perform the literature search, we used the Pubmed™ database and Ichushi™ database, a bibliographic database established in 1903, updated by the Japan Medical Abstracts Society (JAMAS), a non-profit and non-governmental body. Search terms were "Kawasaki disease" and "plasma exchange" to extract articles that describe KD cases treated with PE. Articles published by May 2013 were included. The articles do not include KD patients treated with PE with repeated data, and those who do not fulfill the date of treatment outcome were excluded. Treatment outcome was evaluated based on treatment effectiveness and existence of CALs. Criteria for treatment effectiveness were divided into three types: