CEN Case Reports (2018) 7:13–16
https://doi.org/10.1007/s13730-017-0282-1

CASE REPORT

Relapse of nephrotic syndrome triggered by Kawasaki disease

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Received: 2 August 2017 / Accepted: 26 October 2017 / Published online: 15 November 2017

Abstract
Minor infections, allergies, insect bites, and bee stings are commonly reported causes of nephrotic syndrome (NS). Herein, we report, to the best of our knowledge, the first case of NS relapse due to Kawasaki disease (KD). An 8-year-old boy presented with high fever of 4-day duration. He had developed steroid-dependent NS at the age of 4 years and remained in remission after steroid and mizonbin therapy. Renal biopsy, performed at the age of four, showed minimal change (MC) disease. Upon examination, the patient fulfilled 5 of 6 criteria for KD under the Japanese diagnostic guidelines, with positive proteinuria. He was diagnosed with NS relapse caused by KD. Proteinuria resolved after treatment with intravenous immunoglobulin and cyclosporine A. We present the case of an 8-year-old boy, whose NS relapsed due to KD. To the best of our knowledge, this is the first case report. It is necessary to recognize that KD can trigger relapse of MCNS.

Keywords NS · MCD · Relapse · Kawasaki disease · Cyclosporine A · Intravenous immunoglobulin

Introduction

Nephrotic syndrome (NS) is characterized by proteinuria, hypoalbuminemia, and edema. Minimal change disease (MCD) is a major cause of NS, especially in children. MCD prevalence in patients with NS has been estimated to be 70–90% in children under 10 years, 50% in older children, and 10–15% in adults. The pathogenesis of minimal change NS (MCNS) remains unclear, although dysfunction of T cells may be involved. It has even been postulated that a T-cell-derived plasma permeability factor may induce proteinuria. Minor infections and reactions to insect bites, bee stings, or poison ivy may trigger the initial episode and subsequent relapses.

Kawasaki disease (KD) is an acute febrile vasculitis usually observed in children [1]. Major symptoms include fever, bilateral conjunctival injection without exudate, erythema of the lips and oral mucosa, acral changes, rash, and cervical lymphadenopathy. Although the etiology of KD remains unknown, a partial, functional decline in T cells may be related to this condition. KD can cause acquired heart disease in children, causing coronary artery aneurysms (CAA). CAA or ectasias may occur in 25–30% of children with untreated KD, leading to ischemic heart disease, myocardial infarction, or even sudden death [2]. KD patients are usually treated with intravenous immunoglobulin (IVIG) and high-dose oral aspirin.

We report the case of an 8-year-old boy who experienced a relapse of NS after developing KD and was successfully treated with CyA. To the best of our knowledge, this is the first case of NS relapse due to KD.

Case report

The patient was initially hospitalized with mumps meningitis at the age of 4 and found to have proteinuria. Although chronic nephritis was initially suspected, the development of bilateral leg edema led us to suspect NS and acute nephritis. Leukocyte count was 10,600/mm^3, erythrocyte count 523×10^4/mm^3, platelet count 36.5×10^4/mm^3, and C-reactive protein 0.04 mg/dl, while serum total protein, albumin, creatinine, and total cholesterol levels were 4.2 g/dl, 2.3 g/dl, 0.32 mg/dl, and 342 mg/dl, respectively. Urinary protein excretion was 1.73 g/day with no granular casts. Immunology revealed C3 125 mg/dl, C4 23 mg/dl, CH50 39.9 U/ml,

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and antinuclear antibody titer < 40, with no anti-DNA antibodies. He was diagnosed with NS and treated with 2 mg/kg/day of oral prednisolone (PSL). Proteinuria disappeared 6 days after starting PSL with complete remission of NS. However, NS recurred on 5 occasions when he developed a common cold around the time PSL was discontinued or tapered. He was thus re-diagnosed with steroid-dependent (SD) NS. A renal biopsy at that time revealed MCD. The patient began to exhibit adverse effects of PSL such as moon-face and central obesity, so mizoribine (100 mg/day, trough level 2.76–2.95 μg/ml) was added to the drug regimen when he was 7 years. Remission was achieved and maintained on mizoribine.

At age 8, the patient was admitted to our hospital due to high fever lasting 4 days, cervical lymph node enlargement, and proteinuria. Physical examination revealed left cervical lymphadenopathy, but no conjunctival injection, lip and oral mucosa erythema, acral changes, or rash. Leukocyte count was 18,500/mm^3, erythrocyte count 486×10^4/mm^3, platelet count 20.0×10^4/mm^3, and C-reactive protein 15.95 mg/dl, while serum total protein, albumin, creatinine, and total cholesterol levels were 6.4 g/dl, 3.5 g/dl, 0.40 mg/dl, and 153 mg/dl, respectively. Transaminases were normal (aspartate aminotransferase 20 IU/l and alanine aminotransferase 13 IU/l), while urinary protein excretion was 2.2 g/day.

The patient remained febrile after admission, gradually developing erythema of the lips and oral mucosa, conjunctival injection, and acral changes on day 5 after onset (Fig. 1). High-dose aspirin was started based on a diagnosis of KD. Fever continued and transaminases increased (aspartate aminotransferase 1118 IU/l and alanine aminotransferase 976 IU/l). We administered the first dose of IVIG (2 g/kg in a single infusion) and replaced the aspirin with flurbiprofen. The fever disappeared on day 6, and periungual desquamation began on day 10 after onset. Transaminases normalized after defervescence, with no signs of CAA.

Urinary protein excretion remained high (2.0–3.0 g/day), and the patient was diagnosed with NS relapse 3 days after admission. We observed the patient expecting spontaneous remission of NS as KD improved, since urine output remained stable and he was not edematous. However, the patient developed edema, hypoalbuminemia and proteinuria 8 days after onset (serum albumin 1.9 g/dl and urinary protein excretion 13.6 g/day), and mizoribine was, therefore, replaced with CyA (120 mg/day, trough level 98 ng/ml). Proteinuria resolved after 5 days of CyA administration, and the patient was discharged on day 18 after onset. CyA was discontinued after 9 months of administration, and the patient currently remains in complete remission.

Discussion

Patients with SDNS can relapse when events such as the common cold, other infections, allergies, insect bites, and bee-sting trigger T-cell activation. Shalhoub postulated as far back as 1974 that circulating mediators produced by abnormal T cells may play a role in MCD [3]. Relapses are associated with immune system activation and include expansion of T-cell and B-cell populations, and production of growth factors, macrophages, and many kinds of cytokines such as IL-8, IL-13, and tumor necrosis factor (TNF) α [4]. Glomerular podocyte injury has recently been attributed to a circulating factor produced by T-cell dysfunction in MCD [5]. In the previous studies, the effect of TNF α, a kind of inflammatory cytokines, on podocyte and its role in renal

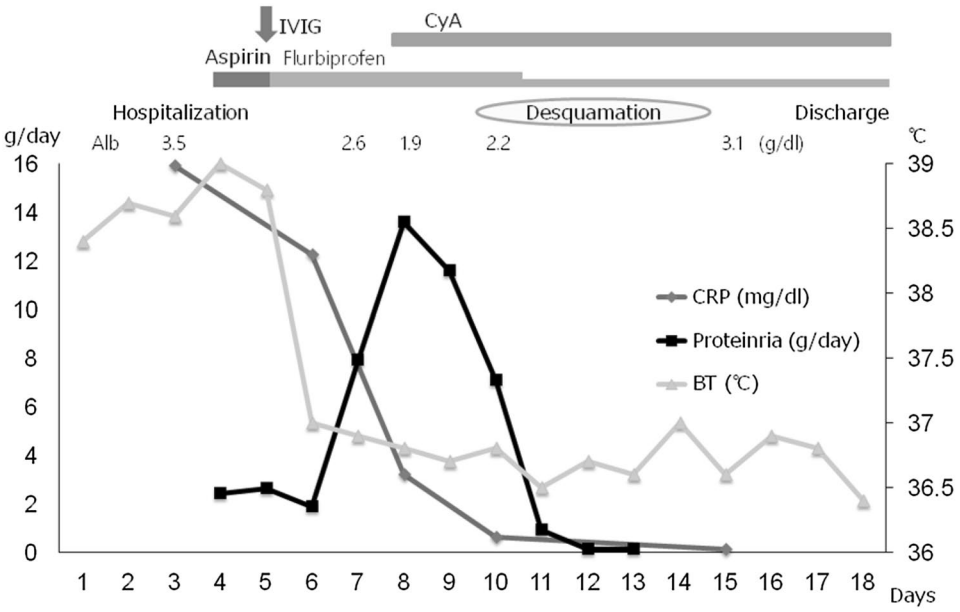

Fig. 1 Clinical course of our patient. *Alb* serum albumin, *CRP* C-reactive protein, *BT* body temperature, *CyA* cyclosporine A, *IVIG* intravenous immunoglobulin

disease have been reported [6]. Another study reported that TNFα may be associated with podocyte cytoskeleton by signaling the nuclear factor (NF)-κB pathway [7].

Renal involvement has been reported in KD, during the course of which sterile pyuria and temporary proteinuria have been the most commonly reported signs [8–10]. Temporary proteinuria, probably of both glomerular and tubular origins, has not been reported to be associated with hypoalbuminemia. Although case reports of KD complicated by NS have been published [4, 11], we found no reports of NS relapse due to KD.

We consider KD was a factor in triggering NS relapse in our patient. In KD, involvement of the immune system and vascular endothelium leads to activation of monocytes and macrophages by cytokines such as TNF α, IL-1β, IL-6 [12], B and T lymphocytes, and endothelial cells. Activated T cells in KD and the effect of cytokines such as TNF α on podocytes may trigger NS relapse; however, the details on this remain unknown. Genetic and infectious factors may also play a role [4].

Our patient had previously presented with NS relapse and proteinuria during colds, but the proteinuria quickly normalized when his cold improved. Although urinary protein excretion had been 2.0–3.0 g/day after admission, we expected NS to resolve spontaneously as in the past relapses. However, edema and oliguria developed, while hypoalbuminemia progressed, and we determined that NS had relapsed due to KD.

Children with SD, frequent relapse (FR), or steroid-sensitive (SS) NS require prolonged corticosteroid therapy, which has been associated with significant adverse effects including impaired glucose tolerance and reduced bone mineral density. To avoid the risk of corticosteroid-related adverse effects, it may be preferable to treat children with FR, SD, and SS NS with immunosuppressants such as CyA [13].

First-line therapy in Japan for KD patients is IVIG with high-dose oral aspirin or flurbiprofen. Second- and third-line therapies for KD patients who remain febrile and symptomatic are additional IVIG, steroids, CyA, infliximab, and plasma exchange. Corticosteroid use in KD has been associated with the development of large CAA. Most fatal cases of KD had ruptured CAA and these patients had been treated with steroid therapy [14]. Kobayashi recently suggested that combining IVIG with PSL may be effective in early stage KD. Although combination therapy reduced IVIG-resistance in early KD, CAA incidence remained unchanged [15]. Lee recently reported large CAA in KD patients who had been treated with steroids, but lacked clinical manifestations such as fever [16]. We, therefore, treated our patient with CyA instead of steroids, since the safety of corticosteroid therapy remains controversial, while CyA is accepted therapy for SDNS and KD in Japan. As a result, CyA proved effective in our patient.

In conclusion, we report what is to the best of our knowledge, the first case of relapsed NS caused by KD. CyA may be effective in patients with relapsed NS due to KD.

Compliance with ethical standards

Conflict of interest All the authors have declared that no conflict of interest exists.

Human and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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