Mod Rheumatol (2004) 14:314–319
DOI 10.1007/s10165-004-0316-3
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CASE REPORT

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An infant with γ-globulin-induced hypersensitivity syndrome who developed Evans' syndrome after a second γ-globulin treatment

Received: August 27, 2003 / Accepted: March 15, 2004

Abstract One month after treatment with γ-globulin for Kawasaki disease, an 18-month-old girl developed Evans' syndrome in addition to drug-induced hypersensitivity syndrome (DIHS) after a second γ-globulin treatment. She suffered from hyperbilirubinemia, hemolytic anemia, and thrombocytopenia. The findings and her clinical course involved plasma exchange and treatment with prednisolone, with good results. Peripheral lymphocyte stimulation tests indicated that γ-globulin was the likeliest cause of the DIHS. A real-time polymerase chain reaction test showed the human herpes virus (HHV)-6 genome in peripheral blood. We demonstrated that a primary infection or infection reactivation by the HHV-6 virus was involved in the development of γ-globulin-induced hypersensitivity and Evans' syndrome.

Key words Autoimmune hemolytic anemia and thrombocytopenia · γ-Globulin · Hypersensitivity syndrome (DIHS) · Intrahepatic cholestasis · Kawasaki disease

Introduction

Drug-induced hypersensitivity syndrome is a multiorgan immune reaction characterized by fever, pleomorphic eruption, lymphadenopathy, hepatitis, and hematologic abnormalities such as eosinophilia and lymphocytosis, including atypical lymphocytes.[1–3] Carbamazepine, sodium valproate, ethosuximide, sulfasalazine, allopurinol, and ibuprofen have been implicated in occurrences of this disease.[1,2] A clinical resemblance to infectious mononucleosis suggests that an underlying viral infection might be involved in triggering the pathophysiological abnormalities underlying these reactions. Recent evidence suggests that primary infection or reactivation with human herpes virus (HHV)-6 may mediate the development of severe drug-induced hypersensitivity.[4,5] However, the mechanisms culminating in drug hypersensitivity reactions are still unknown.

Evans' syndrome, which comprises autoimmune hemolytic anemia accompanied by idiopathic thrombocytopenia,[6,7] represents a small percentage of patients with acute drug-induced immune hemolytic anemia. The syndrome may be divided into three pathophysiological entities[8]: an IgG antierythrocyte antibody type (as induced by methyldopa), a hapten type (as induced by penicillin), and catastrophic intravascular hemolysis (as induced by quinidine). Although the clinical signs and symptoms of the methyldopa type of reaction are identical to those of IgG-induced autoimmune hemolytic anemia, the mechanisms of IgG antibody formation against red blood cells and platelets are poorly understood.

We report the case of an infant in whom i.v. γ-globulin had induced hypersensitivity syndrome and the presence of demonstrable HHV-6 genome in her peripheral blood, and who developed Coombs-positive hemolytic anemia and platelet-associated IgG-positive thrombocytopenia. The progression of hypersensitivity syndrome to Evans' syndrome was mediated by the production of autoantibodies against red blood cells and platelets, and possibly also HHV-6 viral replication during the hypersensitivity reaction.

Case report

An 18-month-old girl was diagnosed with Kawasaki disease based on established criteria (as revised in 1984)[9] at a hospital affiliated to the Yokohama City University School of Medicine. She was treated with i.v. γ-globulin (1 gm/kg for 2 days) and oral aspirin (30 mg/kg per day)and the symptoms subsided (Figs. 1 and 2). There was an elevation of

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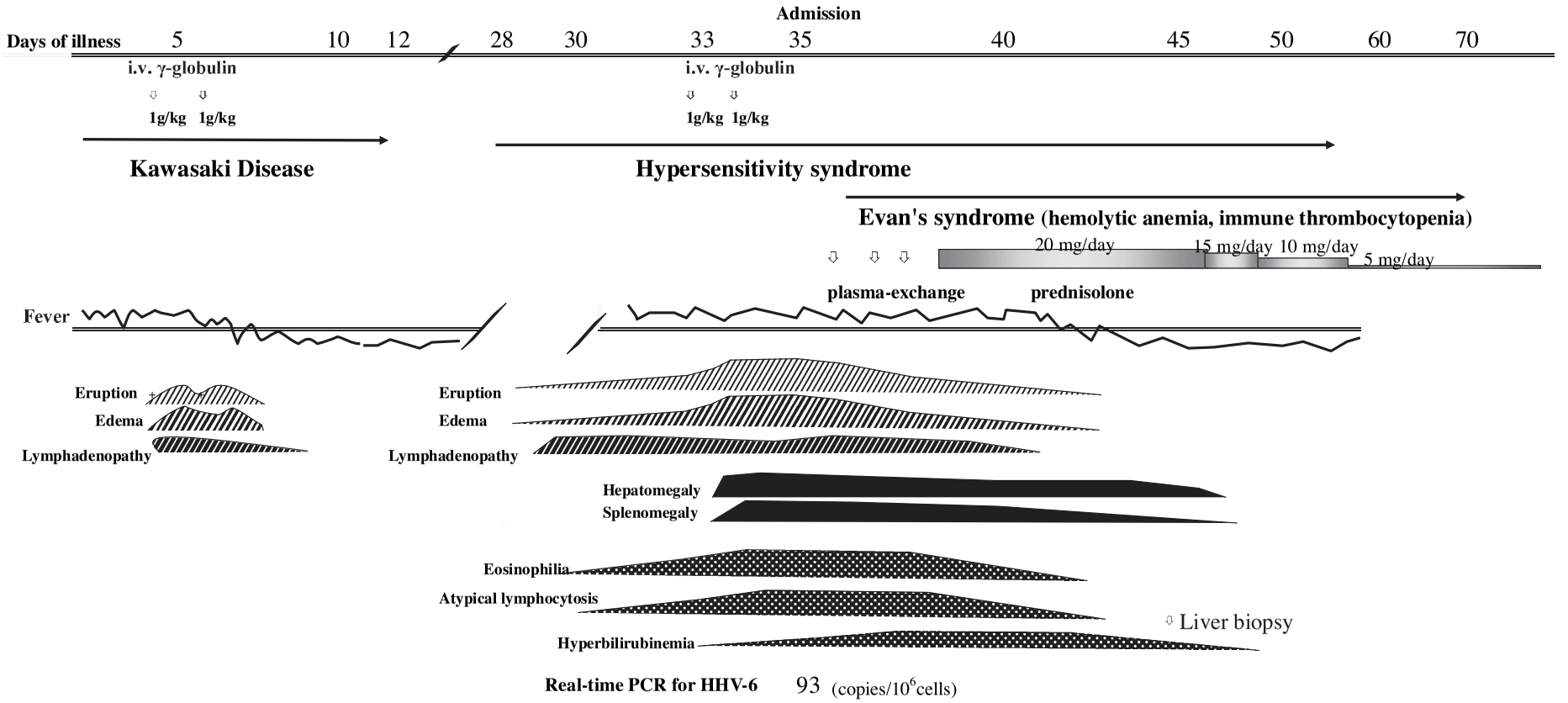
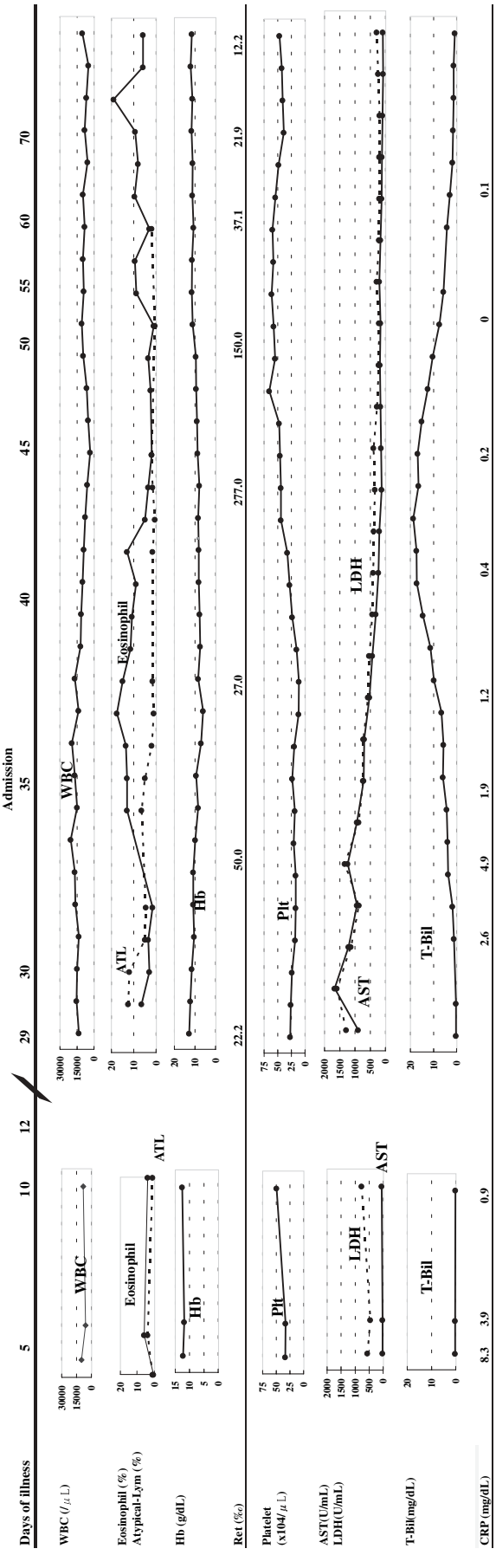


Fig. 1. Clinical course of the patient. One month after treatment with γ-globulin for Kawasaki disease (KD), an 18-month-old girl developed Evans' syndrome in addition to drug-induced hypersensitivity syndrome (DIHS) after γ-globulin was readministered. She suffered from hyperbilirubinemia, hemolytic anemia, thrombocytopenia, eosinophilia, and atypical lymphocytosis. The findings and the disease course indicated treatment with plasma exchange and prednisolone, with good results. Peripheral lymphocyte stimulation tests indicated that γ-globulin was the likeliest cause of DIHS and Evans' syndrome. A real-time polymerase chain reaction (*PCR*) test showed the human herpes virus-6 (*HHV-6*) genome in peripheral blood



inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which decreased to within the normal range within a week. However, a few laboratory abnormalities persisted, and some gradually worsened. Abnormal results 3 weeks after γ-globulin treatment included a white blood cell (WBC) count of 15500/mm^3 (eosinophils 6.5%, atypical lymphocytes 12.5%), asparate aminotransferase (AST) 348 IU/l (normal <38 IU/l), and alanine aminotransferase (ALT) 179 IU/l (normal <44 IU/l). The child was readmitted a month after the initial γ-globulin treatment because of recurrent high fever, skin rash, and fluctuating abnormalities in liver function tests. On the basis of a diagnosis of recurrent Kawasaki disease, a second dose of i.v. γ-globulin (2 gm/kg) was administered. Progressive anemia, jaundice, and hepatosplenomegaly developed, and she was transferred to our University Hospital as an intractable case of Kawasaki disease on day 35 after the onset of the illness.

On admission, the patient was febrile. Hyperemia of the lips, a measles-like maculopapular rash including pigmentation, and jaundice were noted. A physical examination also revealed bilateral cervical lymphadenopathy, edema with induration of the face and extremities, and marked hepatosplenomegaly. A laboratory examination revealed an elevated WBC count (15000/mm^3), including eosinophilia (1950/mm^3) and atypical lymphocytosis (975/mm^3), anemia (hemoglobin 6.1 gm/dl, normal 11.3–14.5 mg/dl; reticulocytes 50‰, normal 6.6–22.1‰), thrombocytopenia (116000/mm^3, normal 180000–390000/mm^3), decreased serum albumin (2.6 gm/dl), and increases in AST (896 IU/l), ALT (332 IU/l), lactate dehydrogenase (LDH) (1297 U/l, normal 106–211 U/l), total bilirubin (6.6 mg/dl, normal, 0.2–1.0 mg/dl), and direct bilirubin (4.5 mg/dl, normal <0.5 mg/dl). Increased concentrations of soluble interleukin (IL)-2 receptor (19000 U/ml, normal 220–530 U/ml), urinary β2-microglobulin (1580 μg/l, normal <230 μg/l), and 2′-5′-adenyl synthetase (781 pmol/dl, normal <100 pmol/dl) indicated hypercytokinemia. Neutrophils accounted for 31% of the total WBC count, and the increase in CRP was mild (1.2 mg/dl). In view of these findings, a diagnosis other than Kawasaki disease was considered and investigated.

To rule out malignant neoplasia and hemophagocytic syndrome, a bone marrow examination was performed; no excessive blasts and no histiocytic hemophagocytosis was found. To further investigate the causes of the progressive anemia, hyperbilirubinemia, and thrombocytopenia, a serologic examination was performed. Direct and indirect anti-globulin tests, as well as a test for cold agglutinins, were positive, pointing to a diagnosis of autoimmune hemolytic anemia, which was also supported by direct anti-globulin tests for IgG and complement on the surfaces of red blood

Fig. 2. The patient's laboratory data. Abnormal data returned to normal, with an improvement in clinical symptoms. *WBC*, white blood cells; *ATL*, atypical lymphocytes; *Hb*, hemoglobin; *Ret*, reticulocytes; *AST*, glutamic-oxaloacetic transaminase; *LDH*, lactate dehydrogenase; *T-Bil*, total bilirubin; *CRP*, C-reactive protein; *Plt*, platelet

Table 1. Real-time polymerase chain reaction (PCR) for human herpes virus (HHV)-6

Day of illness	35	95	116	178	270
Real-time PCR (copies/10^6 cells)	93	86	240	1300	200

Real-time PCR values give DNA copy number per 10^6 white blood cells

cells (RBC). In addition, a large excess of positive platelet-associated IgG (444.4 ng/10^7 cells, normal 9.0–25.0) suggested a diagnosis of autoimmune thrombocytopenia. Reference γ-globulin of the same lot as was used for the therapy for Kawasaki disease was found to be negative for these autoantibodies after extensive investigation. A real-time polymerase chain reaction (PCR) definitively demonstrated HHV-6 viral genome in the peripheral blood (93 copies/10^6 WBC on admission). Repeated examinations for HHV-6 genome showed a gradual increase (240 copies/10^6 WBC on day 116; 1300 copies/10^6 WBC on day 178) (Table 1), suggesting that latent infection with HHV-6 had undergone reactivation at the convalescent phase, not the acute phase, of the drug-induced hypersensitivity syndrome (DIHS). The patient's past history included an episode of exanthema subitum at the age of 6 months.

With a working diagnosis of hypersensitivity syndrome complicated by Evans' syndrome, plasma exchange therapy was initiated to eliminate any previously administered γ-globulin as well as autoantibodies against RBC and platelets, and also to treat progressive hyperbilirubinemia. Approximately 500 ml total circulating plasma was exchanged with 5% albumin solution on 3 consecutive days, resulting in prompt normalization of atypical lymphocytosis, CRP, soluble IL-2-receptor, 2′-5′-adenyl synthetase, and urinary β2-microglobulin. The decreases in reticulocyte number and serum albumin also normalized. However, eosinophilia, hyperbilirubinemia, and the high concentrations of AST and ALT continued to increase. Intravenous prednisolone (2 mg/kg/day) was administered, and then tapered off. The fever and generalized rashes disappeared within a few weeks. Moreover, improvements in the clinical manifestations and laboratory findings (AST, ALT, LDH, total bilirubin, eosinophil count, anemia, and platelet count) were achieved within 2 months. Autoantibodies against RBC and platelets could no longer be detected 3 months after the initiation of prednisolone therapy.

Drug-induced lymphocyte stimulation tests using the reference sample of γ-globulin were positive (stimulation index = 1:316). A liver biopsy specimen showed intrahepatic cholestasis with eosinophil infiltration, which are both typical findings in hypersensitivity syndrome. Hypersensitivity syndrome complicated by Evans' syndrome was therefore the definitive diagnosis.

Discussion

We reported a case of hypersensitivity syndrome developing in an infant as a result of i.v. γ-globulin therapy. The illness then progressed to Evans' syndrome because of her susceptibility to additional treatment with i.v. γ-globulin. The currently recommended i.v. γ-globulin dose for the treatment of Kawasaki disease is 1–2 g/kg.[10–12] Recently, 6000–7000 children per year have been affected with this disease in Japan[13]; most were successfully treated with such a regimen. While occurrences of i.v. γ-globulin-associated hemolytic anemia or of serum sickness have been reported,[14,15] the present case is apparently the first report of hypersensitivity syndrome and Evans' syndrome following i.v. γ-globulin.

Drug-induced hypersensitivity syndrome is considered to be a severe drug allergy, as are Stevens–Johnson syndrome and toxic epidermal necrolysis.[2] Although its precise mechanism remains to be elucidated, the long latent period (3–4 weeks) between the first dose of the drug responsible and the onset of the reaction has been suggested to reflect the contributions of metabolic idiosyncrasies, or factors such as primary infection and reactivation of HHV-6 that trigger and activate the disease in susceptible individuals receiving the drug.[4,5,16] The clinical signs included a maculopapular rash, often progressing to exfoliative erythroderma with fever, adenopathy, and multivisceral involvement. Eosinophilia, atypical lymphocytosis, abnormal liver function tests, and renal impairment were frequent.[17]

Previous reports[2] of patients with drug-induced hypersensitivity syndrome indicated that a limited number of drugs, including carbamazepine, phenytoin, phenobarbital, allopurinol, and dapsone, could trigger the disease. $CD4^+$ as well as $CD8^+$ T cells from patients with allergies to carbamazepine, phenytoin, or sulfamethoxazole have been shown to proliferate in response to in vitro challenge in a drug-specific and dose-dependent manner. These cells showed increased CD25 and HLA-DR expression, suggesting the involvement of drug-specific T cells in drug hypersensitivity.[18]

In the present case, γ-globulin was the probable cause of hypersensitivity, as was demonstrated by a lymphocyte proliferation test against the reference γ-globulin solution. The globulin is a purified protein fraction from human plasma; administration to patients with idiopathic thrombocytopenic purpura or Kawasaki disease has sometimes resulted in anaphylaxis or other allergic reactions.[19,20] The present case suggests that γ-globulin might also be able to cause a drug-induced hypersensitivity syndrome. However, it was ultimately difficult to elucidate which component of γ-globulin was responsible.

As in other reports,[5,21] PCR in our case revealed infection with HHV-6, indicating that an active HHV-6 virus infection acting in concert with T-cell-mediated immune responses against γ-globulin may have been responsible for

the induction of hypersensitivity. One characteristic of this case was the child's history of exanthema subitum 1 year previously. On admission on that occasion, HHV-6 DNA had already been detected by real-time PCR, which eliminates the possibility of primary infection with this virus at the time that drug-induced hypersensitivity developed. DNA copy numbers for HHV-6 in peripheral blood mononuclear cells gradually increased, suggesting latent infection and reactivation. Tohyama et al.[21] reported two adults with sulfasalazine-induced hypersensitivity associated with reactivation of HHV-6; anti-HHV-6 IgG titers in these patients showed a further increase on reexamination 2 weeks after the onset of the hypersensitivity symptoms. Suzuki et al.[19] also described marked increases in anti-HHV-6 IgG 4 weeks after the appearance of symptoms in a patient with hypersensitivity syndrome induced by allopurinol. Latent HHV-6 infection appears to be reactivated in the course of drug-induced hypersensitivity; and the virus, in turn, can modify the disease course. Although Tohyama et al.[22] showed that HHV-6 was usually reactivated 2–3 weeks after the onset of DIHS, in the present case the time-lag between DIHS onset and HHV-6 reactivation was much longer than usual. The reason remained unclear. However, the characteristics of i.v. γ-globulin might be relevant.

On day 35 after the initial γ-globulin treatment, the abrupt onset of high fever, skin rash, and lymphadenopathy suggested a recurrence of Kawasaki disease in the opinion of physicians at the affiliated hospital, and i.v. γ-globulin therapy was administered again. The symptoms failed to subside, and enlargement of the spleen and liver with progressive jaundice and liver function abnormalities continued. Upon the patient's transfer to our university hospital, clinical manifestations including high fever, a maculopapular rash, cervical lymphadenopathy, and massive hepatosplenomegaly, with laboratory findings of eosinophilia, atypical lymphocytosis, increased AST, ALT, and total bilirubin, and a PCR-proven HHV-6 infection indicated a diagnosis of drug-induced hypersensitivity syndrome. However, massive hemolysis and rapid decreases in the number of platelets followed. Positive Coombs tests and platelet-associated IgG tests confirmed an additional diagnosis of Evans' syndrome. Findings in a liver biopsy specimen subsequently indicated that hyperbilirubinemia and liver function abnormalities were related to drug-induced hypersensitivity syndrome rather than Evans' syndrome. Nonetheless, the reactions against RBC and platelets indicated that i.v. γ-globulin readministration induced Evans' syndrome rather than exacerbating the drug-induced hypersensitivity itself.

Hillyer et al.[23] suggested that i.v. γ-globulin administration in patients with Kawasaki disease could promote immune hemolytic anemia via activation of the B lymphocytes responsible for the production of anti-RBC autoantibodies, and that passive transfer of anti-A and -B antibodies and immunomodulation by i.v. γ-globulin might lead to antibody-mediated hemolytic anemia. Thrombocytopenia following γ-globulin treatment has also been reported in a few cases,[15] but the underlying mechanism is still unclear.

In summary, initial i.v. γ-globulin treatment in an infant with Kawasaki disease resulted in drug-induced hypersensitivity syndrome. As the syndrome mimicked recurrent Kawasaki disease, the treatment was repeated, causing a different disease, namely, Evans' syndrome. The precise mechanisms underlying both syndromes remain to be elucidated.

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