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CASE REPORT

**Kakushi Matsushita · Atsuo Ozaki · Hirosaka Inoue
Tomoe Kaieda · Masaki Akimoto · Atsushi Satomura
Naomichi Arima · Heiichiro Hamada · Yukio Suruga
Noriko Aoki · Hiroshi Fujiwara · Chuwa Tei**

Stevens–Johnson syndrome induced by mizoribine in a patient with systemic lupus erythematosus

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Abstract A 32-year-old Japanese woman, who had a treatment history of systemic lupus erythematosus (SLE) with lupus nephritis World Health Organization class IV for 11 months, visited our hospital due to fever, facial erythema, and erosion of the oral cavity on November 10, 2003. Her mucosal erosion and facial skin erythema progressed over the following week, and Stevens–Johnson syndrome was diagnosed due to pathological findings of the skin. Among the administrated drugs, only mizoribine, started 6 months earlier, produced a positive reaction in the drug lymphocyte stimulation test. Increased prednisolone and high dose intravenous γ-globulin were given successfully. Cyclosporine at 50 mg was administered to control the SLE, followed by an increase to 100 mg on January 7, 2004. She suffered from abdominal pain, blindness, and convulsion on January 9. The magnetic resonance image of her brain prompted a diagnosis of reversible posterior leukoencephalopathy syndrome. After withdrawal of cyclosporine and control of hypertension, symptoms disappeared rapidly. Cyclophosphamide pulse therapy was successfully administrated to control lupus nephritis. This is the first report describing the relationship between Stevens–Johnson syndrome and mizoribine. Although the use of mizoribine is thought to be safe, careful observation is necessary.

Key words Mizoribine · Stevens–Johnson syndrome (SJS) · Systemic lupus erythematosus (SLE)

K. Matsushita (✉) · A. Ozaki · H. Inoue · M. Akimoto · N. Arima · H. Hamada · Y. Suruga · N. Aoki · H. Fujiwara
Division of Hematology and Immunology, Internal Medicine, Kagoshima University Hospital, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
Tel. +81-99-275-5934; Fax +81-99-275-5947
e-mail: kaku@m2.kufm.kagoshima-u.ac.jp

T. Kaieda · C. Tei
Cardiovascular, Respiratory, and Metabolic Medicine, Graduate School of Kagoshima University, Kagoshima, Japan

A. Satomura
Department of Nephrology and Endocrinology, Internal Medicine, Itabashi Hospital, Nihon University Medical School, Tokyo, Japan

Introduction

For patients with systemic lupus erythematosus (SLE), the treatment strategy for nephritis with pathological findings of World Health Organization (WHO) class IV is vitally important, as it is one of the major prognostic factors.[1] Cyclophosphamide pulse therapy is widely used for the treatment of class IV lupus nephritis in addition to steroid therapy. The adverse effects of cyclophosphamide therapy are not prominent, except for amenorrhea.[2] In cases of young women patients with SLE who wish to fall pregnant, other immunosuppressive drugs are used, of which mizoribine is preferred because it is generally thought to be safe.[3] Here, we report a patient with SLE who developed Stevens–Johnson syndrome (SJS) induced by mizoribine and reversible posterior leukoencephalopathy related to hypertension during cyclosporine (CyA) administration. This is the first report describing the SJS caused by mizoribine.

Case report

A 32-year-old Japanese woman was diagnosed with SLE and antiphospholipid antibody syndrome due to arthritis, oral ulcer, pleuritis, facial edema, hematological disorders, immunological disorders, and nephrotic syndrome, in October 2002, and her pathological examination revealed lupus nephritis class IVc, based on WHO criteria. Two courses of methylprednisolone pulse therapy and plasma exchange therapy (40 units of fresh frozen plasma for 3 days) were administered successfully. Then 150 mg of mizoribine was added to 22.5 mg of prednisolone to control lupus nephritis.

She was admitted to evaluate her SLE and to consider other immunosuppressive drugs because of general fatigue in July 2003. On admission, she had hypo-oxygenemia of 63 mmHg in arterial blood and interstitial pneumonitis, with thin wall cavity in chest X-ray and chest computed tomography images. Although microorganisms such as bacteria,

fungus, and viruses were not detected, unidentified fungal infection was diagnosed because of an elevated β-D-glucan concentration of 151.8 pg/ml (<11). To control infection, 150 mg of micafangin was administrated in addition to antibiotics and gancyclovir, and mizoribine was discontinued. Although the level of β-D-glucan decreased to within the normal range after 2 weeks, the hypo-oxygenemia and interstitial pneumonia on X-ray had not improved. Therefore, she received half doses of methylprednisolone pulse therapy (500 mg, 3 days) followed by 1 mg/kg of oral prednisolone, and her interstitial pneumonia disappeared in a week. Because her proteinurea and renal dysfunction progressed, 150 mg of mizoribine was restarted on September 12, 2003.

She visited our outpatient clinic due to fever, general fatigue, facial erythema, and erosion of the oral cavity on November 10, 2003 (Fig. 1A). Stevens–Johnson syndrome or viral infection such as measles was suspected. Her mucosal erosion and facial skin erythema progressed in the following week (Fig. 1B). Multiple erosions were recognized in her oral and eye mucosa. She could not take foods due to painful oral lesions. Small bullous eruptions (<5 mm in diameter) were recognized on her face and forearm. The complete peripheral blood counts showed pancytopenia (white blood cells 2500/μl, red blood cells 303×10^4/μl, hemoglobin 10.6 g/dl, hematocrit 32%, platelets 11.7×10^4/μl), and increased concentration of C-reactive protein (3.59 mg/dl) was recognized. Serum examination did not show evidence of recent infections or reactivations of virus such as measles, rubella, cytomegalovirus, Epstein–Barr virus, human herpes virus-6 (HHV-6), or parvovirus B19. Stevens–Johnson syndrome was diagnosed due to pathological findings of the skin. Inflammatory cells such as lymphocytes and neutrophils had aggregated in the dermal area as well as epidermis. Some epidermal cells revealed apoptotic changes without any evidence for viral infection (Fig. 2). Among the administered drugs, only mizoribine produced a positive reaction in the drug lymphocyte stimulation test (DLST). The stimulation index was 2.23, and [^{3}H]thymidine uptake with and without mizoribine was 353 and 158 cpm, respectively. The other drugs were negative in the DLST. Methylprednisolone, 500 mg, was administered for 1 day, followed by 1 mg/kg of intravenous prednisolone and high-dose intravenous γ-globulin (100 mg/kg, 5 days), with the result that the symptoms disappeared within 1 month (Fig. 1C). Cyclosporine A (CyA, 50 mg) was administered to control SLE on December 17, 2003, followed by an increase to 100 mg on January 7, 2004. She then suffered from abdominal pain, blindness, and convulsion on January 9. The magnetic resolution image of her brain prompted a diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS) (Fig. 3). Her blood pressure fluctuated around 150/100 mmHg before CyA administration, and rose to 180–190/100–120 mmHg at onset of RPLS while the serum concentration of CyA was low (23.8 ng/ml); we diagnosed RPLS related to hypertension during CyA administration. After the withdrawal of CyA and subsequent control of hypertension, the RPLS symptoms disappeared rapidly. The involvement of central nervous system (CNS) lupus was not prominent due to normal cerebrospinal fluid data including interleukin-6 and the IgG index. Since she still had impaired renal function (creatinine clearance, 22.3 ml/min) and proteinurea greater than 1 g/day, intermittent intravenous cyclophosphamide pulse therapy was administered to control active lupus nephritis. The clinical course after cyclophosphamide pulse therapy showed improved renal function and proteinurea, and the dose of prednisolone decreased to 5 mg/day in March 2005.

Discussion

We report a patient with SLE who suffered from SJS induced by mizoribine and RPLS related to hypertension during administration of CyA. For patients with SLE, thera-

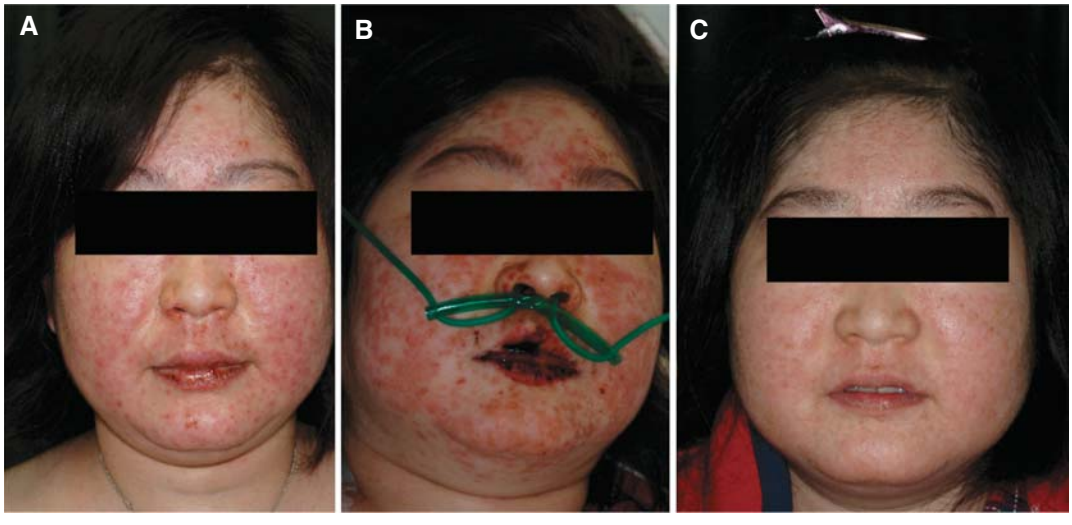

Fig. 1. Erythema of the face and erosion of the lips were documented at onset (**A**), after observation for a week (**B**), and after intravenous gammaglobulin therapy a month after onset (**C**)

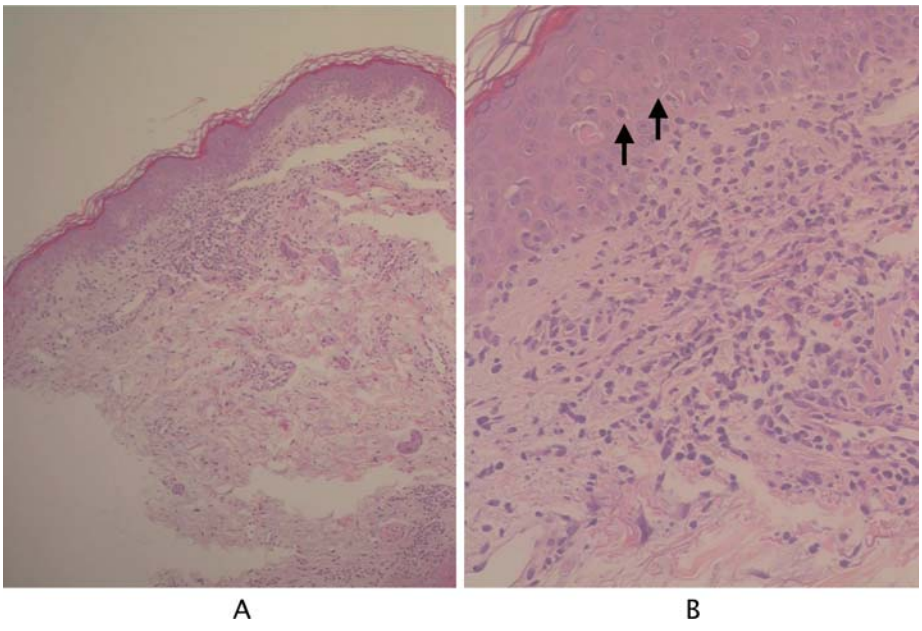

Fig. 2A,B. Pathological findings of erythema of the left forearm, stained by hematoxylin–eosin, were documented. Inflammatory cells, such as lymphocytes and neutrophils, had aggregated in the dermal area as well as epidermis (**A**, ×100). Some epidermal cells revealed apoptotic changes (indicated by *arrows*) (**B**, ×400)

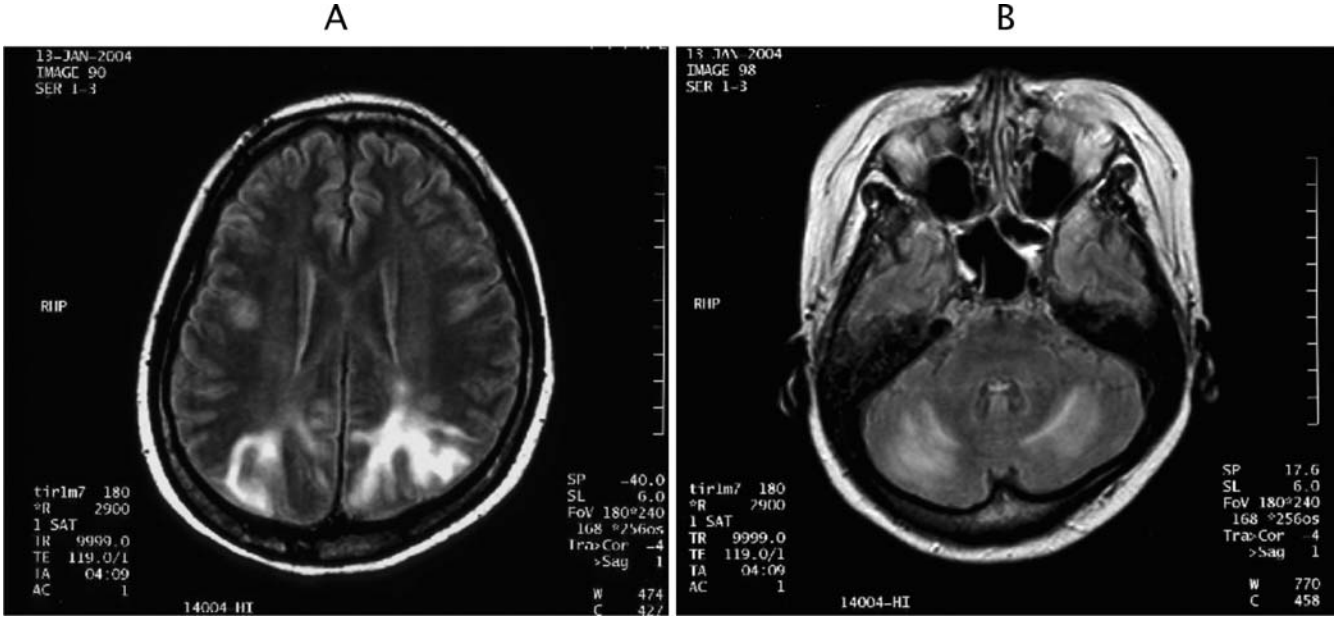

Fig. 3. T2 images of brain magnetic resonance imaging during reversible posterior leukoencephalopathy syndrome revealed a high signal in the bilateral occipital lobes (**A**) and bilateral cerebella (**B**)

peutic measures for lupus nephritis are important, and intravenous cyclophosphamide pulse therapy in addition to steroid therapy is the most effective strategy.[1] Cyclophosphamide therapy causes some adverse effects, such as decreases in blood cells, hemorrhagic urinary cystitis, gastrointestinal injury, immune suppression, secondary malignancies, and ovarian failure.[2] Thus, in a young woman who wants to get pregnant, we approach cyclophosphamide therapy with some hesitancy. Other relevant drugs, such as mizoribine,[3] CyA,[4] and mycophenolate mofetil,[5] have been reported to be effective for lupus nephritis, with mizoribine often being used as it is believed to be relatively safe. Mizoribine is an immunosuppressant drug having selective inhibitory effects on inosine 5-monophosphate dehydrogenase (IMP-DH), an enzyme in the de novo purine nucleotide synthesis system.[6] The compound was first approved for use in the prevention of rejection in patients with renal transplantation, and additional indications are lupus nephritis, rheumatoid arthritis, and primary nephrotic syndrome. The effectiveness and safety of mizoribine has been documented in several studies.[3,7,8] The major side effect of mizoribine is hyperuricemia, with an incidence of about 10%, due to its original mechanism. Although the grade of hyperuricemia varies and is generally controllable, Tanaka

et al. reported a case of acute renal failure with marked hyperuricemia developing during mizoribine administration.[9] The reported case then underwent hemodialysis for 1 month. Other remarkable adverse effects have not been previously reported. However, in a postmarketing survey, one patient revealed severe pneumonia and rash with subsequent discontinuation of mizoribine.[10]

In the present case report, the patient suffered from pneumonia 2 months after the start of mizoribine. The discontinuation of mizoribine, and subsequent application of methylprednisolone semipulse therapy was necessary to control pneumonia. Because we diagnosed the pneumonia as an infection with some involvement of SLE, the mizoribine was readministered to control lupus nephritis. Two months after readministration of mizoribine she suffered from severe SJS. Stevens–Johnson syndrome can have a fatal outcome, with a mortality rate of 10%–15%.[11] A 100 mg/kg dose of intravenous γ-globulin was administered for 5 days successfully, as previously reported.[12] Stevens–Johnson syndrome caused by mizoribine was diagnosed because of the positive DLST. The drug lymphocyte stimulation test was reported to be useful for the diagnosis of SJS caused by drugs, including immunosuppressive drugs.[13] The adverse effects in the present patient appeared about 2 months after the initiation of mizoribine, and the high-dose steroid therapy may have been involved in the delay of SJS appearance. Based on the total clinical course, the adverse effects of mizoribine may have been associated with the pneumonitis in addition to fungal infection in the first admission to our ward. Hypersensitivity syndrome related to viral infection or reactivation is characterized by eruption, internal organ involvement, and eosinophilia.[14] We considered hypersensitivity syndrome in the differential diagnosis because mizoribine possibly caused interstitial pneumonia. However, internal organs involvement and eosinophilia were not prominent during SJS with negative results of virological surveys including HHV-6.

In the present report, we used CyA to control lupus nephritis after removal of mizoribine. Three weeks after the start of CyA therapy, the patient suffered from the RPLS possibly associated with hypertension and CyA. The diagnosis of RPLS is based on the specific symptoms of headache, nausea, abdominal pain, visual disturbance, and seizures, and confirmed by MRI findings of high signal in T2 images.[15] Because of the very low serum level of CyA, hypertension may have played a central role in the pathogenesis of RPLS in this case. In addition to hypertension and CyA administration, the impaired renal function was also reported involved in the pathogenesis of RPLS.[15] Finally, the intravenous intermittent cyclophosphamide therapy improved her lupus nephritis.

We report SJS induced by mizoribine and RPLS related to hypertension during cyclosporine A in a patient with SLE. Since the appearance of the adverse effects of mizoribine might have been delayed by steroid therapy in the present case, careful observation and consideration is recommended. In addition, careful control of blood pressure is required in the case of CyA usage. For female patients with lupus nephritis, alternative therapeutic measures to cyclophosphamide are awaited.

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