CASE REPORT

Maintenance treatment using the purine-synthesis inhibitor mizoribine in a patient with relapsing thrombotic thrombocytopenic purpura

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Abstract Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening disease. Although plasma exchange (PE) therapy and corticosteroids are standard remission induction and maintenance therapies, some patients are easily refractory and frequently relapse under treatment with this therapy, and require additional treatment. However, there are limited data about additional treatment interventions. We report a case of 56-year-old man who was hospitalized for fever, general fatigue and hemoglobinuria. Owing to the symptoms and the laboratory findings of hemolysis, he was diagnosed with TTP. He was treated with PE therapy and corticosteroids, and the TTP went into remission. However, his TTP relapsed and remission induction was attempted again. As a remission maintenance treatment, we used combination therapy with the purine-synthesis inhibitor mizoribine (MZR) and corticosteroids. The administration of MZR maintained disease activity with no adverse event for long periods and allowed us to gradually reduce the corticosteroids dose. Hence, we propose that MZR is an effective treatment for TTP maintenance.

Keywords Thrombotic thrombocytopenic purpura (TTP) · Mizoribine (MZR) · Hemoglobinuria

Introduction

Thrombotic thrombocytopenic purpura (TTP) is characterized by the so-called “classic pentad” of thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, neurological deficits, and fever [1]. TTP is a rare but life-threatening disease. Acquired TTP is due to a deficiency of the von Willebrand factor cleaving protease (ADAMTS13; a disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13). Anti-ADAMTS13 antibody contributes to the pathogenesis of acquired TTP. TTP may be associated with other disorders, such as infections, malignancies, and autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, and antiphospholipid syndrome). Plasma exchange (PE) therapy and corticosteroids are standard remission induction and maintenance therapies. However, some patients are easily refractory and frequently relapse under treatment with this therapy. In particular, a previous study has demonstrated that patients with severe ADAMTS13 deficiency were at higher risk for relapse [2].

Mizoribine (MZR) is an immunosuppressive agent that is known to act on the pathway of purine-synthesis in cells via the selective inhibition of inosine monophosphate dehydrogenase, a rare-limiting enzyme in the de novo synthetic pathway of guanosine monophosphate. MZR selectively inhibits lymphocyte proliferation. Therefore, MZR is used as an immunosuppressant for the control of graft rejection with transplantation and for the treatment of lupus nephritis, rheumatoid arthritis and primary nephrotic syndrome. Combination therapy with MZR and corticosteroids has also been used. To our knowledge, there are no reports about the efficacy of MZR in TTP patients. Here, we report a case of relapsing TTP with severe ADAMTS13 deficiency who was successfully treated and for whom remission was maintained with MZR.

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Case report

A 56-year-old Japanese man was admitted to a local hospital after experiencing cold symptoms, general fatigue and hemoglobinuria. He had a past medical history of hypertension and alcoholic liver injury, and had been treated with bisoprolol fumarate before hospitalization. Although he had fever on admission, his physical examination was normal and his consciousness was clear. Blood tests showed a platelet count of $1.2 \times 10^4/\mu\text{L}$, hemoglobin of 8.3 g/dL (normocytic), and a white blood cell count of 5900/ μL . Lactate dehydrogenase (LDH) was 1901 IU/L, total bilirubin was 2.3 mg/dL, and haptoglobin was decreased to 13 mg/dL, with a negative Coombs' test. Blood urea nitrogen was 31.6 mg/dL, and serum creatinine was 0.99 mg/dL, with normal electrolytes. Urinalysis revealed microscopic hematuria and proteinuria. Moreover, peripheral blood smears disclosed many fragmented red blood cells. Further serum analysis on admission revealed reduced ADAMTS13 activity at 0%. Unfortunately, data on the ADAMTS13 inhibitor were not available (Table 1). Owing to the symptoms and the finding of ADAMTS13 activity, the patient was diagnosed with acquired TTP. We simultaneously considered his background disorder. Because ADAMTS13 activity was severely reduced and there were no reports about bisoprolol fumarate-associated thrombotic microangiopathy (TMA), we excluded the possibility of drug-associated TMA. Serum analysis revealed that he was positive for antinuclear antibody (homogeneous $\times 80$, speckled $\times 160$) and for anti-SSA antibody $\times 4$. Because he also complained of a severely decayed tooth, Sjögren's syndrome (SS) was suspected. However, the pathological findings for a lip biopsy specimen and Schirmer's test were negative. We could not confirm a definite diagnosis of SS. Finally, no relation with autoimmune disease including SS could be proven in this patient; so the standard treatment for idiopathic TTP was selected.

He underwent PE therapy three times a week and received oral prednisolone (PSL) at 60 mg/day. After the initiation of therapy, however, thrombocytopenia, anemia, and the elevation of serum LDH were prolonged. Moreover, he suffered from convulsions and consciousness disorder. He was treated with methylprednisolone pulse therapy (1 g/day for 3 days) as additional treatment. He was transferred to our hospital for further treatment. Serum analysis performed upon transfer revealed that ADAMTS13 activity had recovered to 58.9% without the presence of ADAMTS13 inhibitor. These findings mean that his condition was on the way to recovery. He underwent PE therapy for three consecutive days and was treated with PSL at 60 mg/day. Subsequently, the platelet count increased, LDH decreased, and his consciousness disorder was improved. The inter-PE interval was then gradually lengthened and stopped. The platelet count continued to rise, and the hemolytic findings disappeared. The PSL dose

Table 1 Laboratory findings at the disease onset

Blood count	
WBC	5900/ μL
RBC	$240 \times 10^4/\mu\text{L}$
Hb	8.3 g/dL
Ht	23.2%
Plt	$1.2 \times 10^4/\mu\text{L}$
Blood chemistry	
TP	7.0 g/dL
Alb	3.4 g/dL
AST	116 IU/L
ALT	76 IU/L
LDH	1901 IU/L
T-bil	2.3 mg/dL
BUN	31.6 mg/dL
Cre	0.99 mg/dL
Na	138 mEq/L
K	4.3 mEq/L
Cl	107 mEq/L
CRP	0.7 mg/dL
Immunological	
IgG	1971 mg/dL
IgA	499 mg/dL
IgM	21 mg/dL
C3	84 mg/dL
C4	12 mg/dL
CH50	56.7 U/mL
RF	10.1 U/mL
ANA (Homogeneous)	$\times 80$
(Speckled)	$\times 160$
anti-SSA antibody	$\times 4$
anti-SSB antibody	$\times 1$
anti-dsDNA antibody (ELISA)	< 10 IU/mL
anti-Scl-70 antibody	$\times 1$
Haptoglobin	13 mg/dL
ADAMTS13 activity	0%
ADAMTS13 inhibitor	NA
Urinalysis	
Protein	3+
Occult blood	3+
Red blood cells	50–99/HPF

was gradually reduced to 25 mg/day and the patient's condition remained stable. The patient was discharged.

The patient was followed up as an outpatient, and the oral PSL dose was gradually reduced. At 6 months after disease onset, by which time the oral PSL dose had been reduced to 15 mg/day, his condition was complicated with hemoglobinuria, and his platelet count fell to $0.9 \times 10^4/\mu\text{L}$. As the TTP had relapsed, he was hospitalized, and remission induction therapy was restarted. Further serum analysis on

second admission revealed reduced ADAMTS13 activity at 0.5% with the presence of ADAMTS13 inhibitor. He was treated with a transfusion of fresh frozen plasma and methylprednisolone pulse therapy. In response to this treatment, his platelet count continued to rise and the hemolytic findings disappeared. The steroid pulse was switched to oral PSL at 40 mg/day. The oral PSL dose was gradually reduced to 30 mg/day, and he was discharged again.

The oral PSL dose was gradually reduced again at the outpatient service. At 10 months after disease onset, to reinforce the remission induction treatment, the administration of oral cyclophosphamide (CPA) was started at 50 mg/day. At 13 months after disease onset, oral CPA was stopped. Then total cumulative dose of CPA was 5.1 g. At 18 months after disease onset, by which time the oral PSL

dose had been reduced to 15 mg/day, the dose at which he had previously relapsed, the administration of MZR (out of the insurance coverage in Japan, but with patient's permission) was started at 150 mg/day. The oral PSL was then gradually reduced. At 28 months after disease onset, it had become possible to reduce the oral PSL dose to 5 mg/day. At 5 years after disease onset, by which time the oral PSL dose was 5 mg/day and the MZR dose had been reduced to 75 mg/day, no further relapse of TTP and no adverse events had been observed (Fig. 1). We were able to maintain long-term remission of TTP with MZR and corticosteroids. Although there is a possibility that other treatment interventions, such as administration of CPA and slowly reduction of the oral PSL dose, had favorable effect on maintaining its remission, additional administration of MZR also had effective impact in the present case.

Fig. 1 Clinical course of the case. CPA cyclophosphamide, FFP fresh frozen plasma, LDH lactate dehydrogenase, mPSL methylprednisolone, MZR mizoribine, PE plasma exchange, Plt platelet count, PSL prednisolone

Discussion

In this report, we present a case of relapsing TTP that was maintained by the addition of MZR to corticosteroids, and we address the long-term efficacy, safety and steroid-sparing effect of MZR in our case. We initially used CPA as a maintenance therapy. However, CPA has several side effects. CPA was switched to MZR, which shows a lower risk of side effects. The administration of MZR was able to maintain disease remission and allowed us to gradually reduce the oral PSL dose.

TTP is caused by a deficiency of ADAMTS13. Therefore, the measurement of ADAMTS13 activity and antibodies provides important information for the diagnosis of TTP. Severely reduced ADAMTS13 activity confirms the diagnosis of TTP [3]. Moreover, previous reports have suggested that severely reduced ADAMTS13 activity and the existence of inhibitory anti-ADAMTS13 antibody was associated with poor prognosis and frequent relapse [2, 4]. Although the level of ADAMTS13 inhibitor in our case at disease onset was not available, the presence of this inhibitor at relapse suggested that he already had ADAMTS13 inhibitor at disease onset. Because of the patient's severely reduced ADAMTS13 activity and the existence of ADAMTS13 inhibitor, our case had a high risk of relapse.

As described above, PE therapy and corticosteroids are standard treatments for TTP. PE is thought to work by replacing the deficient ADAMTS13 and removing anti-ADAMTS13 antibody. Corticosteroids are thought to suppress the production of anti-ADAMTS13 antibody. Treatment with PE therapy and corticosteroids reduces mortality to about 10–20% [1, 5]. However, a significant number of patients have disease that is refractory to this treatment or that recurs even under this treatment, then they require additional treatment interventions. The incidence of patients who do not respond to PE therapy and corticosteroids, and require additional treatment varies between 10 and 42% [6]. Previous reports have suggested that patients with poorly responsive disease may benefit from an increased dose of corticosteroids, a greater amount of PE therapy and more frequent PE therapy, splenectomy, and the use of rituximab [7] and other immunosuppressive drugs, such as CPA, cyclosporine, and vincristine [6]. However, there are limited data about these additional treatment interventions. Furthermore, among these drugs, CPA, an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis, has several side effects including myelosuppression, infection, infertility, and malignancy. In our case, the patient was relatively young. Owing to the risk of malignancy, we avoided the long-term use of CPA. The common adverse effects of rituximab, a humanized monoclonal antibody

against the B-cell antigen CD20, are infusion reactions, myelosuppression, hepatitis B virus reactivation and progressive multifocal leukoencephalopathy. In contrast to other drugs, MZR generally shows lower toxicity and myelosuppression. Moreover, previous basic science studies have suggested that MZR regulates the glucocorticoid receptor function and might enhance the efficacy of corticosteroids [8]. Actually, a previous clinical study reported that the use of MZR for the treatment of nephrotic syndrome [9] and immunoglobulin A nephropathy [10]. These drug profiles indicate that MZR could be useful and safe as a treatment for TTP.

Next, we discuss the possible etiology of TTP in our case. As we have mentioned, the occurrence of TTP in the setting of autoimmune disorders is well established. From that viewpoint, our patient was initially suspected of having SS. SS represents a group of chronic autoimmune diseases characterized by the infiltration of lymphocytes into several organs, typically the exocrine glands. The salivary and lacrimal glands are often involved, resulting in dry eyes and a dry mouth. SS is primarily treated with symptomatic treatment for ocular, oral, and other symptoms of dryness. Although patients with extra gland involvement may benefit from systemic therapy, there are no established radical treatments aimed at correcting immunological abnormalities with SS. Nakayamada et al. [11] reported the effectiveness and safety of MZR in SS patients. There are few reports on TTP associated with SS because the association of TTP with SS is rare [12]. Although we could not confirm a definite diagnosis of SS in our case, there is a possibility that the administration of MZR could have corrected the underlying immunological abnormalities and then demonstrated efficacy in our case.

In conclusion, this is the first case report of the successful treatment of relapsing TTP with MZR. We found that MZR may be an effective treatment option for cases of refractory TTP. To confirm the efficacy of MZR for refractory TTP patients, it is necessary to accumulate more cases in the future.

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Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent No identifying information about individuals is included in the article.

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