Mizoribine-induced severe hyperglycemia in a patient with microscopic polyangiitis

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Abstract A 77-year-old woman had been receiving prednisolone (PSL) for 5 months as induction therapy for microscopic polyangiitis. Because of repeated elevation of the antineutrophil cytoplasmic autoantibody titer, we added mizoribine (MZR), and, 2 months later, the patient developed severe hyperglycemia with low serum and urinary C-peptide reactivity (CPR). The MZR was, therefore, withdrawn and insulin therapy was started. One month later, the serum and urinary CPR had increased and postprandial hyperglycemia had improved. Previous in vitro studies have shown that MZR can induce hyperglycemia through at least two mechanisms. One is the alteration of insulin secretion from islet cells, and the other is action via the glucocorticoid receptor (GR). MZR reduces insulin secretion through the depletion of intracellular guanosine triphosphate (GTP), which leads to the inhibition of mitogenesis and induction of beta cell apoptosis. MZR affects insulin resistance by activating the GR through interaction with the 14-3-3 protein, leading to postprandial hyperglycemia. Although postprandial hyperglycemia generally appears between 3 and 7 weeks after PSL administration, that in our patient did not become apparent during 5 months of PSL monotherapy, but was manifested

2 months after the introduction of MZR, and improved after MZR had been withdrawn. We conclude from these findings that MZR had been responsible for the hyperglycemia in our patient.

Keywords Mizoribine · Hyperglycemia · Microscopic polyangiitis

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), which includes Wegener's granulomatosis, Churg–Strauss syndrome, and microscopic polyangiitis (MPA), is characterized by necrotic small-vessel vasculitis with ANCA [1]. In Japan, MPA has been reported to account for 90 % of cases of AAV and 19.4 % of cases of rapidly progressive glomerulonephritis [2]. As maintenance therapy for MPA, immunosuppressive agents such as azathioprine and methotrexate are recommended [1, 3]. Recently, however, some reports have described the efficacy of mizoribine (MZR) in this context [4, 5].

Hyperglycemia is one of the common adverse clinical manifestations during treatment for AAV, and is mainly caused by prednisolone (PSL) administration. However, official safety information from pharmaceutical companies indicates that other types of immunosuppressants recommended for the therapy of AAV, i.e., cyclophosphamide (unknown frequency of occurrence, Shionogi & Co., Ltd., Osaka, Japan) and rituximab (3.3–4.1 %, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan), can also cause hyperglycemia [6–8]. MZR can also induce hyperglycemia, but no previous clinical report on this issue is available.

Here, we report a case of severe hyperglycemia induced by MZR in a patient receiving maintenance therapy for

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MPA. We also discuss the effects of MZR on both the pharmacodynamics of PSL and glucose metabolism based on previous experimental findings.

Case report

A 77-year-old woman, who had been treated for MPA, was admitted to our hospital with severe hyperglycemia. MPA had occurred 7 months previously, and a moderate dose of PSL (30 mg/day) had been started as induction therapy. Other concomitant drugs were atorvastatin 5 mg and rabeprazole 10 mg. Complete remission was achieved initially, but the MPO (myeloperoxidase)-ANCA titer became elevated again when the dose of PSL was reduced. Therefore, MZR (100 mg/day) was added to the PSL (Fig. 1). Two months after the introduction of MZR, the patient complained of general fatigue. Laboratory data showed increases in blood glucose (845 mg/dl) and glycosylated hemoglobin [HbA1c (NGSP); 13.8 %], and the serum and urinary levels of C-peptide reactivity (CPR) were reduced to 1.04 ng/ml and 11.5 μ g/day, respectively. The serum sodium concentration was reduced due to hyperglycemia. Arterial blood gas analysis revealed no ketoacidosis. Other laboratory measurements such as serum creatinine, C-reactive protein, and urinalysis parameters showed no deterioration. In addition, anti-GAD (glutamic acid decarboxylase) antibody was negative (Table 1). Abdominal computed tomography revealed no specific findings. Except for MZR, there had been no changes in the administered drugs during the previous several months.

On the basis of these clinical findings, we concluded that the hyperglycemia had been caused by MZR. Therefore, it

was discontinued and intravenous insulin infusion was started. One month after MZR withdrawal, the serum and urinary CPR data improved to 3.25 ng/ml and 20.6 μ g/day, respectively (Fig. 1). Insulin injection was still needed, but the dose was tapered further.

Discussion

In recent years, it has been recommended that immunosuppressive induction therapy for elderly patients with AAV be mitigated, because serious systemic infection is an independent predictor of death [9, 10]. On the other hand, patients without negative conversion of the ANCA titer during induction therapy sometimes develop MPA relapse [11]. Therefore, it is very important to maintain a balance between the strength of immunosuppressive therapy and the occurrence of serious adverse effects. Some previous reports have indicated that the administration of MZR in addition to PSL can reduce the MPO-ANCA titer and prevent relapse without incurring new serious adverse effects [4, 5].

MZR inhibits inosine monophosphate (IMP) dehydrogenase, a soluble enzyme that converts IMP (derived from either the salvage or de novo synthetic pathways) to xanthosine monophosphate, and subsequently to guanosine triphosphate (GTP) [12]. Nucleic acid synthesis in proliferating lymphocytes depends mainly on the de novo pathway, in which IMP dehydrogenase plays an important role. Therefore, MZR exerts an immunosuppressive effect through the inhibition of lymphocyte proliferation. Within a MZR plasma concentration range of 0.1–5.0 μ g/ml, the rate of suppression of lymphocyte proliferation is 36.4–62.2 % [13].

Fig. 1 Clinical course. severe hyperglycemia was apparent 2 months after the start of MZR administration, and this improved immediately after MZR withdrawal. *Cr* creatinine; *MZR* mizoribine, *MPO-ANCA* myeloperoxidase-antineutrophil cytoplasmic autoantibody, *HbA1c* glycosylated hemoglobin, *PSL* prednisolone

Table 1 Laboratory data on admission

Peripheral blood	
WBC	9300/ μ l
RBC	358×10^4 / μ l
Hb	11.2 g/dl
Ht	34 %
Pit	28.7×10^4 / μ l
Blood chemistry	
TP	6.4 g/dl
AST	18 IU/ml
ALT	15 IU/ml
LDH	265 IU/ml
S-Amy	200 IU/ml
BUN	68 mg/dl
Cr	2.5 mg/dl
Na	123 mEq/l
K	5.5 mEq/l
Cl	88 mEq/l
CRP	0.2 mg/dl
Glu	845 mg/dl
HbA1c (NGSP)	13.8 %
Atrial blood gas analysis	
pH	7.384
pCO ₂	32.9 mmHg
pO ₂	80.9 mmHg
HCO ₃ ⁻	20.2 mmol/l
BE	-3 mmol/l
Serological test	
CPR	1.04 ng/ml
MPO-ANCA	48 U/ml
Anti-GAD Ab	-
Urinalysis	
Gravity	1.013
pH	6.5
Protein	+
Occult blood	+
Glucose	3+
Ketone	-
Sediments	
RBC	0–5/HPF
Urinary chemistry	
Protein	0.15 g/gCr
C-peptide	11.5 μ g/day

BE base excess, Anti-GAD Ab anti-glutamic acid decarboxylase antibody

Experimental findings have suggested at least two candidate mechanisms for MZR-induced hyperglycemia: one is an effect on insulin secretion from islet cells, and the other is an effect on the glucocorticoid receptor (GR) [14–16].

It has been demonstrated in vitro that depletion of the intracellular GTP concentration by MZR causes a reduction of exocytotic insulin secretion from islet cells [15]. The other effect of MZR on islet cells is the inhibition of mitogenesis and induction of apoptosis through depletion of the intracellular GTP concentration [14]. The clinically effective and safe trough plasma concentration of MZR is considered to be 0.1–3.0 μ g/ml [13]. The MZR concentration was higher than the clinical range in the former study, but within the appropriate range in the latter.

Concerning the other effect of MZR on glucose metabolism, it increases GR activity through binding with the 14-3-3 protein, which interacts with the ligand-activated GR and exerts a stimulatory effect on its transcriptional activation. MZR affects 14-3-3/GR interaction and increases GR activity in a serum concentration-dependent manner, resulting in the deterioration of insulin resistance. This effect is observed even if the MZR concentration is 0.26 μ g/ml, i.e., within the range of clinical use [16].

Despite these experimental observations, hyperglycemia as an adverse effect of MZR is rare. Postmarketing product surveillance by a Japanese pharmaceutical company (Asahi Kasei Pharma, Tokyo, Japan) has officially recognized that hyperglycemia as an adverse effect of MZR occurs in 0.11 % of all cases for which the drug is administered. In addition, it occurs within 3 months from the start of administration in most cases. However, we speculate that hyperglycemia as an adverse effect of MZR might be masked or underestimated, as MZR is usually administered in addition to glucocorticoid, and it is difficult to distinguish which drug is the causal one.

In our present patient, the serum and urinary CPR levels were low 2 months after the introduction of MZR, and these parameters were ameliorated one month after its withdrawal, indicating that the impairment of insulin secretion had been attributable to MZR. On the other hand, the hyperglycemia in our patient appeared mainly after lunch and dinner, and, thus, corresponded to glucocorticoid-induced hyperglycemia. Although glucocorticoid-induced hyperglycemia generally appears between 3 and 7 weeks after the start of PSL administration [17], the postprandial hyperglycemia in our patient did not become apparent for 5 months during PSL monotherapy, but appeared 2 months after the introduction of MZR. These findings indicate that activation of the GR by MZR also contributed to the development of hyperglycemia.

In conclusion, when administering MZR in combination with PSL, it should be borne in mind that MZR can cause and accelerate hyperglycemia.

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Lapraik C, Watts R, Bacon P, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. *Rheumatology* (Oxford). 2007;46:1615–6.
2. Koyama A, Yamagata K, Makino H, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. *Clin Exp Nephrol*. 2009;13:633–50.
3. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis*. 2009;68:310–7.
4. Hirayama K, Kobayashi M, Hashimoto Y, et al. Treatment with the purine synthesis inhibitor mizoribine for ANCA-associated renal vasculitis. *Am J Kidney Dis*. 2004;44:57–63.
5. Arimura Y, Yoshihara K, Komiya I, Yamato T, Nakabayashi K, Yamada A. ANCA associated vasculitis—changes of clinical features and outcome in microscopic polyangitis and mizoribine therapy in MPO-ANCA associated vasculitis. *Clin Rheumatol*. 2005;17:290–8.
6. Pengelly CR. Diabetes mellitus and cyclophosphamide. *Br Med J*. 1965;1:1312–3.
7. Cyclophosphamide interview form. Shionogi & Co., Osaka, Japan, 2012.
8. Rituximab interview form. Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, 2010.
9. Chen M, Yu F, Zhang Y, Zhao MH. Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. *Medicine* (Baltimore). 2008;87:203–9.
10. Harper L, Savage CO. ANCA-associated renal vasculitis at the end of the twentieth century—a disease of older patients. *Rheumatology* (Oxford). 2005;44:495–501.
11. Gaskin G, Savage CO, Ryan JJ, et al. Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis. *Nephrol Dial Transplant*. 1991;6:689–94.
12. Kusumi T, Tsuda M, Katsunuma T, Yamamura M. Dual inhibitory effect of bredinin. *Cell Biochem Funct*. 1989;7:201–4.
13. Sonda K, Takahashi K, Tanabe K, et al. Clinical pharmacokinetic study of mizoribine in renal transplantation patients. *Transplant Proc*. 1996;28:3643–8.
14. Li G, Segu VB, Rabaglia ME, Luo RH, Kowluru A, Metz SA. Prolonged depletion of guanosine triphosphate induces death of insulin-secreting cells by apoptosis. *Endocrinology*. 1998;139:3752–62.
15. Metz SA, Rabaglia ME, Pintar TJ. Selective inhibitors of GTP synthesis impede exocytotic insulin release from intact rat islets. *J Biol Chem*. 1992;267:12517–27.
16. Takahashi S, Wakui H, Gustafsson JA, Zilliacus J, Itoh H. Functional interaction of the immunosuppressant mizoribine with the 14-3-3 protein. *Biochem Biophys Res Commun*. 2000;274:87–92.
17. Uzu T, Harada T, Sakaguchi M, et al. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. *Nephron Clin Pract*. 2007;105:c54–7.