Mod Rheumatol (2008) 18:634–638
DOI 10.1007/s10165-008-0106-4

CASE REPORT

A sudden onset of diabetic ketoacidosis and acute pancreatitis after introduction of mizoribine therapy in a patient with rheumatoid arthritis

Shunsuke Mori · Kenji Ebihara

Received: 13 April 2008 / Accepted: 24 June 2008 / Published online: 24 July 2008

Abstract Mizoribine has been recognized to have an acceptable toxicity profile compared with other immunosuppressants. In this study, however, we report a case of diabetic ketoacidosis and acute pancreatitis that suddenly occurred in a rheumatoid arthritis patient 2 weeks after introduction of mizoribine therapy. To the best of our knowledge, this is the first case in the literature to show mizoribine-induced diabetic ketoacidosis. Through prompt diagnosis and treatment, the patient recovered from these extremely rare but potentially lethal complications.

Keywords Acute pancreatitis · Diabetic ketoacidosis · Immunosuppressant · Mizoribine · Rheumatoid arthritis

Introduction

Mizoribine, a nucleotide in the imidazole class of compounds, blocks de novo purine biosynthesis in cells via selective inhibition of inosine-monophosphate dehydrogenase and guanosine-monophosphate synthetase in the guanosine triphosphate (GTP) synthetic pathway, thereby suppressing lymphocyte proliferation [1–3]. Due to its efficacy over long periods and a better toxicity profile when compared to other immunosuppressants, this agent has been widely used in Japan mainly for renal transplant recipients and recently for patients with steroid-resistant lupus nephritis [4], nephrotic syndrome [5], Sjögren's syndrome [6], and rheumatoid arthritis (RA) [1, 7].

RA is a chronic systemic inflammatory disease that primarily targets synovial structures, usually involving peripheral joints in a symmetrical distribution. It is now clear that early initiation of disease-modifying antirheumatic drugs (DMARDs) does alter the disease course [8]. A variety of immunosuppressive agents has been approved as DMARDs in many countries since abnormalities of the immune system are thought to underlie the pathogenesis of RA. In clinical practice, mizoribine is considered to be an immunosuppressant adjunctive to prednisolone therapy since concomitant use of both agents reduces the total amount of prednisolone [9, 10]. Further, a recent prospective cohort study suggested that mizoribine is useful for management of patients with methotrexate (MTX)-refractory RA when used in combination [11].

Critical side-effects of mizoribine have rarely been reported. Here we present a case of diabetic ketoacidosis and acute pancreatitis, occurring suddenly in an RA patient 2 weeks after introduction of mizoribine.

Case report

A 75-year-old man was admitted to the emergency room of our hospital due to severe general fatigue, anorexia, thirst, and an altered level of consciousness. The patient had suffered from seropositive RA for 20 years, and he received a low dose of prednisolone (5 mg/day). During this period, the patient had few articular symptoms. The patient also had a 32-year history of diabetes mellitus, which was well controlled by dietetic treatment alone. Two

S. Mori (✉)
Clinical Research Center for Rheumatic Disease and Department of Rheumatology, Kumamoto Saishunsou National Hospital, 2659 Suya, Kohshi, Kumamoto 861-1196, Japan
e-mail: moris@saisyunsou1.hosp.go.jp

K. Ebihara
Division of Metabolic Medicine, Department of Medicine, Kumamoto Saishunsou National Hospital, 2659 Suya, Kohshi, Kumamoto 861-1196, Japan

weeks before emergency admission, the patient first visited our hospital because of a marked increase in disease activity and exacerbation of joint pain and swelling. At that time, the patient fulfilled the 1987 American College of Rheumatology criteria for diagnosis of RA, and he complained of severe pain and swelling of 12 hand joints (four metacarpophalangeal joints, six proximal interphalangeal joints, and both wrist joints). The disease activity score for 28 joints (DAS28-ESR) was high (6.03). The laboratory data regarding RA were as follows: serum C-reactive protein (CRP), 0.32 mg/dl; erythrocyte sedimentation rate, 70 mm/h; serum matrix metalloproteinase-3 (MMP-3), 327 ng/ml; antinuclear antibody, 1:80; and rheumatoid factor, 75 IU/ml). His white blood cell count was 3,940/μl. Neither ocular nor oral symptoms suggestive of Sjögren's syndrome were observed, nor did the patient exhibit persistent bilateral enlargement of the salivary or lachrymal gland, which is the main manifestation of IgG4-related Mikulicz's disease. Skin ulcers and nail fold infarcts, the most frequently observed features of rheumatoid vasculitis, were not found. The patient had no complaints of fever, weight loss, or general fatigue. A high-resolution computed tomography (HRCT) scan of the lungs indicated a bronchiolitis pattern, but there were no abnormal findings suggesting infectious pulmonary diseases. Data from polymerase chain reactions for mycobacterium tuberculosis, mycobacterium avium-intracellulare complex, and mycobacterium kansasii were negative with induced sputum from the patient. No white blood cells were seen in urinalysis. His glycosylated hemoglobin (HbA_1c) was 6.2%. Mizoribine (150 mg/day) and oral gold (auranofin, 6 mg/day) were added to prednisolone therapy. Since he had chronic hepatitis for 10 years due to a hepatitis C virus infection, methotrexate was not selected as the initial DMARD.

Upon emergency admission, a physical examination showed tenderness of the hypochondrium, but neither abdominal rigidity nor distention was observed. No mass was palpable in the abdomen. His tongue was dehydrated and skin turgor had decreased, but jaundice was not observed. Swelling and tenderness of the right elbow were prominent, and disorientation and confusion were observed. The patient's body temperature, blood pressure, and pulse rate were 36.8°C, 110/81 mmHg, and 109/min with no irregularity, respectively. His body mass index was 14.9 kg/m^2. Laboratory data indicated hyperglycemia (plasma glucose, 829 mg/dl), metabolic acidosis (pH, 7.296; P_{O_2}, 88.7 mmHg; P_{CO_2}, 29.1 mmHg; HCO_3^-, 13.7 mmol/l; base deficit, 11.2 mmol/l; lactate, 17 mg/dl), renal dysfunction (blood urea nitrogen, 83.6 mg/dl; creatinine, 1.79 mg/dl), and electrolyte abnormalities (sodium, 127 mEq/l; potassium, 6.95 mEq/l; chloride, 100 mEq/l). Urinalysis showed ketonuria (ketone bodies, 3+) and glucosuria (glucose, 4+). Urine C-peptide reactivity was low (27.4 μg/day), HbA_1c was 6.6%, and antiglutamic acid decarboxylase (anti-GAD) antibody was negative. Liver function test results were normal. The serum level of amylase was high (3,478 IU/l) and pancreatic-type amylase accounted for 100%. White blood cell count was elevated (12,060/μl) and serum CRP was highly increased (13.3 mg/dl); however, bacterial cultures of specimens from venous blood and sputum showed negative results. There was no evidence of pulmonary infections on HRCT films or urinary infections in urinalysis. HRCT scans revealed enlargement and edema of the pancreas as well as high signals in fat tissues around the pancreas, consistent with pancreatic or peripancreatic inflammation. Pleural effusion was evident bilaterally. No gallstones were seen. From these observations, the patient was diagnosed with diabetic ketoacidosis and acute pancreatitis.

Immediately after diagnosis, the patient intravenously received saline and one injection of insulin (8 U). Mizoribine and auranofin were discontinued and intravenous infusion of insulin (4 U/h) was started. Prednisolone was continued due to severe articular symptoms and high disease activity. Five hours later, plasma glucose decreased to 300 mg/dl and the insulin dose was tapered off to 0.5 U/h. On the following day, plasma glucose was around 200 mg/ml, the metabolic acidosis and electrolyte abnormalities were improved, and the ketone bodies and glucose in urine disappeared. For treatment of acute pancreatitis, we used an inhibitor of proteolytic enzymes, nafamostat mesilate (10 mg of intravenous infusion). After 3 weeks, serum levels of amylase and CRP were normalized and abdominal symptoms disappeared. The intravenous infusion of insulin was replaced with a subcutaneous injection (14 U/day). Two months later, fasting glucose levels were maintained under 100 mg/dl and HbA_{1c} was 5.8%. Fasting plasma C-peptide level returned to normal (2.7 ng/ml). Articular symptoms disappeared and CRP was maintained within the normal range. The patient was eventually discharged.

Discussion

In this case, clinical manifestations indicative of ketoacidosis and acute pancreatitis simultaneously occurred 2 weeks after the introduction of mizoribine. Upon withdrawal of mizoribine, these manifestations disappeared. The patient was diagnosed with diabetes mellitus 32 years earlier, but despite the long-term use of prednisolone, his disease had been well controlled without using any drugs. Since auranofin was prescribed for his RA concomitantly with mizoribine, auranofin might have been implicated in development of the complications. Before his first visit to our hospital, however, the patient had received 6 mg/day

auranofin at another clinic for several months, and during this period, he showed no symptoms suggestive of hyperglycemia or pancreatitis. We therefore considered it unlikely that auranofin was involved in the diabetic ketoacidosis and acute pancreatitis occurring 2 weeks after initiation of the drug. Taken together, we diagnosed this case as mizoribine-induced diabetic ketoacidosis and acute pancreatitis.

Hyperglycemia and diabetes mellitus are relatively frequent adverse effects associated with steroid therapy for RA patients. Tacrolimus and cyclosporin A, potent immunosuppressive agents often used as DMARDs, are also recognized to have diabetogenic potential in organ transplant recipients [12, 13]. Meanwhile, there are only a few cases in the literature that present mizoribine-associated hyperglycemia [14] and we found no case of mizoribine-induced diabetic ketoacidosis in a Medline search. In this case, urine C-peptide reactivity was at a low level, thereby suggesting impairment of insulin synthesis or secretion. We therefore considered that such dysfunction of pancreatic β-cells had led to diabetic ketoacidosis. The patient showed diabetic ketoacidosis and insulin deficiency at the time of diagnosis; however, he was negative for anti-GAD antibody, an islet-related autoantibody, and insulin-secretory capability was recovered after severe diabetic ketoacidosis. These features are different from those of autoimmune type 1 diabetes mellitus. High levels of serum amylase were observed at the onset of symptoms, which is reminiscent of fulminant type 1 diabetes [15]; however, this patient showed HRCT findings characteristic of acute pancreatitis. Since the patient had received low-dose prednisolone for 20 years, we were not able to completely exclude the possibility that increased insulin resistance of peripheral tissues by prednisolone may be, at least in part, involved in the diabetic ketoacidosis occurring in this patient. Furthermore, the patient had a 32-year history of diabetes mellitus although insulin therapy had not been required. Peripheral insulin resistance is a prominent feature of type 2 diabetes mellitus. Thus, the diabetogenic potential of mizoribine may be enhanced when administered to patients with such a predisposing factor for hyperglycemia.

The exact mechanism of mizoribine-induced diabetic ketoacidosis remains an unanswered question. Using isolated rat islets, Metz et al. [16] showed that short-term exposure to mizoribine inhibits nutrient-induced insulin secretion from pancreatic β-cells through selective depletion of cellular GTP, suggesting inhibitory effects of mizoribine on β-cell function. They also indicated that prolonged depletion of GTP induces death of β-cells by apoptosis over 1- to 3-day periods [17]. Such toxic effects of mizoribine on β-cells may lead to an insulin-dependent diabetic condition in patients receiving this drug. Takahashi et al. [18] showed the possibility that mizoribine enhances the transcriptional activity of glucocorticoid receptor via 14-3-3 proteins. Mizoribine may, therefore, increase the diabetogenic activity of both prednisolone used in therapy and endogenous glucocorticoids in patients.

Recently, an association between immunosuppressants and acute pancreatitis has been described [19]. However, only one case of mizoribine-induced acute pancreatitis has been reported in the literature, in which 300 mg/day of mizoribine was administered to an RA patient and no abnormal saccharometabolism was evident [20]. Other immunosuppressive drugs with definitive or probable association with acute pancreatitis were not given to our patient at the onset of symptoms. Corticosteroids have been considered a probable cause of pancreatitis [21]. Our patient had received a low dose of prednisolone for several decades, but his symptoms of pancreatitis were resolved without discontinuation of this drug. Drug-associated acute pancreatitis is thought to be due to a hypersensitivity reaction or generation of toxic metabolites. It was not clear which of these mechanisms had been operative in our case. The two-week interval between the initiation of mizoribine and the onset of pancreatitis suggests an allergic mechanism. Yutsudo et al. also reported that mizoribine-induced pancreatitis occurred 12 days after initiation of the drug [20]. Characteristic time intervals between the drug initiation and the development of acute pancreatitis have been reported for respective drugs, and they may provide possible clues to the discovery of underlying mechanisms in which drugs cause acute pancreatitis [22]. Furthermore, a drug may be strongly suspected if there is a consistent latency period between the time of first exposure to the drug and the onset of acute pancreatitis [19, 23]. Other possible causes of acute pancreatitis include biliary tract diseases such as gallstones, hypercalcemia, hypertriglyceridemia, acute and chronic alcoholism, and infections, etc. Based on clinical and laboratory data, these possibilities were excluded from our case. An association of autoimmune pancreatitis with Sjogren's syndrome or IgG4-related Mikulicz's disease has been noted [24, 25]; however, symptoms characteristic of these conditions, such as dry eyes, dry mouth, or a swelling of the salivary or lachrymal gland, were not seen in our case. Since no clinical, laboratory, or radiological features distinguish drug-induced pancreatitis from pancreatitis caused by other etiologies, awareness and knowledge of this entity is important in making an accurate and timely diagnosis.

Over the past few decades, an association of diabetic ketoacidosis and acute pancreatitis has been documented. Nair et al. reported that acute pancreatitis occurs in at least 10–15% of cases with diabetic ketoacidosis [26]. However, the cause-and-effect relationship of these two conditions is complex. Some studies have stipulated that acute

pancreatitis is a primary event, leading to severe injury of pancreatic islet cells and alterations of insulin and/or glucagon levels. Such hormonal disturbances may induce hyperglycemia and ketoacidosis [27]. Others have concluded that acute pancreatitis in diabetes ketoacidosis is a distinct entity, and that transient and profound hypertriglyceridemia, which often occurs in episodes of diabetic ketoacidosis, precipitates acute pancreatitis [26]. Whether acute pancreatitis may be a primary event in adverse reactions of mizoribine or a sequel to mizoribine-induced diabetic ketoacidosis is not clear in our case. There is also the possibility that a two-way cause-and-effect relationship may be established between acute pancreatitis and diabetic ketoacidosis [28]. Moreover, we cannot rule out the possibility that impairment of insulin synthesis or secretion in β-cells, followed by the onset of diabetic ketoacidosis and acute pancreatitis through a drug-allergic mechanism may have occurred independently during mizoribine therapy. Indeed, several reports have shown mizoribine-induced hyperglycemia without the development of acute pancreatitis [14].

Mizoribine is known as an immunosuppressive agent with an acceptable toxicity profile, compared with other DMARDs. However, rheumatologists should be aware that patients are at risk of diabetic ketoacidosis and acute pancreatitis, both extremely rare but potentially lethal complications, after the introduction of mizoribine therapy for RA.

Conflict of interest statement This research work has received no financial support that may pose any conflicts of interest.

References

1. Yokota S. Mizoribine: mode of action and effects in clinical use. Pediatr Int. 2002;44:196–8.
2. Turka LA, Dayton J, Sinclair G, Thompson CB, Mitchell BS. Guanine ribonucleotide depletion inhibits T-cell activation. mechanism of action of the immunosuppressive drug mizoribine. J Clin Invest. 1991;87:940–8.
3. Kamada H, Itoh H, Shibata H, Koshio T, Hayashi A, Nakagami K. Inhibitory mechanism of mizoribine on the antibody production of mouse B-cells stimulated with lipopolysaccharide. Jpn J Pharmacol. 1997;74:323–30.
4. Kuroda T, Hirose S, Tanabe N, Sato H, Nakatsue T, Ajiro J, et al. Mizoribine therapy for patients with lupus nephritis: the association between peak mizoribine concentration and clinical efficacy. Mod Rheumatol. 2007;17:206–12.
5. Yoshioka K, Ohashi Y, Sakai T, Ito H, Yoshikawa N, Nakamura H, et al. A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. Kidney Int.. 2000;58:317–24.
6. Nakayamada S, Saito K, Umehara H, Ogawa N, Sumida T, Ito S, et al. Efficacy and safety of mizoribine for the treatment of Sjogren's syndrome: a multicenter open-label clinical trial. Mod Rheumatol. 2007;17:464–9.
7. Takei S. Mizoribine in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Pediatr Int. 2002;44:205–9.
8. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis. 2007;66:34–45.
9. Saida K, Zhigang Z, Ozawa K, Konishi T, Saida T. Long-term open-trial of mizoribine with prednisolone in 24 patients with multiple sclerosis: safety, clinical and magnetic resonance imaging outcome. Intern Med. 1999;38:636–42.
10. Yumura W, Suganuma S, Uchida K, Moriyama T, Otsubo S, Takei T, et al. Effects of long-term treatment with mizoribine in patients with proliferative lupus nephritis. Clin Nephrol. 2005;64:28–34.
11. Tanaka E, Inoue E, Kawaguchi Y, Tomatsu T, Yamanaka H, Hara M, et al. Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. Mod Rheumatol. 2006; 16:214–9.
12. Fernandez LA, Lehmann R, Luzi L, Battezzati A, Angelico MC, Ricordi C, et al. The effects of maintenance doses of FK506 versus cyclosporin A on glucose and lipid metabolism after orthotopic liver transplantation. Transplantation. 1999;68:1532–41.
13. Yoshida EM, Buczkowski AK, Sirrs SM, Elliott TG, Scudamore CH, Levin A, et al. Post-transplant diabetic ketoacidosis–a possible consequence of immunosuppression with calcineurin inhibiting agents: a case series. Transpl Int. 2000;13:69–72.
14. Okubo S, Nakatani K. Two cases of rheumatoid arthritis complicated with saccharometabolic abnormality caused by mizoribine (in Japanese). Clinical Rheumatol Related Res. 2000;12:40–4.
15. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM study group. N Engl J Med. 2000;342:301–7.
16. 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.
17. 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.
18. 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.
19. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005;39:709–16.
20. Yutsudo Y, Hasegawa Y, Takada T, Yamada H, Aoyama N, Morita S, et al. A case of rheumatoid arthritis (RA) with drug-induced acute pancreatitis due to mizoribine (in Japanese). Ryumachi. 1997;37:564–7.
21. Felig DM, Topazian M. Corticosteroid-induced pancreatitis. Ann Intern Med. 1996;124:1016–3.
22. Dhir R, Brown DK, Olden KW. Drug-induced pancreatitis: a practical review. Drugs Today (Barc). 2007;43:499–507.
23. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol.. 2007;5:648–61. quiz 4.
24. Yamamoto M, Takahashi H, Naishiro Y, Isshiki H, Ohara M, Suzuki C, et al. Mikulicz's disease and systemic IgG4-related plasmacytic syndrome (SIPS) (in Japanese). Nihon Rinsho Meneki Gakkai Kaishi. 2008;31:1–8.

25. Hayakawa T, Naruse S, Kitagawa M, Kondo T. Clinical aspects of autoimmune pancreatitis in Sjogren's syndrome. Jop. 2001; 2:88–92.
26. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. Am J Gastroenterol. 2000;95:2795–800.
27. Pitchumoni CS, Agarwal N, Jain NK. Systemic complications of acute pancreatitis. Am J Gastroenterol. 1988;83:597–606.
28. Kahn D, Bourgeois JA. Acute pancreatitis and diabetic ketoacidosis in a schizophrenic patient taking olanzapine. J Clin Psychopharmacol. 2007;27:397–400.