Thrombocytopenia Induced by Diazoxide in a Patient with an Insulinoma

Junichiro Adachi¹,², Makiyo Mimura¹, Isao Minami¹,³, Kazuhiko Kakihana¹,² and Takayuki Watanabe¹

Abstract

A 24-year-old healthy woman presented at our hospital due to hypoglycemia. A fasting test provoked spontaneous hypoglycemia, and contrast-enhanced abdominal computed tomography revealed a pancreatic tumor. We diagnosed her with insulinoma and initiated diazoxide treatment to prevent hypoglycemia. After 13 days of treatment, she experienced nasal bleeding, and her platelet count decreased from 186,000/μL to 28,000/μL. The thrombocytopenia was ameliorated five days after diazoxide was discontinued. Although diazoxide has hyperglycemic effects associated with decreased insulin secretion, diazoxide-induced thrombocytopenia is rare. A complete blood count should be obtained periodically in patients receiving treatment with diazoxide.

Key words: diazoxide, drug-induced thrombocytopenia, insulinoma


Introduction

Diazoxide is a non-diuretic benzothiadiazine derivative that decreases insulin secretion by opening K⁺-ATP channels in the membranes of β-cells (1, 2). Diazoxide is widely used to control hypoglycemia in patients with insulinoma. Fluid retention and hirsutism are common but manageable adverse effects (3), whereas thrombocytopenia is a rare and fatal adverse outcome. We herein report a case of thrombocytopenia induced by diazoxide and review the literature on this unusual entity.

Case Report

A 24-year-old woman was admitted to our hospital to be examined and treated for hypoglycemia. The patient had been healthy until two months prior to admission, when she began to have occasional palpitations. She had begun to experience difficulty performing routine activities in the morning after waking one month before admission. The day before admission, the patient’s mother had a difficult time waking the patient from sleep. On the day of admission, the patient was brought to the emergency department due to a disturbance of consciousness and urinary incontinence. Her vital signs were normal upon the examination; however, she was disoriented regarding time and place. Her score on the Glasgow Coma Scale was 12 (eye response, 4; verbal response, 4; and motor response, 4), although other aspects of the neurologic and general examinations were normal. The plasma glucose level was 26 mg/dL (reference range, 70 to 109 mg/dL). Although the intravenous infusion of glucose improved the patient’s level of consciousness, she was admitted to our hospital.

The patient drank alcohol occasionally; however, she took no medications, including oral hypoglycemic agents, and had no known allergies. She did not smoke or use illicit drugs or herbal remedies and had no family history of parathyroid, pancreatic or pituitary tumors. The examination results were as follows: blood pressure, 136/91 mmHg; pulse, 89 beats per minute; weight, 54 kg; height, 165 cm; and body mass index (weight in kilograms divided by the square

¹Department of Internal Medicine, Yokohama City Minato Red Cross Hospital, Japan, ²Department of Internal Medicine, Ohkubo Hospital, Japan, ³Department of Molecular Endocrinology and Metabolism, Graduate School of Tokyo Medical and Dental University, Japan and ⁴Department of Hematology, Tokyo Metropolitan Cancer and Infectious Center Komagome Hospital, Japan

Received for publication June 1, 2013; Accepted for publication October 27, 2013
Correspondence to Dr. Junichiro Adachi, junichirou_adachi@tokyo-hmt.jp
of the height in meters), 19.8. The results of neurologic and general examinations, routine laboratory tests, a complete blood count, assessments of the liver and renal function, chest radiography and electrocardiography were normal. Moreover, the electrolyte, lipid, intact-parathyroid hormone and pituitary hormone levels were normal. The patient was asked to fast for 72 hours to determine whether she had hyperinsulinenic hypoglycemia. After 11 hours of fasting, her plasma glucose level was 28 mg/dL, and she exhibited neuroglycopenic symptoms. Concurrent with hypoglycemia, her insulin and C-peptide levels were 11.0 μU/mL and 2.9 ng/mL, respectively. Contrast-enhanced computed tomography of the abdomen demonstrated a hypervascular lesion measuring 20 mm in diameter in the head of the pancreas during the arterial phase.

We proposed placing a central line because the continuous intravenous glucose infusion (100 mg/day) was initiated, which ameliorated her nocturnal hypoglycemic symptoms. During the arterial phase (Fig. 1). The patient was therefore diagnosed with an insulinoma, and treatment with a continuous intravenous glucose infusion (100 mg/day) was initiated, which ameliorated her nocturnal hypoglycemic symptoms. Moreover, the electrolyte, lipid, intact-parathyroid hormone and pituitary hormone levels were normal. The patient was asked to fast for 72 hours to determine whether she had hyperinsulinenic hypoglycemia. After 11 hours of fasting, her plasma glucose level was 28 mg/dL, and she exhibited neuroglycopenic symptoms. Concurrent with hypoglycemia, her insulin and C-peptide levels were 11.0 μU/mL and 2.9 ng/mL, respectively. Contrast-enhanced computed tomography of the abdomen demonstrated a hypervascular lesion measuring 20 mm in diameter in the head of the pancreas during the arterial phase (Fig. 1). The patient was therefore diagnosed with an insulinoma, and treatment with a continuous intravenous glucose infusion (100 mg/day) was initiated, which ameliorated her nocturnal hypoglycemic symptoms. We proposed placing a central line because the continuous peripheral glucose infusion had induced phlebitis; however, the patient refused the procedure. Therefore, we initiated treatment with diazoxide (250 mg/day) to control her hypoglycemia. The results of a complete blood count were normal prior to the initiation of diazoxide. On day 5 of treatment, the dose of diazoxide was increased to 500 mg/day because the previous dose had little effect on the patient’s hypoglycemia. On day 7 of treatment, she developed a sore throat and general fatigue. However, the diazoxide was increased to 600 mg/day because the drug continued to have only a minor effect on the hypoglycemia. On day 10 of treatment, she gained 4.6 kg due to edema and developed chills with a temperature of 38.0°C (Fig. 2). She subsequently developed purpura on her legs two days later, and the platelet count dropped from 186,000 to 28,000/μL two days thereafter. In contrast, the white blood cell, red blood cell and hemoglobin levels did not show any remarkable changes (5.300/μL to 3.800/μL, 325×10^4/μL to 320×10^4/μL and 9.5 g/dL to 9.1 g/dL, respectively). Bone marrow aspiration demonstrated normal bone cellularity and a normal to increased number of megakaryocytes (Fig. 3), thus indicating that the patient’s thrombocytopenia was due to increased peripheral destruction. We suspected drug-induced thrombocytopenia and discontinued the diazoxide. The next day, her platelet count decreased to 12,000/μL, and nasal hemorrhage occurred; thus, we administered prednisolone (30 mg/day) followed by two days of consecutive platelet transfusions. Following the discontinuation of diazoxide, the platelet count increased to greater than 50,000/μL after five days and was normal after eight days. She lost 3.2 kg eight days

**Figure 1.** Contrast-enhanced computed tomography of the abdomen. A contrast-enhanced computed tomography scan of the abdomen showed a hypervascular lesion (black arrow) measuring 20 mm in diameter in the head of the pancreas during the arterial phase.

**Figure 2.** Course of thrombocytopenia in the patient treated with diazoxide. Diazoxide was used to treat an insulinoma in a 24-year-old woman. The patient developed chills and a fever on day 10 of treatment. She subsequently developed purpura on her legs on day 12 of treatment, and the diazoxide was discontinued thereafter. The platelet count was 28,000/μL. Consecutive platelet transfusions were administered on days 13 and 14; however, they had a minor effect on the platelet count. The thrombocytopenia subsided over the next few days.

**Figure 3.** Bone marrow aspiration. A high number of megakaryocytes with a small and immature morphology was observed. The myeloid: erythroid ratio was 4–5:1. Myeloid precursors were normal in number and left-shifted without a relative increase in the number of promyelocytes or blasts. The number of erythroid precursors was normal.
after diazoxide was discontinued. The dose of prednisolone was tapered 25 days after the drug was first administered, then eventually stopped. The patient was referred to another hospital for enucleation of the pancreatic tumor and did not experience symptoms of hypoglycemia after undergoing this surgical procedure. The pathological findings were indicative of an insulinoma.

Discussion

This case report demonstrates that diazoxide can cause acute thrombocytopenia, as the patient’s platelet count increased following discontinuation of diazoxide. This is the fourth reported case of thrombocytopenia induced by diazoxide (4, 5).

An insulinoma is a pancreatic neuroendocrine tumor that secretes excessive insulin, which is associated with symptoms of hypoglycemia (6, 7). Surgical removal is the best option for treating insulinomas (8); however, the administration of diazoxide to control symptomatic hypoglycemia is an alternative (2). This case was very rare with respect to the patient’s age. The ages of previously reported patients with this condition were 1 month, 15 years and 41 years (4, 5). A review of adverse experience reports of thrombocytopenia induced by diazoxide in Japan (9) indicated that 12 cases have been reported. Of these 12 patients, three were infants and seven were older than 60 years of age. The frequency with which this condition has been reported in these age groups may reflect the background of the patients for several reasons. First, diazoxide is the first choice for treating hyperinsulinemic hypoglycemia in infancy (10). Second, surgery may not be indicated in older patients with insulinoma due to their general condition.

Most patients taking diazoxide experience fluid retention and hirsutism; however, hematological adverse effects are rare. Diazoxide is administered at doses of 100 to 200 mg 3 times a day, or up to 1,500 mg/day (3, 11). The mean reported diazoxide dose is 250 to 400 mg/day (3, 6). In contrast, the mean reported diazoxide dose in cases of thrombocytopenia is 600 to 1,200 mg/day (4, 5). In the present case, the dose of diazoxide was increased up to 600 mg. Therefore, the development of thrombocytopenia may be associated with the dose of diazoxide.

Drug-induced thrombocytopenia is recognized to be an adverse effect of treatment with a broad range of medications (12). Generally, previously reported patients received the sensitizing agents for at least one week before developing petechiae or ecchymoses due to thrombocytopenia. The typical clinical manifestation of drug-induced thrombocytopenia is the detection of isolated thrombocytopenia. The severity of bleeding usually depends on the platelet count. Some severely affected patients (platelets less than 10,000/μL) develop extensive mucous membrane bleeding, including nasal bleeding and gastrointestinal hemorrhage (12, 13). Patients with drug-induced thrombocytopenia can present with faintness, chills, fever, nausea and neutropenia, which often precede bleeding symptoms (13-15). In the present case, chills and fever preceded bleeding.

Small particles derived from these agents can trigger drug-induced thrombocytopenia. Many of these drugs are involved in the induction of immune thrombocytopenia, which occurs via six established pathways (12). Most of these agents, including quinine-type drugs, induce antibodies that bind to platelet membrane proteins (12, 13). These antibodies have a low affinity for these antigens under normal circumstances. Agents that cause drug-induced thrombocytopenia possess structural elements that can fit between drug-dependent antibodies and platelet antigens, thereby increasing the affinity between the antigens and antibodies. These medications affect B-cell functions, such as antibody production and affinity maturation, which cause cell destruction (12-14).

Drug-induced thrombocytopenia should be suspected in patients who exhibit the acute onset of severe thrombocytopenia of unknown etiology. A period of five to seven days of drug exposure is required to sensitize patients who are given a drug for the first time (12). Therefore, the drug history of each patient should be evaluated carefully. Initially, it is difficult to distinguish drug-induced thrombocytopenia from acute autoimmune thrombocytopenia (16); however, the detection of drug-dependent anti-platelet antibodies is helpful for confirming the cause of drug-induced thrombocytopenia (12, 17). It is often possible to distinguish antibodies that respond to normal platelets in the presence, but not absence, of the drug (18). However, detecting drug-dependent anti-platelet antibodies is not always possible in patients with probable drug-induced thrombocytopenia (12). Although we did not detect any drug-dependent antibodies in this case, we speculate that the pathogenesis was Quinine-type immune thrombocytopenia for several reasons. First, Quinine-type immune thrombocytopenia promotes antibody binding at pharmacologic concentrations (12). Second, the thrombocytopenia appeared to develop and progress as the dose of diazoxide was increased in this case.

Discontinuing the sensitizing medication is essential for treating drug-induced thrombocytopenia (13), and the platelet count typically recovers within five to seven days after withdrawing the suspected drug (19). Platelet transfusions should be used in patients with severe thrombocytopenia and extensive mucous membrane bleeding due to the risk of fatal intracranial hemorrhage. Corticosteroids are often administered, although concrete evidence to support their efficacy in cases of drug-induced thrombocytopenia is lacking (12, 19). In the present case, the patient’s platelet count recovered eight days after drug discontinuation. We administered corticosteroids because we were unable to rule out the possibility of immune thrombocytopenic purpura. It is not clear whether the administration of corticosteroids had a beneficial effect on the recovery phase of the diazoxide-induced thrombocytopenia.

In conclusion, this report describes a case of thrombocytopenia induced by diazoxide in a patient with an insuli-
noma. This case suggests that a complete blood count should be obtained periodically in patients taking diazoxide. Furthermore, diazoxide should be discontinued in patients who develop either purpura or a flu-like syndrome after the initiation of treatment.

The authors state that they have no Conflict of Interest (COI).

References