

Case report

Rapid reversal of severe thrombocytopenia after cessation of diazoxide in a 1.7-year-old girl with hyperinsulinemic hypoglycemia

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Abstract:

Background: Hyperinsulinism-hyperammonemia (HI/HA) syndrome is a rare genetic form of hyperinsulinemic hypoglycemia. While diazoxide is the first-line medical therapy for this condition, it has been associated with several adverse effects, ranging from fluid retention to rare hematologic complications. **Case Description:** A 1.7-year-old girl with HI/HA syndrome, confirmed by a monoallelic pathologic variant in the *GLUD1* gene (c.1466C>A, p.Pro-489His), presented with a sudden onset of generalized ecchymoses, petechiae, and wet purpura. These symptoms emerged three weeks after initiating diazoxide therapy at 5 mg/kg/day. Investigations revealed severe isolated thrombocytopenia (platelet count $4 \times 10^9/L$). An elevated immature platelet fraction (10.5%) and a low one-hour corrected count increment following platelet transfusion suggested an immune-mediated destructive process. Diazoxide was immediately discontinued. Following a single platelet transfusion and cessation of the drug, the patient's platelet count recovered rapidly, normalizing within 48 hours and reaching $487 \times 10^9/L$ two weeks after. **Conclusion:** This case highlights a rare but severe presentation of diazoxide-induced thrombocytopenia in a pediatric patient. Laboratory confirmation of an immune process, most likely via a quinine-type mechanism, is consistent with the patient's rapid recovery. Clinicians should maintain a high index of suspicion for hematologic toxicity among patients treated with diazoxide, as prompt discontinuation of the offending agent leads to rapid clinical and laboratory recovery.

Keywords : ● Thrombocytopenia ● Diazoxide ● Hyperinsulinism ● Drug-induced thrombocytopenia

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รายงานผู้ป่วย

ภาวะเกล็ดเลือดต่ำอย่างรุนแรงที่ฟื้นตัวอย่างรวดเร็วหลังหยุดยา Diazoxide ในผู้ป่วยเด็กหญิงที่มีภาวะน้ำตาลในเลือดต่ำจากระดับอินซูลินสูงผิดปกติ

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¹โรงพยาบาลรามธิบดีจักรีนฤเบดินทร์ ²โรงเรียนแพทย์รามธิบดี สถาบันการแพทย์รามธิบดีจักรีนฤเบดินทร์ คณะแพทยศาสตร์โรงพยาบาลรามธิบดี มหาวิทยาลัยมหิดล

บทคัดย่อ

ที่มาและความสำคัญ กลุ่มอาการอินซูลินและแอมโมเนียในเลือดสูง (Hyperinsulinism-hyperammonemia หรือ HI/HA syndrome) เป็นโรคทางพันธุกรรมที่พบไม่บ่อย ส่งผลให้เกิดภาวะน้ำตาลในเลือดต่ำ Diazoxide เป็นยาหลักที่ใช้ในการรักษาภาวะนี้ แต่มีผลข้างเคียงได้หลากหลายตั้งแต่ภาวะบวมน้ำไปถึงภาวะแทรกซ้อนทางโลหิตวิทยาที่รุนแรง **รายงานผู้ป่วย** เด็กหญิงอายุ 1.7 ปี ได้รับการวินิจฉัยกลุ่มอาการ HI/HA ซึ่งยืนยันด้วยการตรวจพันธุกรรมพบ monoallelic pathologic variant ของยีน GLUD1 (c.1466C>A, p.Pro489His) หลังได้รับการรักษาด้วย diazoxide ขนาด 5 มิลลิกรัม/กิโลกรัม/วัน เป็นเวลา 3 สัปดาห์ ผู้ป่วยมีรอยช้ำ จุดเลือดออกตามตัวและในเยื่อช่องปาก

การตรวจทางห้องปฏิบัติการพบภาวะเกล็ดเลือดต่ำรุนแรงโดยมีค่าเกล็ดเลือด $4 \times 10^9/L$ พบค่า immature platelet fraction สูงขึ้น (10.5%) และการตอบสนองต่อการให้เกล็ดเลือดที่ 1 ชั่วโมง (one-hour corrected count increment) ต่ำ บ่งชี้ว่าสาเหตุเกิดจากกระบวนการทำลายเกล็ดเลือดผ่านระบบภูมิคุ้มกัน ผู้ป่วยได้รับการรักษาโดยการหยุดยา diazoxide ทันที และได้รับเกล็ดเลือดทดแทน หลังหยุดยาระดับเกล็ดเลือดของผู้ป่วยเพิ่มขึ้นอย่างรวดเร็ว และกลับมาเป็นปกติภายใน 48 ชั่วโมง

สรุป รายงานผู้ป่วยรายนี้แสดงให้เห็นถึงภาวะเกล็ดเลือดต่ำจากการใช้ยา diazoxide ซึ่งเป็นภาวะที่พบบ่อยแต่มีความรุนแรง การตรวจทางห้องปฏิบัติการสนับสนุนสาเหตุจากกระบวนการทางภูมิคุ้มกันที่ถูกกระตุ้นจากยา โดยเกิดผ่านกลไกแบบ quinine-type ซึ่งสอดคล้องกับการฟื้นตัวของเกล็ดเลือดอย่างรวดเร็วในผู้ป่วยรายนี้ ดังนั้น แพทย์ที่รักษาควรมีความตระหนักและเฝ้าระวังภาวะแทรกซ้อนทางโลหิตวิทยาในผู้ป่วยที่ได้รับยา diazoxide หากเกิดภาวะเกล็ดเลือดต่ำรุนแรงขึ้น การหยุดยาได้ทันท่วงทีจะสามารถช่วยให้ผู้ป่วยฟื้นตัวได้อย่างรวดเร็วและปลอดภัย

คำสำคัญ : ● ภาวะเกล็ดเลือดต่ำ ● ภาวะน้ำตาลในเลือดต่ำ ● อินซูลินในเลือดสูง ● ภาวะเกล็ดเลือดต่ำจากยา

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2569;36:231-7.

Introduction

Hyperinsulinism (HI) is characterized by the dysregulated secretion of insulin, leading to profound hypoglycemia. The genetic etiology of HI frequently involves mutations in genes such as *ABCC8*, *KCNJ11*, *GLUD1*, and *GCK*.¹ Conversely, nongenetic, transient forms are often associated with perinatal stress, intrauterine growth restriction (SGA), or maternal diabetes.

Diazoxide is the first-line treatment for hyperinsulinemic hypoglycemia; however, its efficacy is contingent upon the underlying molecular cause. By binding to the sulfonylurea receptor-1 (SUR1) subunit of the adenosine triphosphate-sensitive potassium (K_{ATP}) channel, diazoxide increases potassium permeability, hyperpolarizing the pancreatic beta cell and subsequently suppressing calcium-dependent insulin secretion.²

While generally well-tolerated, adverse effects such as fluid retention and hypertrichosis are common.³ Thrombocytopenia is a rare complication, occurring in 0 to 4.7% of pediatric cases.³⁻⁷ The underlying pathophysiology remains elusive, though an immune-mediated mechanism has been proposed. Currently, no definitive evidence establishing the cause of diazoxide-induced thrombocytopenia exists, so we present a case of a girl who developed the condition following diazoxide treatment. This report investigates potential mechanisms, the rapid recovery observed, and clinical implications of this rare adverse reaction.

Case report

A 1.7-year-old girl, who was diagnosed with hyperinsulinism-hyperammonemia (HI/HA) syndrome since age of 1.6 years, presented with multiple small ecchymoses three weeks after starting diazoxide. She had recurrent seizures secondary to multiple hypoglycemic episodes. Genetic testing revealed monoallelic pathologic variants of the *GLUD1* gene (c.1466C>A, p.Pro489His), consistent with HI/HA syndrome. With no previous family history of bleeding disorder, she was treated with diazoxide

at a dose of 5 mg/kg/day. No other agents that could cause thrombocytopenia were administered.

Three weeks later, her caretakers noticed ecchymoses on all her extremities. No history of infection was recalled during the past two months before the onset of ecchymoses. Physical examination revealed wet purpura at the buccal mucosa, some petechiae at both forearms, and generalized multiple small ecchymoses, predominantly on the lower extremities. Otherwise, they were unremarkable.

Complete blood count (CBC) showed hemoglobin 115 g/L, white blood cell count $9,610 \times 10^6/L$ (neutrophil 19, lymphocyte 74, monocyte 4, atypical lymphocyte 3%) and platelets $4 \times 10^9/L$. The CBC, at one month prior, revealed a normal platelet count. Peripheral blood smear demonstrated markedly decreased platelet number with normal-to-large size and normal staining without platelet clumping (Figure 1). Immature platelet fraction (IPF) was 10.5% (normal 1.0-5.0), analyzed using an XN-9000 automated hematology analyzer (Sysmex).

Diazoxide was discontinued, and leukocyte-depleted pooled platelet concentrate at 4.8×10^{11} cells (120 mL) was given due to severe thrombocytopenia with mucosal bleeding. Platelet count was slightly increased from 4×10^9 to $6 \times 10^9/L$ within one hour. The efficacy of the platelet transfusion was assessed by calculating the corrected count increment (CCI), defined as the product of the absolute platelet increment (per μL) and the patient's body surface area (m^2), divided by the total number of platelets transfused ($\times 10^{11}$).⁸ Therefore, CCI at one hour after transfusion showed $0.2 \times 10^9/L$ (normal one-hour CCI $> 5 \times 10^9/L$). Platelet counts revealed 49×10^9 , 191×10^9 , and $487 \times 10^9/L$ at 24 hours, 48 hours, and 2 weeks after this event, respectively (Figure 2).

Having discussed with the caretakers, diazoxide was discontinued, and frequent feeding with avoidance of prolonged fasting was advised. Self-monitoring blood glucose was performed without any episode of hypoglycemia.

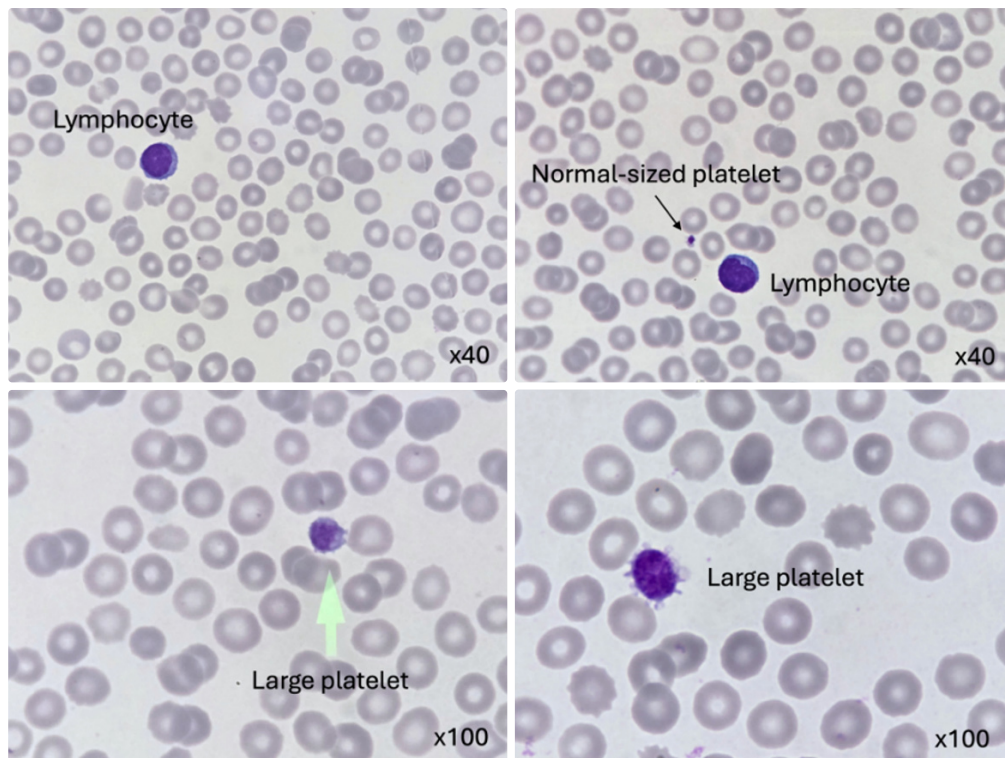


Figure 1 Peripheral blood smear showing markedly decreased platelets without platelet clumping. Large platelets were noted.

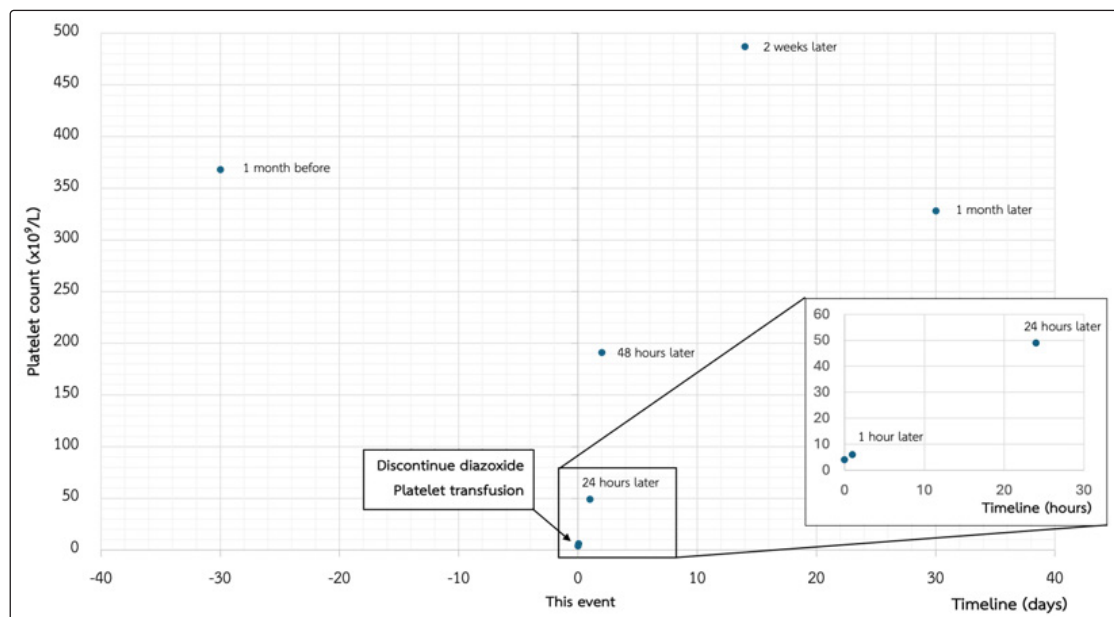


Figure 2 Demonstration of platelet count in this patient. This graph showed rapid recovery of platelet count within 48 hours after discontinuing diazoxide.

Discussion

This patient was diagnosed with HI/HA syndrome, which is congenital HI caused by the *GLUD1* variant. She was initially treated with diazoxide and developed thrombocytopenia three weeks thereafter. Drug-induced immune thrombocytopenia (DITP) was suspected. Platelet

nadir from DITP may be lower than 20,000/L concurrently with clinical bleeding.⁹ Diazoxide was likely the causative drug, as it constituted the only agent introduced to this child at the time of thrombocytopenia. Its onset collided with the manifestation of thrombocytopenia.¹⁰ Related studies reported eight patients with HI who

presented thrombocytopenia while receiving diazoxide. However, the dual use of hydrochlorothiazide (HCTZ) with diazoxide in the treatment of HI made it difficult to define the cause of thrombocytopenia^{6,11} because HCTZ was also reported to have DITP.^{12,13} This study highlighted that diazoxide alone can cause thrombocytopenia. The degree of thrombocytopenia is severe, comparable to that in one related report.¹¹

To determine the mechanism of thrombocytopenia in this patient, IPF played a practical role in distinguishing the causes of thrombocytopenia between increased platelet destruction and decreased platelet production.¹⁴ IPF are young, reticulated platelets, reflecting thrombopoiesis. The use of IPF in clinical practice has increased, for example, to determine the mechanism of thrombocytopenia, to support diagnosis of immune thrombocytopenia or aplastic anemia, to predict the bone marrow recovery after chemotherapy or hematopoietic stem cell transplantation.¹⁴⁻¹⁷ A high IPF count in this case suggests increased platelet destruction supporting the diagnosis of DITP. However, the availability of this specific laboratory test depends on the institution.

To confirm the diagnosis of DITP, a systematic evaluation including the in-vitro evidence of antibody binding that depends on the drug, the specific immunoglobulin binding, and the platelets being the target of immunoglobulin binding, is required.¹⁸ However, these special laboratory tests are not widely available. The basic laboratory investigation, such as CCI, can be helpful to demonstrate the immune destructive process. CCI is generally recommended for patients receiving multiple platelet transfusions and are suspected of having platelet refractoriness. One-hour CCI of less than $< 5 \times 10^9/L$ is suspected to have immune platelet destruction.¹⁹ We use CCI to confirm the underlying mechanism of thrombocytopenia because the mechanism of diazoxide leading to thrombocytopenia remains unclear, which might lead to management decisions

regarding the case of bleeding, for example, high-dose intravenous immunoglobulin.^{10,20} A practical point to calculate CCI is that clinicians must know the exact number of transfused platelets. While some centers count platelets in every bag, others perform random sampling, depending on their policy. When platelet count is unknown, the clinician can request a count from the platelet unit's segment and determine the total platelet dose by multiplying the concentration by the product's volume. The CCI result in this case confirmed the immune platelet destruction from diazoxide.

We propose that DITP in this case was the quinine-type as described in literature.⁹ In quinine-type DITP, the suspicious agent binds to antibodies, inducing an antibody configuration enhancing antibody affinity for the platelet glycoprotein. This results in the formation of a tri-molecular complex consisting of the drug, the antibody, and the platelet. These antibody-sensitized platelets are rapidly destroyed in the reticuloendothelial system. However, the bond between the antibody complementarity-determining regions and platelet epitopes is non-covalent and drug-dependent. Because this interaction is reversible, the antibody's affinity for platelets drops significantly once the drug is cleared from the system.

In our patient, platelet counts began to recover within 24 hours and normalized within 48 hours of discontinuing diazoxide. This timeline is consistent with the drug's clearance, in which platelet recovery typically occurs after four to five half-lives.¹⁰ While diazoxide has a half-life of 28 ± 8.3 hours among adults²¹, it becomes notably shorter among children, ranging from 5.9 to 27.7 hours.²² Our patient's recovery was faster than the seven to eight days reported in previous reported cases.^{11,23} This accelerated recovery may be attributed to more rapid drug metabolism among children, who typically possess a higher hepatic volume-to-weight ratio, increased hepatic blood flow, and lower plasma protein binding.^{24,25}

Onset of thrombocytopenia in our case occurred late at about three weeks after starting diazoxide, while thrombocytopenia occurred as early as 3 to 14 days in other studies.^{11,23} According to the Pediatric Endocrine Society, CBC should be tested before treatment as a baseline, five to seven days after diazoxide administration, and every three to six months thereafter.²⁶ In addition, we suggest CBC monitoring five to seven days after dosage increment. Immediate cessation of the suspicious drug was warranted after thrombocytopenia occurred.^{10,27}

After exclusion of other possible causes, rechallenge of the suspicious agent helps confirm the diagnosis of DITP.^{10,27} However, rechallenging is limited in many settings, and false negatives occur frequently.^{9,10,27} In our case, after thoroughly discussing with parents, rechallenge was deemed improper as the risk outweighed the benefits. Fortunately, conservative management sufficed for this patient. Her hypoglycemia improved with frequent feeding.

Genetic analysis helps determine the causes of hyperinsulinemic hypoglycemia; therefore, treatment differs according to genetic types. The *GLUD1* variant found in our patient is reported to be diazoxide-responsive, whereas recessive variants in the K_{ATP} channel (*ABCC8*, *KCNJ11*) do not respond well to diazoxide treatment.²⁶ When available, determining the genetic cause may help avoid unnecessary use of diazoxide, preventing the risk of thrombocytopenia.

Conclusion

This case highlights a rare but life-threatening complication of diazoxide therapy in a pediatric patient with HI/HA syndrome. While diazoxide is a first-line treatment, clinicians should monitor CBC during the initial weeks of therapy to detect thrombocytopenia. The rapid recovery of platelet counts following drug withdrawal suggests a reversible, immune-mediated mechanism. Therefore, immediate cessation of diazoxide is mandatory upon suspicion, necessitating a shift to alternative glycemic management such as dietary intervention.

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