

Case report

Drug-induced immune hemolytic anemia from piperacillin-tazobactam

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Abstract:

Drug-induced immune hemolytic anemia (DIIHA) is an uncommon medical condition occurring in approximately 1 to 4 cases per 1,000,000 individuals. DIIHA can occur through various mechanisms. One of the mechanisms is the antibody production against red blood cells, leading to immune hemolysis. This case report describes a patient who, after receiving piperacillin-tazobactam (Tazocin®), developed clinical anemia and hemolysis. A direct antiglobulin test was positive for IgG, and the elution test was negative to all the panel cells. We then performed the drug-treated and presence of drug test to confirm the DIIHA diagnosis. After discontinuing piperacillin-tazobactam, the patient's clinical condition was improved.

Keywords : ● Drug-induced immune hemolytic anemia ● Antibiotics ● Piperacillin-tazobactam
● Drug adverse reactions

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รายงานผู้ป่วย

รายงานผู้ป่วยที่มีภาวะเม็ดเลือดแดงแตกจากยา piperacillin-tazobactam

ปริญธร นาคดี กัญยาพร สุขสอาด และ เจนจิรา กิตติวรภัทร

ภาควิชาเวชศาสตร์การธนาคารเลือด คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

ภาวะเม็ดเลือดแดงแตกจากยาเป็นภาวะที่พบได้ไม่บ่อย พบในอัตราส่วน 1-4:1,000,000 ประชากร สามารถเกิดได้จากหลายกลไก หนึ่งในนั้นคือเกิดจากยากระตุ้นทำให้ร่างกายสร้างแอนติบอดีต่อเม็ดเลือดแดงโดยตรง และเกิดการทำลายเม็ดเลือดแดง รายงานผู้ป่วยฉบับนี้ เป็นการรายงานผู้ป่วยหลังได้รับยา piperacillin-tazobactam (Tazocin®) แล้วมีภาวะช็อค เม็ดเลือดแดงแตก ตรวจพบ direct antiglobulin test ให้ผลบวกชนิด IgG และการตรวจ elution test ให้ผลลบกับเซลล์มาตรฐาน เมื่อนำไปตรวจด้วยวิธี drug treated และ presence of drug ให้ผลเข้าได้กับภาวะเม็ดเลือดแดงแตกจากยา หลังจากหยุดยา อาการช็อคและภาวะเม็ดเลือดแดงแตกของผู้ป่วยดีขึ้น

คำสำคัญ : ● ภาวะเม็ดเลือดแดงแตกจากยา ● ยาปฏิชีวนะ ● เพิเพอราซิลลิน-ทาโซแบ็กแทม ● ภาวะแทรกซ้อนจากยา
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Introduction

Drug-induced immune hemolytic anemia (DIIHA) is an uncommon medical condition occurring in approximately 1 to 4 cases per 1,000,000 individuals¹. Currently, over 140 drugs have been reported to cause DIIHA². DIIHA can be classified into three categories: 1) drug-dependent category which was further divided into drug-treated and presence of soluble drug mechanisms; 2) drug-independent category and 3) non-immunologic protein adsorption (NIPA)². The first category requires the interaction between the implicated drug and the red blood cell (RBC) membrane. This category can occur either by hapten-specific mechanism, i.e., drug-treated or immune complex mechanism, i.e., presence of soluble drug. The prototypes for the former are penicillin or piperacillin and the latter are cephalosporin antibiotics^{1,2}. Meanwhile, the drug-independent category was first identified in a patient who received methyldopa in 1966³. The mechanism involves the formation of cross-reactive antibodies to RBCs which is difficult to differentiate from an autoimmune hemolytic anemia (AIHA). The prototype of NIPA category is platinum-based chemotherapy. The affected drug alters the RBC membrane, causing the proteins in plasma to be adsorbed onto RBCs. In a previously reported case of NIPA from cephalothin antibiotic, the direct antiglobulin test (DAT) was positive, but hemolytic anemia did not occur. *In vitro*, RBCs incubated in plasma containing cephalothin were coated with various proteins. Agglutination was not often observed when the eluate was tested with cephalothin-treated RBCs at 37°C due to the low level of proteins in the eluate¹.

Case report

A 32-year-old Thai female with underlying diseases of non-transfusion dependent thalassemia (NTDT) hemoglobin H/Constrant Spring (HbH/CS) disease and paroxysmal atrial fibrillation, was admitted to the hospital due to dengue infection with anemia, hemoglobin (Hb) level of 5.2 g/dL. Her baseline Hb was approximately 6.0

g/dL. She received one unit of RBC transfusion during the admission. One week after discharge, the patient presented to the hematology clinic with low-graded fever and progressive dyspnea. She also had jaundice with darkening of urine. Her blood test showed Hb 2.7 g/dL, hematocrit (Hct) 5.6%, reticulocyte count 6.6%, LDH 970 U/L, total bilirubin 2.73 mg/dL and indirect bilirubin 1.9 mg/dL. She was diagnosed with acute hemolytic anemia and treated as an inpatient. An attending physician ordered one unit of RBC transfusion and started piperacillin-tazobactam (Tazocin[®]) as a prophylaxis antibiotic to cover hospital-acquired infection. A summary of her diagnosis, laboratory findings, treatments, and transfusions during this period is described in Table 1. An automated column agglutination test, CAT (IH-500; Bio-Rad, Cressier Switzerland) of current pre-transfusion testing this time was shown in Table 2.

ABO discrepancy and positive autocontrol were identified. We hypothesized that they were an effect of cold autoantibody. We then retested with warmed and washed RBCs using conventional tube test (CTT). The cell grouping was negative with anti-A, 4+ agglutinate with anti-B and anti-D. Due to insufficient plasma, we were unable to perform the reverse grouping and antibody identification. However, the previous blood group of the patient was group B, RhD+ with a history of developing anti-Mi^a, anti-S, anti-Jk^b, anti-Fy^b and unidentified antibodies. Her RBC phenotyping was recorded as C+C+D+e+e+, K-, Mi(a-). Two compatible RBC units (one group B and one group O RBCs) were transfused to the patient with no reported of transfusion reaction. The following day, an attending physician ordered three more units of RBCs. The pre-transfusion testing, antibody screening, and identification were performed and suspected of drug interference as demonstrated in Table 3, 4a, 4b, and 4c.

The reactions to all panel cells were positive with different grading and we could not specify the antibody at that time. Since the autocontrol showed positive results, the direct agglutination test (DAT) was performed

Table 1 Clinical course of the patient

Date	Diagnosis	Lab investigation	DAT	Treatment	Transfusion
4/9/2023	Dengue infection with menstrual period with anemia	Hb 2.2 g/dL	Not tested	Pip/tazo 1 dose	Prestorage filter blood (PFB) 1 unit - compatible
12/9/2023	Acute anemia with anemic symptom	Hb 2.7 g/dL reticulocyte count 6.6% LDH 970 (mg/dL) indirect bilirubin 1.9 mg/dL	DAT 2+	Pip/tazo 3 dose	PFB 1 unit - compatible leukocyte poor blood (LPB) 1 unit - compatible
13/9/2023		Hb 3.7 g/dL	Not tested		PFB 2 units - compatible
15/9/2023	DIHA	Hb 4.5 g/dL	Not tested	Stop pip/tazo	
18/9/2023		Hb 4.9 g/dL	DAT 3+		
28/9/2023		Hb 3.3 g/dL	DAT 2+		PFB 1 unit - compatible
5/10/2023		Hb 5.3 g/dL	negative		

Table 2 Pre-transfusion testing of the patient by column agglutination test (CAT) automation (IH-500; Bio-Rad)

Date	Cell grouping			Ctrl	Serum grouping	
	Anti-A	Anti-B	Anti-D		A ₁ cells	B cells
	2+	4+	4+	2+	3+	2+
12/09/2023	Screening Cells					
	O ₁	O ₂	O ₃			
	1+	+/-	0			

Ctrl = control

Table 3 Pre-transfusion testing of the patient by CTT

Date	Cell grouping			Ctrl	Serum grouping	
	Anti-A	Anti-B	Anti-D		A ₁ cells	B cells
	0	mf	4+	0	3+	2+
13/09/2023	Screening Cells					
	O ₁	O ₂	O ₃			
	2+	w+	w+			

mf = mixed field; Ctrl = control

and yielded a 2+ reaction. We did the acid elution test to exclude the delayed hemolytic transfusion reaction. Unexpectedly, the eluate gave negative results with all the panel cells as illustrated in Table 5.

One of the frequent findings of panreactive antibody identification and positive autocontrol, but showed negative reactions from an eluate sample is DIHA. The

patient did not have a history of recent incompatible blood component transfusion or intravenous immunoglobulin (IVIG) treatment. We then reviewed all the medications administered to the patient in the past months (supplemental data). Piperacillin/tazobactam (pip/tazo; Tazocin[®], Wyeth Lederle S.r.l. Catania, Italy) was the only suspected drug that caused DIHA in this

Table 4a Antibody identification with an in-house panel cells

No.	Rh-hr				MNS				P		Lewis		Kidd		Duffy		Kell				Diego		Lutheran		Xg	Test result by CAT							
	D	C	E	c	e	C ^w	f	V	M	N	S	s	MI ^a	P ₁	Le ^a	Le ^b	Jk ^a	Jk ^b	Fy ^a	Fy ^b	K	k	Kp ^a	Kp ^b	Js ^a		Js ^b	Di ^a	Di ^b	Lu ^a	Lu ^b	Xg ^a	
1	+	+	+	+	+	/	/	/	0	+	0	+	+	+	0	+	+	+	+	0	0	+	+	/	/	/	/	0	+	0	+	/	1+
2	+	0	+	+	+	/	+	/	+	0	0	+	0	0	+	0	+	+	+	+	+	+	+	/	/	/	/	0	+	0	+	/	1+
3	+	+	0	0	+	/	/	/	+	+	0	+	+	+	+	0	+	+	+	0	0	+	+	/	/	/	/	0	+	0	+	/	2+
4	0	0	+	+	+	/	+	/	+	+	0	+	0	0	0	+	0	+	+	0	0	+	+	/	/	/	/	0	+	0	+	/	w+
5	+	+	0	+	+	/	+	/	+	+	0	+	+	+	0	+	0	+	+	0	0	+	+	/	/	/	/	0	+	0	+	/	1+
6	+	0	+	+	0	/	/	/	+	0	+	+	0	0	0	0	0	+	0	0	0	+	+	/	/	/	/	0	+	0	+	/	w+
7	0	0	0	+	+	/	+	/	+	0	0	+	0	0	0	+	+	+	+	+	0	+	+	/	/	/	+	+	0	+	/	w+	
8	+	+	0	+	+	/	+	/	+	0	0	+	+	0	0	+	+	0	0	0	0	+	+	/	/	/	/	0	+	0	+	/	1+
9	+	+	0	0	+	/	/	/	+	+	+	0	0	0	0	+	0	0	+	+	0	0	+	/	/	/	/	0	+	0	+	/	1+
10	+	+	+	0	0	/	/	/	+	0	0	+	0	+	0	0	0	+	+	0	0	+	+	/	/	/	/	0	+	0	+	/	1+
11	+	+	0	0	+	/	/	/	+	0	+	+	0	0	0	0	0	+	+	0	0	+	+	/	/	/	/	+	+	0	+	/	0
Autocontrol																												2+					

CAT = column agglutination technique; reaction was graded as 0 = negative; / = not tested; w+ = weakly positive, 1+, 2+, 3+, 4+

Table 4b Antibody identification with CAT, automation (Vision max; Ortho Clinical Diagnostics) panel cells Lot No. 8RA21

No.	Rh-hr				MNS				P	Lewis		Kidd		Duffy		Kell				Diego	Lutheran		Xg	Test result by										
	D	C	E	c	e	C ^w	f	V		M	N	S	s	Mi ^a	P ₁	Le ^a	Le ^b	Jk ^a	Jk ^b		Fy ^a	Fy ^b			K	k	Kp ^a	Kp ^b	Js ^a	Js ^b	Di ^a	Di ^b	Lu ^a	Lu ^b
1	+	+	0	0	+	+	0	0	+	+	+	+	/	+	+	0	+	+	+	0	0	+	0	+	+	/	+	/	/	0	+	+	+	2+
2	+	+	0	0	+	0	0	0	0	+	0	+	/	0	0	+	0	+	0	+	+	+	+	0	0	+	/	/	/	0	+	0	0	FIB
3	+	0	+	0	+	0	0	0	+	+	+	+	/	+s	0	+	+	0	+	0	0	+	0	+	0	+	/	/	/	0	+	0	0	FIB
4	+	0	0	+	+	0	+	0	0	+	0	+	/	+s	0	0	+	0	0	0	0	0	+	0	+	/	/	/	0	+	0	+	+	FIB
5	0	+	0	+	+	0	+	0	+	+	0	+	/	0	0	+	0	+	+	0	0	0	+	0	+	/	/	/	0	+	+	+	+	FIB
6	0	0	+	+	+	0	+	0	+	0	+	+	/	+	0	+	+	0	+	0	0	0	+	0	+	/	/	/	0	+	0	+	+	2+
7	0	0	0	+	+	0	+	0	+	0	+	+	/	0	0	+	+	+	0	+	+	+	0	+	0	+	/	/	/	0	+	+	+	1+
8	0	0	0	+	+	0	+	0	+	+	0	+	/	0	+	0	+	+	0	+	0	0	+	0	+	/	/	/	0	+	+	+	+	1+
9	0	0	0	+	+	0	+	0	+	0	+	0	/	+	0	0	+	0	+	+	+	0	0	+	0	+	/	/	/	0	+	+	+	0.5+
10	0	0	0	+	+	0	+	0	0	+	0	+	/	0	0	+	0	+	+	0	0	0	+	0	+	/	/	/	0	+	0	0	0	1+
11	+	+	0	0	+	0	0	0	0	+	0	+	/	0	0	+	+	+	0	+	+	+	0	0	+	/	/	/	0	+	+	+	+	FIB
Autocontrol																												2+						

CAT = column agglutination technique; FIB = fibrin; reaction was graded as 0 = negative; / = not tested; 0.5+ = weakly positive, 1+, 2+, 3+, 4+

Table 4c Antibody identification with CAT, automation (IH-500; Bio-Rad) panel cells Lot No. 645713 75 2

No.	Rh-hr				MNS				P		Lewis		Kidd		Duffy		Kell				Diego		Lutheran		Xg	Test result by							
	D	C	E	c	e	C ^w	f	V	M	N	S	S	MI ^a	P ₁	Le ^a	Le ^b	Jk ^a	Jk ^b	Fy ^a	Fy ^b	K	k	Kp ^a	Kp ^b	Js ^a		Js ^b	Di ^a	Di ^b	Lu ^a	Lu ^b	Xg ^a	
1	+	+	0	0	+	+	/	/	+	+	0	+	/	0	0	+	+	0	+	0	+	0	+	0	+	/	/	/	/	0	+	+	1+
2	+	+	0	0	+	0	/	/	+	0	0	+	/	+	0	+	+	+	0	+	+	+	0	+	/	/	/	/	/	0	+	/	2+
3	+	0	+	+	0	0	/	/	+	0	0	+	/	0	0	0	0	+	0	+	0	+	0	+	/	/	/	/	/	0	+	+	1+
4	0	+	0	+	+	0	/	/	0	+	0	+	/	+	0	+	+	0	+	0	+	0	+	0	+	/	/	/	/	0	+	+	2+
5	0	0	+	+	+	0	/	/	+	0	+	+	/	0	0	+	+	0	+	+	0	+	0	+	/	/	/	/	/	0	+	+	1+
6	0	0	0	+	+	0	/	/	+	0	+	0	/	+	0	+	0	+	0	+	0	+	0	+	/	/	/	/	/	0	+	+	1+
7	0	0	0	+	+	0	/	/	+	+	0	+	/	+	0	0	+	0	+	0	+	0	+	+	/	/	/	/	/	0	+	/	2+
8	+	0	0	+	+	0	/	/	+	+	+	0	/	+	0	+	+	+	0	0	0	0	+	0	+	/	/	/	/	0	+	+	1+
9	0	0	0	+	+	0	/	/	+	0	+	0	/	+	0	0	+	0	+	0	+	0	+	0	+	/	/	/	/	0	+	+	1+
10	0	0	0	+	+	0	/	/	0	+	0	+	/	0	+	0	0	+	0	+	0	+	0	+	/	/	/	/	/	0	+	/	2+
11	0	0	0	+	+	0	/	/	+	0	0	+	/	+	+	0	0	+	+	0	0	0	+	0	+	/	/	/	/	+	+	0	3+
Autocontrol																												2+					

CAT = column agglutination technique; reaction was graded as 0 = negative; / = not tested; w+ = weakly positive, 1+, 2+, 3+, 4+

Table 5 Antibody identification of the eluate used the in-house panel cells

No.	Rh-hr				MNS				P	Lewis		Kidd		Duffy		Kell				Diego		Lutheran		Xg	Test result by								
	D	C	E	c	e	C ^w	f	V	M	N	S	s	Mi ^a	P ₁	Le ^a	Le ^b	Jk ^a	Jk ^b	Fy ^a	Fy ^b	K	k	Kp ^a	Kp ^b	Js ^a	Js ^b	Di ^a	Di ^b	Lu ^a	Lu ^b	Xg ^a	CAT	
1	+	+	+	+	0	/	/	/	+	0	0	+	0	+	0	+	+	+	+	0	0	+	+	/	/	/	/	0	+	0	+	/	0
2	+	+	+	+	+	/	/	/	0	+	+	+	0	0	0	+	+	+	+	+	0	+	/	/	/	/	/	0	+	0	+	/	0
3	0	+	0	0	+	/	/	/	+	+	0	+	+	+	0	+	+	+	+	0	0	+	/	/	/	/	/	0	+	0	+	/	0
4	+	+	+	0	+	/	/	/	+	+	0	+	0	+	0	+	+	+	+	0	+	+	/	/	/	/	/	0	+	0	+	/	0
5	0	0	0	+	+	/	+	/	+	0	0	+	+	+	0	+	+	+	+	+	0	+	/	/	/	/	/	0	+	0	+	/	0
6	+	+	0	+	+	/	+	/	+	+	+	+	0	+	+	0	+	0	0	0	+	0	/	/	/	/	/	+	+	0	+	/	0
7	+	+	0	0	+	/	/	/	+	0	+	0	0	0	0	+	+	+	+	0	0	+	/	/	/	/	/	0	+	0	+	/	0
8	+	0	+	+	0	/	/	/	+	+	0	+	0	0	0	+	+	+	+	0	0	+	/	/	/	/	/	0	+	0	+	/	0
9	+	+	+	0	+	/	/	/	+	0	0	+	0	+	+	0	+	0	0	0	0	+	/	/	/	/	/	0	+	0	+	/	0
10	+	+	0	+	+	/	+	/	+	0	0	+	0	+	0	0	0	0	+	0	0	+	/	/	/	/	/	+	+	0	+	/	0
11	+	+	0	0	+	/	/	/	+	+	0	+	0	0	0	+	0	0	+	0	0	+	/	/	/	/	/	0	+	0	+	/	0
Autocontrol																												NT					

CAT = column agglutination technique; NT = not tested; / = not tested; reaction 0 = negative; + = positive

patient. The patient received one dose of the pip/tazo on the previous admission (29/08/2023) and three doses during this admission (12/09/2023 to 14/09/2023).

The pip/tazo was the antibiotics previously reported as a cause of DIIHA by a drug-dependent immunization mechanism⁴. We then confirmed the diagnosis of DIIHA by pip/tazo in this patient by using drug-treated RBC and the presence of a solution of drug test.

Materials and Methods⁵

Red cells and reagents preparation

The patient's clotted blood sample was separated into packed red cells and serum. Then the aliquot serum was diluted at 1:20 with normal saline. The red cell sample was eluted using acid elution technique; the eluate and last wash were collected for further testing. The control red cells were prepared from pooling less than 7-day-old phenotype-matched group O RBCs. The pooled serum using as a control was prepared from less than 7-day-old group AB serum without an unexpected antibody.

Drug-treated red cells

Drug-treated RBC sample was prepared by dissolving 600 mg of pip/tazo in 15 mL of 0.1 M sodium barbital buffer (BB) and added 1 mL of red cells. After incubated for 1 hour at room temperature with occasional mixing, the samples were washed three times and prepared as a final solution, 5% RBC suspension in phosphate-buffered saline (PBS).

The presence of a soluble drug

The presence of a soluble drug test is an *in vitro* assay to simulate the *in vivo* immune response to the drug. We used pooled group O RBCs mixed with the patient's serum with and without adding the drug. The pooled group AB serum and PBS were used as negative controls. Enzyme treatment increases hemolysis reaction at 37°C compared to the untreated sample.

Results

The drug-treated RBCs sample reacted strongly to the patient's serum at the antiglobulin (AHG) phase when compared to the untreated RBCs. The reaction was also observed in the 1:20 diluted serum. These reactions suggest that the strong antibody to the drug is present in the patient's serum. There might be the pip/tazo antibody present in the normal serum, but it is usually weaker and would disappear upon dilution (Table 6). The eluate, last wash, and PBS served as negative controls of the test.

According to the presence of a soluble drug test, as demonstrated in Table 7, the patient's serum produced similar results with and without the added drug. This finding is explained by the presence of the specific drug in the patient's serum. The papain-treated RBCs facilitate the reactions of the tests (Figures 1a and 1b). The weakly positive reactions observed in the AHG phase of the pooled serum sample are due to antibodies to pip/tazo in a normal population.

Table 6 The drug-treated RBCs test

Sample tested	Drug-treated RBCs			Untreated RBCs		
	37°C (60 min)	AHG	CCC	37°C (60 min)	AHG	CCC
Patient's serum	w+	3+	NT	0	w+	NT
Patient's serum diluted 1:20	0	1+	NT	0	0	1+
Eluate	0	0	1+	0	0	1+
Last wash	0	0	1+	0	0	1+
Pooled normal serum	0	1+	NT	0	0	1+
Pooled normal serum diluted 1:20	0	0	1+	0	0	1+
PBS	0	0	1+	0	0	1+

PBS = phosphate buffer solution; AHG = antihuman globulin; CCC = Coombs control cells; NT = not tested; RBCs = red blood cells

Table 7 The presence of the soluble drug test

Sample tested	Papain-treated RBCs			Untreated RBCs		
	37°C (90 min)	AHG	CCC	37°C (90 min)	AHG	CCC
Patient's serum + Drug	PH	4+	NT	0	1+	NT
Patient's serum + PBS	PH	4+	NT	0	w+	NT
Patient's serum + Pooled serum + Drug	PH	4+	NT	0	1+	NT
Patient's serum + Pooled serum + PBS	PH	4+	NT	0	w+	NT
Pooled serum + Drug	0	1+	NT	0	0	1+
Pooled serum + PBS	0	1+	NT	0	0	1+

PBS = phosphate-buffered saline; AHG = antiglobulin test; PH = partial hemolysis; CCC = coombs control cells; NT = not tested; RBCs = red blood cells

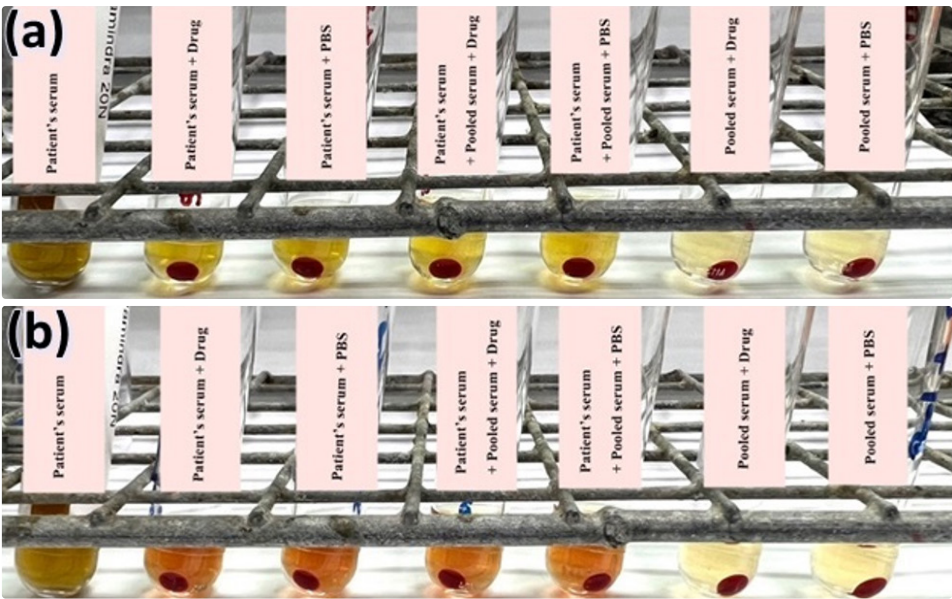


Figure 1 Presence of a soluble of drug test of the patient's serum against (a) the untreated RBCs and (b) the papain-treated RBCs at 37°C, incubated for 90 minutes

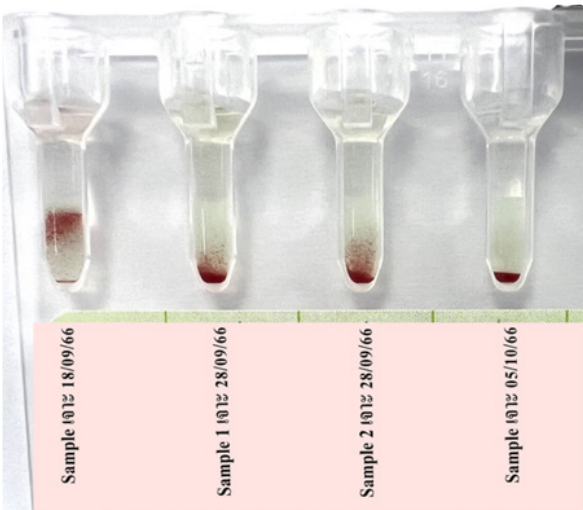


Figure 2 DAT of the patients on days 4, 14, 14, and 21 post-cessation of piperacillin/tazobactam. The reactions were graded as 3+, 2+, 2+, and negative, respectively

Thus, the drug-treated RBCs and the presence of soluble drug assays confirmed the DIIHA of the patient from pip/tazo. The blood bank had informed the physician to discontinue the pip/tazo and follow up DAT along with antibody screening. The intensity of DAT was weakening and became undetectable on day 21 (Figure 2 and Table 8). Similarly, the antibody became undetectable on day 14 after cessation of pip/tazo (Table 8).

Discussion

This case study represents a DIIHA observed in a HbH/CS spring disease patient. The patient was presented with hemolytic anemia 1 week after RBC transfusion (4/9/2023). Her Hb level was 2.7 g/dL, Hct 5.6% from the pre-transfusion Hb of 5.2 g/dL, Hct 15.8%. The differential diagnoses of this hemolytic crisis are 1) acute hemolysis from sepsis and fever in a thalassemic patient, but this diagnosis cannot explain the positive

Table 8 Timeline of the reactions of DAT and antibody screening results

Days after cessation of drug	Polyspecific DAT	Antibody screening
-9	Negative	NT
-2	2+	Positive
(12/09/2023) Start pip/tazo		
-1	2+	Positive
0	NT	NT
(14/09/2023) Off pip/tazo		
+4	3+	Positive
+14	1+	Weakly positive
+21	Negative	NT

DAT = direct agglutination test; NT = not tested

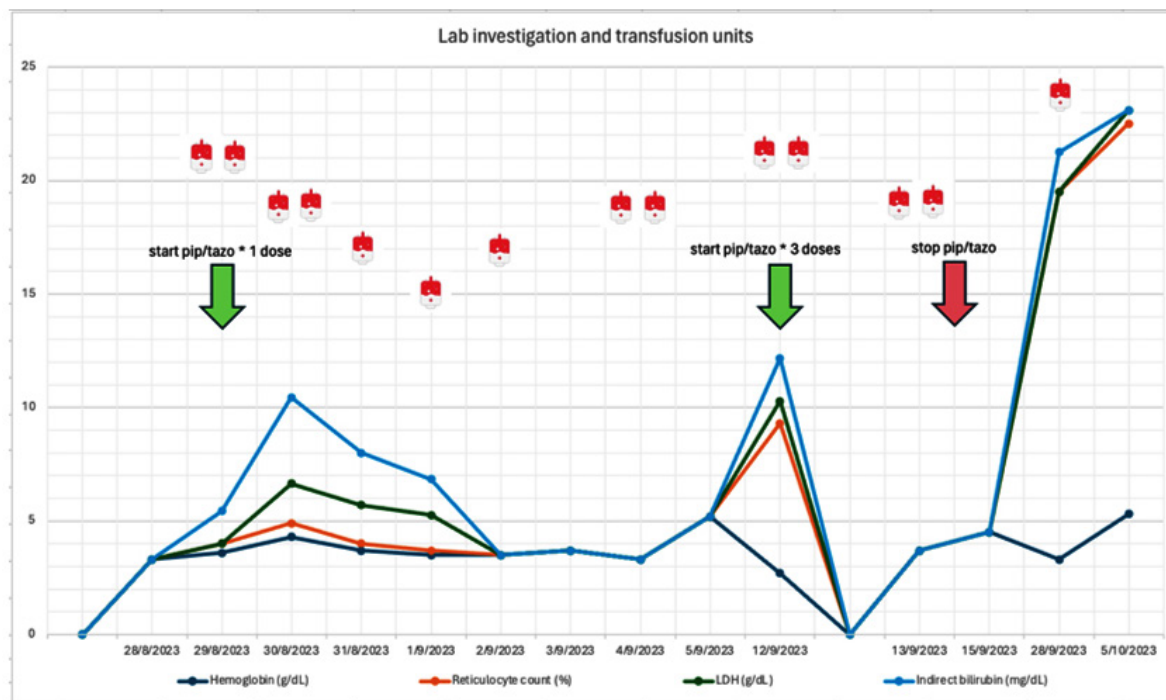


Figure 3 Timeline of the patient receiving piperacillin/tazobactam (pip/tazo), transfusion support, and the relevant laboratory parameters. The initial Hb before receiving pip/tazo was 5.2 g/dL (05/09/2023) then the Hb was decreased to 2.7 g/dL (12/09/2023). The reticulocyte count and bilirubin increased; the hemolysis laboratory markers were elevated. Once the drug was stopped, all the parameters returned to pre-exposure levels

DAT of the patient, 2) secondary AIHA triggered by infection; this is the most likely diagnosis, 3) delayed hemolytic transfusion reaction; because the hemolysis developed during 24 hours to 28 days after blood transfusion. Antibody screening was positive after receiving blood compared to the previous antibody screening result, which was still negative.

During this admission, the patient received 4 units of RBC over 2 days, but the Hb increased by only 2 g/dL (Hb 2.7 g/dL to 4.5 g/dL). The investigation showed evidence of hemolysis, including positive monospecific IgG DAT. However, the eluate was negative with all panel cells. The diagnosis of DIIHA was proposed and after reviewing all the medication records, pip/tazo is suspected as a causation. The patient had received one dose of pip/tazo on her last visit (August 2023). We performed drug-treated RBCs and the presence of a soluble drug assays as serological tests confirming the diagnosis. The patient received pip/tazo for three days. After cessation of the drug, the Hb gradually increased without blood transfusion. The clinical and laboratory findings of hemolysis also improved. The antibody screening and DAT became undetectable after 14 and 21 days after withholding pip/tazo, respectively.

Pip/tazo is a combined drug between piperacillin and tazobactam sold under the brand Tazocin®. Piperacillin is a semi-synthetic penicillin against pseudomonas and tazobactam is a beta-lactamase broad-spectrum antibiotic. The pip/tazo is a broad-spectrum antibiotic, typically used in critical patients or immunocompromised hosts. However, piperacillin is common to cause DIIHA and can lead to fatal hemolytic anemia⁴. This case report is an example of a patient who developed DIIHA from pip/tazo and improved after discontinuing the drug. Several cases of pip/tazo causing DIIHA have been reported^{4,6-8}. All of the cases were presented with acute anemia within one or two weeks after drug exposure. The pip/tazo antibody identified can be either IgG or IgM and occasionally have a specificity for Rh e+ RBCs⁷.

Once the diagnosis of DIIHA from pip/tazo is suspected; the patient should be discontinued of the drug and switched to pseudomonas-covered antibiotics as indicated. In cases of mild hemolysis, discontinuing the implicated drug and providing transfusion support would be sufficient. Other options for treatment include IVIG administration, corticosteroids, and erythropoietin injection^{4,6-8}.

A diagnosis of DIIHA is challenging and likely underdiagnosed. The clinical presentations of DIIHA can be varied from mild anemia to fatal complications. However, once the diagnosis is suspected, the laboratory investigator team and physicians should discuss the possibility. Discontinuation of the implicated drug and other alternative treatments are considered along with providing supportive care. The authors hope this case report will raise awareness of the DIIHA risk associated with commonly prescribed medications.

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