

Research Article

A case of Ceftriaxone-induced immune thrombocytopenia: A diagnostic and therapeutic dilemma

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Introduction

Drug-induced immune thrombocytopenia (DITP) is a rare and often difficult-to-diagnose cause of thrombocytopenia, caused by drug-dependent platelet antibodies leading to increased platelet consumption and destruction. DITP evolves within 7 days of initiation of the offending drug and is characterized by thrombocytopenia, with or without bleeding manifestations. Immediate discontinuation of the inciting drug remains the cornerstone of management. Although the most commonly identified drugs are quinine, penicillamine, and valproic acid, isolated cases of ceftriaxone-induced immune thrombocytopenia have been reported.

Case Report

A 60-year-old female presented with fever, dysuria, and fatigue for 3 days with associated proximal muscle weakness for a few weeks. She was diagnosed with right pyelonephritis with urine cultures growing non-ESBL (extended-spectrum beta-lactamase) Escherichia Coli for which she was started on Ceftriaxone 2g daily. She was also started on low-dose prednisone 20mg daily for fibromyalgia. Her platelet count continued to downtrend and on day 7 of treatment reached a nadir of 18K/µL. Heparin-induced thrombocytopenia (HIT) was excluded. She received one unit of platelets and ceftriaxone was switched to ceftazidime, with which her platelet counts improved. Owing to the temporal relationship between the development and resolution of thrombocytopenia with the commencement and withdrawal of ceftriaxone, drug-induced thrombocytopenia was diagnosed. Naranjo's algorithm revealed a probable adverse drug reaction but confirmatory tests for ceftriaxone-induced platelet antibodies could not be performed.

Discussion

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DITP remains a diagnosis of exclusion and poses a significant therapeutic challenge. Clinicians need to have a high index of suspicion to rule out common causes of unexplained thrombocytopenia before diagnosing DITP.

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Introduction

Drug-induced immune thrombocytopenia (DITP) has been identified as a rare cause of isolated thrombocytopenia among in-hospital patients [1]. It can often be severe and life-threatening in the setting of persistent thrombocytopenia, with a platelet nadir reaching as low as 20,000/μL [2]. DITP occurs due to the formation of drug-dependent platelet reactive antibodies, activating platelet consumption signaling and leading to accelerated platelet destruction. This etiology is unique from other causes of isolated thrombocytopenia, such as heparin-induced thrombocytopenia (HIT) which leads to platelet activation and thrombosis [3]. The reported incidence is 10 in 1,000,000 cases, and the diagnosis is that of exclusion, established by clinical correlation and temporal profile of drug initiation. In cases of DITP, the thrombocytopenia occurs within 7-10 days of drug initiation and resolves within 5-7 days after discontinuation, but this has been known to vary [4]. The most commonly implicated drugs are quinine, valproic acid, vancomycin, penicillamine, and clotrimazole [4].

Ceftriaxone is a third-generation cephalosporin, which is usually known for causing drug-induced hemolytic anemia, but a few cases of DITP have been reported [5]. Hereby, we report a case of a 60-year-old female who developed ceftriaxone-induced thrombocytopenia while receiving antibiotic therapy for pyelonephritis.

Case Presentation

A 60-year-old female presented with complaints of fever, dysuria, and generalized weakness for 3 days. However, prior to presentation, she had ongoing complaints of progressively worsening back pain, myalgia, lower extremity pain, difficulty ambulating and getting up from sitting position along with some near-falls caused by her knees giving way for the last few weeks. She had a history of hypertension and dyslipidemia well controlled on medications, a remote history of secondary hemochromatosis due to blood transfusions which was treated and presently not on any chelator therapy, and alcohol use in a dependent pattern leading to fatty liver. She had maintained her sobriety for the past 3 years. She also had a hospital admission with multiple diffuse neurological symptoms 3 years ago, during which an MRI brain ruled out any intracranial abnormality and she was diagnosed with a functional neurological disorder. She denied any over-the-counter or herbal medication use. Her vital signs revealed a temperature of 97.6 F, heart rate of 110 beats/min in sinus rhythm, blood pressure of 96/64 mmHg, BMI of 28 kg/m2, and oxygen saturation of 98% on room air. Physical exam was significant for impaired attention and concentration, a myopathic pattern of weakness characterized by proximal muscle weakness in bilateral upper and lower limbs, and otherwise normal respiratory, cardiac, and abdominal exam with no renal angle tenderness. Laboratory investigations demonstrated normal blood counts which were at baseline. The chemistry panel was significant for normal electrolytes, and mildly increased total and direct bilirubin levels with elevated liver enzymes. Inflammatory markers including Erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) were also increased (Table 1). Tick-borne illness panel, including babesiosis and Lyme disease, was negative. CT brain without contrast was unremarkable. CT of the abdomen and pelvis revealed hepatic steatosis and right-sided pyelonephritis but no features of a renal abscess. She was started on intravenous ceftriaxone 2g daily. Blood cultures were sterile and urine cultures grew non-ESBL (extended-spectrum beta-lactamase) Escherichia Coli. MRI of the brain showed signs of chronic white matter angiopathy with unremarkable MRI of the whole spine. She was also started on low-dose steroids with Prednisone 20mg daily for possible polymyalgia rheumatica and was continued on ceftriaxone to complete a planned 10-day course.

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Laboratory investigations/Day	1	2	3	4	5	6	7	8	9	10	11
Hemoglobin (11-15 g/dL)	13.2	11.4	11.2	10.8	11.1	12.4	11.0	10.5	11.3	12.1	11.8
WBC (4-11 x1000/uL)	10.0	7.6	6.5	8.1	7.4	7.2	7.8	6.4	6.1	7.1	5.8
Platelets (150-450 x1000/uL)	134	95	58	51	48	35	18	24	20	36	47
Sodium (134-144 mEq/L)	134	135	138	139	137	140	139	144	142	138	139
Potassium (3.5-5.5 mEq/L)	4.3	4.5	4.2	4.4	4.1	3.8	3.9	4.6	4.0	3.9	4.4
Creatinine (0.5-1.5 g/dL)	1.56	1.53	1.49	1.34	1.08	0.94	0.84	0.76	0.71	0.54	0.51
Calcium (8.3-10 mg/dL)	9.3	9.1	8.7	8.5	8.4	9.2	9.5	8.9	8.4	9.0	9.1
Total Bilirubin (0.1-1.2 mg/dL)	1.7	1.3	1.1	0.9	0.8	0.6	0.5	0.5	0.3	0.2	0.3
Direct Bilirubin (0-0.4 mg/dL)	1.1	0.5	0.3	0.2	0.1	0.1	0.2	0.1	0	0	0.1
AST (0-40 U/L)	213	201	122	74	38	34	30	24	26	31	28
ALT (0-32 U/L)	117	83	81	72	50	40	31	28	24	20	21
Alkaline Phosphatase (25-150 U/L)	357	299	284	231	217	184	146	121	108	97	102
Total Protein (6-8.5 g/dL)	5.7	4.8	4.6	5.1	5.3	5.0	5.2	5.4	4.9	5.7	5.8
Albumin (3.5-5 mg/dL)	2.9	2.8	3.1	2.8	2.9	2.7	3.0	3.1	3.2	3.8	3.8
ESR (2-15 mm/hr)	66	-	-	-	-	-	-	41	-	-	-
CRP (0-5 mg/L)	212	-	-	-	-	-	-	109	-	-	-

Table 1. Laboratory investigations during the course of hospital admission.

Her platelet levels continued to downtrend during antibiotic therapy without any bleeding manifestations, reaching a nadir of 18000/μL on day 7 (Figure 1). A peripheral smear was significant for a diminished number of platelets per high power field, but no platelet clumps or schistocytes were visualized. Reticulocyte count was elevated suggestive of an appropriate bone marrow response. The disseminated intravascular coagulation panel was negative with normal fibrinogen and negative D-Dimer and fibrin degradation products. Her hemoglobin and white blood cell count remained stable. She was also found to have normal iron stores, vitamin B12, and folic acid levels. She was on subcutaneous heparin for deep vein thrombosis prophylaxis which was discontinued, and her 4T score was calculated to be 3. PF4 (Platelet Factor-4) antibodies and serotonin release assay were negative, ruling out HIT (Heparin-induced thrombocytopenia). She was transfused with 1 unit of platelets which improved the platelet count transiently to 24000/ μL, but it kept downtrending again. DITP was suspected due to the temporal profile of the thrombocytopenia after antibiotic initiation and the exclusion of all other potential causes. Her ceftriaxone was discontinued and switched over to ceftazidime. The day post-antibiotic change, platelet counts began to improve. She overall had significant symptomatic improvement and an MRI abdomen revealed improving pyelonephritis with no other intra-abdominal pathology. Her kidney function and liver function tests also normalized during the period of admission. Her platelet count on discharge was 47,000/μL and was found to be 114,000/μL at a two-week follow-up.

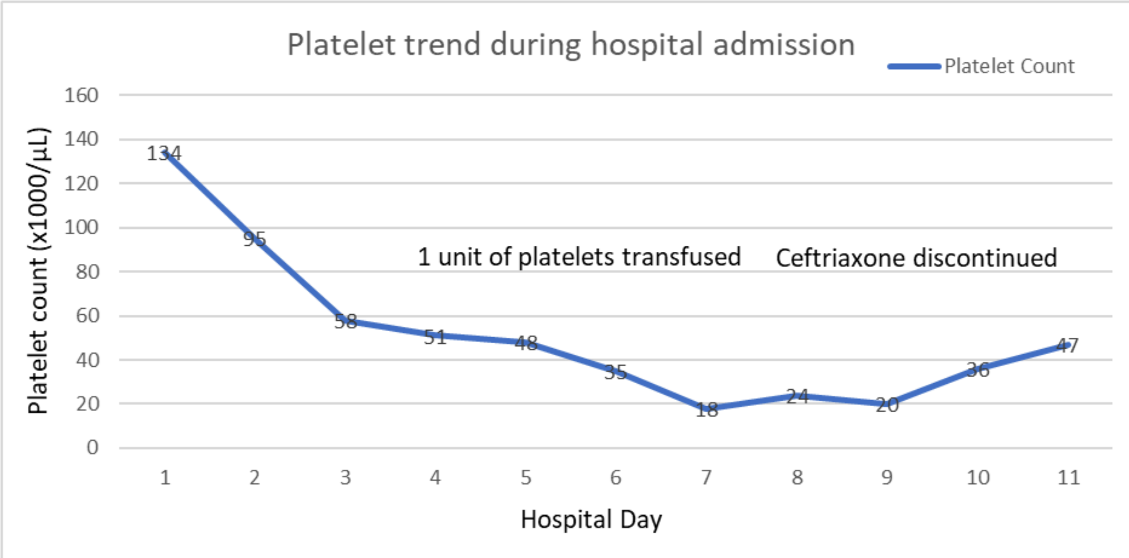

Figure 1. Trend of platelet count during the course of hospital admission.

Discussion

DITP is a life-threatening adverse reaction caused by drug-dependent antibodies and can have a multitude of causes. The etiology of thrombocytopenia is classified into four categories, namely platelet underproduction, splenic sequestration, pseudothrombocytopenia caused by platelet clumping, and peripheral destruction. The principal mechanism behind DITP is platelet destruction, with possible contribution by nutritional deficiencies and bone marrow involvement [1][2].

In our case, the peripheral smear was unremarkable for schistocytes or platelet clumps, vitamin levels were normal, there was appropriate bone marrow response, and the HIT panel was negative. DITP caused by the newly initiated antibiotic ceftriaxone was considered the most likely diagnosis owing to the significant temporal relationship of the occurrence of thrombocytopenia which coincided with the commencement of ceftriaxone and resolved when it was discontinued. It remains a diagnosis of exclusion, and confirmation requires the presence of drug-dependent platelet reactive antibodies in the serum. Another method of confirmation involves rechallenge, requiring restarting the suspected culprit drug and observing for a repeat drop in platelet level, which is rarely done to avoid potential catastrophic complications [3][6]. As per the Naranjo algorithm, this was considered a probable adverse drug reaction with a score of 6, but due to the lack of laboratory facilities, the presence of ceftriaxone-dependent antiplatelet antibodies could not be confirmed.

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DITP typically develops within 5 to 7 days of initiation of the potential offender drug, but can also be caused by sporadic exposure to the same drug over a period of time. The most common manifestation is thrombocytopenia diagnosed only on laboratory investigations without any clinical manifestations, but can sometimes even lead to frank bleeding [6]. A review of 247 case reports found incidence rates of major and fatal bleeding of 9% and 0.8%, respectively [7]. In comparison to other potential causes of isolated thrombocytopenia, the platelet nadir usually reaches less than 20,000/μL in DITP.

Re-exposure to the potential causative drug often leads to thrombocytopenia which is more acute in onset and often more severe. This has been attributed to a potential persistence of the reactive antibodies or an unexplained anamnestic response. Most drug-dependent reactive antibodies require the presence of the offending agent to function, which assists to mediate their interaction with the target platelet antigens. This is why most of the cases of DITP are self-resolving once the potential offending drug is discontinued. As the concentration of the drug diminishes in the serum over time, the antibodies are unable to bind to the platelets as effectively, leading to an improvement in platelet count. However, the culprit antibody continues to remain in circulation for a period of a few months, which is usually responsible for repeated episodes. In most cases, as the serum concentration of the drug decreases, the platelet count starts improving within 1 to 2 days and often normalizes within a week. However, impaired drug clearance due to hepatic or renal impairment can lead to persistent thrombocytopenia, which has also been reported [8].

There have been reports of DITP attributed to the first three generations of cephalosporins in literature. In some cases, certain cephalosporin-dependent antibodies have also been found to cross-react with others. This is the probable mechanism behind the development of DITP in patients receiving a particular generation of cephalosporins, who may have had some past exposure and sensitization to a potentially different but epitope-related drug [4]. We were unable to confirm if our patient had previously received any beta-lactam antibiotic, hence the possibility of being sensitized to the same could not be ruled out.

Ceftriaxone-induced immune thrombocytopenia has been described in a few case reports in the literature, including six cases identified between the time frame of 1991 and 2013, by a database maintained by the university of Oklahoma which is responsible for keeping a track of DITP cases attributed to a particular drug. Out of the mentioned 6 cases, only 3 were confirmed with the presence of ceftriaxone-dependent antiplatelet reactive antibodies. There have been a few more case reports recently describing this phenomenon, including one in a 2-year-old child [5][9][10][11]. The particular epitopes found on the GPIX complex and the GPIIb/IIIa subunit of the platelets were identified as potential targets for the antibodies, but the exact mechanism remains unknown [12].

Immediate discontinuation of the potential causative drug remains the cornerstone of management. Platelets should be transfused if the thrombocytopenia is severe and the platelet level falls below 10,000/μL, or if there are clinical signs and symptoms of ongoing bleeding. DITP and Immune Thrombocytopenic Purpura (ITP) both have very similar manifestations and are both diagnoses of exclusion, and hence it becomes extremely difficult to differentiate between the two. In some cases, steroids and intravenous immunoglobulin have been used as immunosuppressive agents with varying responses [8][9][10].

Ceftriaxone is one of the most common antibiotics initiated in hospitalized patients for empirical treatment of a multitude of infections, including community-acquired pneumonia and urinary tract infections. Clinicians need to have a high index of suspicion and a broad differential diagnosis to rule out other contributing causes of thrombocytopenia before diagnosing DITP. The development of ceftriaxone-induced immune thrombocytopenia also poses a significant therapeutic challenge, necessitating alternative antibiotic therapy. Our literature search reported only one case of ceftazidime-induced immune thrombocytopenia, which was chosen as an alternative antibiotic regimen for our patient, even though there was a potential risk of cross-reactivity [13]. Determining the most effective antibiotic regimen in such cases is often challenging and needs further data.

Conclusion

We present the case of a woman who developed ceftriaxone-induced immune thrombocytopenia while being treated for pyelonephritis. It highlights the importance of maintaining a high clinical suspicion and ruling out other potential common causes before attributing unexplained thrombocytopenia to DITP. The identification of the exact drug responsible for causing DITP is challenging in most scenarios because most of these patients are admitted to the hospital with some form of acute illness and are usually started on a few new medications for the management of the underlying condition. This often poses a significant therapeutic challenge with limited data to guide therapy in such circumstances.

Informed consent statement

Informed consent was obtained from the patient over a telephonic conversation for the publication of this report and any accompanying images.

Conflict-of-interest statement

The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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