Digging into the Cause of Drug-Induced Thrombocytopenia: A Case Report

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Abstract

Thrombocytopenia can be caused by various etiologies, one of which is immune-mediated destruction. Within the realm of immune thrombocytopenia, there can be multiple pathways and mechanisms that lead to platelet destruction. Finding the exact mechanism can be a crucial diagnostic step in deciding the most appropriate treatment of the platelet loss and in the therapeutic planning of a patient's comorbidities, especially in patients with malignancies. In this case report, we describe a patient with metastatic clear cell renal cell carcinoma who developed acute thrombocytopenia while preparing to initiate therapy for his malignancy.

CASE STUDY

A 48-year-old male patient with a past medical history of hypertension and chronic kidney disease presented to an outside facility on October 10, 2022, with hematuria and acute urinary retention. During this admission, imaging revealed a large right renal mass with bulky retroperitoneal lymphadenopathy that was suspicious for malignancy. The patient received a 7-day course of cefdinir for his urinary symptoms. Following a radical nephrectomy, a diagnosis of clear cell renal cell carcinoma (ccRCC) was confirmed. Over the next 3 months, the patient developed ascites and spinal metastasis as complications of his disease. During this period, the patient required multiple paracenteses, each time receiving either penicillin (piperacillin-tazobactam) or cephalosporin antibiotics (multiple doses each of cefdinir and ceftriaxone) for spontaneous bacterial peritonitis (SBP) prophylaxis. The patient also received two doses of cefazolin for surgical prophylaxis for his nephrectomy in November and a vertebroplasty in December to repair compression fractures due to metastatic cancer.

Onset of Acute Thrombocytopenia

In January, the patient presented to the oncology clinic to initiate therapy with ipilimumab and nivolumab for his metastatic ccRCC. On baseline laboratory monitoring, he was found to have a platelet count of 3 × 10^9/L. He was admitted to the hospital for further workup of his acute thrombo-

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cytopenia. The most recent platelet count from 3 days prior had been 170 × 10^9/L. Figure 1 depicts the patient's platelet count over this time period. No clinical signs or symptoms of thrombocytopenia or overt bleeding were present.

Diagnostic Workup

Given the sudden onset of thrombocytopenia, the differential diagnosis included immune thrombocytopenia (ITP), and more specifically drug-induced thrombocytopenia (DITP), disseminated intravascular coagulopathy (DIC), thrombotic microangiopathy (TMA), heparin-induced thrombocytopenia (HIT), and splenic sequestration. The latter were ruled out due to high fibrinogen and normal prothrombin time (PT) and partial thromboplastin time (PTT), no hemolysis or schistocytes on the peripheral smear, and no splenomegaly on the abdominal CT, respectively. Copper deficiency was also investigated. The patient did have low copper levels and was instructed to start an over-the-counter supplement following discharge; however, the platelet count had stabilized prior to that time.

During his recent multiple admissions, the patient had received the following medications known to cause DITP: enoxaparin, piperacillin-tazobactam, ceftriaxone, cefazolin, and cefdinir. Table 1 depicts all the medications the patient received that have been linked with thrombocytopenia along with administration dates. Evaluation of the 4Ts score (thrombocytopenia, timing of thrombocytopenia, thrombosis, and other reason) ruled out HIT, as the patient's score was a 1, indicating low risk based on zero points due to a nadir < 10, zero points for the presence of any new or worsened thrombosis, and 1 point for other possible cause of thrombocytopenia. In regard to timing, the patient's platelet count fall did occur after approximately 30 doses of 300 units of heparin as IV line flushes that were received during admission in early January, with the last being about 4 days prior to the platelet drop. However, no decrease in platelet count was seen until after discharge and without readministration of any heparin-containing products, earning a zero for timing as well. With a total score of 1 on the 4Ts score for HIT, further testing was not pursued.

Consequently, antibody testing was performed for piperacillin-tazobactam and cefdinir, as the highest suspicion of DITP was associated with these antibiotics. Cefazolin and ceftriaxone had the lowest risk of thrombocytopenia, as the patient received only one or two doses of these

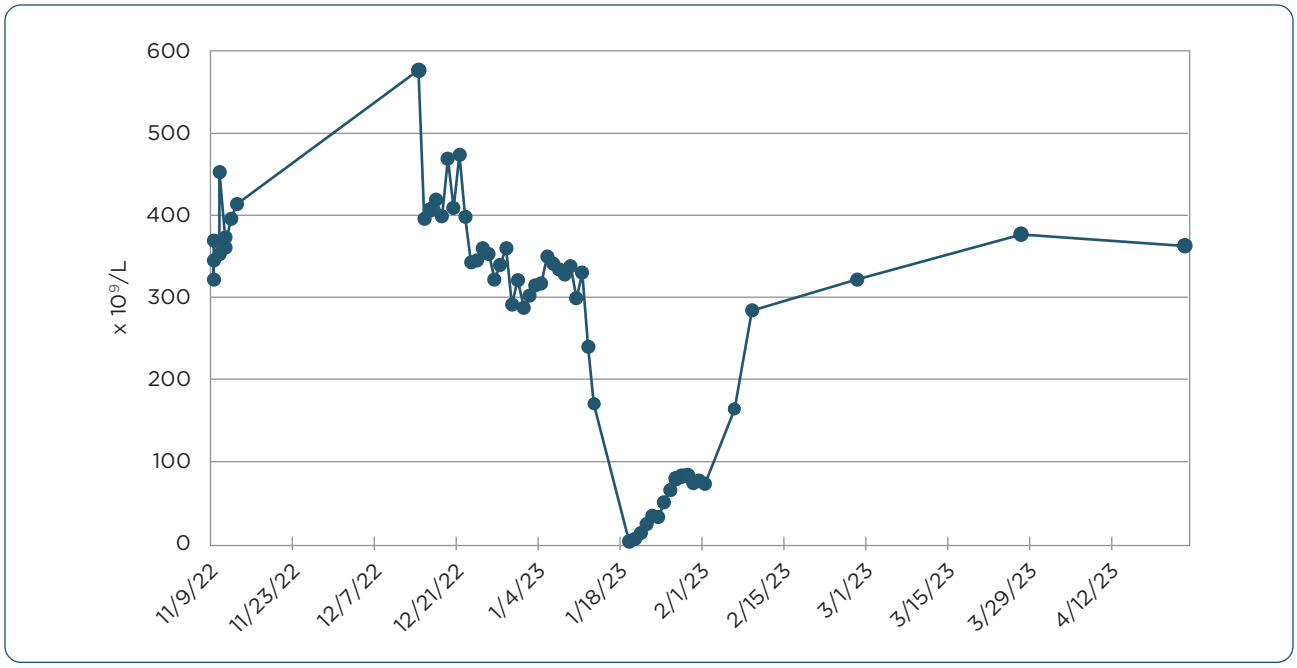

Figure 1. Patient's platelet count over time.

medications and were not tested specifically. The piperacillin-tazobactam and cefdinir tests were sent to an off-site facility on January 20.

Treatment and Management

While awaiting lab results, the patient received treatment with four doses of IV dexamethasone (40 mg each) and two doses of intravenous immunoglobulin (IVIg). Consequently, the patient's platelet count increased to 79 × 10^9/L within 7 days of starting said treatment. This normalization occurred without the use of any blood factor products, including platelets, as Hematology recommended to withhold platelet transfusion unless bleeding was noted. At the end of January, the lab results confirmed the presence of platelet-dependent antibodies to cefdinir. The patient was medically stable and was transferred to a rehabilitation center at this time. There, the patient continued to receive supportive care and was later discharged after 1 week to initiate systemic therapy for his cancer. At the infusion center in early February, the patient had labs checked prior to starting anticancer therapy. His platelets were within normal limits, at 289 × 10^9/L. Due to the aggressive nature of the patient's disease and the lag time from diagnosis to finally being able to safely initiate treatment, the patient's oncologist initiated treatment with the immune checkpoint inhibitor nivolumab and the tyrosine kinase inhibitor cabozantinib. The patient would go on to receive four cycles of nivolumab and remain on cabozantinib over 9 months later.

Platelets play a crucial role in the process of clotting (Jurk & Kehrel, 2005). Thrombocytopenia, characterized by a platelet count less than 100 to 150 × 10^9/L, is of clinical concern due to the increased risk of bleeding without the normal number of functional platelets (Aster et al., 2009; Smock & Perkins, 2014).

THROMBOCYTOPENIA MECHANISMS

In general, thrombocytopenia can occur due to the following mechanisms: decreased platelet production, splenic sequestration, dilution, or a decrease in circulating platelets (Smock & Perkins, 2014). Decreases in platelet production are often seen by oncology providers, due to either myeloid malignancy, aplastic anemia, or marrow infiltration of a solid tumor, via a disruption in normal hematopoietic function, or as a toxicity of myelosuppressive chemotherapy. Other etiologies outside of the malignancies and their treatments include chronic alcohol abuse, liver disease, congenital platelet production disorders, infection, and nutritional

Table 1. Drugs Received by Patient Known to Cause Drug-Induced Thrombocytopenia

Date	Drug	Estimated dose(s)	DITP mechanism	Indication
10/10	Ceftriaxone 1 g IV once	1	Hapten-induced antibody	Empiric treatment of pyelonephritis
10/10	Cefdinir 300 mg every 12 hours by mouth	14	Hapten-induced antibody	Discharge home medication
11/9	Cefazolin 2 g IV once	1	Hapten-induced antibody	Surgical infection prophylaxis
12/15	Ceftriaxone 2 g IV once Ceftriaxone 1 g IV once	1 1	Hapten-induced antibody	Surgical infection prophylaxis
12/15	Enoxaparin 40 mg SQ every 24 hours	16	Immune complex (HIT)	VTE prophylaxis
12/26	Piperacillin-tazobactam 3.375 g every 8 hours	4	Hapten-induced antibody	SBP prophylaxis
12/29	Cefazolin 2 g IV once	1	Hapten-induced antibody	Surgical infection prophylaxis

Note. DITP = drug-induced thrombocytopenia; HIT = heparin-induced thrombocytopenia; VTE = venous thromboembolism; SBP = spontaneous bacterial peritonitis.

deficiencies, such as copper (Gauer & Braun, 2012; Smock & Perkins, 2014; Uchino et al., 2021).

In terms of splenic sequestration, normally, about 30% of the total platelet volume can be found within the spleen. This number increases in patients with splenomegaly, and most patients with an enlarged spleen will have a concomitant decrease in platelet count (Smock & Perkins, 2014). Dilution is another possibility that could explain rapidly decreasing platelet count. This can occur when large volumes of fluids that do not contain platelets are administered. This can often occur with large amounts of IV fluid, as well as during large transfusions of red blood cells, as 10 to 12 units of packed red blood cells could cause a decrease in plate count of approximately 50% (Wong & Rose, 2012).

In the case study, while the patient had a metastatic malignancy, there was no marrow involvement, he had a normal liver function on laboratory evaluation and no splenomegaly was seen on multiple CT scans of the abdomen and pelvis, he had not received large-volume IV fluids or blood products, and he reported no alcohol abuse. While he was suspected of having a bacterial infection, his thrombocytopenia developed following the resolution of his infectious symptoms, so it was unlikely to be due to sepsis.

Decreases in circulating platelets may be caused by the consumption or destruction of platelets. Common causes include disseminated intravascular coagulopathy (DIC), infection, preeclampsia/hemolysis, elevated liver enzymes, and low platelet count (HELLP), hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), or immune-mediated thrombocytopenia (ITP; Gauer & Braun, 2012; Smock & Perkins, 2014). The pathogenesis of ITP is due in part to the loss of immune tolerance of platelet autoantibodies, whereby autoantibodies are able to directly target platelet membrane glycoproteins, causing macrophage-led destruction via Fcγ receptors (Bussel et al., 2021; Liu et al., 2020). Platelet production is also suppressed, in part, by megakaryocyte damage by these autoantibodies (Bussel et al., 2021). Immune-mediated thrombocytopenia can typically be managed by corticosteroids, intravenous immunoglobulin (IVIg), or other means of immunosuppression to blunt the body's attack on its own cells (Gauer & Braun, 2012).

DRUG-INDUCED THROMBOCYTOPENIA

Drug-induced thrombocytopenia (DITP) occurs when this immune cascade is triggered by medications that a patient is taking (Aster et al., 2009). Literature describes at least seven different potential mechanisms that may lead to DITP (Bougie et al., 2015). This condition affects one out of 100,000 people annually and is most commonly seen in patients treated with sulfamethoxazole-trimethoprim, quinidine-quinine, or vancomycin (Aster et al., 2009; Aster & Bougie, 2007).

The diagnostic criteria for DITP involve the occurrence of thrombocytopenia while taking the drug, exclusion of other etiologies, and resolution following drug cessation (Arnold et al., 2013; Aster & Bougie, 2007). Drug-induced thrombocytopenia typically occurs 5 to 10 days after the first exposure to a sensitizing drug with platelets falling below 20×10^9/L. In contrast to initial exposure, re-exposure to the medication can lead to platelet counts falling below the normal range within a few hours (Arnold et al., 2013; Aster et al., 2009). As with other types of ITP, platelet counts can drop precipitously and deeply, with severe drops to $< 20 \times 10^9$/L commonly occurring. As a result, patients may present with ecchymosis and petechiae, or with wet purpura, gastrointestinal bleeding, or intracranial hemorrhage in more severe cases (Aster et al., 2009; Aster & Bougie, 2007).

Certain medications, like quinine, penicillins, and cephalosporins, cause DITP via hapten-induced antibodies (Aster et al., 2009; Aster & Bougie, 2007). This involves a small molecule, the drug, that triggers a humoral immunological response by covalently binding to a large carrier protein, forming a hapten. This hapten allows for the loss of immune tolerance to circulating autoantibodies, which are now able to bind to platelet membrane glycoproteins, leading to platelet-hapten complex destruction.

Another cause of immune platelet destruction is drug-dependent antibodies (DDAbs; Bougie et al., 2015). In this case, binding occurs directly between the drug and autoantibody without a third-party hapten and only in the presence of the offending drug (George & Aster, 2009). This drug-antibody complex then binds to glycoproteins on platelets, leading to immune-mediated

destruction. This has been reported most frequently with monoclonal antibody-based medications such as rituximab (Rituxan), bevacizumab (Avastin), adalimumab (Humira), infliximab (Remicade), and immune checkpoint inhibitors such as ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda; Vayne et al., 2020). There is some evidence that these drug-dependent antibody complexes may also target and destroy megakaryocytes or platelet precursor cells, leading to deceased platelet production as well. This could be one reason that antibody testing is not always clinically fruitful, as decreased platelet production could leave fewer circulating platelets to be bound to the specific antibody during a thrombocytopenia event (Vayne et al., 2020). While DDAbs can cause a platelet count decrease within days of exposure to the offending agent, the antibodies themselves have been shown to persist in patients for many years following their formation, meaning strict avoidance of the causative agent is necessary to prevent another sudden and acute drop in platelets (George & Aster, 2009).

These immune complexes typically form when the individual is first exposed to the drug (Aster & Bougie, 2007). Then, upon re-exposure, platelet destruction occurs due to the reformation of platelet-targeting autoantibodies and the complexes binding to glycoproteins on platelets (Aster et al., 2009; Aster & Bougie, 2007).

Diagnosis

The diagnosis of hapten-induced DITP can be challenging, as specific antibody testing is required (Arnold et al., 2013). The International Society on Thrombosis and Haemostasis (ISTH) has developed a recommendation for the standardization of DITP laboratory testing for quinine, vancomycin, sulfamethoxazole-trimethoprim, and piperacillin-tazobactam (Arnold et al., 2015). Testing involves either flow cytometry or enzyme-linked immunosorbent assay (ELISA) to determine the presence of anti-human IgG and IgM to diagnose DITP (Arnold et al., 2013, 2015; Aster et al., 2009). Especially for cephalosporins, antibody testing is not common practice to determine DITP (Arnold et al., 2013, 2015). Instead, in cases where no other plausible causes are identified, and DITP is suspected, common practice dictates to discontinue the offending agent and initiate therapy for ITP, if needed, without antibody testing (Arnold et al., 2013, 2015; Aster & Bougie, 2007). The depth of the thrombocytopenia and the clinical presentation of bleeding guide the therapeutic choice for ITP (Neunert et al., 2019).

CASE STUDY DISCUSSION

One other cause of thrombocytopenia, which is rare but possible, is paraneoplastic autoimmune thrombocytopenia. Paraneoplastic hematologic changes occur more frequently in hematologic malignancies, such as lymphoma, compared to solid tumors, although they can present with any type of malignancy. In a meta-analysis of 68 cases of paraneoplastic autoimmune thrombocytopenia, 7 cases (10.3%) were found in patients with renal carcinomas (Krauth et al., 2012). Six of these renal cell carcinoma patients achieved a complete response of their platelet count for ≥ 6 months following tumor resection, further highlighting the link between the cancer and the thrombocytopenia (Krauth et al., 2012). As paraneoplastic syndromes occur secondary to a malignancy, cancer-directed therapy may be enough to reverse the syndrome. However, many patients in the meta-analysis did require traditional ITP treatment with steroids and/or IVIg to normalize their platelets counts. As paraneoplastic syndromes can be difficult and/or lengthy to diagnose, many providers may not feel comfortable initiating cancer therapy in a patient with such low platelet counts.

In this case, the patient's decline in platelets was acute, and thus ITP was suspected based on clinical and laboratory data. Based on the patient's planned immunotherapy, the treatment team needed a definitive answer to the question of how and why this patient's platelets were being destroyed.

The patient was scheduled to begin nivolumab and ipilimumab, immune checkpoint inhibitors targeting PD-L1 and CTLA-4, respectively, to enhance the immune response against cancer, both of which have been implicated in DDAb-induced thrombocytopenia. While the patient in question had not received either of these medications to cause antibodies to form to their specific structure, it was felt best not to start new medications that also carry the risk, although quite rare, of immune-

mediated platelet destruction until the treatment team had a better understanding as to the cause of the patient's platelet count drop (National Cancer Institute, 2023). Commonly, stopping a medication suspected of causing DITP and monitoring for clinical and laboratory improvement can be used to determine the cause. However, due to the autoimmune nature of ITP and the fact that planned treatment agents for this patient could also contribute to thrombocytopenia through similar mechanisms that could exacerbate the overall recovery process, it was crucial to determine the cause of the patient's thrombocytopenia.

This case was also complex due to the number of medications that the patient had previously received that are known to cause DITP. This included cefazolin, cefdinir, ceftriaxone, piperacillin-tazobactam, and enoxaparin (Arnold et al., 2013, 2015; Aster et al., 2009). While a scoring system confirmed a low risk of HIT, no such system exists for antibiotics causing DITP (Aster et al., 2009). Therefore, testing was essential to pinpoint the cause if it was indeed medication related, rather than nutritional or due to malignancy. While piperacillin-tazobactam were the only medication tested directly, the flow cytometry–based test came back positive for antibodies to cefdinir. For future cases, comprehensive in vitro testing for all antibiotics is advised for precise assessment.

The test results returned in 10 days and confirmed that the patient was positive for platelet-dependent antibodies for cefdinir. However, it must be pointed out that when this sample was collected, the patient had not received cefdinir in 38 days, and no other cephalosporins in the past 22 days. The patient and their spouse were asked by numerous providers to ensure no doses of the patient's previously prescribed cefdinir had been taken recently, to which both the patient and spouse remained resolute that no doses had been taken at home, as the patient completed his 7-day course of cefdinir in its entirety at the time of prescription. This time course does not fit with the expected course of DDAb-based ITP. Patients with drug-dependent antibodies typically see a platelet decrease within hours to days of exposure to the offending medication. It is possible that this patient developed DDAbs to cefdinir following a prior administration of the medication, which persisted in the serum but may not have been driving the acute platelet decrease in the absence of cefdinir exposure. This would mean that the patient had a second autoimmune process occurring that actually caused the acute drop in counts, such as a paraneoplastic process. A paraneoplastic antibody panel was not tested for this patient.

To be cautious, cefdinir was added to the patient's allergy list, primarily to prevent future utilization. Following platelet recovery, the patient was able to initiate anticancer therapy with cabozantinib (Cabometyx) and nivolumab. This outcome led to the patient receiving the best treatment for their metastatic clear cell renal cell carcinoma. Additionally, if the patient develops an infection in the future, this testing allows us to prevent the use of cefdinir since it is now listed on the patient's allergy list, as the hapten complex is likely to reform and lead to platelet destruction within hours to days. While not all patients require antibody-specific testing, in this case, using in vitro testing allowed the team to proceed to cancer therapy with less concern for sudden thrombocytopenia and aided future treatment teams by identifying a possible reaction with cefdinir.

CONCLUSION

In cancer patients with unexplained thrombocytopenia, that is, not due to marrow involvement or cancer treatment, some sort of autoimmune process is the most likely contributor and should be investigated thoroughly so that best management and recurrence prevention strategies can be detailed, including the discontinuation of possible offending agents and future avoidance of causative agents. In the near term, a short burst of dexamethasone and IVIg can be effective in reversing the autoimmune process at play, regardless of the exact cause of the autoimmune activity. ●

Disclosure

The authors have no conflicts of interest to disclose.

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