CLINICAL CASE DISCUSSION

Thrombocytopenia in the Critically Ill: An Animal with Several Heads

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Abstract

A 59-year-old male with a history of systemic hypertension and fever presented as an interesting patient with thrombocytopenia. While fever with thrombocytopenia is a common presentation, this patient's course in the hospital took multiple twists and turns, taking us through a tutorial in thrombocytopenia.

Keywords: Fever, Myalgia, Systemic hypertension, Thrombocytopenia.

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Main Text

A 59-year-old gentleman with a past medical history of systemic hypertension presented to an outside hospital with acute onset fever, myalgia, and lethargy for 3 days. His neurological and cardiorespiratory status were unremarkable. Initial workup revealed thrombocytopenia (platelet count: 60,000) and acute kidney injury (AKI) (creatinine: 2 mg/dL). Other cell lines and organ functions were normal.

What Other Information would You Like to Elicit in History to Help You in This Patient's Evaluation?

In the above patient, we have the following information—59/M hypertensive with fever, myalgia, lethargy, thrombocytopenia, and AKI.

Further history should include obtaining detailed information about each of the symptoms. A history of fever should include—onset, duration, degree of fever (high grade vs low grade), presentation of fever (intermittent vs continuous vs diurnal variation of temperature), association with chills, and/or rigors. Fever history by itself can give us plenty of information about the possible disease etiology. A high-grade fever with chills/rigors would be suggestive of an acute bacterial infection. Fever occurring at a particular time of the day with rigors would suggest malaria. A low-grade, evening rise in temperature is typical of tuberculosis, whereas a persistent low-grade fever with constitutional symptoms would be suggestive of a noninfective cause such as lymphomas.

It would be important to inquire if the patient has any localizing symptoms associated with fever, such as new onset of alteration in mentation, rash, chest pain, joint pain, headaches, nausea, vomiting, diarrhea, cough, or shortness of breath. Recent travel history, exposure to animals, sick contacts, and any previous hospitalization with low platelets mandating blood transfusions also need to be inquired about.

In view of thrombocytopenia, a history of any complication due to bleeding (thrombocytopenia-associated), such as gum bleed, epistaxis, ecchymosis, hematemesis, hematochezia, melena, and hemoptysis, should be elicited. Additionally, it would be important to elicit history evaluating the causes and/or complications of AKI, such as urinary urgency, painful micturition, blood in urine, duration of decreased urine output, pedal edema, difficulty in breathing, anorexia, nausea, and vomiting.

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What are Some of the Important Clinical Signs That You would Look for in This Patient?

Given the patient's clinical presentation of fever, myalgia, lethargy, thrombocytopenia, and AKI, there are several clinical signs that should be looked for to identify potential underlying conditions. These include the following.

- Neurological symptoms: These may include changes in consciousness, altered mental status, seizures, or focal neurologic deficits, which can be indicative of central nervous system involvement and may be present in severe form of sepsis, vasculitis, or certain conditions like hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).
- Respiratory distress: One must think of pneumonia, pleural effusion, and pulmonary edema secondary to AKI or acute respiratory distress syndrome (ARDS) complicating a systemic illness.
- Petechiae or ecchymoses: These may manifest as a sign of thrombocytopenia, platelet dysfunction, or a coagulopathy,

wherein one must think of possibilities such as dengue or other viral hemorrhagic fevers, leukemias, and vasculitis.
- Jaundice: Indicative of hyperbilirubinemia, which can be either due to hemolytic anemias or liver involvement due to viral hepatitis or infiltrative diseases such as lymphomas.
- Lymphadenopathy: Based on the location and size of lymph nodes, one can consider tuberculosis, lymphomas, hematological malignancies, or localized skin/soft tissue infections.
- Splenomegaly: This can occur in several conditions, including tropical infections, autoimmune diseases, or hematologic disorders, and can be identified clinically at the bedside.

What are the Probable Differential Diagnoses in This Patient?

There are several potential diagnoses for a patient presenting with fever, thrombocytopenia, and AKI. It is important for a healthcare professional to conduct a thorough evaluation, including laboratory tests and imaging studies, to arrive at an accurate diagnosis and provide appropriate treatment.

- Viral infections: Some viral infections, such as dengue fever or Zika virus, can cause fever, thrombocytopenia, and AKI.
- Tropical infections like leptospirosis or scrub typhus should be thought of in this patient, and appropriate antibiotic cover should be initiated.
- Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterized by the formation of blood clots in small blood vessels throughout the body, classically manifesting as fever, altered mentation, AKI, thrombocytopenia, and hemolytic anemia. However, not all five manifestations need to be present to make the diagnosis.
- Disseminated intravascular coagulation (DIC) is a condition characterized by abnormal blood clotting throughout the body, which can lead to organ damage and thrombocytopenia. DIC is usually a part of a systemic illness with multi-organ involvement commonly associated with AKI.
- Heparin-induced thrombocytopenia (HIT) is a potentially serious complication of heparin therapy, in which the patient develops antibodies against heparin that lead to platelet activation and thrombosis. Fever, when present, is usually noninfective. Organ damage, including AKI, can occur, albeit rarely.
- Drug-induced hypersensitivity syndrome (DIHS) is a rare, severe drug reaction that can cause fever, thrombocytopenia, acute liver injury, and AKI, among other symptoms. It is typically caused by certain medications, such as dapsone, anticonvulsants, or antibiotics.

What was the Initial Thrombocytopenia Attributed to, and What did the Workup Reveal?

Initial evaluation of this patient revealed a positive NS1 antigen at an outside hospital, but workup for other tropical infections and blood cultures were negative. He was diagnosed to be having dengue and was being managed accordingly. However, his renal functions worsened progressively, for which he underwent four sessions of heparin-free hemodialysis at the outside facility. He was referred to our hospital for further workup and management of his worsening renal function. On presentation to our hospital, he was anuric with a high serum creatinine of 7.4 mg/dL. The extremely high serum creatinine, along with proteinuria on urine routine analysis, was unusual for dengue-related AKI, and hence, further workup to evaluate the etiology of AKI was planned. He underwent a renal biopsy, which revealed postinfectious glomerulonephritis (PIGN).

How was the PIGN Treated, and What was the Patient's Immediate Hospital Course?

He was treated with pulse dose steroid (methylprednisolone 500 mg once a day for 4 days) and cyclophosphamide (500 mg single dose), and maintenance steroids (prednisolone 80 mg once a day) continued. With these interventions, his renal functions gradually improved, and his thrombocytopenia resolved with his platelet count improving to 3.2 lakhs. However, he continued to need hemodialysis for his AKI. His dialysis catheter in the left internal jugular vein was removed on day 4 due to inadequate flow, and a new catheter was placed in right femoral vein. The new dialysis catheter was locked with heparin as per usual protocol to prevent catheter clotting and regular dialysis continued. Despite this, patient developed dialysis catheter dysfunction with poor flows in the newly placed femoral dialysis catheter. A venous Doppler done at this time point to evaluate this revealed a venous thrombus in the right femoral vein. A hemogram done revealed a platelet count of 1.5 lakhs, a steep drop from 3.2 lakhs.

What are the Possible Causes of Acute Drop in Platelet Count with New Onset Thrombosis in the Intensive Care Unit (ICU)?

The etiology of acute drop in platelet count in an ICU is often multifactorial. Thrombocytopenia in the ICU could be secondary to thrombin-mediated platelet activation, platelet adhesion to endothelial cells and leukocytes, platelet aggregation by increased von Willebrand factor release, red cell damage, and histone release or platelet destruction by the complement system.[1]

However, this patient manifested acute drop in platelet count in association with new-onset thrombosis. Although such a manifestation is uncommon, when it occurs, the clinician should consider and rule out the following diagnoses.

- Disseminated intravascular coagulation (DIC): DIC can cause combined bleeding and thrombosis along with thrombocytopenia and derangement in coagulation parameters. Prolongation of prothrombin time, increased D-dimer, and decreased fibrinogen point toward this diagnosis. However, thrombosis is often microvascular in nature.
- Heparin-induced thrombocytopenia (HIT): HIT is a well-known complication of heparin therapy that can lead to thrombocytopenia and arterial or venous thrombosis.
- Vaccine-induced thrombotic thrombocytopenia (VITT): Coronavirus disease 2019 (COVID-19) VITT is an incompletely understood syndrome that is emerging as an extremely rare complication in recipients of certain adenovirus-based COVID-19 vaccines.
- Autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and vasculitis may cause thrombocytopenia and thrombosis through autoimmune mechanisms such as antiphospholipid antibody syndrome.

- Drug-induced thrombocytopenia can result in both thrombocytopenia and thrombosis, especially with the use of chemotherapeutic agents.
- Malignancies can lead to both thrombocytopenia and hypercoagulability, with solid tumors and leukemia being the most common culprits.
- Catheter-related thrombosis is associated with both thrombocytopenia and thrombosis locally in the vein, especially in patients with central venous catheters in place, which is a possibility in this patient.

When would You Suspect HIT, and How do You Diagnose It?

Heparin-induced thrombocytopenia (HIT) is a serious adverse effect of heparin therapy that can occur in 1–5%[2] of patients receiving unfractionated heparin (UFH) and is less common with low-molecular-weight heparin (LMWH). The diagnosis of HIT can be challenging and is based on clinical suspicion and laboratory tests. Key findings that should prompt a consideration of HIT include thrombocytopenia that develops within 5–10 days of starting heparin therapy, a platelet count of <150,000/mm^3 or a decrease in platelet count of greater than 50% from the baseline, new onset of arterial and/or venous thrombotic events, such as deep vein thrombosis, pulmonary embolism, or arterial thrombosis, and skin lesions such as petechiae or purpura. A scoring system (such as the 4T score) is a useful bedside tool to screen for HIT in patients suspected to have HIT.[3] This score takes into account the timing of the thrombocytopenia, the presence of thrombotic events, the degree of thrombocytopenia, and the presence of other causes of thrombocytopenia. A score of ≥6 carries a high probability of HIT, with the risk being almost 50% (Table 1).

However, it is important to note that not all patients with HIT will have all of these features. Diagnosis of HIT requires a sequence of laboratory tests for confirmation. The first step would be to look for presence of anti-PF4/heparin antibodies. However, presence of anti-PF4/heparin antibodies alone does not confirm the diagnosis of HIT, while the absence of anti-PF4/heparin antibodies almost always rules out HIT. The positive antibody test should be followed up by the platelet activation assay, such as serotonin release assay (SRA) or heparin-induced platelet aggregation (HIPA) assay. If platelet activation is confirmed in the presence of anti-PF4/heparin antibodies, it confirms the diagnosis of HIT.[4]

What are the Key Principles in Treating HIT?

The management of HIT typically involves a combination of measures to both stop heparin therapy in all forms, including removal of any heparin-coated catheters, and treat the hypercoagulable state aggressively with anticoagulation to prevent new thrombotic episodes. Anticoagulation therapy must be initiated immediately using alternate anticoagulants.[5] Usual treatment options include direct thrombin inhibitors such as argatroban or bivalirudin infusion, fondaparinux, or direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and endoxaban.[6,7] Careful monitoring of patients on treatment of HIT is imperative to assess response to treatment, adequacy of anticoagulation, and ongoing thrombotic burden (Table 2).

It is important to monitor patients with HIT closely as they are at a high risk of thrombotic events. Evidence of new thrombi and platelet count as an indicator of ongoing HIT and response to therapy should be actively followed. Appropriate coagulation tests like activated partial thromboplastin time (aPTT) and anti-Xa assay should be monitored to assess the effectiveness of anticoagulation therapy.

On further questioning, our patient later revealed that he had a previous exposure to heparin (LMWH), during which he had a thrombocytopenia, which got corrected after stopping LMWH. The 4T score of this patient was 8, and the heparin platelet factor 4 antibody was positive. Platelet activation assay was not immediately available and, hence, could not be performed. Patient was immediately treated with removal of dialysis catheter and argatroban infusion for the hypercoagulable state.

Procoagulant workup (antiphospholipid antibody, homocysteine, and ADAMTS 13) was negative. After ruling out other causes of thrombocytopenia, including thrombotic microangiopathy, DIC, and sepsis, a diagnosis of HIT was made. Patient's platelet count gradually improved with the above measures, but on day 3 of this treatment, he had a large volume of melena with another drop in platelet count. Argatroban infusion was stopped in view of active gastrointestinal bleed and endoscopy planned.

Table 1: 4T score for diagnosis of HIT

4Ts	*2 points*	*1 point*	*0 point*
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20	Platelet count fall 30–50% or platelet nadir 10–19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall ≤1 day (prior to heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts); onset after day 10; or fall ≤1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous UFH bolus	Progressive or recurrent thrombosis; nonnecrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Table 2: Key points in managing HIT

Diagnosis	4T score
Investigation	Antiplatelet factor 4 antibody assay Followed by platelet activation assays
Treatment of choice	Stop heparin in all forms Remove any heparin-coated devices Immediately initiate anticoagulation
Anticoagulation in a patient with HIT	Drugs can be direct thrombin inhibitors, DOACs, or fondaparinux
HIT not responsive to usual care	PLEX Rituximab

What could be the Causes of Drop in Platelets while This Patient is on Argatroban?

Some possible causes of progressive thrombocytopenia that should be considered include progression of HIT despite optimal therapy, new onset sepsis, thrombotic microangiopathy, or drug-induced thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) is a dynamic process, and platelet count can continue to decline despite the initiation of argatroban therapy. New thrombi in the arterial or venous system would favor this diagnosis. Thrombotic microangiopathy is a rare but serious complication of HIT that can cause a decline in platelet count, as well as other laboratory abnormalities, such as hemolytic anemia and renal dysfunction. Presence of multisystem involvement with increasing schistocytes in peripheral smear would suggest such a possibility. New onset bacterial or fungal sepsis should be part of the differential in any critically ill patient with an acute drop in platelet count. New onset fever with or without localizing symptoms and signs, leukocytosis, hypotension, and evidence of DIC, if any, will suggest sepsis. Multiple medications can cause thrombocytopenia in the ICU—the most common among them being antibiotics.

How do You Manage Bleeding while the Patient is on Argatroban, and What was the Further Clinical Course of This Patient?

The principles of managing clinically significant bleeding in a patient on argatroban infusion include stopping the infusion, reversing its effect, definitive control of the bleeding and interim support with blood, and blood products to replace blood loss and depleted coagulation factors. Argatroban has a relatively short half-life of 40–50 minutes, but its clearance may be prolonged in patients with AKI or liver failure. Reversal agents such as vitamin K, recombinant activated factor VII (rVIIa), and prothrombin complex concentrate (PCC) have been evaluated. Vitamin K is a cofactor in the synthesis of clotting factors II, VII, IX, and X and can help restore their levels. rVIIa is a potent activator of factor VII and can help initiate coagulation in the absence of sufficient levels of other clotting factors. PCC is a concentrate of vitamin K-dependent clotting factors that can help replenish coagulation factors and restore hemostasis without causing fluid overload. Antifibrinolytics such as tranexamic acid or aminocaproic acid can also be considered in the management of bleeding in patients on argatroban. These agents act by inhibiting the breakdown of fibrin clots and can help stabilize clots and prevent further bleeding.

In our patient, argatroban infusion was immediately stopped, and he was started on pantoprazole infusion for gastrointestinal bleeding. Urgent upper and lower gastrointestinal tract endoscopies were done but were negative for any active source of bleeding. His dialysis line was removed for possible suspicion of line-related sepsis and blood cultures sent, which revealed *Klebsiella pneumonia* in two out of four bottles. His steroid (initiated for PIGN) was stopped in view of bacteremia and meropenem initiated. With these interventions, his thrombocytopenia gradually improved. Hence, argatroban infusion was first restarted, and maintenance dose of steroid was resumed after sepsis was adequately treated. As all the catheter sites were thrombosed, he was initiated on peritoneal dialysis.

After a brief stable course in the ICU, he subsequently developed an episode of hemoptysis. Argatroban infusion had to be temporarily withheld again, and a computed tomography (CT) angiogram chest was done, which revealed a new right segmental pulmonary thrombus. Progressive HIT with formation of new clots was thought of, and hence, argatroban infusion was restarted and a course of intravenous immunoglobulin (IVIg) initiated. With the above measures, the platelet count gradually improved to 1 lakh. As his platelet count did not improve further, a bone marrow biopsy was done, which showed a hypercellular marrow and mild hemophagocytic picture without any evidence of malignancy. His AKI also improved, with creatinine levels stabilizing at 4–5 mg/dL and a urine output of around 1 L per day.

What Management Strategies are Available to Manage a Patient with HIT Refractory to Stopping Heparin and Anticoagulation?

In cases where initial nonheparin anticoagulation with argatroban fails, there are several alternative anticoagulation options that can be considered.[7,8] These include lepirudin, bivalirudin, fondaparinux, or danaparoid and DOACs like apixaban, rivaroxaban, or dabigatran. Bivalirudin is a direct thrombin inhibitor, similar to argatroban, and has been shown to be effective in the treatment of HIT. Fondaparinux is a synthetic pentasaccharide that selectively binds to antithrombin III and inhibits factor Xa and has been used as an alternative to heparin in patients with HIT. Danaparoid is a heparinoid that does not cross-react with HIT antibodies and has been shown to be effective in the treatment of HIT.

In addition to alternative anticoagulation options, blood product transfusion can be considered in emergency situations to manage thrombocytopenia, especially in actively bleeding patients when the platelet count is <50,000/μL. This may also be more appropriate in patients who require invasive procedures.[9,10]

Intravenous immunoglobulin (IVIg) has also been used to manage HIT refractory to heparin cessation and anticoagulation, although its efficacy is not well established.[11] Plasma exchange (PLEX) has also been used to remove HIT antibodies from circulation, but its role in the management of HIT is still controversial.[12] Finally, immunosuppression with rituximab has been used in cases where

there is evidence of thrombosis or other manifestations of HIT that are refractory to standard therapy.[13] A bone marrow biopsy may also be considered to rule out other causes of thrombocytopenia as was done in this patient.

Course of Our Patient

Our patient did not completely recover from the HIT episode. His platelets continued to be on the lower side (80,000–90,000/dL) without any bleeding manifestations. He was discharged on tapering steroids with a plan to shift him onto steroid-sparing agents. He had a partial renal recovery requiring dialysis. His serum creatinine remained at 4 mg/dL, and he had a urine output of around 1.75 L per day. In view of recurrent thrombosis of the hemodialysis catheters, he was being maintained on peritoneal dialysis at the time of discharge, which was planned to be tapered based on his renal recovery.

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