A Case-Based Approach to Thrombocytopenia in Adults

Part 2: Additional Cases and Conclusion

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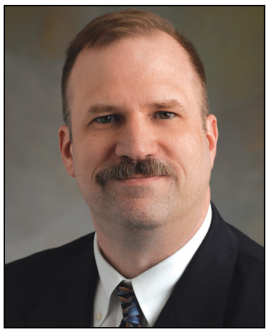

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Thrombocytopenia is a vast topic with a differential ranging from lab artifacts like pseudothrombocytopenia to immediately life-threatening events such as microangiopathic hemolytic anemia. This case-based discussion demonstrates key aspects of common and uncommon causes of thrombocytopenia in adults. Etiologies may be delineated as the result of decreased production or increased consumption.

In the first part of this series published last year, we reviewed the differential diagnosis and an approach to thrombocytopenia using four cases (numbered 1-4) to illustrate key points.[1] In this second part, we conclude with four additional cases (numbered 5-8) that exemplify the broad differential and nuances of approaching thrombocytopenia in the adult.

CASE 5: A 37-year-old male with a history of cryptogenic strokes and chronic kidney disease (CKD) with a baseline creatinine of 1.4 mg/dL presents to the Emergency Department with bright red blood per rectum. He is already on chronic anticoagulation with warfarin. Labs done at the time of presentation demonstrate severe thrombocytopenia with a normal hemoglobin.

WBC Count (4.8-10.8 10*3/µL)	7.2
Hgb (14.0-18.0 g/dL)	14.8
MCV (80.0-100.0 fL)	88.2
Platelet Count (150-450 10*3/µL)	4▼
Neutrophils Absolute (2.20-8.00 10*3/µL)	5.04
Creatinine (0.7-1.2 mg/dL)	1.4▲
Protein Total Serum (5.6-7.9 g/dL)	6.2
Albumin (3.5-4.9 g/dL)	4.3
Bilirubin Total (0.2-1.2 mg/dL)	2.4▲
Alkaline Phosphatase (34-104 U/L)	56
AST (SGOT) (13-40 U/L)	34
ALT (SGPT) (7-52 U/L)	44
INR (PT) (0.9-1.2)	3.0▲
PTT (23.9-30.7 s)	45.5▲

Prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged consistent with the use of the vitamin K antagonist. The presumed diagnosis is immune thrombocytopenic purpura, for which intravenous immunoglobulin (IVIG) and pulse dexamethasone are initiated; this results in a transient increase in platelet count to 15,000/µL, which then quickly returns to less than 10,000/µL.

The patient then develops stroke-like symptoms, and the differential is broadened to include thrombotic thrombocytopenic purpura (TTP). The diagnostic test of choice, an ADAMTS13 level, may take three days or more, so a PLASMIC score is calculated and indicates a high pretest probability prompting therapeutic plasma exchange (TPE) to treat for TTP. Furthermore, a peripheral smear shows an increase in schistocytes and microspherocytes and a mean corpuscular volume (MCV) of <90 fL. This case illustrates that a normal hemoglobin does not eliminate the possibility of a microangiopathic process, and because the total bilirubin is elevated, further workup is initiated.

His lactate dehydrogenase (LDH) is found to be extremely high at 1,517 U/L (normal <260 U/L), while the haptoglobin is undetectable; later it is noted that these labs had been drawn after IVIG was given. IVIG can result in a hemolytic anemia, so it is important to check these hemolytic values prior to initiating IVIG, if at all possible.

The ADAMTS13 level subsequently demonstrates very low activity consistent with the diagnosis of TTP:

Result Name	Value	Unit	Reference Value
▼ LOW **ADAMTS13 Activity Assay**	9	%	≥70
▲ HIGH **ADAMTS13 Inhibitor Bethesda Titer**	1.5	Bethesda units	≤0.4

Plasma exchange results in the rapid resolution of thrombocytopenia; following this, the patient receives rituximab, which returns the ADAMTS13 to a normal level. Given the prior stroke-like symptoms, his ADAMTS13 level is monitored periodically, and the patient receives rituximab every one to two years

when levels are dropping. Fortunately, he has not had a stroke in the more than five years since he first presented with TTP.

Discussion

The PLASMIC score is much like the 4T score for heparin-induced thrombocytopenia in that it gives a pretest probability of TTP — one point each is assigned for the following: platelet count <30,000/µL, hemolysis, no active cancer, no solid organ or stem cell transplant, MCV <90 fL, international normalized ratio (INR) <1.5, creatinine <2 mg/dL. Those with a low score are unlikely to have TTP, but those with intermediate or high scores should have their ADAMTS13 levels tested and should receive therapy for TTP until another diagnostic conclusion is reached.[2]

ADAMTS13 is a protease that cleaves ultra-large von Willebrand multimers. Without this activity, von Willebrand multimers continue to activate platelets, resulting in a microangiopathic process. TTP can be hereditary due to deficiencies in ADAMTS13 itself, or TTP can be immune mediated, such as in the case described here, in which an acquired inhibitor against the ADAMTS13 molecule prevents its function. Critical illness can result in lower-than-normal levels. Yet in true TTP, levels are often critically low (<10%). Asking Hematology services to help interpret findings may be beneficial when the ADAMTS13 activity level is >10%.[3]

Immune TTP has an incidence of 3 in 1,000,000 individuals, and the clinical presentation is often multisystemic. Common symptoms include nausea and abdominal pain, bleeding and purpura, weakness, neurologic findings — including headache, confusion, stroke, or seizure — and cardiac ischemia.[4,5] Mild renal insufficiency is common, but more severe renal injury should raise the concern for an alternative microangiopathic process such as Shiga toxin-induced hemolyticuremic syndrome (HUS), complement-mediated HUS, or drug-induced thrombotic microangiopathy. These symptoms may not be seen early in the course; severe thrombocytopenia should always result in a consideration of the diagnosis of TTP.

Treatment involves a high clinical suspicion and may need to be initiated prior to results of confirmatory testing with ADAMTS13 since untreated TTP has a mortality rate as high as 90%. TPE removes ultra-large von Willebrand multimers, in place of which the patient is given donor plasma that contains normal von Willebrand multimers. At the same time, corticosteroids suppress the immune system. When TPE is completed, rituximab is initiated to further suppress the immune-initiated pathophysiology.

Caplacizumab is a monoclonal antibody that blocks the activity of von Willebrand interactions with platelets and is used in severe or relapsing cases.[6] Finally, if there is serious bleeding or the need for an invasive procedure, platelet transfusion appears to be safe and effective.[7]

Diagnosis: thrombotic thrombocytopenic purpura

- Consider hemolysis labs (LDH and haptoglobin) in severe thrombocytopenia.
  - Check prior to IVIG.
- PLASMIC scores help evaluate the pretest probability of TTP.
  - Intermediate or high-risk scores can be assessed with an ADAMTS13 and should lead to presumptive treatment with plasma exchange.
- Check HBcAb prior to IVIG.

CASE 6: An 86-year-old female who lives alone presents to the Emergency Department with several weeks of right leg pain and swelling due to a deep vein thrombosis. Her son notes she has unintentionally lost 20 pounds over the past few months and is becoming increasingly forgetful.

A computed tomography (CT) scan of the chest, abdomen, and pelvis shows no malignancy. Pancytopenia noted with a macrocytic anemia and elevated total bilirubin raises the possibility of a hemolytic process; that is confirmed when lab results further show a very high LDH (1,836 U/L, normal <260 U/L) and undetectable haptoglobin. A direct antiglobulin test is negative, and coagulation studies are unremarkable.

WBC Count (4.8-10.8 10*3/µL)	2.4▼
Hgb (12.0-16.0 g/dL)	8.1▼
MCV (80.0-100.0 fL)	105.4▲
Platelet Count (150-450 10*3/µL)	123▼
Neutrophils Absolute (2.20-8.00 10*3/µL)	1.39▼
Lymphocytes Absolute (0.90-5.00 10*3/µL)	0.93
Monocytes Absolute (0.20-0.80 10*3/µL)	0.05▼
Eosinophils Absolute (0.00-0.40 10*3/µL)	0.03
Basophils Absolute (0.00-0.40 10*3/µL)	00.0
Creatinine (0.6-1.1 mg/dL)	0.6
Protein Total Serum (5.6-7.7 g/dL)	5.7
Albumin (3.5-4.9 g/dL)	3.4▼
Bilirubin Total (0.2-1.1 mg/dL)	1.8▲
Alkaline Phosphatase (34-144 U/L)	62
AST (SGOT) (13-40 U/L)	40
ALT (SGPT) (7-52 U/L)	17

When subsequently checked, the patient's B_{12} level is undetectable. Treatment with B_{12} supplementation results in resolution of the patient's cytopenia and improvement in fatigue and memory.

Discussion

In this age group, a pancytopenia with macrocytic anemia and weight loss is often a sign of an underlying hematologic malignancy such as myelodysplastic

syndrome (MDS) or a metastatic carcinoma. Yet, severe B12 deficiency can also result in ineffective erythropoiesis and intramedullary hemolysis.

B12 deficiency is often caused by a loss of intrinsic factor due to autoimmune atrophic gastritis, also known as pernicious anemia. Other causes include a chronic deficiency, such as can occur when maintaining a vegan diet or in the setting of a patient with a history of gastric bypass, short gut syndrome, inflammatory bowel disease, Imerslund-Gräsbeck syndrome, or chronic use of metformin. Prolonged use of nitrous oxide, as may be seen in patients who use this drug recreationally, may further result in a functional B12 deficiency.

Clinical features are megaloblastic anemia with a hypercellular and dysplastic bone marrow that can look like MDS or leukemia, as well as demyelination of the cervical and thoracic dorsal and lateral columns of the spinal cord and white matter of the brain. Subacute combined degeneration can result in symmetric paresthesia, impaired position and vibration sensation, gait disorders, or memory issues.[8]

Testing the serum B12 levels is subject to spuriously reduced and elevated levels due to fluctuations in binding proteins. Therefore, interpreting the value in the clinical context is essential. For example, pregnancy can be a time of falsely low levels, and malignancy can result in falsely elevated levels.

Furthermore, anti-intrinsic factor antibodies in pernicious anemia can compete with the chemiluminescence assay and result in a spuriously normal level. Checking methylmalonic acid (MMA) levels can aid in the diagnosis of B12 deficiency as MMA is high in B12 deficiency. Providers must remember, however, that MMA can be falsely elevated in the setting of renal insufficiency.[7]

Treatment involves intramuscular or subcutaneous injection of B12 in severe/symptomatic cases to quickly raise the B12 level. Oral supplementation with 1,000 mcg daily of cyanocobalamin is typically sufficient to overcome absorption issues thereafter. When there is clinical uncertainty of B12 deficiency, replacement is indicated since missing the diagnosis may result in significant long-term consequences.

DIAGNOSIS: severe B12 deficiency with associated ineffective erythropoiesis and intramedullary hemolysis

- Check B12 during the workup of thrombocytopenia and consider checking MMA or empirically treating with B12 to gauge the symptom response.

CASE 7: A 79-year-old male with a history of severe aortic stenosis presents with one week of nausea/vomiting that initially improved until he developed a fever to 102°F and confusion. Vital signs include a blood pressure of 108/72 with pulse of 90 beats per minute. A CT of the chest, abdomen, and pelvis without intravenous or oral contrast demonstrates bibasilar atelectasis versus pneumonia, borderline hepatomegaly, and possible right perinephric stranding. Labs performed during admission show severe thrombocytopenia with neutrophilia, acute kidney injury, hyponatremia, and transaminitis.

WBC Count (4.8-10.8 10*3/µL)	17.0▲
Hgb (14.0-18.0 g/dL)	13.9▼
MCV (80.0-100.0 fL)	93.5
Platelet Count (150-450 10*3/µL)	48▼
Neutrophils Absolute (2.20-8.00 10*3/µL)	12.84▲
Lymphocytes Absolute (0.90-5.00 10*3/µL)	3.83
Monocytes Absolute (0.20-0.80 10*3/µL)	0.29
Glucose (serum) (65-140 mg/dL)	118
Sodium (135-145 mmol/L)	130▼
Potassium (3.4-5.3 mmol/L)	3.7
Chloride (98-107 mmol/L)	87▼
CO2 Venous (21.0-31.0 mmol/L)	31.0
Anion Gap (5-15 mmol/L)	12
Creatinine (0.80-1.30 mg/dL)	3.92▲
BUN/Creatinine Ratio (10-20 Ratio)	19
Protein Total Serum (5.6-7.7 g/dL)	6.1
Albumin (3.5-4.9 g/dL)	3.5
Bilirubin Total (0.2-1.2 mg/dL)	1.5▲
Alkaline Phosphatase (34-104 U/L)	328▲
AST (SGOT) (13-40 U/L)	117▲
ALT (SGPT) (7-52 U/L)	104▲

In the Emergency Department, he is given ceftriaxone and azithromycin and soon switched to piperacillin/tazobactam and vancomycin for presumed sepsis. Blood and urine cultures are subsequently negative, and a viral panel including COVID-19 testing is negative as well; urine legionella and pneumococcal antigens are negative.

Given that the patient has mental status changes, an elevated total bilirubin, and thrombocytopenia in the setting of acute kidney injury requiring dialysis, the differential diagnosis includes the possibility of a microangiopathic hemolytic anemia. Further lab analysis reveals that LDH is elevated to 563 U/L (normal <260 U/L) and the haptoglobin and reticulocyte counts are normal. PT/PTT are also normal, and the fibrinogen is appropriately elevated.

Broad-spectrum antibiotics do not seem to help the fever. In the setting of borderline hepatomegaly, hemophagocytic lymphohistiocytosis is also considered. His ferritin is elevated to 6,222 ng/ml (normal <336 ng/ml), and the triglycerides are also elevated at 216 mg/dL (normal <150 mg/dL). Soluble IL2r alpha (CD25) is sent, and although it does not result until days after a diagnosis is ultimately made, it is highly elevated at 28,950 pg/ml (upper limit of normal 1,891 pg/ml).

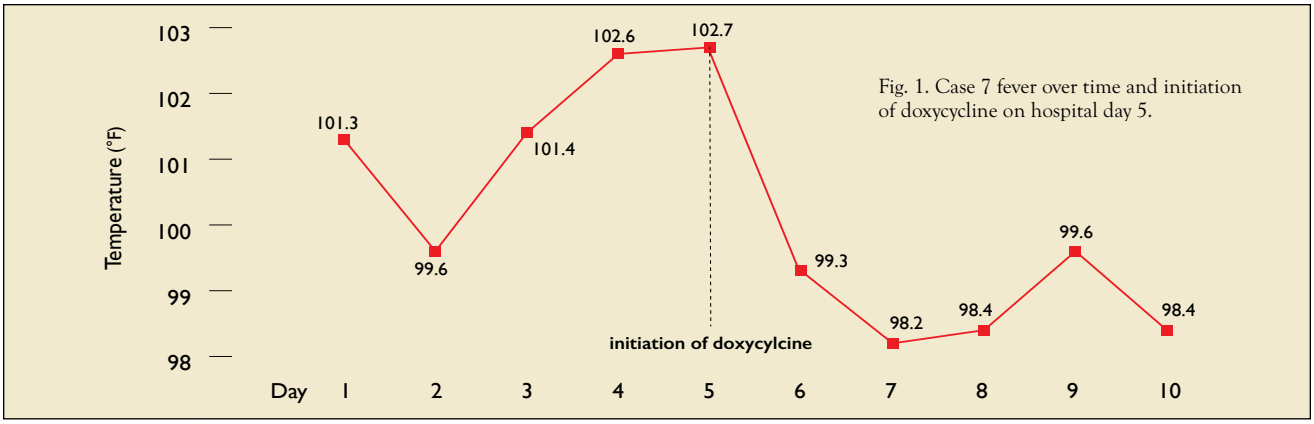

Fig. 1. Case 7 fever over time and initiation of doxycycline on hospital day 5.

Specialists from the Infectious Diseases and Hematology services are consulted, and a tickborne illness is also considered in the differential; empiric doxycycline is started on hospital day five. Immediate defervescence is noted. Lab analysis demonstrates that the platelet count starts recovering 48 hours later and is back to normal range within five days (see Fig. 1 above).

Additional lab results are revealed several days after the diagnosis of human granulocytic anaplasmosis is made — including *Ehrlichia* human granulocytic ehrlichiosis immunoglobulin M (IgM) antibody at a ratio of 1:80 and IgG antibody at a ratio of 1:64. The following lab results are negative: *Ehrlichia* IgM and IgE, *Rickettsia rickettsii* panel, Lyme titers, and Babesia titers. Q fever IgM stages I and II are negative, while IgG stages I and II are positive, suggesting either a past exposure or a false positive. Epstein-Barr virus titers suggest a prior infection. On further review of the history when his sensorium improves, the patient relates that he had gone camping in the woods one week prior to the onset of these symptoms, although he does not recall any tick bites.

Discussion

Human granulocytic anaplasmosis is caused by *Anaplasma phagocytophylum* and has an incubation of one to two weeks. It is more commonly seen in the northeastern United States.[9,10] The diagnosis can be made if Wright- or Giemsa-stained peripheral blood during the early stage of infection demonstrates the obligate intracellular parasite, or morulae, in the cytoplasm of neutrophils. Fig. 2 (at right above) demonstrates a case of *Ehrlichia*.

Acute and convalescent serologic testing may demonstrate a four-fold change or seroconversion; this is the most sensitive and most widely used test. Treatment decisions typically need to be made prior to knowing the results of testing; the serology can be negative in the first one to two weeks of infection. Polymerase chain reaction amplification for specific DNA may be positive in the first week of infection but is not widely available.

In symptomatic patients, doxycycline is the treatment of choice. Empiric therapy with doxycycline is justified when considering this diagnosis because it will cover other tickborne illnesses — with the exclusion of *Babesia* — which occur in 2% to 12% of cases.[10,11] Quick resolution of fever after starting doxycycline can be "diagnostic" of tickborne illness, and if symptoms are not improving within 48 hours, an alternative diagnosis should be considered.

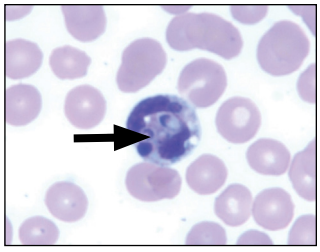

Fig. 2. Case 7 morulae at 1000x. This peripheral smear demonstrates the intracytoplasmic morulae within a monocyte from a case of *Ehrlichia*. Note that *Anaplasma* as described in this case infects the neutrophil lineage.

Image courtesy Angie Ha, LG Health Core Lab supervisor.

The constellation of non-specific flu-like symptoms including fever, muscle aches, and nausea, along with transaminitis, acute kidney injury, and hematologic derangements including leukopenia, atypical lymphocytosis, bandemia, and thrombocytopenia as described in this case, should prompt the care team to consider tickborne illness among many other life-threatening etiologies. The non-specific presentation makes it tempting to assume thrombocytopenia is consumptive, such as might occur in a patient who is septic. The presentation is variable from asymptomatic to life threatening in 3% of cases.[10]

DIAGNOSIS: tickborne Illness — human granulocytic anaplasmosis

- Include a history of outdoor activity in the evaluation of thrombocytopenia during tick exposure months.
- Rapid resolution of symptoms and thrombocyto-

penia with doxycycline can be diagnostic of a tickborne illness.

CASE 8: A 62-year-old male presents to the Hematology clinic prior to having a right total knee arthroplasty. He has a long-standing history of platelets in the 60,000-90,000/µL range. He explains that when his father had a myocardial infarction, it was noted that the father's platelets were in the 70,000-80,000/µL range; subsequently, the patient's brother was noted to have platelets in the 40,000/µL range.

The patient states that when he was a child, he was told he has an autosomal dominant trait most consistent with hereditary macrothrombocytopenia. He has had multiple hemostatic challenges in the past without excessive bleeding including a circumcision, a dental extraction, several broken bones including a C5 fracture, an ACL repair, and a vasectomy.

Von Willebrand testing is normal, and platelet aggregation studies are overall unremarkable. A peripheral smear shows enlarged platelets with an absolute thrombocytopenia (see Fig. 3).

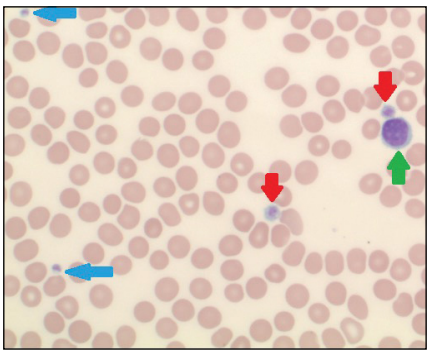

Fig. 3. Case 8 peripheral smear at 60x shows macrothrombocyte (red arrows) and more normal size platelets (blue arrows), as well as a lymphocyte (green arrow) in a background of red blood cells.

He proceeds with knee surgery without any bleeding complications and tolerates prophylactic aspirin.

Discussion

Hereditary macrothrombocytopenia can be found in patients of a variety of genetic heritages and is characterized by large to giant platelets with an absolute thrombocytopenia that is either clinically insignificant or results in a mild bleeding disorder.[12] Heterozygous mutations in GP1BA or GP1BB likely account for this condition, and there is overlap genetically with patients who have Bernard-Soulier syndrome.[13]

DIAGNOSIS: congenital thrombocytopenia most consistent with hereditary macrothrombocytopenia

- A long-standing history of stable thrombocytopenia in a young person should prompt consideration of a congenital etiology.

CONCLUSION

As these cases demonstrate, the differential diagnosis for thrombocytopenia can be broad and complex. Understanding the differential as presented in these two articles will allow a clinician to consider life-threatening etiologies and initiate the appropriate workup. Astute clinicians should keep in mind the need to have a high index of suspicion for heparin exposure, microangiopathic hemolytic processes, and tickborne illness.

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