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Clinicopathological Conference

Warren Alpert Medical School of Brown University: Clinicopathologic Conference: September 20th, 2024. A Woman in her 20s with Abdominal Pain, Anemia and Thrombocytopenia.

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Abstract

A case conference describing the presentation of a woman in her 20's with anemia, abdominal pain and thrombocytopenia who was diagnosed with paroxysmal nocturnal hemoglobinuria and likely aplastic anemia.

CASE PRESENTATION

A woman in her 20s presented to hospital with nausea, vomiting, epigastric pain that was progressively worsening over the previous month. She reported associated fatigue, mild lightheadedness, and episodes of easy bruising. She reported heavy menses, lasting 4-5 days on average with heavy menstrual flow on days one through two. She recalled an attempt to donate blood several years prior when she was told she was ineligible due to a red blood cell count in the lower range of normal. She denied hematemesis, melena, hematochezia, constipation, diarrhea, and hematuria. She denied chest pain and shortness of breath, sick contacts, and foreign travel.

She had no other past medical history, including blood transfusions. She did not take any prescribed or over-the-counter medications. She reported no allergies. She denied a family history of bleeding or prothrombotic disorders. She denied use of tobacco, alcohol, cannabinoid, and other substances. She was sexually active with a partner and used barrier protection methods of birth control. She was a resident of the State of Rhode Island.

Physical examination revealed blood pressure 118/78 mmHg, pulse rate 72/min, respiratory rate of 14/min and temperature of 98°F. The patient appeared generally well. Scleral pallor was noted without icterus. Pulmonary, cardiovascular, and abdominal examinations were unremarkable. Organomegaly was absent. Skin was warm and dry, without rashes. Extremities were without evidence of edema with 2+ radial and pedal pulses. No lymphadenopathy was noted in the cervical, axillary, inguinal and other usual nodal bearing areas.

See Table 1 for laboratory findings respectively. Computed tomography (CT) scan of abdomen and pelvis with intravenous contrast revealed unremarkable lower thoracic organs, normal liver, spleen, pancreas, adrenal glands, kidneys but did show mild proximal small bowel enteritis. Pelvis organs were unremarkable. Chest radiography was unremarkable.

WARREN ALPERT MEDICAL SCHOOL STUDENT PRESENTATIONS

Student (The Miriam Hospital, Providence, RI)

Working Diagnosis: Myelodysplastic Syndrome due to Benzene Exposure

The patient presents with a month of fatigue, easy bruising, vomiting, and epigastric pain, as well as anemia and thrombocytopenia. A hemolytic cause of anemia is possible due to the elevated D-dimer but seems significantly less likely due to the normal bilirubin, negative direct antiglobulin test, and lack of schistocytes on peripheral smear. Common causes of megaloblastic anemia including B12 and folate deficiency are ruled out with normal

Table 1. Laboratory findings

Laboratory Result	Reference Range, Adult	On Presentation
White blood cell count	3.5-11.0 x 10^9/L	4.3 x 10^9/L
Hemoglobin, serum	13.5-16.0 g/dL	5.4 g/dL
Hematocrit, serum	37.0-47.0%	16.8%
Platelets	150-400 x 10^9/L	55 x 10^9/L
Sodium, serum	135-145 mEq/L	135 mEq/L
Potassium, serum	3.6-5.1 mEq/L	3.5 mEq/L
Chloride, serum	98-110 mEq/L	103 mEq/L
Blood Urea Nitrogen (BUN), serum	6-24 mg/dL	9 mg/dL
Creatinine, serum	0.64-1.27 mg/dL	0.6 mg/dL
Glucose, serum	67-99 mg/dL	109 mg/dL
Calcium, serum	8.5-10.5 mg/dL	9.0 mg/dL
Aspartate aminotransferase (AST), serum	10-42 IU/L	31 IU/L
Alanine aminotransferase(ALT), serum	6-45 IU/L	11 IU/L
Alkaline Phosphatase, serum	34-104 IU/L	68 IU/L
Protein, total, serum	6.0-8.0 g/dL	7.9 g/dL
Albumin, serum	3.5-5.0 g/dL	4.7 g/dL
Bilirubin, total, serum	0.2-1.3 mg/dL	0.7 mg/dL
Lipase, serum	10-60 IU/L	24 mg/dL
Vitamin B-12	227-1053 pg/mL	412 pg/mL
Iron, serum	37-170 ug/dL	55 ug/dL
Transferrin, serum	179-371 mg/dL	406 mg/dL
Transferrin Saturation	15-50%	14%
Ferritin, serum	22-322 ng/mL	10 ng/mL
Folate, serum	3.5 - 14.7 ng/mL	20.4 ng/mL
D-Dimer, serum	0 - 300 ng/mL	4314 ng/mL
International normalized ratio (INR)		1.1
Lactate dehydrogenase (LDH)	119-265 IU/L	627 IU/L
Stool Occult Blood		Negative
Direct Antiglobulin Test		Negative
Thyroid-stimulating hormone (TSH), serum	0.330-4.120 U/mL	1.017 U/mL
Peripheral Blood Smear		Macrocytic anemia with moderate anisocytosis, thrombocytopenia. No over schistocytes.

plasma levels. Her peripheral blood smear findings are concerning for aplastic anemia and/or myelodysplastic syndrome (MDS). Toxin exposure such as benzene may lead to bone marrow injury and premature development of MDS in a younger patient. Although benzene exposure is relatively rare, the patient may live or work in proximity to facilities involved in the processing or manufacture of petrochemicals or other processes leading to exposure. In terms of workup, I would recommend further occupational and exposure history with particular regard to benzene, and a bone marrow biopsy.

Student (Veterans Affairs Medical Center, Providence, RI)

Working Diagnosis: Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired hematologic disorder caused by deficiency of CD55 and CD59, which allows for increased complement-mediated hemolysis. PNH can cause anemia and thrombocytopenia. The patient's report of having "low blood counts" when younger suggests that her current disorder is chronic rather than acute, supporting PNH. Her abdominal pain, nausea, and vomiting could be explained by severe anemia causing hypoperfusion of the intestine. Refuting evidence includes absence of blood on the urine dipstick, and no reported change in the color of her urine, particularly in the morning. We would also expect an elevated unconjugated bilirubin. I would recommend peripheral blood flow cytometry analysis to detect absence of CD55 and/or CD59.

Student (Rhode Island Hospital, Providence, RI)

Working Diagnosis: Systemic Lupus Erythematosus

This presentations of a woman in her 20's admitted with nausea, vomiting, and epigastric pain along with fatigue, lightheadedness, and easy bruising that has worsened over the past month is most concerning for systemic lupus erythematosus (SLE). SLE is the most likely diagnosis as the patient has a history of low blood counts which

has reportedly prevented her from donating blood in the past, indicating a chronic nature of her disease process. The patient's gender and younger age fit the demographic profile for SLE. Anemia and thrombocytopenia are commonly seen in SLE due to autoimmune hemolysis of red blood cells and platelets. It is possible that SLE is driving the elevated serum inflammatory markers including D-dimer and LDH. The patient's gastroenterological symptoms may be explained by lupus enteritis, a condition known to affect the bowel and associated with vasculitis. Next steps in workup would include a serum anti-nuclear antibody (ANA), anti-double stranded DNA, and anti-Smith antibody titers.

Student (Kent County Hospital, Warwick, RI)

Working Diagnosis: Parvovirus B19 infection

The most likely diagnosis for this patient is a parvovirus B19 infection causing an aplastic crisis and mild small bowel enteritis. Parvovirus B19 classically presents with symmetric polyarthritis, it is not required for diagnosis and can cause other symptoms such as the enteritis we see in this patient. Parvovirus B19 can cause anemia and thrombocytopenia as it primarily infects progenitor cells of erythrocytes (such as myeloid stem cells) and would fit the timeline of the patient's symptoms. Additional features of the patient's presentation such as macrocytosis can be explained by recovery of the bone marrow and increased reticulocyte counts (reactive macrocytosis). Although other viral infections (e.g. cytomegalovirus, Ebstein-Barr virus) can cause aplastic anemia, these usually occur in immunocompromised patients. To workup the Parvovirus B19, I would send for antibody testing for Parvovirus B19 IgM and IgG serologies as well as a reticulocyte count to show bone marrow recovery.

Dr. Andrew Hsu (Department of Medicine, Division of Hematology and Oncology, Warren Alpert School of Medicine, Brown University)

The most striking finding in this case is bicytopenia, involving two lines of bone marrow production, the red blood cells and platelets. It raises concern for conditions affecting bone marrow production such as nutritional deficiencies, such as B12 and copper deficiencies, perhaps associated with malabsorption such as celiac disease. This patient has enteritis on imaging which could perhaps be associated with inflammatory bowel disease. I would also want to collect more history about her heavy menses and better quantify the menstrual flow. Lactate dehydrogenase (LDH) elevation and a peripheral blood smear with anisocytosis but without premature myeloid cells or nucleated red cells points away from myelodysplastic syndrome. The absence of schistocytes on the peripheral smear and a negative direct antiglobulin test point away from thrombotic microangiopathy and other autoimmune hemolytic anemias. In the absence of evidence of hemolysis, my top differential would be aplastic anemia, followed by acute human immunodeficiency virus infection (HIV). I would perform a bone marrow biopsy as well as human immunodeficiency virus (HIV) serological testing.

CLINICAL COURSE

The patient underwent esophagogastroduodenoscopy with findings consistent with chronic gastritis secondary to *H. pylori* infection. Other laboratory testing included a normal level of ADAMSTS13 enzyme activity, negative cold agglutinins, and normal serum protein electrophoresis. Peripheral blood flow cytometry showed granulocytes with partial CD24 and decreased CD16 expression consistent with a diagnosis of paroxysmal nocturnal hemoglobinuria. The patient was started on ravulizumab, and red blood cell and platelet counts improved. She received meningococcal vaccination and completed a course of treatment for *H. pylori*.

FINAL DIAGNOSIS

Paroxysmal Nocturnal Hemoglobinuria (PNH)

DISCUSSION

Paroxysmal nocturnal hemoglobinuria is a clonal, hematopoietic disorder in which a mutation in the phosphatidylinositol glycan class A (PIGA) gene on the X chromosome affects the synthesis of glycosylphosphatidylinositol (GPI) anchors, specialized lipids which help attach CD59, a cell surface receptor that protects cells from the complement system, onto red blood cells (RBCs). The PIGA gene mutation must occur in a hematopoietic stem cell and then undergo clonal expansion to affect mature blood cells. Lack of CD59 attachment on RBCs results in complement-mediated hemolysis leading to the range of signs and symptoms seen in PNH. PNH is rare in children and mostly seen in adults (median age of 30) with no significant difference in prevalence by sex, race, or geography.[1]

PNH often presents with clinical signs of hemolytic anemia, pancytopenia, and venous thrombosis. This includes symptoms of anemia such as fatigue, along with signs of hemoglobinuria due to hemolysis. Although PNH is classically associated with symptoms of morning red/pink urine (hemoglobinuria), the color change is only present in a small subset of patients. The release of hemoglobin from RBC breakdown leads to vasospasm and a hypercoagulable state, which can lead to thromboses and related sequelae. This commonly causes intra-abdominal thrombi or pulmonary emboli, resulting in symptoms like abdominal/chest pain and dyspnea.[2] This

can also lead to strokes in patients' whose thrombi are in the cerebral arteries. Other common vessel-related problems seen in these patients with PNH include renal insufficiency and erectile dysfunction. Bone marrow dysfunction/suppression, leading to pancytopenia due to defects in synthesis, is also observed. Patients may present with infections due to leukopenia, along with easy bruising/bleeding due to thrombocytopenia.

Laboratory testing for diagnosing PNH should confirm hemolysis and exclude other causes for anemia. Common findings for PNH include a low hemoglobin, low serum haptoglobin, high reticulocyte count, negative direct Coombs test, elevated lactate dehydrogenase (LDH), and the presence of hemoglobin and/or hemosiderin in the urinalysis. Flow cytometry is the key to diagnosis and is performed on the RBCs and granulocytes using reagents that bind to CD59 and CD55, among others. The FLAER reagent is also used in PNH diagnosis as it directly binds the GPI anchor. Diagnosis is established via flow cytometry findings showing deficiency in GPI linked proteins such as CD55 and CD59 along with clinical findings such as hemolytic anemia, hemoglobinuria, myelodysplastic syndrome, aplastic anemia, or thrombosis.[3]

Aplastic anemia is characterized by hypocellular (dearth of hematopoietic stem cells and progenitor cells), fatty bone marrow without fibrosis or unusual infiltrates, and it is defined by the presence of two out of three of the following: hemoglobin less than 10 g/dL, platelets less than 50,000/L, and neutrophils less than 1500/L. It can be categorized as acquired aplastic anemia when it is not an inherited condition such as Diamond-Blackfan Anemia, among others. Though the exact pathophysiological mechanism is not clear, acquired aplastic anemia appears to be associated with PNH. In fact, many patients with newly diagnosed PNH have either historical or current bone marrow suppression, and they can even go on to develop myelodysplastic syndromes further on in their life as well, leading to subsequent acquired aplastic anemia. Patients with newly diagnosed aplastic anemia are also often found to have clonal populations of cells affected by the PIGA mutation seen in PNH.[4]

Management of PNH often depends on how its severity is characterized by objective findings. In cases where the condition is subacute and there are no substantial symptoms of hemolysis, bone marrow suppression, or thrombosis, the patient can remain under observation to assess for worsening of symptoms.[1] For patients with symptoms of hemolysis, the aim is to inhibit complement mediated hemolysis, and C5 inhibitors such as ravulizumab or eculizumab are effective.[5,6] For patients with severe bone marrow failure, hematopoietic cell transplantation should be considered if they are eligible.[7] Other complications of PNH are treated similarly to when they present in isolation, such as thrombosis which should be treated with appropriate anticoagulation and thrombolysis based on severity/indication.[5] Since the advent of C5 inhibitor treatment, patients have morbidity and mortality similar to age matched controls, however prognosis can be worse for patients with severe infections, thrombosis, renal failure, and bone marrow failure.[8,9]

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- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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