CME CREDIT

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A 61-year-old woman with thrombocytopenia and a rash

A 61-YEAR-OLD WOMAN with a history of seizures was transferred to our facility from another hospital for further evaluation and management of a rash and a low platelet count.

The woman was initially admitted to the other hospital 4 weeks earlier due to the onset of focal seizures. An extensive evaluation revealed no etiology for the seizures. She was discharged home with her seizures well controlled with phenytoin. Approximately 3 weeks later, she noticed a diffuse rash without any other associated symptoms. Her primary physician discontinued the phenytoin and substituted carbamazepine. Two days later she felt that her rash had worsened, and she became frustrated and stopped taking all of her medications. She presented to the emergency department 2 days later with diarrhea, polyuria, and polydypsia. At that time a blood workup revealed a plasma glucose level of 824 mg/dL and a platelet count of 10×10^9/L. She was admitted to the hospital and was later transferred to our facility.

Medical history. A review of her medical history showed type 2 diabetes requiring insulin; asthma; and the focal seizures mentioned above. Current and recent medications included NPH insulin 40 U every morning and 20 U every evening; carbamazepine (stopped 2 days prior to transfer); phenytoin (stopped 9 days prior to being transferred to our facility); and albuterol and ipratropium bromide inhalers. Her only known drug allergy was to glipizide. She did not smoke or drink alcohol.

Physical findings. On physical examination, she appeared comfortable. Her temperature was 37.2°C, heart rate 100 bpm (regular), blood pressure 142/84 mm Hg, and respiratory rate 20. She was not in acute distress. Examination of her skin revealed confluent macular purpuric lesions involving the entire body and face, with relative sparing of the palms and soles. Purpuric papules were also found on the back of her hands and legs. There was also conjunctival injection with periorbital edema, but mucous membranes were clear. The chest was normal on auscultation, and no wheezes were heard. Her cardiac examination was normal. There was no detectable organomegaly, and a stool test for occult blood was positive. She had strong peripheral pulses with no edema.

LABORATORY RESULTS AT ADMISSION

Laboratory results at the time of her admission to our facility are listed in TABLE 1. Her white blood cell count was 21.4×10^9/L (54% neutrophils, 19% lymphocytes, and 15% eosinophils), with a hemoglobin (Hgb) of 11.8 g/dL and a platelet count of 5×10^9/L. Results of coagulation studies were normal.

A peripheral blood smear was immediately reviewed, showing leukocytosis with immature neutrophils (ie, left shift), eosinophils, and decreased platelets. There was no evidence of red cell fragments, target cells, or schistocytes.

Platelet destruction can be due to immune or nonimmune processes

LOW PLATELET COUNT

1 This patient's low platelet count might result from each of the following, except which one?

- ❑ Drug effect
- ❑ Pseudothrombocytopenia
- ❑ Immune platelet destruction
- ❑ Nonimmune platelet destruction

TABLE 1

Laboratory test results at the time of hospital admission

STUDY	VALUE	NORMAL RANGE
Sodium	124 mmol/L	132–146
Potassium	4.5 mmol/L	3.5–5.0
Chloride	94 mmol/L	98–110
Carbon dioxide	23 mmol/L	24–32
Blood urea nitrogen	46 mg/dL	8–25
Creatinine	1.5 mg/dL	0.7–1.4
Glucose	685 mg/dL	65–110
Bilirubin	1.4 mg/dL	0–1.5
Lactate dehydrogenase (LDH)	685 U/L	100–220
Alkaline phosphatase	340 U/L	20–120
Aspartate aminotransferase (AST)	35 U/L	7–40
Hemoglobin	11.8 g/dL	12–16
White blood cells	21.4×10^9/L	4.0–11.0
Neutrophils	54 %	40–70
Lymphocytes	19 %	15–45
Eosinophils	15 %	1–6
Platelets	5×10^9/L	150–400
Red blood cells	4.05×10^{12}/L	4.2–5.4

Investigating a low platelet count requires an organized approach, making efficient and accurate use of available diagnostic tests and treatments.

First, one must determine if the low platelet count signifies true thrombocytopenia or pseudothrombocytopenia. Pseudothrombocytopenia occurs when platelets clump in an EDTA anticoagulated tube. Platelet clumps are seen on the peripheral smear, and a normal platelet count is obtained from a heparinized tube.

Our patient's peripheral smear revealed a decreased number of platelets without platelet clumping. Thus, it appears that she had true thrombocytopenia, making pseudothrombocytopenia the correct choice above.

Causes of thrombocytopenia

Thrombocytopenia can be secondary to decreased production of platelets, sequestration of platelets, or destruction of platelets (TABLE 2).

Decreased production of platelets can be caused by an insult to the hematopoietic cells (eg, from cytotoxic therapy, drugs, toxins, infections, aplasia) or replacement of otherwise normal marrow (eg, as in infiltration of the marrow by malignant cells, myelofibrosis).

Platelet sequestration is usually due to functional hypersplenism (eg, as in cirrhosis, passive congestion, malignancy, infections).

Platelet destruction can be due to immune or nonimmune processes. Immune causes include idiopathic thrombocytopenic purpura, transfusion-related alloimmune thrombocytopenia, and drugs. Nonimmune processes include disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, sepsis, mechanical destruction, and again, drugs.

THE INITIAL HOSPITAL COURSE

On admission to our hospital, the patient underwent hydration with normal saline and received insulin intravenously. Phenobarbital was substituted for her prescription for carbamazepine.

A hematology consultation was obtained. Bone marrow aspiration was performed, and microscopic examination of the aspirate revealed a cellular marrow with megakaryocytes. These findings suggested a peripheral loss of platelets. The clinical picture and the results of bone marrow analysis were felt to be consistent with idiopathic thrombocytopenic purpura. Treatment with intravenous immunoglobulin and two units of platelets was started.

Over the next 2 days the patient complained of a sore throat and was noted to have a temperature of 38.3°C. She was drowsy.

Several laboratory values during this time were notable: the Hgb fell from 11.8 g/dL to 10.0 g/dL, then 8.9 g/dL. The platelet count remained below 10×10^9/L (6×10^9/L).

Her lactate dehydrogenase (LDH) increased to 1844 U/L, bilirubin to 2.4 mg/dL, and AST to 105 U/L. Alkaline phosphatase decreased to 263 U/L. A dipstick urinalysis found 3+ Hgb and no bilirubin. A microscopic examination of the urine found more than 25 red blood cells and 11 to 25 white blood cells per high-powered field.

HEMOLYSIS

2 A decreasing level of which of the following would provide evidence that hemolysis is occurring?

- ❑ Urine hemosiderin
- ❑ LDH
- ❑ Methemalbumin
- ❑ Haptoglobin

Several of the above laboratory results suggest hemolysis. When evaluating a patient for hemolysis, several tests should be considered.

During hemolysis, the reticulocyte count increases to compensate for the falling Hgb level. LDH and bilirubin are released and thus elevated, whereas the haptoglobin and hemopexin levels fall as they bind to free hemoglobin and are quickly cleared in the liver. Free hemoglobin is oxidized to methemoglobin, which subsequently splits from the globin portion and binds to free albumin, causing a rise in methemalbumin levels. The heme tetramer splits to a dimer, is filtered in the kidney, and is absorbed by the renal tubules, where the iron is stored as hemosiderin. As the tubular cells die, they slough into the urine, leading to an elevated urine hemosiderin level.

Thus, of the choices above, haptoglobin is the only one that decreases during hemolysis.

ANALYZING THE CAUSES OF HEMOLYSIS

There are several ways to organize the causes of hemolysis. One way is to divide the causes into intrinsic red blood cell abnormalities and abnormalities not intrinsic to red blood cells (TABLE 3).

Intrinsic abnormalities can be congenital, such as membrane defects (eg, spherocytosis, elliptocytosis) and enzymopathies (eg, glucose-6-phosphate dehydrogenase deficiency), or acquired, such as lead poisoning, paroxysmal nocturnal hemoglobinuria, and renal failure.

Extrinsic abnormalities include microangiopathy (eg, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, eclampsia, and malignant hypertension), hypersplenism, sepsis, and immune causes (eg, drugs, infections, lymphoma, collagen vascular diseases).

TABLE 2

Differential diagnosis of thrombocytopenia by cause

Caused by decreased platelet production
Hematopoietic cell insult
- Cytotoxic therapy
- Drugs
- Toxins
- Infections
- Aplasia

Bone marrow replacement
- Malignant cells
- Myelofibrosis

Caused by platelet sequestration
Functional hypersplenism
- Cirrhosis
- Passive splenic congestion
- Malignancy
- Infection

Caused by platelet destruction
Immune processes
- Idiopathic thrombocytopenic purpura
- Transfusion related
- Drugs

Nonimmune processes
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Sepsis
- Mechanical destruction
- Drugs

During hemolysis, the reticulocyte count rises to counter the falling Hgb

Review of our patient's subjective and objective problems revealed the characteristic pentad of thrombotic thrombocytopenic purpura (see below).

THROMBOTIC THROMBOCYTOPENIC PURPURA

3 Most patients with thrombotic thrombocytopenic purpura will have all of the following laboratory results, except which one?

- ❑ Low hemoglobin
- ❑ Creatinine above 1.5 mg/dL
- ❑ Normal coagulation studies
- ❑ Elevated LDH

TABLE 3

Differential diagnosis of hemolysis

Intrinsic red blood cell abnormalities

Congenital
- Membrane defects (eg, spherocytosis, elliptocytosis)
- Enzymopathies (eg, glucose-6-phosphate dehydrogenase deficiency)

Acquired
- Lead poisoning
- Paroxysmal nocturnal hemoglobinuria
- Renal failure

Extrinsic red blood cell abnormalities

Microangiopathy
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Eclampsia
- Malignant hypertension

Hypersplenism

Sepsis

Immune causes
- Drugs
- Infections (eg, Epstein-Barr virus, Mycoplasma)
- Lymphoma
- Collagen vascular diseases

Biopsy of the skin, muscle, and gingiva has a low diagnostic yield

Thrombotic thrombocytopenic purpura is a syndrome of disseminated thrombotic occlusions of the microcirculation, with five characteristics:

- Hemolytic anemia
- Thrombocytopenia
- Neurologic symptoms
- Fever
- Renal dysfunction

Microthrombi and fibrin networks are laid down in the small vessels, although the reason is unclear. Red blood cells are damaged by these networks and are destroyed in the spleen or the microcirculation. Platelets are either consumed in the microthrombi or damaged and removed by the reticuloendothelial system.

Only 40% of patients go on to develop the full pentad, and even fewer have the full pentad at initial presentation. Anemia and thrombocytopenia are usually severe at presentation. Fever is uncommon initially but invariably develops. Neurologic manifestations, including headache, confusion, cranial nerve palsies, seizures, and coma can progress rapidly. Renal dysfunction is manifested by an abnormal urinary sediment. Fewer than 20% of patients develop a serum creatinine above 1.5 mg/dL; therefore, this is the correct answer.

Associated underlying disorders

Thrombotic thrombocytopenic purpura is associated with a definable underlying disorder in 15% of cases. Pregnancy, collagen vascular diseases, allograft rejection, and infection (*Escherichia coli* O157:H7) lead the list. Laboratory findings include evidence of hemolysis (see above), normal coagulation studies, and a peripheral blood smear showing polychromasia, stippling, nucleated red cells, and schistocytes. Bone marrow aspirate reveals normoblastic hyperplasia and increased megakaryocytes. Biopsy of the skin, muscle, and gingiva has a low diagnostic yield.

TREATMENT OF CHOICE

Exchange plasmapheresis is the treatment of choice for thrombotic thrombocytopenic purpura, although its exact mechanism of action is unknown. Plasmapheresis is felt to be more effective than plasma infusion alone. Many other therapies have been used, either with disappointing results or with success in only a few cases. These include splenectomy, prostacyclin, antiplatelet drugs, corticosteroids, and vincristine. Platelet transfusions should be avoided unless evidence of life-threatening hemorrhage is present, as acute deterioration in status has been reported (more platelets available to form microthrombi, leading to further end-organ damage). Intravenous immunoglobulin has not been proven effective and may even be harmful.

Currently, after treatment with plasmapheresis, 80% to 90% of patients survive the first episode with no sequelae or minimal sequelae. Approximately one third experience a relapse within 10 years, usually responding to the same therapy as the initial episode.

FURTHER HOSPITAL COURSE

The next day the patient again was drowsy and complained of "feeling down." Her laboratory values continued to deteriorate. Her LDH increased to 2149 U/L, bilirubin increased to 2.9 mg/dL, and her AST decreased slightly to 98 U/L. Her hemoglobin continued its fall, to 7.4 g/dL, as did her platelet count, to 6×10^9/L.

Her haptoglobin was less than 6 mg/dL (normal range 37–246 mg/dL), and her peripheral blood smear revealed red blood cell fragments. As she was being prepared for plasmapheresis, she went into cardiopulmonary arrest. Resuscitation efforts were unsuccessful.

It appears that the patient had thrombotic thrombocytopenic purpura. However, this does not explain all of her problems, such as rash and eosinophilia. These raise the suspicion of a drug reaction.

PHENYTOIN'S ADVERSE EFFECTS

4 Which of the following adverse effects of phenytoin is idiosyncratic?

- ❑ Nystagmus
- ❑ Ataxia
- ❑ Nausea
- ❑ Gingival hyperplasia

The adverse effects of phenytoin can be divided into those that increase in frequency and severity with the plasma concentration of the drug and those that are idiosyncratic (TABLE 4). Nystagmus, ataxia, incoordination, dysarthria, lethargy, nausea, vomiting, and epigastric pain are all concentration-dependent.

Idiosyncratic reactions include gingival hyperplasia, hirsutism, acne, many varieties of rash (including toxic epidermal necrolysis and Stevens-Johnson syndrome), aplastic anemia, hepatitis, and the phenytoin hypersensitivity syndrome. Thus, of the choices listed, gingival hyperplasia is the only idiosyncratic adverse effect.

Phenytoin hypersensitivity syndrome

The phenytoin hypersensitivity syndrome occurs in 1 in 1,000 to 1 in 10,000 patients within 3 weeks to 3 months after starting phenytoin therapy. African Americans have the highest incidence. Rash is one manifestation: erythema or maculopapules may be seen, and the rash may exfoliate, show follicular accentuation with pustules, or lead to erythema multiforme or toxic epidermal necrolysis.

Other manifestations include edema (prominent facial edema is characteristic), pharyngitis, conjunctivitis, adenopathy, hepatosplenomegaly, fever, anorexia, myopathy, and diarrhea.

Laboratory manifestations of phenytoin hypersensitivity syndrome include leukocytosis with eosinophilia, elevated transaminases, Coombs-negative hemolytic anemia, interstitial nephritis, and thrombocytopenia.

Phenobarbital and carbamazepine can cause a similar reaction that is indistinguishable from phenytoin hypersensitivity syndrome. In susceptible patients, the detoxification of the reactive arene oxide metabolites of these aromatic anticonvulsants is abnormal.

TABLE 4

Adverse effects of phenytoin

Concentration-dependent reactions

Nystagmus
Ataxia
Incoordination
Dysarthria
Lethargy
Nausea
Vomiting
Epigastric pain

Idiosyncratic reactions

Gingival hyperplasia
Hirsutism
Acne
Rash
  Toxic epidermal necrolysis
  Stevens-Johnson syndrome
Aplastic anemia
Hepatitis
Phenytoin hypersensitivity syndrome

The rash and eosinophilia point to a drug reaction

This is inherited in an autosomal-codominant pattern.

Immediate discontinuation usually leads to total recovery without sequelae. Deaths have been reported with severe liver disease, coagulopathy, or sepsis, or upon accidental reexposure. Corticosteroids are not effective.

Our patient's clinical presentation and course are in keeping with thrombotic thrombocytopenic purpura secondary to the phenytoin hypersensitivity syndrome, of which there is one previous case report by Hirsh (see Suggested Reading). Unfortunately, although phenytoin therapy was discontinued early in her course, both of the drugs that were substituted—ie, carbamazepine and phenobarbital—can lead to the same reaction in susceptible patients.

SUGGESTED READING

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