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A 74-year-old woman with abdominal pain and fever

A 74-YEAR-OLD WOMAN was transferred from a local hospital for further evaluation and management of abdominal pain with fever.

The patient had presented to the local hospital 11 days before with a 1-day history of bilateral upper-quadrant abdominal pain. She described the pain as a constant ache with intermittent sharper pains accompanied by nausea, but she could not identify any precipitants of the pain. She was also constipated.

A few days after being admitted to the local hospital, the patient had developed a fever and mild shortness of breath. She was treated empirically for a possible pulmonary infection with a variety of antibiotics (ceftriaxone, ticarcillin-clavulanate, erythromycin, metronidazole, cefazolin, and vancomycin). Blood, urine, and sputum cultures remained negative throughout her hospitalization.

At the local hospital she had also undergone an upper gastrointestinal (GI) series, a small bowel follow-through, a barium enema, and computed tomography (CT) of the abdomen. These revealed colonic diverticulosis and a dilated gallbladder with no gallstones. A hepato-iminodiacetic acid scan was reported as suspicious for acute cholecystitis. CT-guided aspiration of the gall bladder revealed "non-purulent fluid." Cultures of the fluid from the gallbladder were negative. A chest radiograph revealed only small bilateral pleural effusions.

During the barium enema the patient had become hypoxic, requiring supplemental oxygen and transfer to the intensive care unit. Her physicians started intravenous heparin therapy empirically while investigations were performed. A ventilation-perfusion scan was interpreted as showing a low probability of pulmonary embolism, and a subsequent pulmonary angiogram was read as normal. A chest CT scan did not reveal anything other than the small bilateral pleural effusions seen on the chest radiograph. A thoracentesis revealed transudative fluid only. Intravenous heparin was discontinued.

Past history. The patient had had essential thrombocythemia for 5 years, for which she took hydroxyurea until 2 months before admission. Hydroxyurea was restarted at the local hospital because her platelet count was high at 750×10^9/L (normal 150–400 $\times$ 10^9/L), but it was stopped 3 days later because of mucositis. More than 30 years ago, the patient had been diagnosed with "pernicious anemia."

Family history was unremarkable. The patient lived with her husband on a farm, had two healthy children, and had not recently traveled.

Physical examination

On presentation to our hospital the patient was experiencing diffuse abdominal pain, nausea, vomiting, fatigue, and sweats.

On physical examination, the patient appeared ill. Her temperature was 38.2°C, heart rate 102/minute and regular, blood pressure 123/67 mm Hg, respiratory rate 16/minute, and oxygen saturation 96% by pulse oximetry while receiving oxygen at 2 L/minute per nasal cannula. She had mild oral mucositis, decreased basal breath sounds bilaterally, and a grade 2/6 systolic ejection murmur (reported in the past). Her abdomen was soft with diffuse tenderness but without palpable organomegaly or peritoneal signs. Her stool was negative for occult blood. She had no focal neurologic

Her platelet count dropped from 750 to 272 x 10⁹/L in only a few days

TABLE 1

The patient's laboratory values at the time of admission

TEST	VALUE	UNITS	NORMAL RANGE
White blood cell count	4.07	$\times 10^9$/L	4.2–5.4
Hemoglobin	9.2	g/dL	12.0–16.0
Platelet count	272	$\times 10^9$/L	150–400
Sodium	135	mmol/L	132–148
Potassium	4.5	mmol/L	3.5–5.0
Chloride	108	mmol/L	98–110
Carbon dioxide	22	mmol/L	24–32
Blood urea nitrogen	11	mg/dL	8–25
Creatinine	1.0	mg/dL	0.7–1.4
Glucose	112	mg/dL	65–110

deficits. TABLE 1 shows her laboratory values at the time of admission. Coagulation studies were normal.

Her medications on transfer included ticarcillin-clavulanate and heparin in prophylactic, subcutaneous doses.

Fever of unknown origin has a new set of criteria

■ HOSPITAL COURSE

We continued to give ticarcillin-clavulanate, performed bone marrow aspiration to assess the patient's essential thrombocythemia and to look for a cause of her fever, and obtained a general surgery consult. The surgeons believed that the patient might have acute cholecystitis and so scheduled her for a laparoscopic cholecystectomy the following day. The patient tolerated the operation well. The initial pathology study suggested an acute exacerbation of chronic cholecystitis.

Two days passed, but the patient's condition did not change significantly. She continued to spike fevers with temperatures as high as 39°C and complained of nausea, vomiting, abdominal pain, and weakness. Blood, urine, and sputum cultures remained negative, and her laboratory values remained about the same. She noted some swelling of her right lower extremity. A duplex ultrasound scan revealed a popliteal deep venous thrombosis, which we monitored by serial duplex ultrasound examinations. Her bone marrow aspiration results were consistent with the prior diagnosis of essential thrombocythemia.

At this point our patient had had an upper GI series, a small bowel follow-through, a barium enema, CT scans of the chest and abdomen, a hepato-iminodiacetic acid scan, aspiration and later removal of her gallbladder, a pulmonary angiogram, a bone marrow aspiration, and multiple cultures, none of which provided an adequate explanation for her symptoms and fever.

■ FEVER OF UNKNOWN ORIGIN

1 Which of the following choices is not part of the standard definition of fever of unknown origin?

❑ Temperature greater than 38.3°C
❑ Fever for at least 3 weeks
❑ Fever that defies diagnosis after 1 week of inpatient investigation
❑ Fever that cannot be suppressed by antipyretics

The standard definition of fever of unknown origin has been a temperature higher than 38.3°C for at least 3 weeks that defies diagnosis after 1 week of inpatient investigation. The ability of antipyretics to suppress the fever is not part of the definition.

A new classification scheme divides fever of unknown origin into four categories: classic, nosocomial, neutropenic, and HIV-associated. In each, the definition differs somewhat from the older, standard definition.

Classic fever of unknown origin (an unexplained temperature higher than 38.3°C for at least 2 weeks, or three outpatient visits, or 3 days in the hospital). There are many potential causes. Infectious causes are numerous (tuberculosis being the most common). If a typical infection cannot be found, occult infections must be considered (eg, abscesses, osteomyelitis, endocarditis, prostatitis), as should viral infections (eg, cytomegalovirus, Epstein-Barr virus) and infections with less common organisms such as fungi, *Plasmodium* (the agents of malaria), or *Rickettsia*. Some neoplastic diseases can cause fever; the most common being lymphomas, leukemias, renal cell carcinoma, and hepatomas. Collagen vascular diseases, granulomatous disorders, and miscellaneous

causes such as drug fever, gout, cirrhosis, recurrent pulmonary emboli, and metabolic disorders round out the list.

Nosocomial fever of unknown origin (an unexplained temperature higher than 38.3°C in a hospitalized patient in whom fever was not present at admission; there must be at least 3 days of investigation with 2 days of culture incubation). Investigation should focus on sites where occult infections might be sequestered, such as intravascular lines, sinuses (with nasogastric tubes), prosthetic devices, acalculous cholecystitis, and *Clostridium difficile* colitis. Drugs and transfusion-related fevers must also be considered.

Neutropenic fever of unknown origin (a temperature higher than 38.3°C in a patient with a neutrophil count lower than 500/μL after 3 days of investigation with 2 days of culture incubation). All types of infections, including fungal, viral, and gram-positive and gram-negative bacterial organisms, must be considered. A cause of the fever is often not found. In general, patients do well with supportive care, including empiric antimicrobial therapy, while awaiting a rise in the neutrophil count.

HIV-associated fever of unknown origin (a temperature higher than 38.3°C for more than 4 weeks for outpatients or 3 days of in-hospital investigation with 2 days of culture incubation). HIV itself, *Mycobacterium avium intracellulare*, toxoplasmosis, tuberculosis, *Pneumocystis carinii* pneumonia, cryptococcus, histoplasmosis, non-Hodgkin lymphoma, and drug fever are just some of the many diagnostic possibilities. The differential diagnosis depends on the degree of immunosuppression, as reflected by the CD4+ count.

Hospital course (continued)
The patient's condition did not change. In spite of persistent vomiting her sodium level was 134 mmol/L, potassium 4.5 mmol/L, and CO_2 20 mmol/L. (With persistent vomiting one would expect the potassium level to fall and the CO_2 to rise.)

Given the above findings and her persistent GI complaints and weakness, we considered the possibility of adrenal insufficiency.

■ **ADRENAL INSUFFICIENCY**

2 Which of the following laboratory findings is consistent with a diagnosis of primary adrenal insufficiency?

❏ Increased serum sodium
❏ Increased serum chloride
❏ Increased serum carbon dioxide
❏ Increased serum potassium

Failure of the adrenal glands may be either primary or secondary.

Primary adrenal insufficiency
More than 150 years ago, Richard Addison described primary adrenal insufficiency as "general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of the color of the skin." It is rare and affects both sexes equally, across all age groups.

Causes of primary adrenal insufficiency can be divided into those leading to anatomic destruction of the glands (more than 90% of the glands' volume must be destroyed before symptoms of adrenal insufficiency appear) and those resulting from metabolic failure of the gland (**TABLE 2**).

In spite of persistent vomiting, her potassium level remained 4.5

Most cases of anatomic adrenal destruction are idiopathic, although half of patients with idiopathic anatomic destruction have circulating adrenal antibodies. Some of these destroy the adrenal glands directly while others block the binding of ACTH. These autoimmune forms of primary adrenal insufficiency are part of both type 1 (characterized by mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency) and type 2 (thyroiditis, type 1 diabetes mellitus, and adrenal insufficiency) polyglandular autoimmune syndromes.

The next most common causes of anatomic destruction are infections (tuberculosis, fungal, viral, opportunists in AIDS), invasion by tumors, surgery, hemorrhage with necrosis, and invasion by nonmalignant processes (amyloid, sarcoid).

Metabolic failure is rare. Congenital adrenal hyperplasia, cytotoxic agents, and drugs that act as enzyme inhibitors fall into this category.

Symptoms and signs of primary adrenal insufficiency vary in spectrum and severity, depending on the duration and degree of adrenal hypofunction. Frequently seen are weakness, weight loss, GI complaints, abnormal pigmentation of the skin and mucous membranes, hypotension, syncope, and vitiligo.

Laboratory findings. Early on, only the cosyntropin stimulation test may be abnormal. With more advanced disease, serum levels of sodium, chloride, and CO_2 are often low, and potassium is often high. ("Increased serum potassium" is the correct answer to QUESTION 2, above.) Decreased renal blood flow may lead to elevated vasopressin and angiotensin II levels (the reason for low sodium). Mild hypercalcemia can be seen, for reasons that are unclear. Electrocardiographic and electroencephalographic findings are nonspecific. Normocytic anemia and moderate eosinophilia (10% to 20%) are frequent.

In mild adrenal insufficiency all values may overlap with normal. Thus, the diagnosis can only be made by corticotropin (ACTH) stimulation testing. The screening cosyntropin stimulation test is performed by giving 0.25 mg cosyntropin intravenously or intramuscularly and measuring the cortisol level at baseline, 30 minutes, and 60 minutes. A normal response consists of a stimulated cortisol level greater than 18 µg/dL and at least 7 µg/dL higher than at baseline.

Treatment. Education is an important part of any comprehensive treatment program. The patient should wear a medic alert bracelet. A glucocorticoid (hydrocortisone 25–37.5 mg/day or prednisone 7.5 mg/day) should be given in divided doses, with the larger portion in the morning. A mineralocorticoid is often needed as well, even if the patient takes in ample sodium (3–4 g per day). Fludrocortisone 0.05 to 0.2 mg/day usually suffices. The baseline doses are adjusted on the basis of clinical status, blood pressure, and electrolyte levels.

During illness the glucocorticoid dose may need to be increased to two to five times that at baseline. After major surgery, five to 10 times the maintenance dose should be given in divided doses and tapered by approximately 20% to 30% per day, depending on the postoperative course. Sodium intake and fludrocortisone levels may need to be increased during times of heavy exercise in hot weather.

Secondary adrenal insufficiency

Secondary adrenal insufficiency may be due to isolated ACTH deficiency, a panhypopituitary disorder, or exogenous corticosteroids. Most of the symptoms and signs are the same as in primary adrenal insufficiency, but patients with secondary adrenal insufficiency have near-normal aldosterone levels and generally do not have excess pigmentation, severe dehydration, or hyperkalemia. Thus, mineralocorticoid replacement is unnecessary.

Hospital course (continued)

A cosyntropin stimulation test was performed. The baseline level of cortisol was 6.4 µg/dL (normal morning range 3.4–26.9), and the stimulated level was 6.1 µg/dL (normal > 18 and at least 7 µg/dL higher than at baseline). Glucocorticoid replacement was given, and the patient's fever, GI symptoms, and laboratory abnormalities quickly disappeared.

Although the patient's original presentation was probably due to cholecystitis, the persistence of her fever after cholecystectomy, the finding of adrenal insufficiency, and the resolution of her symptoms (including fever) after

Mild adrenal insufficiency can only be diagnosed by ACTH stimulation

glucocorticoid replacement confirm the diagnosis of adrenal insufficiency as the cause of her fever. This is indeed a rare cause of fever of unknown origin. The question remained: Why did the patient develop adrenal insufficiency?

Two findings gave some insight into the cause: the rapid drop in platelets from approximately $750 \times 10^9/L$ to $272 \times 10^9/L$ after only a few days of hydroxyurea therapy, and the finding of a below-the-knee DVT. Because the patient had received heparin, we decided to investigate the possibility of heparin-induced thrombocytopenia leading to hemorrhage and necrosis of the adrenal glands.

■ HEPARIN-INDUCED THROMBOCYTOPENIA

3 Which of the following is not true of heparin-induced thrombocytopenia?

❑ There are two types
❑ The nonimmune type is readily reversible
❑ The IgG-mediated immune type leads to a substantial risk of thrombotic complications
❑ The immune type of heparin-induced thrombocytopenia is usually seen within 12 hours of starting heparin

Two types of heparin-induced thrombocytopenia have been described: an early, benign, readily reversible, "nonimmune" type and a later, more-serious "immune" type that is mediated by IgG and that paradoxically leads to a substantial risk of thrombotic complications.

The immune type of heparin-induced thrombocytopenia has an estimated incidence of 1% at 7 days and 3% at 14 days. It usually arises 5 to 15 days after starting heparin (not within 12 hours, as listed in the question above), but may occur sooner if the patient has taken heparin previously.

This disorder is caused by IgG and IgM antibodies directed against heparin-platelet factor 4 complexes, leading to immune platelet destruction. The antibodies may also activate the endothelium by binding to platelet factor 4 on endothelial cell surface heparin. The net result is a highly prothrombotic state. Patients have a risk of thrombosis that is 37 times normal, with both venous and
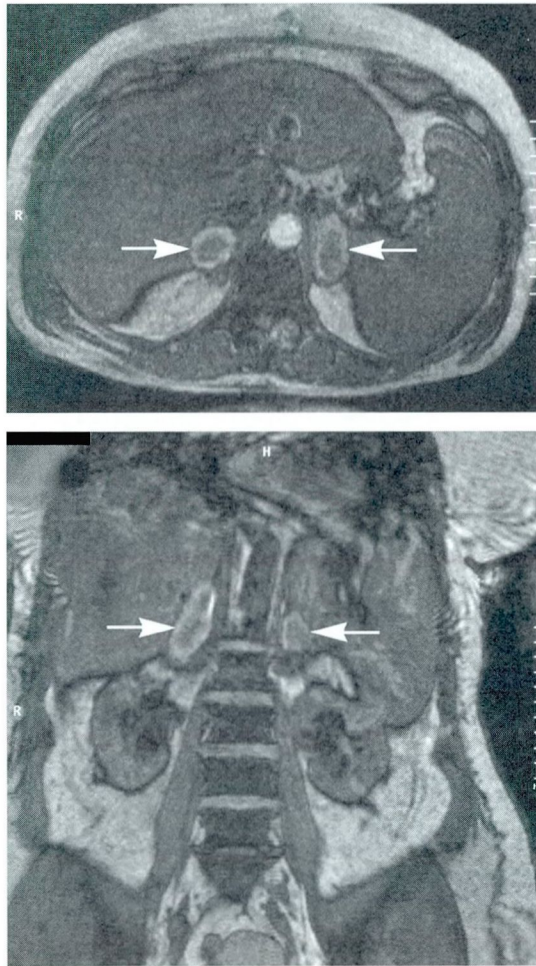

FIGURE 1. Axial and coronal T1-weighted MRI images showing increased density of the adrenal glands (arrows) typical of adrenal hemorrhage.

arterial ("white clot syndrome") thromboses being noted. Bleeding complications have also been described but are much less frequent and important than the thrombotic complications.

Platelet counts usually reach a nadir of between 20 and $150 \times 10^9/L$, but they return to baseline within 1 week of stopping heparin. A fall in the platelet count without overt thrombocytopenia may be noted—in itself an indication to stop heparin treatment. Heparin-associated antiplatelet antibody tests are assays of platelet activation that look for platelet aggregation in the presence of heparin. An enzyme-linked immunosorbent assay has been developed that detects the target antigen on the platelets.

Paradoxically, heparin-induced thrombocytopenia increases the risk of thrombosis

The main treatment is to stop the heparin. As a substitute, warfarin has been used but has uncertain efficacy, and the white clot syndrome may require surgery if severe. Danaparoid (a heparinoid with little cross-reactivity), ancrod (a proteinase obtained from snake venom that specifically breaks down fibrinogen), and argatroban have been used with some success. Recently, the direct thrombin inhibitor lepirudin has been approved for use in this condition.

Multiple case reports have documented heparin-induced thrombocytopenia leading to adrenal hemorrhagic necrosis. Adrenal vein thrombosis is frequently found in these cases. It is felt that this is the inciting event, with subsequent necrosis and hemorrhage of the adrenal glands.

Hospital course (continued)

The patient's abdomen was imaged again with an MRI study, revealing enlarged, dense adrenal glands consistent with bilateral adrenal hemorrhage (**FIGURE 1**). A heparin-associated antiplatelet antibody test was positive. Heparin was discontinued and the patient's platelet count rose to 441×10^9/L within 2 days. She was discharged home in good condition.

Diagnosis
- Cholecystitis
- Primary adrenal insufficiency from necrosis and hemorrhage secondary to heparin-induced thrombocytopenia syndrome.

■ SUGGESTED READING

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