Progressive Neutropenia in a Young Woman

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HISTORY
The patient has bipolar disorder, for which she takes lamotrigine, and untreated hepatitis C. She is an injection drug user and has smoked 1 pack of cigarettes a day for more than 10 years. She lives with her parents and does not work.

PHYSICAL EXAMINATION
Temperature is 38.3°C (101°F); heart rate, 110 beats per minute; respiration rate, 18 breaths per minute; blood pressure, 110/65 mm Hg; and oxygen saturation level, 99% on room air. No rashes, lymphadenopathy, or oral lesions are evident. A 3/6 holosystolic murmur is audible over the tricuspid area, and chest auscultation reveals bibasilar crackles. There is no splenomegaly or hepatomegaly, and no joint tenderness or petechiae are noted. No focal neurologic deficits are detected.

LABORATORY AND IMAGING RESULTS
White blood cell (WBC) count is 17,600/µL; hemoglobin level, 12.5 g/dL; and platelet count, 175,000/µL. Creatinine level is 0.8 mg/dL. The remaining chemistry panel results are normal, as are results of liver function tests. On day 2, blood cultures reveal methicillin-sensitive Staphylococcus aureus (MSSA). A 2-dimensional echocardiogram shows moderate-sized mobile tricuspid valve vegetation with severe tricuspid regurgitation. A CT scan of the thorax shows multiple lesions consistent with septic pulmonary emboli.

HOSPITAL COURSE
The patient is given oxacillin, and she improves clinically. A peripherally inserted central catheter is placed, and the patient is transferred to a convalescent facility to complete the duration of the course of antibiotics.

After 10 days, she is transferred back to the hospital with complaints of new-onset fatigue, weakness, and chest pain. Her WBC count on readmission is 2200/µL, with a differential of 35% segmented neutrophils, 56% lymphocytes, and 4% monocytes. A review of laboratory studies from the convalescent facility shows that her WBC count dropped steadily while she was there, reaching a nadir of 1100/µL, with an absolute neutrophil count (ANC) of 125/µL. A peripheral smear shows no blast forms, nucleated red blood cells, or teardrop cells.

What is the most likely cause of the patient’s neutropenia?
A. Hepatitis C.
B. New onset of leukemia.
C. Oxacillin.
D. MSSA infection with bone marrow involvement. CORRECT ANSWER: C

Neutropenia, usually defined as an ANC of less than 1500/µL, can have a variety of causes. The hepatitis C virus (choice A) is very hematologically active and can cause a variety of cytopenias. Common hematologic manifestations of hepatitis C include essential mixed cryoglobulinemia, monoclonal gammapathies, autoimmune thrombocytopenia, and B-cell non-Hodgkin lymphoma. However, this patient has had hepatitis C for years; thus, it is unlikely to have caused neutropenia while she was in the hospital. Moreover, the specific blood effect, neutropenia, is not typical. Leukemia can cause neutropenia, but it is rare for a new onset of leukemia (choice B) to occur in the hospital. In addition, this patient has no other signs of malignancy. The peripheral smear shows no morphologic abnormalities; there are no blasts or other findings typical of bone marrow disease. Neutropenia is also associated with infections that infiltrate the bone marrow. However, in a bone marrow infection (choice D), decreases in platelet and red blood cell counts would be expected, as well as findings of myelophthisis (eg, immature forms and teardrop cells on the peripheral smear). None of these are seen here. Moreover, the organisms most commonly associated with bone marrow infiltration are Mycobacterium avium complex, HIV, and Histoplasma capsulatum--not S aureus.
Drug-related neutropenia: epidemiology. More than 70% of cases of neutropenia are associated with a drug. Risk factors for the development of drug-related neutropenia include advancing age, female gender, associated infectious mononucleosis, renal failure, and underlying autoimmune disease. Patients with the HLA-B38 phenotype and the combination of alleles DR4 and DQW3 are also at increased risk.1 Drugs commonly associated with neutropenia include clozapine, sulfasalazine, thionamides, and ticlopidine. Other drugs that occasionally cause neutropenia include angiotensin-converting enzyme inhibitors, H2 blockers, NSAIDs, and flecainide. Antibiotics associated with neutropenia include macrolides, trimethoprim/sulfamethoxazole, chloramphenicol, sulfonamides, cephalosporins, and semi-synthetic penicillins. 

Pathophysiology. The 2 basic mechanisms by which drugs cause neutropenia are:

- Immune-mediated destruction of the circulating neutrophil by drug-dependent or drug-induced antibodies.2
- Direct toxic effects on the marrow granulocyte precursors.2

Bone marrow aspiration and biopsy findings vary with the mechanism of action. Normal or mildly reduced cellularity with myeloid aplasia or hypoplasia is seen if the culprit drug is acting as a direct toxin. Arrest of myeloid maturation at a later stage is seen if the damage is immune-mediated.

This patient has been receiving 2 medications: oxacillin and lamotrigine. Lamotrigine is known to cause neutropenia—and probably does so more often than oxacillin. However, she has been taking lamotrigine for 2 years, making it an unlikely cause of the neutropenia that developed in the hospital. Oxacillin (choice D) is a commonly used antibiotic that can cause hematologic problems, including neutropenia, leukopenia, thrombocytopenia, and agranulocytosis. Oxacillin was started in the hospital, and the time course of the drop in the WBC count was appropriate.

Treatment. Once severe neutropenia is documented, the offending drug should be withdrawn whether or not the patient has symptoms. The neutropenia usually resolves within 1 to 3 weeks after the drug is discontinued, although the timetable for resolution varies substantially from patient to patient.

The use of granulocyte colony-stimulating factor is somewhat controversial. The advantages cited include shorter recovery times, less antibiotic use, and shorter hospital stays compared with historic controls. However, survivorship benefits are more difficult to prove.3 Because of their minimal toxicity, growth factors are used for patients with an ANC of less than 1000/µL who have fever or other signs of infection. Growth factors are also given to patients with an ANC of less than 500/µL that persists for longer than 5 days after the suspect drug has been withdrawn.

Outcome of this case. A presumptive diagnosis of drug-induced neutropenia was made. The patient's lamotrigine was stopped, but her neutrophil count continued to fall. Results of HIV testing as well as testing for antineutrophil antibodies were negative. Oxacillin was stopped, and vancomycin was started. Within 48 hours after oxacillin was discontinued, the patient's WBC count began to increase; it had reached a level of 7200/µL by the time she was discharged.

References:
REFERENCES:

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