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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2024, 41(4):570–572

Hematology Quiz – Case 66

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A previously-well 79-year-old woman was transferred to the emergency department with a one-week history of ecchymoses and purpuric rash on her lower extremities associated with shortness of breath and a cough that was productive of small quantities of blood-tinged sputum. On examination, the patient was lethargic but arousable and oriented. She was afebrile. Laboratory evaluation showed a hemoglobin level of 9.6 g/dL, a white-cell count of 3.0×10^9/L, a platelet count of 23×10^9/L, mean corpuscular volume (MCV) 93 fL (79–98), lactate dehydrogenase (LDH) 2,859 IU/L (reference range: 134–279), creatinine 1.87 mg/dL (0.6–1.2), alanine aminotransferase (ALT) 26 IU/L (0–55), aspartate aminotransferase (AST) 50 (5–34), alkaline phosphatase 99 IU/L (40–150), and total bilirubin 2.7 mg/dL (0.2–1.2) with direct bilirubin 0.4 mg/dL (<0.5). The reticulocyte count was 2.66% (0.5–2.0) and the Coombs test was negative. Coagulation studies revealed a normal international normalized ratio (INR) of 1.1 (0.8–1.2) with activated partial thromboplastin time of 33 s, and a normal fibrinogen level (309 mg/dL). Examination of the blood smear revealed thrombocytopenia, schistocytes, and nucleated red blood cells (figures 1, 2); the bone marrow aspirate smear is shown in figures 3–6.

Comment

A thorough evaluation is required in all patients suspected of having thrombotic thrombocytopenic purpura (TTP) in order to rule out alternative diagnoses. As with all laboratory tests, the decision to perform bone-marrow biopsy should be considered on a patient-by-patient basis, and it should be performed only if clinically indicated. The test for ADAMTS13 activity usually takes some time to come back. In view of the patient's microangiopathic blood film, urgent total plasma exchange was initiated, as well as high-dose methylprednisolone. However, a bone marrow aspiration was

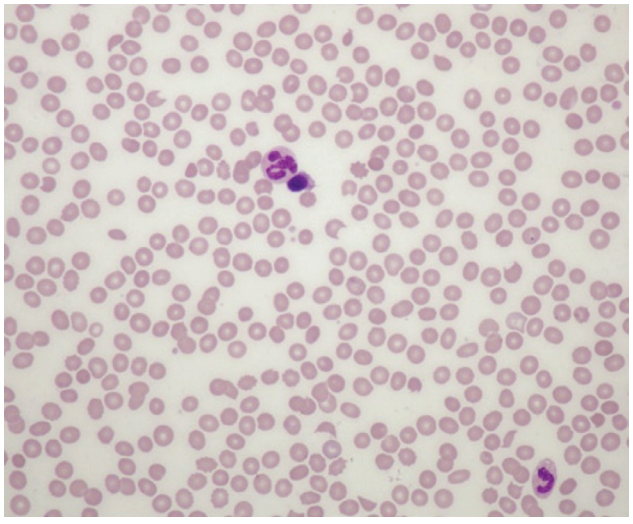

Figure 1.

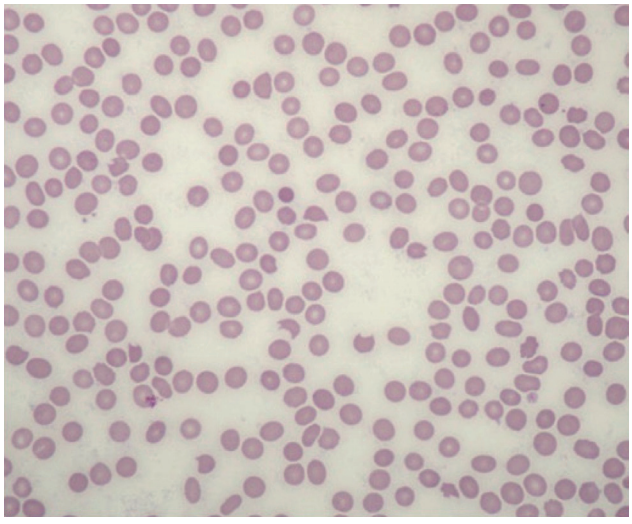

Figure 2.

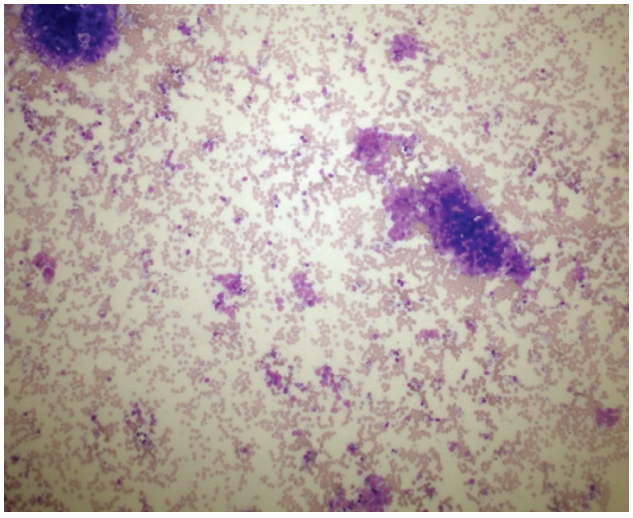

Figure 3.

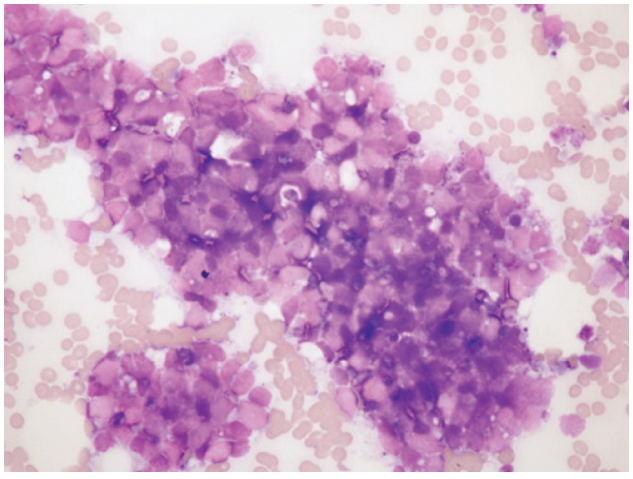

Figure 4.

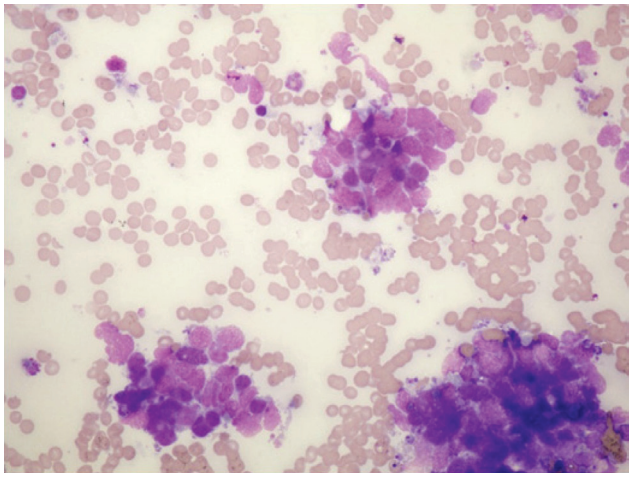

Figure 5.

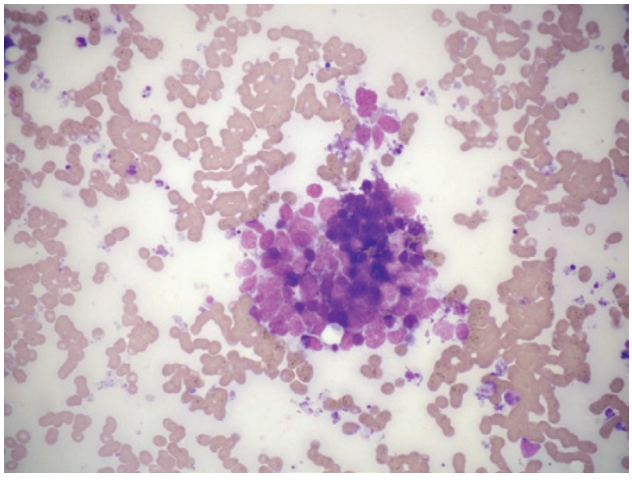

Figure 6.

also performed pending the results for ADAMTS13 activity (figures 3–6). Total plasma exchange was discontinued on the basis of the bone-marrow-aspiration findings.

The correct diagnosis is thrombotic microangiopathy (TMA) secondary to high-grade adenocarcinoma metastatic to the bone marrow. Furthermore, a contrast enhanced computed tomography (CT) scan showed hepatomegaly, small volume cervical, mediastinal and abdominal lymphadenopathy, as well as findings consistent with small pulmonary emboli. The anatomical site of origin of the carcinoma remained occult. She was treated with chemotherapy for carcinoma from an unknown primary site (CUP). ADAMTS13 activity returned normal. CUP is an uncommon cancer accounting for approximately 3% of all diagnoses of cancer.

It should be noted that TMA is a clinical syndrome consisting of hemolytic anemia (LDH >500 U/L), thrombocytopenia (<50,000/μL), and presence of schistocytes on peripheral blood smear owing to systemic microvascular occlusion. The most common causes of TMA include TTP and hemolytic uremic syndrome (HUS). Malignancy-associated TMA is a rare entity that shares clinical features with that of HUS and TTP. It is usually seen in older patients with metastatic cancer with marked elevations in LDH. Tumor-cell infiltration of the bone marrow or response to cancer-directed therapy are key distinguishing factors from other TMA syndromes.

Schistocytes are fragments of red blood cells, produced by extrinsic mechanical damage within the circulation. In healthy individuals, the percentage of schistocytes varies from 0.2–0.5%, likely caused by manual fragmentation of red blood cells during venesection or manual spreading of the blood smear. Three types of schistocytes are seen in TMA: triangular erythrocytes or kite cells, helmet cells, and keratocytes. The International Council for Standardization in Hematology (ICSH) Schistocyte Working Group has agreed that a schistocyte percentage ≥2% in a peripheral-blood smear in adults is a strong indication in favor of a diagnosis of TMA, when additional features suggesting an alternative diagnosis are absent.

Causes of TMA include TTP (acquired, hereditary), Shiga (or Shiga-like) toxinmediated HUS (ST-HUS) (i.e., HUS associated with infections

by Shiga toxin-producing E. coli O157:H7), complement-mediated TMA (previously referred to as atypical HUS), drug-induced TMA, post-transplant TMA (after solid-organ or stem-cell transplantation), and malignancy-associated TMA. Other conditions in which schistocytes are also seen (but usually at a lower percentage) include disseminated intravascular coagulation (DIC), malignant hypertension, scleroderma renal crisis, severe vitamin B_{12} deficiency, mechanical hemolysis ("Waring blender" syndrome), HELLP (hemolysis, elevated liver-enzyme levels, and low platelets) syndrome of late pregnancy, and catastrophic antiphospholipid syndrome (CAPS).

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