CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 7-2025: A 65-Year-Old Woman with Weakness, Back Pain, and Pancytopenia

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PRESENTATION OF CASE

Dr. Daniel Leonard (Medicine): A 65-year-old woman was transferred to this hospital for evaluation of pancytopenia and back pain.

The patient had been in her usual state of health until 3 weeks before the current evaluation, when midline cervical, thoracic, and lumbar back pain developed after she had rolled a patient over during her work as a home health aide. She was evaluated by her primary care physician. On neurologic examination, her strength was preserved and symmetric, and her gait was normal; no spinal or paraspinal tenderness was present on palpation. Treatment with prednisone, tramadol, and cyclobenzaprine was initiated, along with physical therapy. However, her pain persisted, prompting referral to a sports medicine specialist. Radiographs of the cervical, thoracic, and lumbar spine reportedly showed diffuse osteopenia and moderate degenerative disk disease with cervical osteophytes at the C5–C6 and C6–C7 levels. There was no evidence of acute fracture. Treatment with a higher dose of prednisone and oxycodone was prescribed.

Four days before the current evaluation, the patient was transported by ambulance to the emergency department of another hospital after her sister had found her lying on the floor of her home, with immobility from back pain. She had had a bowel movement while lying on the floor, and her house was in disarray. On examination, the oral temperature was 36°C, and the remainder of the vital signs and physical examination were reportedly normal. The complete blood count was notable for a platelet count of 14,000 per microliter (reference range, 150,000 to 450,000), a hemoglobin level of 8.9 g per deciliter (reference range, 12.0 to 16.0), and a white-cell count of 5100 per microliter (reference range, 4500 to 11,000). An automated differential count revealed the presence of immature granulocytes and nucleated red cells.

Additional laboratory studies showed a prothrombin time of 15.7 seconds (reference range, 9.1 to 12.1), which corresponded to an international normalized ratio of 1.3 (reference range, 0.9 to 1.2). The partial-thromboplastin time and the

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fibrinogen level were normal. The lactate dehydrogenase level was greater than 2500 U per liter (reference range, 110 to 210), the ferritin level 24,325 μg per liter (reference range, 10 to 200), and the haptoglobin level 91 mg per deciliter (reference range, 30 to 200). The vitamin B_{12}, folate, and copper levels were normal. Nucleic acid amplification testing for babesia and anaplasma species was negative, as was serologic testing for Lyme disease.

Computed tomography (CT) of the abdomen and pelvis, performed after the administration of intravenous iodinated contrast material, reportedly showed nodules at both lung bases, as well as areas of hepatic nodularity and enhancement. There was a well-circumscribed, hypoattenuating lesion at the pancreatic head that was related to a known intraductal papillary mucinous neoplasm, which had not changed from imaging obtained 3 years earlier. A peripheral-blood smear reportedly showed schistocytes. After consultation with the hematology service was obtained, fresh-frozen plasma and packed red cells were transfused, and intravenous methylprednisolone was administered. The patient was transferred to this hospital to be evaluated for thrombotic thrombocytopenic purpura (TTP).

On the patient's arrival at this hospital, she reported diarrhea, epigastric abdominal pain, and profound fatigue, in addition to persistent spinal pain, night sweats, and cough during the preceding month. She did not have leg weakness, saddle anesthesia, or fecal incontinence. She noted an unintentional weight loss of approximately 9 kg during the past 6 weeks. Her medical history was notable for primary hypothyroidism, type 2 diabetes, migraines, and intraductal papillary mucinous neoplasm. An episode of complicated diverticulitis had been treated with sigmoid colectomy and partial small-bowel resection. Hysterectomy and cholecystectomy had been performed in the remote past. Medications included escitalopram, topiramate, levothyroxine, and pancreatic enzyme–replacement therapy.

The patient lived alone in Massachusetts and worked as a home health aide. She had smoked two packs of cigarettes per day for 40 years but had quit smoking 3 years before the current evaluation. She did not drink alcohol or use recreational drugs. Her mother had had breast cancer at 70 years of age, and her niece had received a diagnosis of colorectal cancer at 40 years of age. A colonoscopy performed 18 months before the current evaluation was notable for hyperplastic polyps and tubular adenomas, which were resected. Her most recent mammogram, performed 5 years before the current evaluation, was normal.

On examination, the oral temperature was 36.2°C, the heart rate 89 beats per minute, the respiratory rate 16 breaths per minute, the blood pressure 167/71 mm Hg, and the oxygen saturation 95% while the patient was breathing ambient air. She appeared pale and tired. There was tenderness on deep palpation of the epigastrium; Murphy's sign was absent. No ecchymoses or petechiae were present. The platelet count was 10,000 per microliter (reference range, 150,000 to 450,000), the hemoglobin level 7.5 g per deciliter (reference range, 12.0 to 16.0), and the white-cell count 2860 per microliter (reference range, 4500 to 11,000). A manual differential count showed 9.4% nucleated red cells, 1.0% plasma cells (reference value, 0.0), and 1.0% metamyelocytes (reference value, 0.0). The reticulocyte count was 1.9% (reference range, 0.7 to 2.5).

The aspartate aminotransferase level was 102 U per liter (reference range, 9 to 32), the alanine aminotransferase level 64 U per liter (reference range, 7 to 33), the alkaline phosphatase level 308 U per liter (reference range, 45 to 115), and the lipase level greater than 3000 U per liter (reference range, 13 to 60). Results of a basic metabolic panel and direct antiglobulin testing were otherwise unremarkable; the bilirubin levels were normal. Antinuclear antibody testing was positive at a titer of 1:40. Results of serum protein electrophoresis were normal, as were levels of free light chains, the kappa:lambda ratio, and the IgG4 level. A peripheral-blood smear showed basophilic stippling, hypolobated neutrophils with prominent granules, and thrombocytopenia with occasional large platelets. No blasts or schistocytes were seen.

Dr. Brandon H. Messick: CT of the abdomen and pelvis, performed after the administration of intravenous iodinated contrast material, revealed a subcentimeter hypodense lesion on the pancreatic head, which had not changed from

previous imaging and was most likely indicative of a side-branch intraductal papillary mucinous neoplasm. Diffuse parenchymal hypoattenuation was present in the liver, a finding compatible with hepatic steatosis. In addition, focal fat stranding and fluid surrounded the pancreatic tail; these features were consistent with acute pancreatitis.

The patient was admitted to the hospital, and diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Rebecca K. Leaf: I participated in the care of this patient and am aware of the final diagnosis. This 65-year-old woman with an 80-pack-year history of cigarette smoking, as well as a history of type 2 diabetes and diverticulitis, presented with fatigue, low-back pain, and diarrhea. Notable findings included leukopenia, anemia, thrombocytopenia, the presence of circulating nucleated red cells and schistocytes, and a markedly elevated lactate dehydrogenase level. The patient was transferred to this hospital to be evaluated for TTP.

PANCYTOPENIA

Pancytopenia is defined as low levels of all three blood-cell lines and has an expansive differential diagnosis, which includes processes that hamper cell production as well as those that may shorten the life span of cells in circulation. In many cases, the pattern of cell lines involved can help shape the differential diagnosis (Fig. 1). In this patient's case, I will consider disorders that globally affect hematopoiesis or cause peripheral destruction of all three cell lines.

NUTRITIONAL DEFICIENCIES

Adequate nutritional stores are vital for blood-cell production, and various hematinic deficiencies are associated with characteristic clinical and laboratory findings. For instance, cobalamin (vitamin B_{12}) and folate (vitamin B_9) are integral components of one-carbon metabolism, and deficits in either vitamin impair DNA synthesis and lead to the arrest of cell maturation.[1,2] The characteristic finding with both vitamin B_{12} and folate deficiencies is megaloblastic anemia due to ineffective erythropoiesis, although leukopenia, thrombocytopenia, and neurologic complications may also develop.[3] With long-standing and severe deficiency, intramedullary hemolysis with thrombocytopenia may occur, with a clinical appearance similar to that of thrombotic microangiopathy.[4] Although this patient had several risk factors for vitamin B_{12} deficiency, including partial small-bowel resection and pancreatic insufficiency, the vitamin B_{12} and folate levels were measured and reported as normal.

Copper deficiency, which can develop after gastric surgery or excess zinc supplementation, is less common than vitamin B_{12} and folate deficiencies but can be associated with similar findings in peripheral-blood and bone marrow–biopsy specimens.[5] Although this patient had risk factors for copper deficiency such as bowel resection, the copper level was normal, which rules out this diagnosis.

Restrictive eating disorders may cause cytopenias, most commonly leukopenia, although macrocytic anemia and thrombocytopenia have also been reported.[6] This patient did not have a history of restricted eating.

TOXINS

Numerous toxins are associated with pancytopenia, including medications, radiotherapy, and alcohol. The patient history should include a comprehensive list of all medications and supplements, as well as details regarding alcohol use. Many medications can cause pancytopenia, but the most common culprits by far are antineoplastic agents, immunosuppressants, antibiotic agents, and antiseizure medications.[7] Alcohol is directly toxic to the bone marrow and is associated with histologic changes, including megaloblastosis and the development of ringed sideroblasts and vacuolated erythroid and granulocyte precursors.[8,9] This patient was taking no medications that are typically associated with pancytopenia, and she had no history of clinically significant alcohol use.

INFECTIONS

Viral infections can also lead to pancytopenia, and the patient history should indicate the presence of risk factors for certain infectious diseases. The most recognized infectious causes of pancytopenia are Epstein–Barr virus infection,

cytomegalovirus infection, human immunodeficiency virus infection, and viral hepatitis, although any acute viral infection may result in transient bone marrow suppression and hypoproliferation. Infection with parvovirus B19 can result in pure red-cell aplasia, which could explain anemia but would not account for decreases in the other two cell lines. The patient

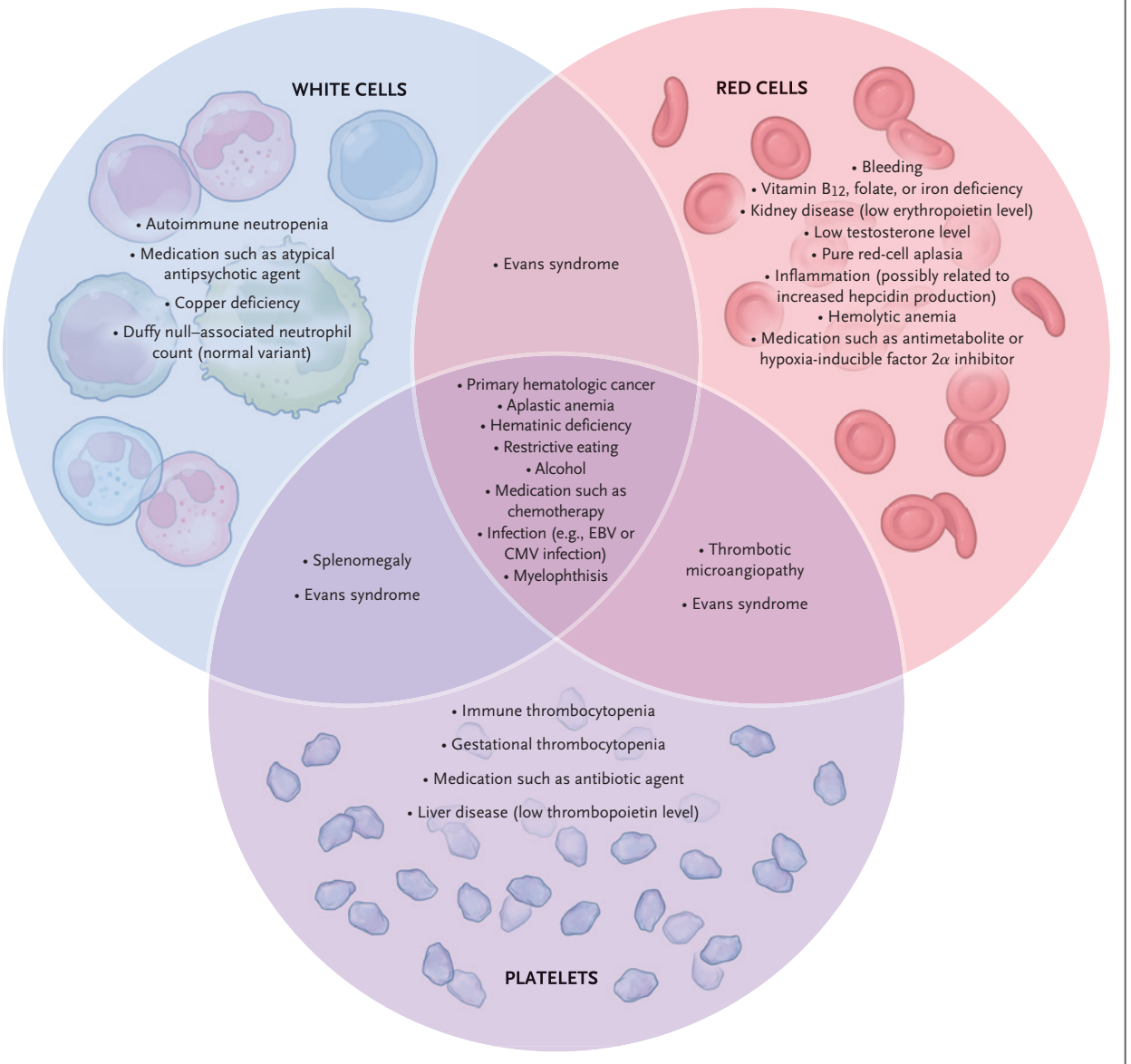

Figure 1. Causes of Acquired Cytopenias.

Each set (circle) shows conditions that cause a low count in a given cell line (white cells, red cells, or platelets). The combined regions, where the sets overlap, show conditions that cause low counts in a given combination of cell lines. The region where all three sets overlap shows conditions that cause pancytopenia, defined as low counts in all three cell lines. Evans syndrome is typically associated with low counts in two cell lines but can affect all three cell lines in rare instances. Not all causes of acquired cytopenias or set overlap are shown. EBV denotes Epstein–Barr virus and CMV cytomegalovirus.

history can be used to guide additional workup, indicating whether the patient should be evaluated for tickborne diseases (e.g., anaplasmosis or ehrlichiosis), tuberculosis, or malaria. This patient underwent an extensive evaluation for viral and tickborne diseases, which was negative.

AUTOIMMUNE OR AUTOINFLAMMATORY DISEASE

Cytopenias associated with autoimmune conditions are common and may result from autoantibody formation, elevated levels of proinflammatory cytokines and proteins (e.g., interleukin-6) that up-regulate hepcidin production, a decreased erythropoietin level due to kidney disease, or splenic sequestration. In addition, bone marrow failure may be directly immune-mediated, as in the case of aplastic anemia, or may be due to immune dysregulation, as in the case of hemophagocytic lymphohistiocytosis.[10] This patient's markedly elevated ferritin level suggested considerable inflammation, which was most likely contributing to her hypoproliferative anemia. However, she had no other systemic manifestations of autoimmune disease. Aplastic anemia would not have such a fulminant course and would not explain the strikingly elevated lactate dehydrogenase level, the immature cells in the peripheral blood, or the pulmonary nodules. Hemophagocytic lymphohistiocytosis is a diagnosis that is considered after other, more common disorders have been ruled out, and underlying drivers of the condition (e.g., infection and cancer) should be investigated.

MICROANGIOPATHIC HEMOLYTIC ANEMIA

Microangiopathic hemolytic anemia is a Coombs'-negative hemolytic disorder that is characterized by erythrocyte destruction within small blood vessels, which results in the presence of schistocytes on a peripheral-blood smear. When microangiopathic hemolytic anemia is observed in combination with thrombocytopenia, thrombotic microangiopathy — the pathophysiology of which involves endothelial-cell activation, fibrin deposition, and thrombus formation — must be considered.[11] Well-recognized types of thrombotic microangiopathy include TTP, typical and atypical hemolytic–uremic syndromes, and drug-induced thrombotic microangiopathy, which can occur with the use of antineoplastic or immunomodulatory agents, such as gemcitabine or tacrolimus. These disorders can affect any organ and can result in end-organ complications, such as kidney dysfunction, neurologic compromise, or myocardial injury.

This patient was initially transferred to this hospital to be evaluated for TTP — specifically immune TTP, a life-threatening disorder that develops when autoantibodies bind to and result in the clearance of the von Willebrand factor–cleaving protease ADAMTS13. Although some aspects of this patient's case could be explained by TTP, schistocytes were not present in the peripheral-blood smear obtained on the day of admission to this hospital. In addition, TTP would not explain the patient's leukopenia, weight loss, or pulmonary nodules. Given the patient's extensive smoking history and constitutional symptoms, cancer-associated thrombotic microangiopathy should be considered.

PRIMARY HEMATOLOGIC DISEASE

Primary cancers of the bone marrow interfere with normal hematopoiesis, replacing hematopoietic stem cells and disrupting the bone marrow microenvironment.[12] Malignant cells may also produce cytokines that inhibit hematopoietic-cell maturation[13] and co-opt immune mechanisms to promote their own expansion.[14] Acute leukemia or aggressive lymphoma could lead to rapid weight loss and constitutional symptoms over a short period, but the results of blood tests and imaging in this patient did not clearly support these diagnoses.

MYELOPHTHISIS

The term "myelophthisis" comes from the Greek *myelo*, which means "marrow," and *phthisis*, which means "wasting away" or "decay." Myelophthisis refers to the replacement of normal bone marrow architecture by infiltrating tissue or nonhematopoietic cells. Myelophthisis may reflect a process that originates within the marrow, as in the case of primary myelofibrosis, or may be due to a systemic condition such as a granulomatous disease, a lipid-storage disorder, endocrinopathy, or metastatic carcinoma.[15] In addition, ineffective blood-cell production in the bone marrow may lead to extramedullary hema-

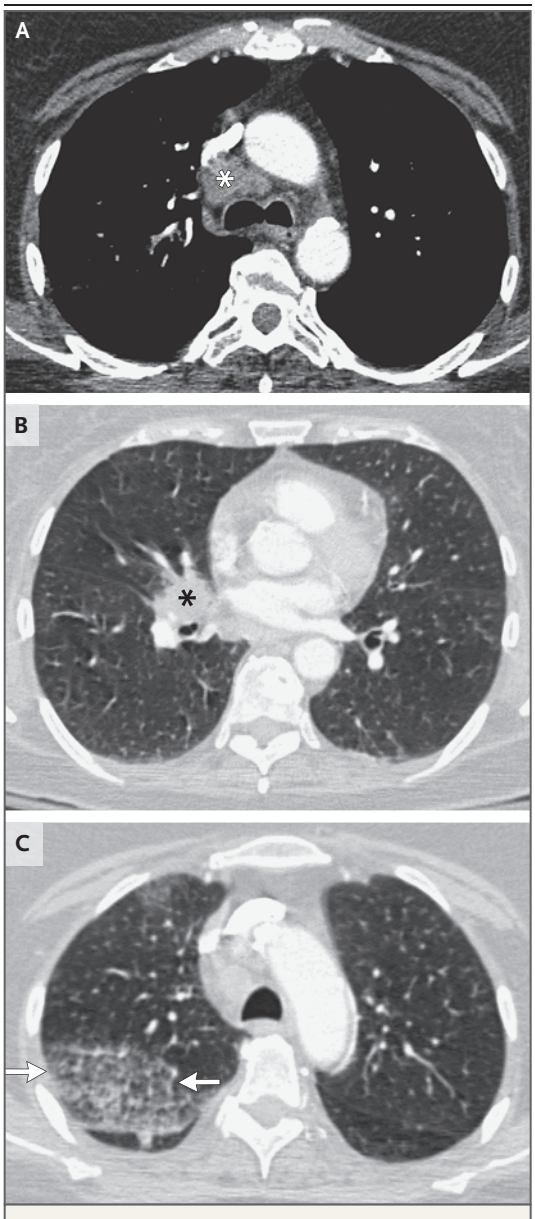

Figure 2. CT of the Chest.

CT of the chest was performed after the administration of intravenous iodinated contrast material. Supraclavicular, mediastinal, and hilar lymphadenopathy is present; the enlarged lymph nodes have abnormal morphologic features and measure up to 26 mm (Panel A, asterisk). An infrahilar lobulated, solid nodule measuring 11 mm is present (Panel B, asterisk). Additional findings include nodular interlobular septal thickening and ground-glass opacities involving the right upper lobe (Panel C, arrows), findings that can be seen with infection, sarcoidosis, or lymphangitic carcinomatosis.

topoiesis in the spleen and subsequent splenomegaly, which further exacerbates the cytopenias.

In patients with myelophthisis, the sine qua non finding on a peripheral-blood smear is leukoerythroblastosis, which is characterized by the presence of nucleated red cells, dacrocytes (teardrop-shaped red cells), immature myeloid white cells, and large platelets. However, a leukoerythroblastic picture is not specific for bone marrow infiltration because it may occur with any condition that puts severe strain on the bone marrow, including hemorrhage and sepsis.[16]

Myelophthisis is a rare, albeit well-described, presenting feature of metastatic carcinoma.[17,18] In addition to cytopenias and leukoerythroblastosis, features suggestive of metastatic carcinoma in this case include weight loss, bone pain, pulmonary nodules, and a long history of tobacco use. Solid-tumor infiltration of the bone marrow leads to ineffective erythropoiesis, intramedullary hemolysis, and in some instances, bone marrow necrosis. With widespread metastatic disease, solid tumors may embolize into small vessels, which causes tumor microthrombi, erythrocyte shearing, and platelet consumption — the characteristic features of cancer-associated thrombotic microangiopathy.[19-21] I suspect that cancer-associated thrombotic microangiopathy explains this patient's clinical presentation. In addition, red-cell fragmentation can result from the deposition of fibrin thrombi in the vessel walls,[22] and tumor cells themselves can cause dysregulated coagulation through the secretion of tissue factor–bearing microparticles, the up-regulation of von Willebrand factor synthesis, and the induction of tissue hypoxia.[23-25]

The solid tumors that most commonly infiltrate the bone marrow and cause cancer-associated thrombotic microangiopathy include lung, breast, gastric, and prostate cancers. Given this patient's long smoking history, weight loss, night sweats, and pancytopenia, I thought that metastatic lung adenocarcinoma with infiltration of the bone marrow was the most likely diagnosis in this case. To establish this diagnosis, I performed a bone marrow biopsy to look for evidence of bone marrow infiltration by a solid tumor and cancer-associated thrombotic microangiopathy.

REBECCA K. LEAF'S DIAGNOSIS

Bone marrow infiltration by a solid tumor (most likely lung adenocarcinoma) and cancer-associated thrombotic microangiopathy.

INITIAL HOSPITAL COURSE

Dr. Leonard: On admission to the hospital, the patient underwent additional imaging of the chest. A bone marrow biopsy was also performed.

Dr. Messick: CT of the chest (Fig. 2), performed after the administration of intravenous iodinated contrast material, revealed a lobulated, solid nodule measuring 11 mm in the greatest dimension at the infrahilar area of the right middle lobe. Mediastinal, hilar, and supraclavicular lymphadenopathy was present, with enlarged lymph nodes measuring up to 26 mm in the greatest dimension. In addition, there was focal, nodular interlobular septal thickening involving the right upper lobe. The differential diagnosis

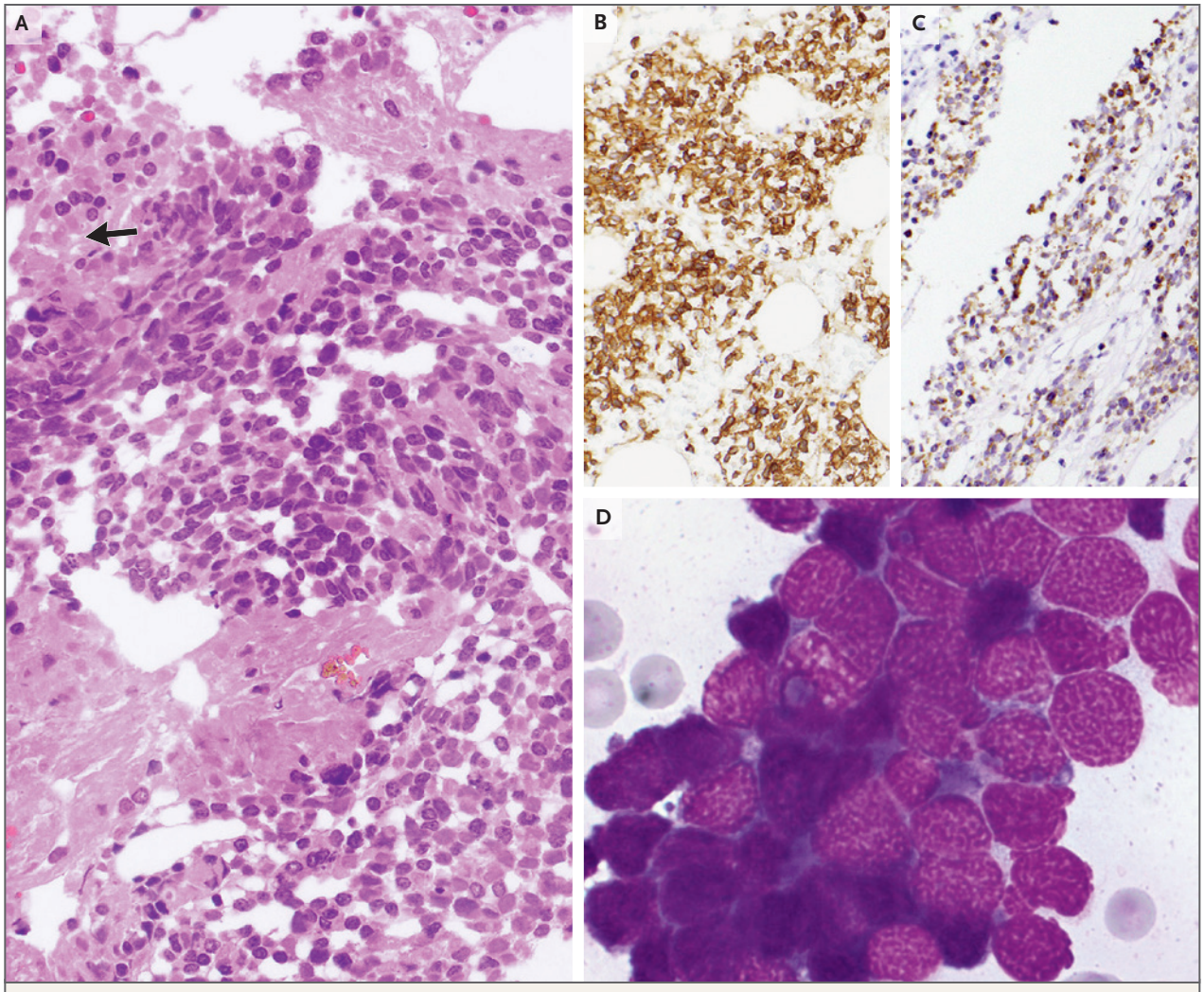

Figure 3. Bone Marrow–Biopsy Specimen.

Hematoxylin and eosin staining of a bone marrow–biopsy specimen shows extensive infiltration by atypical cells with speckled chromatin, nuclear molding, and areas of necrosis (Panel A, arrow). On immunohistochemical staining, the atypical cells are positive for CD56 (Panel B) and synaptophysin (Panel C), markers of neuroendocrine differentiation. Wright–Giemsa staining of a bone marrow–aspirate smear shows rare clusters of carcinoma cells with scant cytoplasm, fine chromatin, and nuclear molding (Panel D).

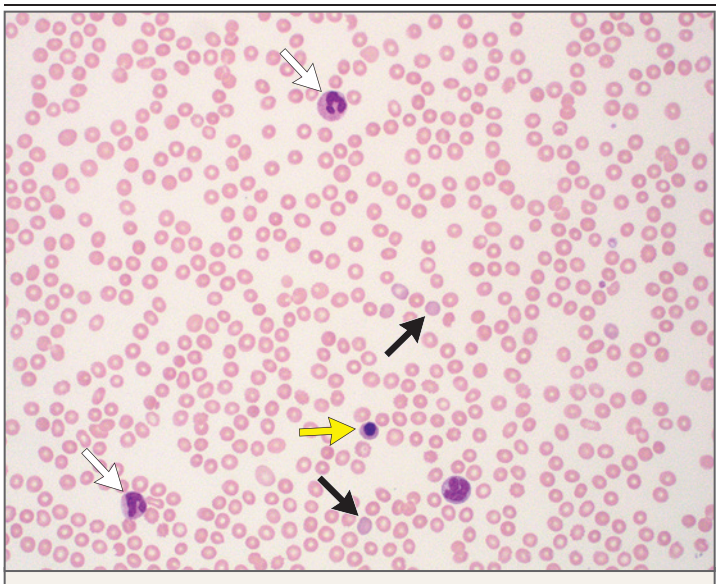

Figure 4. Peripheral-Blood Specimen.

Wright–Giemsa staining of a peripheral-blood smear shows evidence of a leukoerythroblastic reaction in which bone marrow infiltration by metastatic carcinoma has resulted in premature expulsion of maturing bone marrow elements. Findings include polychromatic red cells (black arrows), nucleated red cells (yellow arrow), and left-shifted granulocytic precursors, including band neutrophils (white arrows), metamyelocytes, and myelocytes.

for this constellation of findings includes metastatic lung cancer, metastatic disease related to a primary cancer other than lung cancer, lymphoma, and less likely, an infectious cause such as tuberculosis.

PATHOLOGICAL DISCUSSION

Dr. Derek Loneman: Examination of the bone marrow–biopsy specimen (Fig. 3) revealed an age-adjusted hypercellular marrow with an atypical infiltrate of medium-sized cells with round-to-oval nuclei, speckled chromatin, and scant-to-moderate cytoplasm that constituted approximately 80% of the marrow cellularity. There was also necrosis, nuclear molding, and crush artifact. The findings were suggestive of metastatic carcinoma, particularly neuroendocrine carcinoma, although the differential diagnosis also included lymphoma and metastatic melanoma. On immunohistochemical staining, the atypical cells were positive for CD56, synaptophysin, and chromogranin, findings consistent with neuroendocrine differentiation. The atypical cells were negative for CD3, CD20, MNF116, and SOX10. Examination of the corresponding bone marrow aspirate revealed rare clusters of large cells with nuclear molding and scant basophilic cytoplasm, features consistent with metastatic carcinoma.

The peripheral-blood smear (Fig. 4) showed a leukoerythroblastic picture with left-shifted (immature) granulocytes, nucleated red cells, and polychromasia. The pathological diagnosis was metastatic high-grade neuroendocrine carcinoma. In combination with the imaging findings, which were consistent with primary lung cancer, the findings were most suggestive of metastatic small-cell carcinoma of pulmonary origin.

PATHOLOGICAL DIAGNOSIS

Metastatic small-cell carcinoma of the lung with associated myelophthisis.

DISCUSSION OF MANAGEMENT

Dr. Catherine B. Meador: Small-cell lung cancer (SCLC) is an aggressive neuroendocrine cancer that accounts for approximately 10 to 15% of lung cancer diagnoses. Known for its high proliferative index, SCLC is most often diagnosed as metastatic disease, also known as extensive-stage disease. For several decades, the first-line treatment for extensive-stage SCLC was platinum-based doublet chemotherapy (the combination of a platinum-based agent and etoposide), a regimen associated with high initial response rates. In two phase 3 randomized trials conducted in the past several years,[26,27] the addition of immune checkpoint inhibition to chemotherapy increased overall survival, and thus platinum-based chemotherapy plus immunotherapy became the current standard of care for extensive-stage SCLC.

Although most patients with extensive-stage SCLC have an initial reduction in tumor burden with first-line platinum-based doublet chemotherapy plus an immune checkpoint inhibitor, the regimen is not curative in the context of metastatic disease. Relapse occurs for most patients within 1 year. Treatment approaches for relapsed or refractory disease include single chemotherapeutic agents, such as topoisomerase 1 inhibitors[28,29] and lurbinectedin,[30] but unfortu-

nately, these regimens rarely lead to a durable response. Most recently, tarlatamab, a DLL3-targeted bispecific T-cell engager, was granted accelerated approval by the Food and Drug Administration for the treatment of relapsed extensive-stage SCLC. Tarlatamab has been associated with a 40% objective response rate and has the potential for sustained benefit, with a median duration of response of 14.9 months among patients who could be evaluated for a response.[31,32] These findings suggest a promising new class of treatment for extensive-stage SCLC.

Patients with SCLC commonly present with a clinically significant burden of metastatic disease. Patients often have bulky hilar and mediastinal lymphadenopathy and distant sites of disease, frequently in the absence of a dominant primary lung lesion visible on imaging studies. Bone marrow biopsy is rarely needed for the diagnosis of extensive-stage SCLC; however, in some patients (<5%), metastatic disease involves only the bone marrow at diagnosis.[33] Bone marrow biopsy is still included in staging guidelines for patients with evidence of limited-stage disease on imaging and with findings suggestive of bone marrow infiltration on a peripheral-blood smear.

In patients with SCLC, first-line platinum-based doublet chemotherapy can lead to a rapid disease response and to a decrease in symptoms within days to weeks. Therefore, we often administer such chemotherapy even to patients with poor performance status if their clinical decompensation is deemed to be primarily disease-related (and thus at least temporarily reversible with systemic therapy). However, one of the primary toxic effects of platinum-based doublet chemotherapy is bone marrow suppression and resulting cytopenias. In this patient, who presented with profound pretreatment cytopenias stemming from malignant bone marrow infiltration, the risk of treatment outweighed even the palliative benefit. Although single immune checkpoint inhibitors typically do not cause clinically significant cytopenias and have been approved as first-line treatment for other solid tumors, including non–small-cell lung cancer, data from phase 3 randomized trials have not shown a benefit with respect to overall survival for single immune checkpoint inhibitors in patients with extensive-stage SCLC.[34] Therefore, for patients who are ineligible for first-line platinum-based doublet chemotherapy, supportive care is often the most appropriate treatment strategy.

FOLLOW-UP

Dr. Leonard: On the first hospital day, the patient had multiple episodes of profound melena with a decreased hemoglobin level as low as 5.7 g per deciliter, for which she received red-cell transfusions. She concomitantly had worsening fatigue, inattentiveness, and confusion, as well as increasing signs of discomfort. After lengthy discussions with the patient's children and siblings, the goal of care was changed to comfort measures only. Although this final transition was based on a decision made by the patient's family, the patient had given clear instruction earlier in life that she did not want to live in a state of helplessness or pain — an insight that she had gained as a caregiver and home health aide. The patient died on the sixth hospital day, surrounded by her children and siblings. The family consented to an autopsy.

AUTOPSY

Dr. Loneman: Shortly after the patient's death, an autopsy was performed (Fig. 5). On gross examination, tumor deposits could be identified in numerous organs. The right lung was involved by relatively few small, scattered intraparenchymal and pleural deposits, whereas the left lung was involved predominantly by pleural-based nodules, a finding consistent with lymphangitic spread. Thoracic lymph nodes were involved by tumor deposits that measured up to 6.5 cm in greatest dimension. An isolated deposit that was relatively large (3.5 cm in greatest dimension) was identified in the tail of the pancreas, and the liver was extensively involved by tumor, as were the vertebral bodies. Other areas involved by tumor included the left adrenal gland and the left breast. Microscopic examination of the tumor deposits revealed atypical cells with speckled chromatin and scant cytoplasm that were similar to those identified on bone marrow biopsy. There were also conspicuous areas of

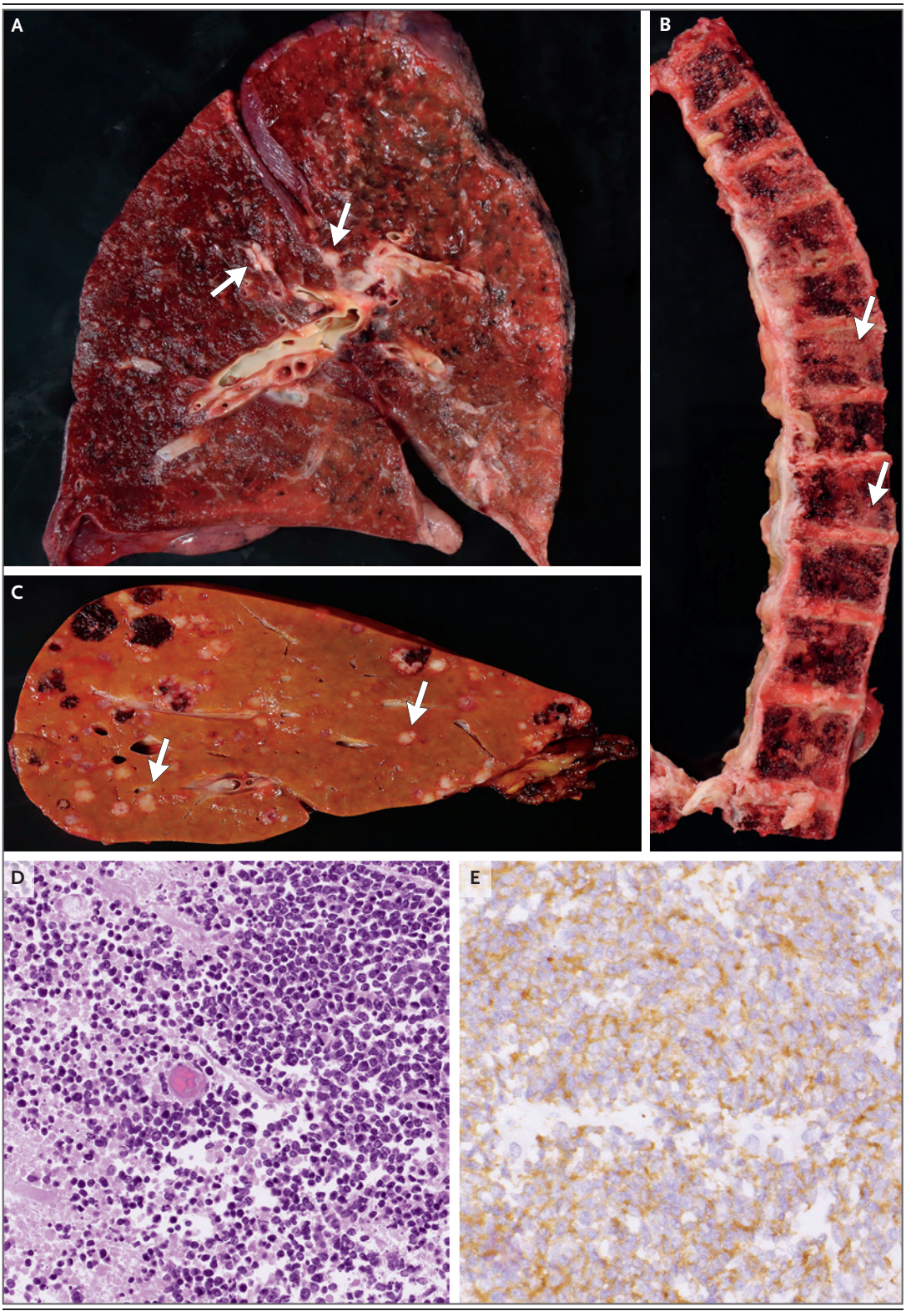

Figure 5 (facing page). Autopsy Specimens.
Scattered tumor deposits are present in the right lung (Panel A, arrows). Extensive tumor involvement is present in the vertebral bodies (Panel B, arrows) and the liver (Panel C, arrows). Hematoxylin and eosin staining of a tumor deposit shows atypical cells with nuclear molding and areas of necrosis (Panel D). Immunohistochemical staining for synaptophysin is positive in the atypical cells (Panel E), a finding consistent with neuroendocrine differentiation.

hemorrhage and necrosis. Immunohistochemical staining again revealed a neuroendocrine immunophenotype and was negative for other melanoma markers (S100 and MART-1), in addition to those assessed in the bone marrow. In combination with the smoking history and the pattern of involvement seen on imaging, the histologic features were consistent with primary lung cancer. However, the largest tumor deposits were extrapulmonary, and other sites of primary origin, especially the pancreas, could not be fully ruled out.

FINAL DIAGNOSIS

Metastatic small-cell carcinoma of the lung.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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