CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 10-2020: An 83-Year-Old Man with Pancytopenia and Acute Renal Failure

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PRESENTATION OF CASE

Dr. Christian C. Mewaldt (Medicine): An 83-year-old man was transferred to this hospital because of pancytopenia and acute renal failure.

Five days before this presentation, the patient was found conscious on his bedroom floor; he had been well the previous evening. A caregiver noticed that the patient had new generalized weakness and unsteadiness and was unable to walk with a walker. He was taken to the emergency department of another hospital for evaluation.

The temperature was 38.1°C, the pulse 103 beats per minute, the blood pressure 165/55 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 95% while the patient was breathing ambient air. He was alert and oriented to self and date of birth. The cardiac, pulmonary, and abdominal examinations were normal. The creatinine level was 3.2 mg per deciliter (283 μmol per liter; reference range, 0.7 to 1.2 mg per deciliter [62 to 106 μmol per liter]), increased from his baseline level of 2.4 mg per deciliter (212 μmol per liter). Other laboratory test results are shown in Table 1. A chest radiograph showed mild pulmonary congestion. Computed tomography (CT) of the head, performed without the administration of intravenous contrast material, revealed a right parietal ventriculoperitoneal shunt terminating in the left lateral ventricle that had been placed 2 years earlier because of normal pressure hydrocephalus. The bilateral ventricles were smaller than they had been on previous imaging studies. An infusion of sodium bicarbonate, a single dose of ceftriaxone, and subcutaneous heparin were administered.

On the second day at the other hospital, the white-cell count was 3800 per microliter (reference range, 4500 to 10,500), the hemoglobin level 12.8 g per deciliter (reference range, 13.3 to 16.3), and the platelet count 75,000 per microliter (reference range, 150,000 to 400,000). The D-dimer level was 229,926 ng per milliliter (reference range, 0 to 500), the fibrinogen level 180 mg per deciliter (reference range, 200 to 393), the international normalized ratio 1.2 (reference range, 0.9 to 1.1), and the prothrombin time 13.5 seconds (reference range, 10.6 to 13.4). Subcutaneous heparin was stopped. During the next 3 days, pancytopenia worsened

Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	On Admission, Other Hospital	Reference Range, This Hospital†	On Admission, This Hospital
Hemoglobin (g/dl)	13.3–16.3	12.8	13.5–17.5	9.6
Hematocrit (%)	40.0–49.0	37.8	41.0–53.0	27.8
Platelet count (per μl)	150,000–400,000	121,000	150,000–400,000	21,000
White-cell count (per μl)	4500–10,500	4500	4500–11,000	3710
Differential count (per μl)				
Neutrophils	1500–7800	4000	1800–7700	3370
Lymphocytes	850–4100	200	1000–4800	270
Monocytes	200–1100	300	200–1200	70
Eosinophils	50–600	0	0–900	0
Reticulocytes (%)			0.5–2.5	<0.5
Prothrombin time (sec)			11.5–14.5	14.8
Prothrombin-time international normalized ratio			0.9–1.1	1.2
Activated partial-thromboplastin time (sec)			22.0–36.0	61.8
D-dimer (ng/ml)			<500	>10,000
Fibrinogen (mg/dl)			150–400	144
Sodium (mmol/liter)	136–145	139	135–145	150
Potassium (mmol/liter)	3.5–5.1	4.6	3.4–5.0	3.1
Chloride (mmol/liter)	98–107	100	98–108	111
Carbon dioxide (mmol/liter)	22–29	21	23–32	21
Anion gap (mmol/liter)	6–18	18	3–17	18
Urea nitrogen (mg/dl)	6–20	44	8–25	95
Creatinine (mg/dl)	0.7–1.2	3.2	0.60–1.50	6.28
Glucose (mg/dl)	74–109	158	74–109	122
Calcium (mg/dl)	8.6–10.0	9.8	8.5–10.5	7.2
Uric acid (mg/dl)			3.6–8.5	8.5
Lactic acid (mmol/liter)	0.2–2.0	2.4	0.5–2.0	3.1
Creatine kinase (U/liter)	39–308	9390	60–400	6290
Lactate dehydrogenase (U/liter)			110–210	2592
Protein (g/dl)				
Total	6.6–8.7	7.5	6.0–8.3	5.3
Albumin	3.5–5.2	4.8	3.3–5.0	2.5
Globulin			1.9–4.1	2.8
Alanine aminotransferase (U/liter)	5–41	118	10–55	195
Aspartate aminotransferase (U/liter)	10–50	38	10–40	583
Alkaline phosphatase (U/liter)	40–129	101	45–115	100
Haptoglobin (mg/dl)			30–200	277
C-reactive protein (mg/liter)			<8.0	156.5

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for uric acid to micromoles per liter, multiply by 59.48. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

and the creatinine level increased. On the fifth hospital day, doxycycline was administered, and the patient was transferred to this hospital for further treatment.

The patient had a history of benign prostatic hypertrophy, chronic kidney disease, normal pressure hydrocephalus, mild dementia, hypertension, hyperlipidemia, and coronary artery disease, which had led to multivessel coronary-artery bypass grafting 14 years earlier and to the placement of drug-eluting coronary stents 11 months before this evaluation. He had been treated for Lyme disease 3 years before this evaluation. Medications included aspirin, clopidogrel, atorvastatin, ezetimibe, isosorbide mononitrate, metoprolol succinate, and amlodipine. Penicillin had reportedly caused anaphylaxis. The patient was a widower and lived in a house in New England with his son, daughter-in-law, and grandson, without pets. He had previously worked as a home inspector; in retirement, he enjoyed reading and spending time outside. The patient used a walker for ambulation and was able to perform most activities of daily living; he required assistance from his family and home health services for activities requiring more advanced executive function. He did not use alcohol, tobacco, or illicit drugs. His mother had had heart disease; his father had had dementia.

The temperature was 37.3°C, the pulse 93 beats per minute, the blood pressure 153/68 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 90% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.7. On examination, the patient was oriented to self and location. The mucous membranes were dry, and the neck was supple. There was no palpable lymphadenopathy, bruising, or rash. The remainder of the physical examination was normal.

Blood cultures were obtained. Blood levels of vitamin B_{12} and folate were normal. Other laboratory test results are shown in Table 1.

Dr. Eric W. Zhang: CT of the chest (Fig. 1A), performed without the administration of intravenous contrast material, revealed symmetric pulmonary edema and bilateral pleural effusions. There were scattered mildly enlarged mediastinal lymph nodes, measuring up to 1.4 cm in short-axis diameter. CT of the abdomen and pelvis (Fig. 1B and 1C), performed without the administration of intravenous contrast material, showed cholelithiasis with trace pericholecystic fluid and mild gallbladder-wall thickening. Follow-up ultrasonography of the right upper quadrant revealed cholelithiasis without evidence of cholecystitis; Murphy's sign was negative.

Dr. Mewaldt: Doxycycline and intravenous fluids containing sodium bicarbonate were continued. Metoprolol, amlodipine, and isosorbide mononitrate were administered.

On the second day at this hospital, the hematology service was consulted. Examination of a peripheral-blood smear revealed red cells with hypochromic forms, scattered schistocytes (3 per high-power field), and echinocytes. Atypical neutrophils without dysplasia were present, and there were no immature forms or blasts. The platelets were decreased in number and well granulated, without clumping and with some scattered larger forms.

On the third hospital day, tretinoin (often called all-*trans* retinoic acid) was administered because of concerns about acute promyelocytic leukemia (APL). On the fourth hospital day, additional diagnostic test results were received.

DIFFERENTIAL DIAGNOSIS

Dr. David B. Sykes: This elderly man suddenly became ill and was admitted to this hospital in the context of an undiagnosed systemic process associated with multiple laboratory abnormalities, including pancytopenia, with concerns about possible hemolysis and disseminated intravascular coagulation (DIC). In complex medical cases in which teams from multiple medical subspecialties may be consulted, it can be tempting to formulate a long list of potential diagnoses; however, it is often more useful to consider the available information with the goal of moving diagnoses down or completely off the list. With this case, we are charged with determining whether this patient's constellation of symptoms and laboratory abnormalities are related to a primary hematologic problem or are secondary to a nonhematologic process.

To start building a differential diagnosis, we can focus on two features of this case: pancytopenia and renal failure. The patient's laboratory test results initially suggest dysregulated coagulation and the potential for hemolysis. These results prompt us to assemble a list of "can't miss" hematologic conditions — conditions that, if untreated, could rapidly result in compli-

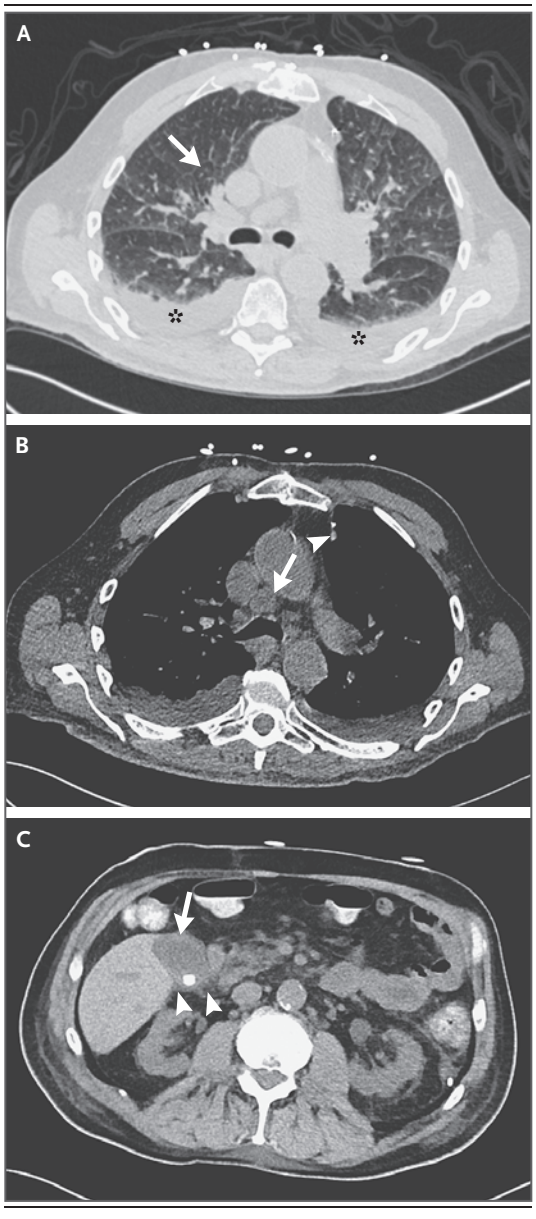

Figure 1. CT Scans of the Chest, Abdomen, and Pelvis.
An axial image of the chest obtained with lung windows at the level just below the carina (Panel A) shows bilateral smooth interlobular septal thickening (arrow) with patchy ground-glass opacities. There are bilateral small pleural effusions (asterisks) with associated relaxation atelectasis. An axial image of the chest obtained with soft-tissue windows at the level of the carina (Panel B) shows a mildly enlarged low right paratracheal lymph node (arrow). There are also changes related to previous coronary-artery bypass grafting, with a left internal thoracic artery graft (arrowhead) in the left anterior mediastinal fat and a healed median sternotomy incision. Bilateral small pleural effusions are again visible. An axial image of the abdomen obtained with soft-tissue windows at the level of the gallbladder fossa (Panel C) shows circumferential gallbladder-wall thickening (arrow) with mild pericholecystic edema (arrowheads). The gallbladder is not distended and contains a calcified gallstone.

cations or death (Table 2). Many of these diagnoses stick in the memory as convenient three-letter acronyms, with destructive processes such as thrombotic thrombocytopenic purpura and hemolytic–uremic syndrome at the top of the list of diagnoses that can result in pancytopenia and renal failure.

HEMOLYSIS

Does this patient have hemolysis? He presented with progressive anemia and an elevated lactate dehydrogenase level, findings that prompt consideration of hemolysis. Of note, his serum haptoglobin level was slightly elevated at 277 mg per deciliter (reference range, 30 to 200 mg per deciliter). Haptoglobin is a protein produced by the liver that forms a complex with free plasma hemoglobin, and the haptoglobin–hemoglobin complex is cleared by CD163-expressing macrophages of the reticuloendothelial system. This process, which protects organs from the highly oxidative nature of hemoglobin, lowers the serum haptoglobin level.

What is the likelihood that a patient with clinically significant hemolysis would have a normal serum haptoglobin level? The interpretation of a low haptoglobin level (<30 mg per deciliter) or low-normal haptoglobin level (30 to 100 mg per deciliter) is subject to confounding variables, including liver dysfunction, chronic hemolysis, mechanical hemolysis, recent transfusion, and congenital anhaptoglobinemia. However, an elevated haptoglobin level, as seen in this patient, is more reliable.

In realizing that this one laboratory value dramatically alters the differential diagnosis, I would obtain the measurement again, thereby avoiding the rare but real possibility of a preanalytical error, such as the presence of the wrong patient's blood in the tube.[1] Under the assumption that the correct patient's blood was tested, a haptoglobin level of 277 mg per deciliter argues strongly against the possibility of hemolysis.

LACTATE DEHYDROGENASE LEVEL

This patient's lactate dehydrogenase level was markedly elevated at 2592 U per liter, a level that is more than 10 times the upper limit of the normal range. Although an elevated lactate de-

Table 2. "Can't Miss" Hematologic Diagnoses.

Process	Acronym	Hallmark Findings
Destructive processes associated with pancytopenia		
Hemolytic–uremic syndrome	HUS	Hemolysis, schistocytes, and renal failure
Thrombotic thrombocytopenic purpura	TTP	Hemolysis, schistocytes, and classically, a pentad of fever, anemia, thrombocytopenia, renal failure, and neurologic change; coagulation test results are normal
Disseminated intravascular coagulation	DIC	Schistocytes and abnormal coagulation test results
Hemophagocytic lymphohistiocytosis	HLH	Hemophagocytosis, hepatomegaly, and splenomegaly
Infiltrative processes associated with pancytopenia		
Acute promyelocytic leukemia	APL	Often associated with DIC
Other cancers: acute myeloid leukemia, acute lymphocytic leukemia, Burkitt's lymphoma, and myeloma		Rapid proliferation and infiltration of the bone marrow compartment, which can lead to pancytopenia
Destructive processes associated with individual cytopenias		
Heparin-induced thrombocytopenia	HIT	Isolated thrombocytopenia
Immune thrombocytopenic purpura	ITP	Isolated thrombocytopenia
Paroxysmal nocturnal hemoglobinuria	PNH	Isolated anemia
Processes often in the hematologic differential diagnosis that may be indirectly associated with cytopenias		
Antiphospholipid antibody syndrome	APS	Protean manifestations, multiorgan involvement, and profound inflammatory state
Porphyria		Neurovisceral symptoms, which cause it to appear on the hematologic differential diagnosis in many cases

hydrogenase level is most often attributed to the breakdown of erythrocytes, it is important to remember that lactate dehydrogenase activity is present in all tissues. Lactate dehydrogenase, which catalyzes the bidirectional conversion between lactate and pyruvate, is an enzyme tetramer composed of H and M subunits. Five isoforms of lactate dehydrogenase can be distinguished in the blood on the basis of the composition of the subunits. Isoform 1 (H4) predominates in cardiac myocytes and erythrocytes, whereas isoform 5 (M4) is found in hepatocytes and skeletal myocytes.

Given the concomitant elevation of this patient's creatine kinase level (6290 U per liter), alanine aminotransferase level (195 U per liter), and aspartate aminotransferase level (583 U per liter), the lactate dehydrogenase isoform detected in his blood is most likely isoform 5, released from cells in his liver and skeletal muscle. Specialized testing can be performed to distinguish the lactate dehydrogenase isoform, but I do not think such testing is clinically necessary in this case.

PANCYTOPENIA

Over the course of the 5-day admission at the other hospital, the patient's hematocrit fell from 37.8% to 27.8%, his platelet count fell from 121,000 to 21,000 per microliter, and his white-cell count fell from 4500 to 3710 per microliter. At this hospital, examination of a peripheral-blood smear revealed a few schistocytes (3 per high-power field) but was otherwise unrevealing. Is there a primary hematologic cause underlying this patient's worsening pancytopenia, or are these changes consistent with what we would expect in the context of another critical illness?

I suspect that this patient's anemia is due to the combination of three factors: decreased erythrocyte production, increased erythrocyte turnover, and iatrogenic enthusiasm (i.e., anemia associated with excessive phlebotomy). He almost certainly had anemia associated with inflammation, in which increased levels of hepcidin, interleukin 6, interferon-γ, and tumor necrosis factor α led to temporary inhibition of new red-cell

production (reticulocyte count, <0.5%), as well as a shortened erythrocyte life span and increased erythrophagocytosis within the reticuloendothelial system.[2]

The combination of a patient with an undiagnosed condition and involvement of multiple subspecialty consultant teams often leads to a broad diagnostic laboratory workup, including the usual daily tests and blood counts as well as an extensive search for infectious or rheumatologic causes. In this case, the workup was probably repeated at both hospitals. Using a rough calculation, I estimate that this patient's iatrogenic blood loss over the course of 5 days would have easily exceeded 500 ml, with a resultant predictable contribution to his anemia.

Thrombocytopenia in a critically ill patient can be due to several causes.[3] In this case, a diagnosis of immune thrombocytopenic purpura seems unlikely, and the timing of heparin exposure makes a diagnosis of heparin-induced thrombocytopenia also unlikely.

ACUTE PROMYELOCYTIC LEUKEMIA AND DISSEMINATED INTRAVASCULAR COAGULATION

APL is high on the list of "can't miss" hematologic diagnoses, given its association with DIC and the potential for rapid decompensation and death early during the disease. Current treatment of APL with prodifferentiation therapy (e.g., tretinoin) is a success story in oncology. Before the identification of tretinoin, a diagnosis of APL was akin to a death sentence, with low survival rates. Now, APL is the most treatable form of adult acute leukemia, with survival rates higher than 90%.[4]

A diagnosis of acute leukemia is usually considered when the white-cell count is highly elevated and circulating blasts are identified on examination of a peripheral-blood smear. However, APL has the potential to manifest in an unusual fashion, with a low white-cell count in peripheral blood and an absence of circulating leukemic blasts, a combination of findings that is sometimes referred to as aleukemic leukemia. In such cases of APL, the bone marrow may still be packed with malignant promyelocytes that crowd out the normal progenitors (with resulting pancytopenia), but these promyelocytes remain tethered within the marrow, as would be expected of their normal promyelocyte counterparts.

It is with this possibility in mind that we evaluate this patient's laboratory test results in order to consider underlying DIC. Although the partial-thromboplastin time is quite prolonged (61.8 sec) and the D-dimer level is markedly elevated (>10,000 ng per milliliter), these values are out of proportion to the nearly normal international normalized ratio (1.2) and fibrinogen level (144 mg per deciliter). DIC involves the nonspecific consumption of clotting factors and would not be expected to disproportionately consume factors involved in the partial-thromboplastin time relative to factors involved in the prothrombin time. The extent of elevation of the D-dimer level argues in favor of a widespread infection, metastatic cancer, or inflammation in the context of a fulminant autoimmune process. Although the prolonged partial-thromboplastin time remains puzzling, I wonder whether it could be a residual effect of use of subcutaneous heparin with a prolonged half-life in the context of a very low creatinine clearance. Overall, with regard to consideration of APL, this would be a very atypical presentation of a rare disease, with unexplained muscle and liver involvement despite the absence of circulating blasts and with coagulation test results that are inconsistent with DIC.

SUMMARY

With some sense of relief, when we return to a careful review of this patient's history, we find a couple of important clues: the patient enjoyed spending time outside and had been treated for Lyme disease 3 years earlier. These features raise the question of whether another tickborne disease would explain his acute illness, widespread inflammation, and multiorgan (muscle, liver, and kidney) involvement, in addition to his bone marrow suppression and hematologic abnormalities.

Infection with *Anaplasma phagocytophilum* — a type of intracellular bacteria that is endemic in the New England area and is transmitted by the same ixodes tick species that transmits Lyme disease — would be a unifying diagnosis in this case, which has features consistent with other reported cases.[5,6] As a hematologist, I would try to make the diagnosis of anaplasmosis by reviewing the peripheral-blood smear to identify morulae in the cytoplasm of circulating neutrophils. However, the peripheral-blood smear was prepared after the administration of doxycycline, which reduces the sensitivity of this evaluation, and therefore, nucleic acid testing would be

more reliable; it would also be helpful in ruling out infection with ehrlichia species.

CLINICAL IMPRESSION

Dr. Rebecca S. Karp Leaf: When the patient was transferred to this hospital, he appeared well clinically but had laboratory test results showing pancytopenia, elevated aminotransferase levels, acute kidney injury, an elevated lactate dehydrogenase level, a low fibrinogen level, and a markedly high D-dimer level. Although his clinical presentation was consistent with some aspects of DIC, the serum haptoglobin level was elevated, which argued against a robust hemolytic process. Included in the paperwork from the other hospital was a handwritten note scrawled on the discharge summary that read, "smear positive."

Our initial differential diagnosis was broad, including infectious processes such as tickborne illnesses, toxic exposures, nutritional deficiencies, and primary hematologic cancer. In the context of pancytopenia and DIC, we considered a diagnosis of APL, although neither promyelocytes nor Auer rods were observed on the peripheral-blood smear. APL is a life-threatening hematologic emergency that leads to early death due to hemorrhage in as many as 25% of patients[7]; as such, practice guidelines recommend initiation of treatment immediately on first suspicion of this condition.[8] APL is characterized by translocation of the retinoic acid receptor α gene (on chromosome 17) and most often the promyelocytic leukemia gene (on chromosome 15), leading to fusion proteins that block retinoic acid–induced myeloid differentiation.[9] Tretinoin, a widely available medication with few toxic effects, induces myeloid differentiation and remains a cornerstone of treatment in APL.[10] The patient started empirical treatment with tretinoin, supported with cryoprecipitate and other blood products, while bone marrow biopsy and additional tests were performed. Doxycycline was continued, given the high suspicion for tickborne illness.

CLINICAL DIAGNOSIS

Acute promyelocytic leukemia or tickborne disease.

DR. DAVID B. SYKES'S DIAGNOSIS

Anaplasma phagocytophilum infection.

PATHOLOGICAL DISCUSSION

Dr. Sarah E. Turbett: The diagnostic test was a nucleic acid test of whole blood for *A. phagocytophilum*, which was positive. Nucleic acid testing for *Ehrlichia chaffeensis*, *E. ewingii*, *E. canis*, and *E. muris*–like agent was negative, as was examination of a blood smear for intraerythrocytic parasites. An immunoassay for Lyme IgM and IgG was positive, as was a confirmatory Western blot test for Lyme IgG, with only five IgG bands present.

The diagnosis of human granulocytic anaplasmosis is often made by means of examination of a peripheral-blood smear, serologic testing, or whole-blood nucleic acid testing. Although culture is the most accurate method, its use is often limited to research settings, given the expertise and specific culture requirements needed.[11] Examination of a peripheral-blood smear can be a useful tool for the diagnosis of human granulocytic anaplasmosis but is limited by variable sensitivity (ranging from 20 to 80%); in addition, this method is labor intensive and requires a high degree of expertise, and these factors limit its use in the clinical setting.[12] On serologic testing, documentation of a rise in titer by a factor of 4 between the acute and convalescent phases of infection is required for diagnosis confirmation, and antibody responses can persist for months or years after infection.[11] Of the available diagnostic methods, nucleic acid testing is the most widely used, with high sensitivity within the first week of illness.[11]

The diagnosis of Lyme disease is most commonly made with a two-tiered approach to serologic testing, with an initial immunoassay followed by either a Western blot test or a second approved immunoassay, as recommended by the Centers for Disease Control and Prevention.[13] In this case, the patient's initial and confirmatory serologic test results for Lyme disease met criteria for positivity, with the presence of five IgG bands, a pattern most commonly seen in late infection. The patient had a known history of treated Lyme disease, and both IgM and IgG can persist for years after successful treatment of infection.[14] There is no current commercially available diagnostic test that can be used to distinguish past infection with *Borrelia burgdorferi* from recurrent infection.

Given the patient's history of treated Lyme disease and the time course of his symptoms,

his serologic test results for Lyme disease seemed most consistent with past, treated infection. Active coinfection with *B. burgdorferi*, however, could not be completely ruled out.

Dr. Valentina Nardi: The bone marrow–biopsy specimen and bone marrow aspirate showed marrow that was hypercellular for the patient's age, with maturing trilineage hematopoiesis and no evidence of cancer (Fig. 2A and 2B). The peripheral-blood smear showed mature leukocytes with abundant toxic granulation. Very rare neutrophils (approximately 1 in 500) in the peripheral blood and bone marrow aspirate had basophilic intracytoplasmic inclusions that were suggestive of morulae of *A. phagocytophilum* (Fig. 2B and 2D). These findings, in conjunction with the positive blood nucleic acid test for *A. phagocytophilum*, were consistent with *A. phagocytophilum* infection.

DISCUSSION OF MANAGEMENT

Dr. Turbett: Human granulocytic anaplasmosis was first described in Wisconsin in 1990. The majority of cases occur in the upper Midwest and northeastern regions of the United States, and incidence has steadily increased in these regions since 2000.[15] Transmission most often occurs by the bite of an infected tick, but mother-to-child transmission, transmission by blood

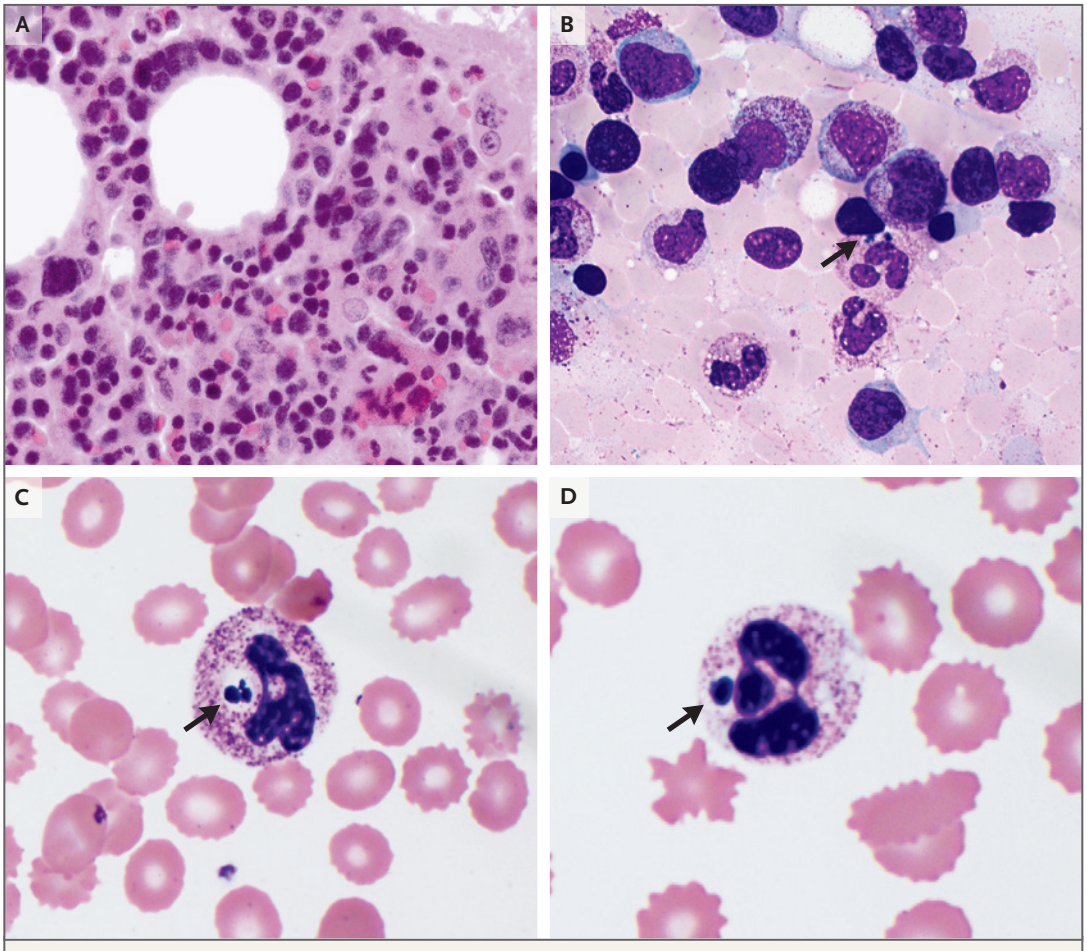

Figure 2. Bone Marrow–Biopsy Specimen, Bone Marrow Aspirate, and Peripheral-Blood Specimen.

Hematoxylin and eosin staining of a bone marrow core-biopsy specimen (Panel A) and Wright–Giemsa staining of a bone marrow aspirate smear (Panel B) show maturing trilineage hematopoiesis. On the bone marrow aspirate smear (Panel B) and on Wright's staining of a peripheral-blood smear (Panels C and D), most neutrophils show nonspecific toxic granulation; rare ones have intracytoplasmic inclusions (arrows), which are suggestive of human granulocytic anaplasmosis.

transfusion, and transmission by the slaughtering of infected animals have also been reported.[11]

Common symptoms include fevers, malaise, headaches, and myalgias; rash is an uncommon finding.[11] Laboratory abnormalities often include leukopenia, anemia, thrombocytopenia, and elevated aminotransferase levels. In fact, white-cell and platelet abnormalities are so often present that normal values can be used to rule out this infection in most populations.[16]

Doxycycline is considered to be first-line therapy for treatment of *A. phagocytophilum* infection in both adults and children. This recommendation is based on in vitro data and published reports that show clinical efficacy.[17] There are no current guidelines regarding the treatment of pregnant women with human granulocytic anaplasmosis, although small case series have shown successful treatment with the use of doxycycline.[18] Alternatives to doxycycline include rifampin, which has in vitro activity against this organism, although overall clinical data are lacking.[19] The duration of rifampin therapy has not been formally established; however, a 7-to-10-day course is recommended on the basis of clinical experience.[17] Shorter courses of 4 to 7 days can be used in children in an effort to reduce toxic effects.[17] With appropriate therapy, fevers tend to resolve within 24 to 48 hours, and the majority of patients have a complete recovery after 2 months.[11] Chronic infection has never been documented.[11]

FOLLOW-UP

Dr. Karp Leaf: Results of the bone marrow evaluation were not consistent with a diagnosis of APL, and treatment with tretinoin was discontinued. The patient continued to receive doxycycline, and within 3 days after the initiation of treatment, his pancytopenia and coagulopathy diminished. Unfortunately, his renal function did not substantially improve, and he continues to receive hemodialysis. The patient lives at home with his family and continues to enjoy spending time outdoors.

FINAL DIAGNOSIS

Anaplasma phagocytophilum infection.

This case was presented at the Medicine Case Conference.

No potential conflict of interest relevant to this article was reported.

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

REFERENCES

1. Dzik WH, Murphy MF, Andreu G, et al. An international study of the performance of sample collection from patients. Vox Sang 2003;85:40-7.

2. Ganz T. Anemia of inflammation. N Engl J Med 2019;381:1148-57.

3. Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. Hematology Am Soc Hematol Educ Program 2017;2017:660-6.

4. Lo-Coco F, Di Donato L, Schlenk RF. Targeted therapy alone for acute promyelocytic leukemia. N Engl J Med 2016;374:1197-8.

5. Case Records of the Massachusetts General Hospital (Case 16-2018). N Engl J Med 2018;378:2023-9.

6. Case Records of the Massachusetts General Hospital (Case 6-2011). N Engl J Med 2011;364:759-67.

7. Lehmann S, Deneberg S, Antunovic P, et al. Early death rates remain high in high-risk APL: update from the Swedish Acute Leukemia Registry 1997-2013. Leukemia 2017;31:1457-9.

8. Tallman MS, Wang ES, Altman JK, et al. Acute myeloid leukemia, version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:721-49.

9. Kakizuka A, Miller WH Jr, Umesono K, et al. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RAR alpha with a novel putative transcription factor, PML. Cell 1991;66:663-74.

10. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-21.

11. Bakken JS, Dumler JS. Human granulocytic anaplasmosis. Infect Dis Clin North Am 2015;29:341-55.

12. Bakken JS, Dumler JS. Clinical diagnosis and treatment of human granulocytotropic anaplasmosis. Ann N Y Acad Sci 2006;1078:236-47.

13. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep 2019;68:703.

14. Kalish RA, McHugh G, Granquist J, Shea B, Ruthazer R, Steere AC. Persistence of immunoglobulin M or immunoglobulin G antibody responses to Borrelia burgdorferi 10-20 years after active Lyme disease. Clin Infect Dis 2001;33:780-5.

15. Anaplasmosis: epidemiology and statistics. Atlanta: Centers for Disease Control and Prevention, 2019 (https://www.cdc.gov/anaplasmosis/stats/index.html).

16. Turbett SE, Anahtar MN, Pattanayak V, et al. Use of routine complete blood count results to rule out anaplasmosis without the need for specific diagnostic testing. Clin Infect Dis 2020;70:1215-21.

17. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1089-134.

18. Dhand A, Nadelman RB, Aguero-Rosenfeld M, Haddad FA, Stokes DP, Horowitz HW. Human granulocytic anaplasmosis during pregnancy: case series and literature review. Clin Infect Dis 2007;45:589-93.

19. Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). Clin Infect Dis 2013;57(4):e22-e121.