CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 6-2024: A 21-Year-Old Man with Fatigue and Night Sweats

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PRESENTATION OF CASE

Dr. Ben Ouyang (Medicine): A 21-year-old man was admitted to this hospital in the summer because of pancytopenia.

The patient had been in his usual state of good health until 4 weeks before the current presentation, when nausea and vomiting developed. The nausea and vomiting resolved after 1 day, but fatigue developed. Two weeks before the current presentation, lightheadedness associated with changing positions developed, as well as night sweats; fatigue persisted. On the morning of the current presentation, the patient had lightheadedness while lying down, and he presented to the emergency department of another hospital for evaluation.

At the other hospital, the patient reported ongoing lightheadedness. The temporal temperature was 37.2°C, the blood pressure 131/68 mm Hg, the pulse 121 beats per minute, the respiratory rate 12 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The weight was 91.2 kg, the height 192 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 24.7. The conjunctivae were pale. Laboratory studies revealed pancytopenia and an elevated blood bilirubin level. The blood lactate dehydrogenase level was greater than 2500 U per liter (reference range, 135 to 225). Blood levels of glucose, electrolytes, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, D-dimer, and fibrinogen were normal, as were the results of kidney-function tests; other laboratory test results are shown in Table 1. Imaging studies were obtained.

Chest radiography reportedly showed no abnormalities. Intravenous fluids were administered, and the pulse decreased to 100 beats per minute. Oral doxycycline was administered for possible tickborne illness. One unit of packed red cells was transfused, and the patient was transferred to the emergency department of this hospital for further evaluation.

On evaluation at this hospital, the patient reported that the lightheadedness had abated. He had no history of fever, hematuria, blood in the stool, or bleeding from other sites. He worked as a carpenter and spent minimal time outside. He

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Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	On Presentation, Other Hospital	Reference Range, This Hospital†	On Presentation, This Hospital
Hematocrit (%)	42.0–52.0	14.3	41.0–53.0	17.1
Hemoglobin (g/dl)	14.0–18.0	5.1	13.5–17.5	5.7
White-cell count (per μl)	4800–10,800	1900	4500–11,000	2110
Differential count (per μl)				
Neutrophils	1900–7800	960	1800–7700	990
Lymphocytes	1000–4500	640	1000–4800	820
Monocytes	100–800	160	200–1200	150
Eosinophils	0–500	30	0–900	0
Basophils	0–200	10	0–300	40
Immature granulocytes	0–50	80	0–50	0
Platelet count (per μl)	150,000–400,000	125,000	150,000–400,000	141,000
Mean corpuscular volume (fl)	80.0–100.0	105.9	80.0–100	101.8
Mean corpuscular hemoglobin (pg)	28.0–34.0	37.8	26.0–34.0	33.9
Mean corpuscular hemoglobin concentration (g/dl)	32.0–36.0	35.7	31.0–37.0	33.3
Red-cell distribution width (%)	11.5–13.5	17.3	11.5–14.5	20.9
Reticulocyte count (%)	—	—	0.5–2.5	3.8
Prothrombin time (sec)	—	—	11.5–14.5	15.6
Prothrombin-time international normalized ratio	0.9–1.1	1.2	0.9–1.1	1.3
Activated partial-thromboplastin time (sec)	22.0–30.0	21.0	22.0–36.0	28.1
Haptoglobin (mg/dl)	—	—	30–200	<10
Lactate dehydrogenase (U/liter)	135–225	>2500	110–210	2947
Ferritin (μg/liter)	30–388	—	10–200	185
Total bilirubin (mg/dl)	0.1–1.0	1.5	0.0–1.0	1.9
Direct bilirubin (mg/dl)	0.0–0.2	—	0.0–0.4	0.2
Creatinine (mg/dl)	—	—	0.60–1.50	0.89

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† 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.

lived with his parents and brother and had two cats and a dog. He took no medications. There were no known drug allergies. He did not smoke cigarettes, drink alcohol, or use illicit drugs. His maternal grandmother had had lymphoma.

The temporal temperature was 36.4°C, the blood pressure 131/64 mm Hg, the pulse 89 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The results of pulmonary, cardiovascular, and abdominal examinations were normal. Areas of hypopigmentation of the skin were detected near the elbows, fingers, and feet. Cranial nerve function was intact, and strength was 5 out of 5 in the arms and legs.

Dr. Maria Y. Chen: Examination of a peripheral-blood smear (Fig. 1) revealed evidence of macrocytic anemia with anisopoikilocytosis. Few white cells were present. There were neutrophils with variable segmentation and occasional immature forms, as well as platelets that were normal in terms of number and morphologic features.

Dr. Ouyang: A direct antiglobulin test was negative for IgG; C3 was detected on microscopic examination. Screening tests for Lyme disease, human immunodeficiency virus, and severe acute respiratory syndrome coronavirus 2 RNA were negative. Urinalysis showed 2+ urobilinogen (reference value, negative), without bilirubin, blood, glucose, ketones, protein, or nitrates; the specific gravity and pH were normal. Other laboratory test results are shown in Table 1. Imaging studies were obtained.

Dr. Madeleine M. Sertic: A sagittal ultrasound image of the abdomen (Fig. 2) showed mild splenomegaly, with the spleen measuring 15.8 cm on the long axis (reference value with adjustment for sex and height, <14.1). There was an incidental rounded echogenic lesion in the left hepatic lobe that measured up to 1.3 cm in diameter, a finding consistent with a hepatic hemangioma.

Dr. Ouyang: A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Jonathan C.T. Carlson: I participated in the care of this patient, and I am aware of the final diagnosis in this case. This 21-year-old man presented with fatigue and night sweats, and pancytopenia was detected. These nonspecific symptoms and signs invoke a broad differential diagnosis, which can be narrowed when we consider that he had been previously healthy, with no known tick or toxin exposures, and that his illness had developed over the course of weeks, not months or years.

We could generate a differential diagnosis

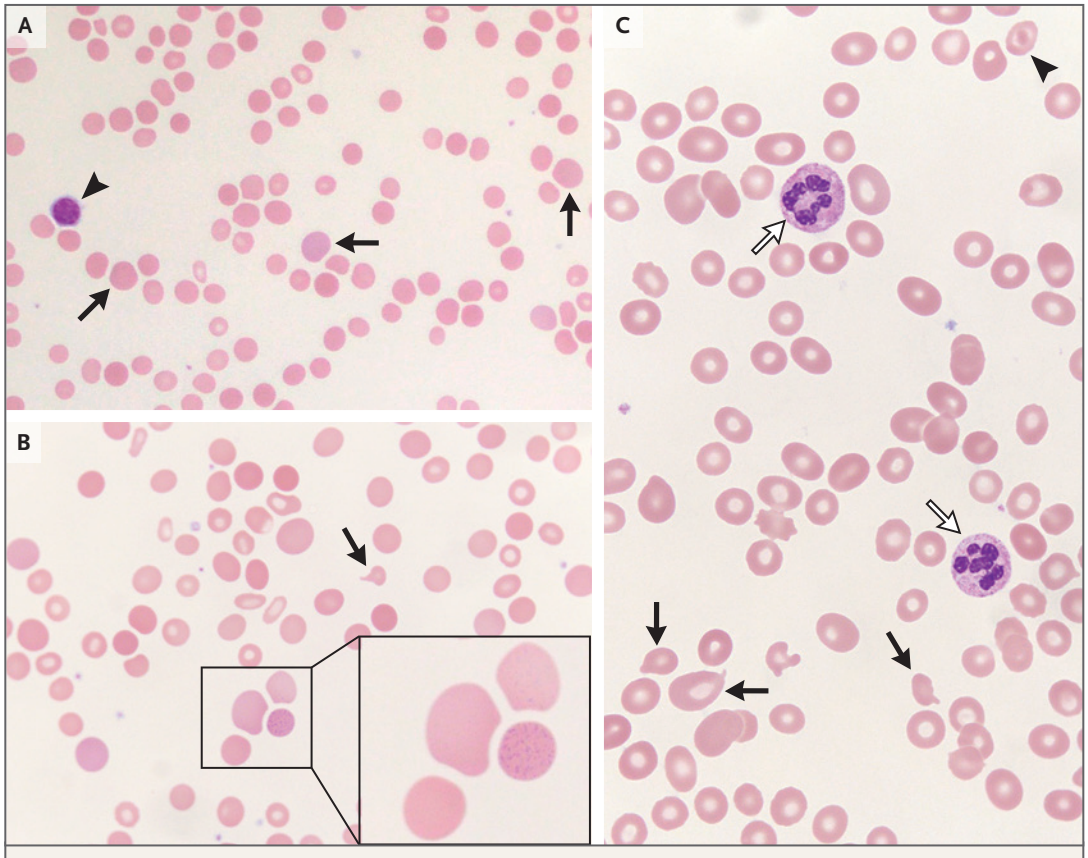

Figure 1. Peripheral-Blood Smear.

Wright–Giemsa staining of a peripheral-blood smear shows marked anisopoikilocytosis with occasional macroovalocytes (Panel A, black arrows), which are red cells larger than a lymphocyte nucleus (Panel A, black arrowhead) that lack central pallor. Also shown are rare red cells with fine basophilic stippling (Panel B, inset); dacrocytes, which are red cells in the shape of a teardrop (Panels B and C, black arrows); rare target cells (Panel C, black arrowhead); and some neutrophils that have increased segmentation, with six or more nuclear lobes (Panel C, white arrows).

around these features alone. However, they can be juxtaposed with a constellation of striking laboratory abnormalities, including pronounced leukopenia, symptomatic macrocytic anemia, and a markedly elevated blood lactate dehydrogenase level. It can be particularly useful to consider the "scaling functions" of these laboratory test results — that is, their relative magnitude, including where exactly they land within or outside the normal range, and more important, how they scale in proportion to each other and to the severity of illness. The interpretation of laboratory test results in pathologic or physiological clusters often reveals characteristic patterns that can unravel a case (Fig. 3). Analyzing the lactate dehydrogenase level in the context of the bilirubin level and reticulocyte count will help us test hypotheses about the scale and sites of cellular injury. In addition, measuring the reticulocyte count alongside the mean corpuscular volume, red-cell distribution width, and ferritin level will provide a nuanced view of nutritional status.

The interpretation of such multidimensional hematologic data is a task in which basic science has thus far outstripped our clinical approach. High-dimensional RNA sequencing and flow cytometry, for example, are routinely analyzed with clustering algorithms that help us both decode and visualize key cellular relationships[1,2] — a practice that portends a future in which clinical laboratory tests are used to compute a probabilistic differential diagnosis. Until such methods are developed, we will need to leverage a version of this approach that is grounded in clinical experience. For each of the categories of causes of pancytopenia that are described below, consideration of the scaling functions for key hematologic measures will help us adjudicate the relative likelihood and potential mechanisms.

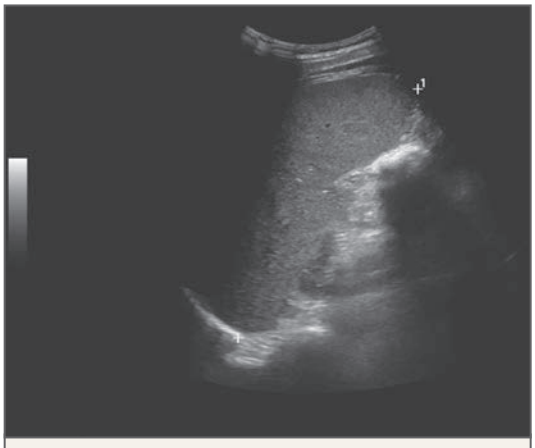

Figure 2. Ultrasound Image.

A sagittal ultrasound image of the abdomen shows mild splenomegaly, with the spleen measuring 15.8 cm on the long axis (reference value with adjustment for sex and height, <14.1).

CONGENITAL DISEASES

Given this patient's young age, the adult onset of a pediatric syndrome that causes pancytopenia must be considered. An entity such as *GATA2* deficiency, Fanconi's anemia, the Wiskott–Aldrich syndrome, or a ribosomopathy or telomeropathy could cause pancytopenia, and an elevation in the mean corpuscular volume would occur with some of these disorders. However, few aspects of the patient's history would provide further support for such a process; he had no recurrent infections, developmental abnormalities, or other chronic organ dysfunction. The tempo of symptom onset, over a period of 4 weeks, would be too fast for these entities, and the blood lactate dehydrogenase level of nearly 3000 U per liter would be uncharacteristically high in the absence of a hematologic cancer.

INFECTIONS

In contrast, the subacute onset of illness, the history of nausea and vomiting early in the presentation, and the good health at baseline are all consistent with an infectious cause of the patient's pancytopenia. Infection with a viral pathogen such as cytomegalovirus or Epstein–Barr virus could also account for his splenomegaly. An atypical presentation of infection with parvovirus or adenovirus should also be considered. The laboratory scaling functions, however, substantially decrease the likelihood of these viral infections. None of these infections are likely to result in a blood lactate dehydrogenase level of nearly 3000 U per liter. In addition, a hemoglobin level of 5.1 g per deciliter would be very low, and a mean corpuscular volume of 105.9 fl would be atypically high. A viral infection associated with bone marrow suppression would not typically induce macrocytosis or an

elevated red-cell distribution width. Parvovirus-induced pure red-cell aplasia can cause profound anemia, but the reticulocyte count is usually undetectable. This patient's reticulocyte count of 3.8% will require further interpretation but does not fit that pattern.

What about infection with nonviral pathogens? The indolent course of illness in an otherwise healthy patient is not consistent with bacteremia or sepsis. An atypical mycobacterial or fungal infection is unlikely in the absence of other evidence of immunodeficiency and without

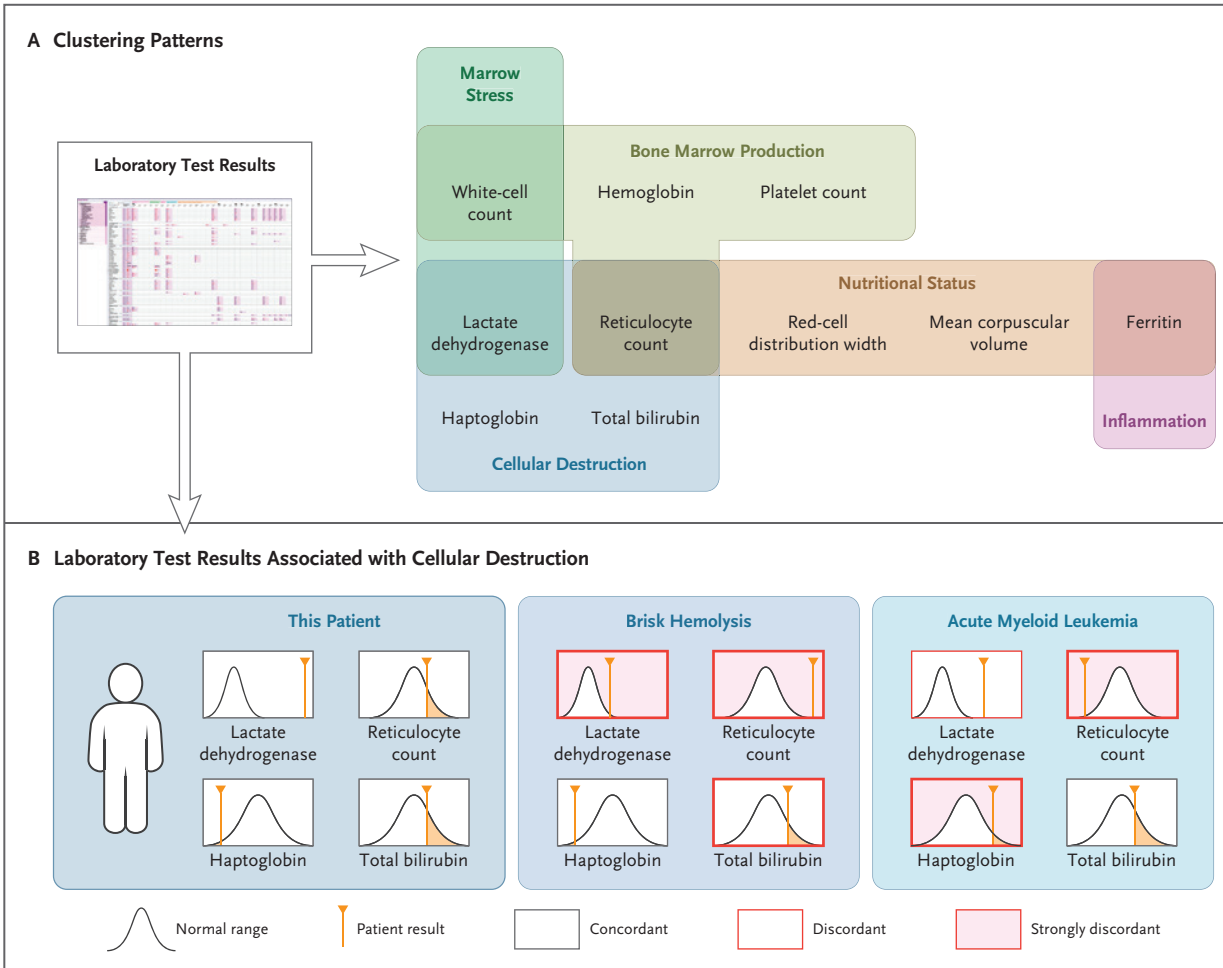

Figure 3. Clustering of Laboratory Test Results.

Results of routine laboratory tests can be conceptualized in clusters that reflect underlying physiological processes in order to guide diagnostic reasoning (Panel A). Results within a cluster characteristically vary proportionally in tandem with pathologic changes, helping to identify the mechanism. An illness with a systemic effect on bone marrow production, such as severe aplastic anemia, routinely yields pancytopenia with a concordantly low reticulocyte count. If bone marrow injury or stress is causing a high level of lactate dehydrogenase, the white-cell count is likely to be abnormal as well. If the reticulocyte count is low but the red-cell distribution width, mean corpuscular volume, and ferritin level are normal, a nutritional deficiency is unlikely. Several patterns of laboratory test results can be observed in patients with processes that cause cellular destruction, with the pattern depending on the locus of injury and the types of cells that are affected (Panel B). This patient's test results included a profoundly elevated lactate dehydrogenase level that was discordant with the kinetics of both hemolysis and leukemia. Even brisk red-cell lysis rarely causes the degree of elevation in the lactate dehydrogenase level seen in this case, but if it did, it would provoke a proportionally dramatic elevation in both the reticulocyte count and the bilirubin level. Likewise, a lactate dehydrogenase level of nearly 3000 U per liter would be somewhat atypical even in a patient with acute myeloid leukemia, in whom the reticulocyte count would be low (not high), reflecting bone marrow filled with blasts, and the haptoglobin level would be elevated (not suppressed).

suspicious imaging findings. Although the patient presented in the summer, tickborne illness is also improbable; screening tests for Lyme disease were negative, and he had no known exposures or environmental risk factors. Babesiosis with erythrocyte destruction is highly unlikely to be the cause of a blood lactate dehydrogenase level of nearly 3000 U per liter in the absence of marked hyperbilirubinemia, other signs of tissue injury, and critical illness.

It would be reasonable to perform nucleic acid testing for Epstein–Barr virus, cytomegalovirus, and parvovirus. However, my overall suspicion for an infectious process is low in this case.

CANCER

The subacute onset of illness in this patient is compatible with a diagnosis of a hematologic cancer, and night sweats are often associated with cancer, particularly lymphomas. The strikingly abnormal lactate dehydrogenase level, hemoglobin level, and white-cell count are concordant with cancer as a potential cause of his pancytopenia. However, other laboratory test results are more reassuring. The reticulocyte and platelet counts were relatively preserved; these findings suggest that the bone marrow has not been completely infiltrated by tumor and that marrow production has not been interrupted at a systemic level. Likewise, no clear population of circulating immature cells was seen on a peripheral-blood smear, and the mean corpuscular volume of 105.9 fl would be atypical for any of the hematologic cancers. In addition, no lymphadenopathy was detected on examination. Nevertheless, leukemia or lymphoma remains a possibility, and given the risk of missing such a diagnosis, it would be reasonable to perform a bone marrow biopsy.

INFLAMMATORY AND AUTOIMMUNE DISEASES

This patient's constellation of night sweats, fatigue, and pancytopenia could be explained by an autoimmune disease, and examination findings consistent with vitiligo further suggest an autoimmune process. Systemic lupus erythematosus could account for several of this patient's laboratory abnormalities but is unlikely in the absence of other evidence of a connective-tissue disorder. Hemophagocytic lymphohistiocytosis can cause extreme elevation in the blood lactate dehydrogenase level, severe cytopenias, and varied clinical symptoms. However, normothermia and a normal (or not elevated) blood ferritin level would be highly unusual in a patient with hemophagocytic lymphohistiocytosis, and macrocytosis would be atypical.

Could the patient have immune-mediated hemolysis? Paroxysmal nocturnal hemoglobinuria can be ruled out on the basis of the laboratory scaling functions. In order for paroxysmal nocturnal hemoglobinuria to account for the degree of elevation in the blood lactate dehydrogenase level seen in this patient, exceptionally brisk intravascular hemolysis would need to be present. In turn, the brisk intravascular hemolysis would be expected to cause clinically significant kidney injury, which would be inconsistent with the normal creatinine level and urinalysis results.

Could the patient have antibody-mediated hemolysis? He had the classic quartet of findings: a positive direct antiglobulin test, an elevated lactate dehydrogenase level, an elevated indirect bilirubin level, and a low haptoglobin level. The quantitative pattern, however, does not fit with this mechanism. The blood lactate dehydrogenase level is atypically high; a level of less than 1000 U per liter would be typical. In addition, the reticulocyte count is discordantly low, given that florid red-cell destruction (i.e., red-cell destruction occurring at a rate compatible with the degree of anemia and elevation in the lactate dehydrogenase level in this patient) characteristically provokes a vigorous marrow response. The same argument applies to the bilirubin level, which is proportionate to the amount of hemoglobin being recycled and would have to be higher for the pathophysiological kinetics — the rates at which pathophysiological events, such as red-cell destruction, and compensatory physiological processes, such as clearance of metabolites, are proceeding — to align. Because the direct antiglobulin test was only positive microscopically, a clinically significant autoimmune hemolytic process is unlikely.

NUTRITIONAL DEFICIENCIES

In a patient with a normal diet and no alcohol consumption, there might at first be little concern regarding nutritional deficiencies. Yet, a closer

look is warranted in this case because several aspects of the patient's presentation could be associated with vitamin deficiency. In the context of severe vitamin B_{12} or folate deficiency, ineffective hematopoiesis can lead to the death of precursor cells in bone marrow and to marked elevation in the lactate dehydrogenase level. Because some of the precursor cells in bone marrow that die are developing erythrocytes, a low haptoglobin level may occur. Incorporating the degree of anemia in this patient, we can calculate a corrected reticulocyte count of 1.3%, which is much lower than the count that would be expected with the peak response by healthy and nutritionally replete bone marrow to such a severely depressed hemoglobin level.[3] In addition, an association is well established between vitiligo and pernicious anemia.[4] Pernicious anemia wields a unique mechanism as a cause of vitamin B_{12} deficiency that is capable of exhausting nutrient stores even in the context of robust vitamin B_{12} intake; macrocytic anemia and an elevated red-cell distribution width are classic findings.

Although this patient's neurologic status appeared to be normal, the hematologic and neuropsychiatric manifestations of vitamin B_{12} deficiency are substantially independent, each mediated by mechanisms that remain to be fully elucidated. The onset of clinical symptoms over a period of weeks to months would not fit the underlying biochemical progression of vitamin B_{12} deficiency, in which the depletion of physiological stores occurs over a period of 2 to 5 years.[5] However, a clinical deficiency can be a threshold phenomenon, in which symptoms occur abruptly when compensatory mechanisms are exhausted. Given this possibility, the constellation of laboratory test results obtained thus far would support a diagnosis of vitamin B_{12} deficiency.

The critical next steps in this patient's evaluation included obtaining blood levels of vitamin B_{12} and folate, as well as performing a detailed review of the peripheral-blood smear, with a focus on the segmentation of neutrophils and the morphologic features of erythrocytes. Although vitamin B_{12} deficiency was a compelling potential explanation for his presentation, cancer remained a possibility, and a bone marrow biopsy was performed.

DR. JONATHAN C.T. CARLSON'S DIAGNOSIS

Vitamin B_{12} deficiency.

DIAGNOSTIC TESTING

Dr. Chen: The vitamin B_{12} level was less than 150 pg per milliliter (111 pmol per liter; reference value, >231 pg per milliliter [170 pmol per liter]). The folate level was 4.9 ng per milliliter (11.1 nmol per liter; reference value, >4.7 ng per milliliter [10.7 nmol per liter]). The methylmalonic acid level was elevated (1.00 nmol per milliliter; reference value, <0.40), as was the homocysteine level (21.5 μmol per liter; reference range, 0 to 14.2).

The peripheral-blood smear showed features consistent with megaloblastic anemia, including clinically significant anisopoikilocytosis and morphologically abnormal neutrophils. Neutrophils have an average of three nuclear lobes, with a typical range of two to five. The presence of six or more lobes in more than 1% of neutrophils, or the presence of five or more lobes in more than 5% of neutrophils, is consistent with hypersegmentation. In this patient, a large portion of neutrophils had five or more nuclear lobes.

The bone marrow–biopsy specimen (Fig. 4A) showed normocellularity for the patient's age. Left-shifted erythroid hyperplasia and maturing trilineage hematopoiesis were detected. On E-cadherin staining (Fig. 4B), there was striking hyperplasia of early erythroid precursor cells. On CD34 staining (Fig. 4C), the level of CD34+ blasts was not increased, accounting for less than 5% of the overall cellularity in the bone marrow. Aspirate smears (Fig. 4D and 4E) showed erythroid cells with megaloblastic changes, including nuclear–cytoplasmic asynchrony, nuclear budding, binucleation, and other nuclear irregularities. There were scattered giant band forms. Nuclear hypersegmentation was seen in a few megakaryocytes. Flow cytometry performed on the bone marrow showed no evidence of acute leukemia or other hematopoietic neoplasms. Cytogenetic testing showed a normal male karyotype (46,XY) in 20 metaphases, and no alterations in genes that are commonly implicated in hematopoietic cancers were detected on a DNA-

based next-generation sequencing panel (Rapid Heme Panel, version 3).[6] The findings of erythroid hyperplasia with prominent dyserythropoiesis and mild morphologic abnormalities in the myeloid and megakaryocytic lineages are consistent with vitamin B_{12} deficiency.

Additional serologic testing revealed the presence of both anti–parietal cell antibodies and anti–intrinsic factor antibodies, a combination of findings that has a high sensitivity and specificity for the diagnosis of pernicious anemia.[7,8] The serum gastrin level was elevated (594 pg per milliliter; reference value, <100), and the serum pepsinogen level was below the limit of quantification; these findings are suggestive of atrophic gastritis.[9] Taken together, the laboratory and histopathological findings are consistent with vitamin B_{12} deficiency due to pernicious anemia.

Dr. Ouyang: After the results of vitamin B_{12} testing were received, a more detailed neurologic examination was performed. Tone and cerebellar function were normal. Proprioception and vibration sense were intact, as were sensation to light touch and pinprick. Temperature sensation was impaired in the feet and legs. Deep-tendon reflexes were 3+ at the patellae but were 2+ elsewhere.

PATHOLOGICAL DIAGNOSIS

Vitamin B_{12} deficiency due to pernicious anemia.

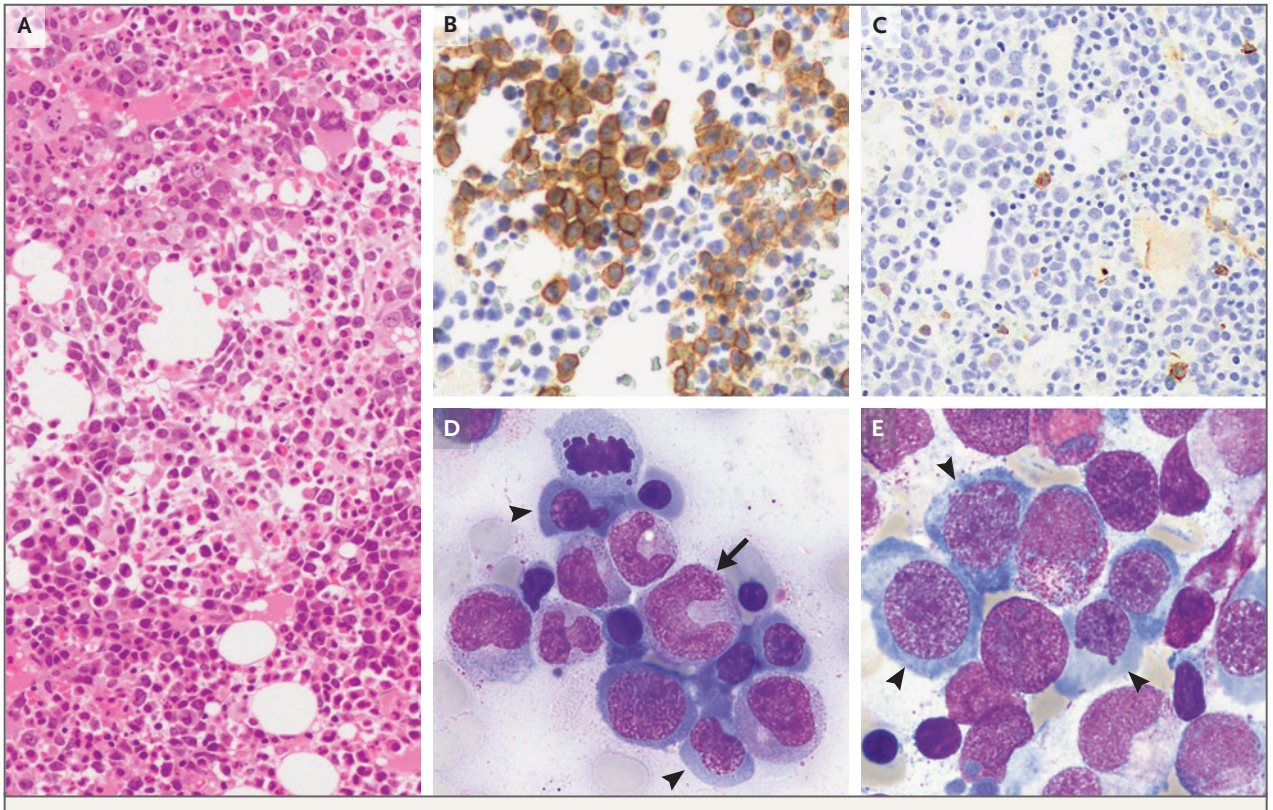

Figure 4. Bone Marrow–Biopsy Specimen and Bone Marrow Aspirate.

Hematoxylin and eosin staining of a bone marrow–biopsy specimen (Panel A) shows approximately 80% cellularity, which reflects normocellularity for the patient's age. The myeloid-to-erythroid ratio is reversed, with an increase in erythroid forms. Mature segmented granulocytes are decreased but present. Megakaryocytes with overall normal morphologic features are also present. There is an abundance of left-shifted forms, many of which are erythroid precursor cells. Immunohistochemical staining for E-cadherin (Panel B) is positive in the erythroid precursor cells. Immunohistochemical staining for CD34 (Panel C) is positive in less than 5% of the cells overall, which does not indicate an increased level. Wright–Giemsa staining of bone marrow aspirate smears (Panels D and E) shows an increase in erythroid cells with megaloblastic changes, including nuclear–cytoplasmic asynchrony, binucleation, nuclear budding, and other irregularities (arrowheads). There are also scattered giant band forms (Panel D, arrow).

DISCUSSION OF MANAGEMENT

Dr. Carlson: In a patient with a new diagnosis of pernicious anemia or another cause of severe vitamin B_{12} deficiency, replacement therapy typically begins with an intensive phase that involves the administration of intramuscular cyanocobalamin for 4 to 8 weeks. Intramuscular cyanocobalamin is administered at a dose of 1000 μg daily for a week and then at a dose of 1000 μg weekly through completion of the course.[5,10] Concomitant folic acid supplementation is routinely used to ensure an adequate supply of folate, given that accelerated hematopoiesis can lead to the rapid depletion of short-term folate stores.

For the indefinite maintenance phase of replacement therapy, both intramuscular cyanocobalamin (1000 μg monthly) and oral cyanocobalamin (1 to 2 mg daily) are validated options. The typical level of vitamin B_{12} intake attained through diet is 5 to 10 μg daily. At the level of vitamin B_{12} intake achieved through oral repletion, which is more than 200 times the level attained through diet, diffusion-limited passive uptake of vitamin B_{12} throughout the gastrointestinal tract is sufficient to maintain physiological stores, and no protein cofactors are needed, even with just 1% absorption efficiency.[5,11,12] Repletion of vitamin B_{12} leads to a rapid physiological and metabolic response; reticulocytosis is evident within 4 to 5 days.[13]

In the long term, the choice of intramuscular or oral therapy can be made on an individual basis with consideration of cost, comfort, and the need for supervision. Achlorhydria from autoimmune parietal-cell destruction may result in concomitant iron deficiency; routine monitoring is warranted. The autoimmune gastritis that underlies pernicious anemia increases the risk of cancer by a factor of approximately 7, with an estimated incidence of 0.27% per patient-year.[14] Screening endoscopy after diagnosis is recommended,[15] and the threshold for performing repeat endoscopy is low if pertinent symptoms occur. In young patients, long-interval surveillance is of particular relevance, although follow-up intervals have not yet been defined.

In this patient, vitamin B_{12} replacement therapy with intramuscular cyanocobalamin at a dose of 1000 μg daily was initiated, and there was a plan to transition his treatment to weekly doses after discharge from the hospital. The blood counts stabilized, and the blood lactate dehydrogenase level trended rapidly downward after the third hospital day. By the fifth hospital day, 4 days after treatment with intramuscular cyanocobalamin was started, there was a 22% increase in the absolute reticulocyte count. With reassuring results from the bone marrow biopsy and improving laboratory test results, the patient was discharged home.

Five weeks after discharge, the patient was evaluated by his primary care physician. He felt well and had returned to work. The complete blood count was normal, as was the blood vitamin B_{12} level.

FINAL DIAGNOSIS

Vitamin B_{12} deficiency due to pernicious anemia.

This case was presented at the Medicine Case Conference.

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

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