CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 38-2020: A 52-Year-Old Man with Cancer and Acute Hypoxemia

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PRESENTATION OF CASE

Dr. Margaret B. Allison (Medicine): A 52-year-old man was urgently evaluated because of hypoxemia that occurred on the fifth day he was at this hospital for suspected cancer.

The patient had been in his usual state of health until 2 months before presentation to this hospital, when pain on the right side of the back developed. The pain began gradually after the patient had moved heavy furniture, worsened with activity and coughing, sometimes radiated down the back of the right arm to the elbow, and occasionally awakened him from sleep. During the next 2 months, the pain waxed and waned. Ice, ibuprofen, naproxen, cyclobenzaprine, and physical therapy were prescribed but did not lead to any improvement.

One day before presentation to this hospital, the patient was seen in his primary care clinic because the severity of the back pain had increased and numbness and weakness of the right hand had developed. Radiography of the cervical and thoracic spine revealed spondylolisthesis, degenerative changes, and an anterior wedge deformity of the T9 vertebral body of indeterminate duration. The following day, after the imaging results were reviewed, the patient was referred to the emergency department of this hospital for further evaluation.

In the emergency department, the patient reported severe, sharp, burning pain in the right shoulder, triceps, and upper and middle back. He also noted fatigue and increased urinary frequency. He had hypertension, dyslipidemia, obesity, and hyperthyroidism. Medications included amlodipine, metoprolol, topiramate, ranitidine, ibuprofen, and naproxen. Peanuts and latex had caused urticaria. Multiple relatives had hypertension and diabetes mellitus. The patient worked in security and did not use alcohol, tobacco, or illicit substances. He identified as Black and as a Jehovah's Witness; he stated that receiving blood transfusions was incompatible with his beliefs.

On examination, the temperature was 37.1°C, the heart rate 95 beats per minute, the blood pressure 162/88 mm Hg, the respiratory rate 19 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The paraspinal muscles were tender, more so on the right side than on the left side. Strength was 4 out of 5 when the patient extended his right shoulder and when he gripped the examiner's fingers with his right hand. Straight leg raising was normal bilaterally. Oral acetaminophen, ibuprofen, oxycodone, and diazepam and transdermal lidocaine were administered, and the patient was observed overnight in the emergency department. The next morning, the pain persisted; magnetic resonance imaging (MRI) was performed.

Dr. F. Joseph Simeone: MRI of the spine (Fig. 1A, 1B, and 1C), performed before and after the administration of intravenous gadolinium, revealed an enhancing, marrow-replacing mass involving the right posterior aspect of the T1 vertebral body, with resultant severe stenosis of the spinal canal and right neural foramen. The bone marrow signal was diffusely heterogeneous, and there were mild compression deformities of multiple thoracic vertebral bodies, including T9, as seen on radiography.

Dr. Allison: The blood calcium level was 19.7 mg per deciliter (4.92 mmol per liter; reference range, 8.5 to 10.5 mg per deciliter [2.12 to 2.62 mmol per liter]). The anion gap, platelet count, erythrocyte sedimentation rate, and urinalysis were normal, as were blood levels of magnesium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, total protein, albumin, globulin, lactate dehydrogenase, thyrotropin, and prostate-specific antigen; other laboratory test results are shown in Table 1. Serum and urine samples were obtained for protein electrophoresis and immunofixation, and another serum sample was obtained to be analyzed for kappa and lambda free light chains. Additional imaging studies were obtained.

Dr. Simeone: Computed tomography (CT) of the chest, abdomen, and pelvis (Fig. 1D), performed after the administration of intravenous contrast material, confirmed the lytic lesion at T1 and the compression deformities of multiple thoracic vertebral bodies. Multiple small osteolytic skeletal lesions were identified. There was no evidence of other mass lesions or lymphadenopathy.

Dr. Allison: The patient was admitted to the hospital on the second hospital day; a diagnosis of cancer was suspected. On examination, he appeared fatigued and uncomfortable and had a flat affect. There was diminished sensation of the pads of the second and third fingers on the right hand; the remainder of the examination was unchanged. Oral acetaminophen, subcutaneous calcitonin, and intravenous lactated Ringer's solution, hydromorphone, diazepam, and zoledronic acid were administered. Overnight, the patient became increasingly somnolent, and the oxygen saturation decreased to 91%.

The following morning, on the third hospital day, auscultation of the lungs revealed bibasilar crackles. Laboratory test results are shown in Table 1. Supplemental oxygen was administered through a nasal cannula at a rate of 2 liters per minute, and the oxygen saturation increased to 94%. Lactated Ringer's solution and zoledronic acid were stopped, and intravenous normal saline, furosemide, and dexamethasone were begun.

On the fourth hospital day, a CT-guided bone marrow biopsy was performed. Afterward, trace edema in the legs was noted. Examination of the urinary sediment revealed barrel-shaped crystals, and a 24-hour urine sample contained more than 5 g of protein; other laboratory test results are shown in Table 1. A stool sample was guaiac-negative. Oral cholecalciferol and intravenous rasburicase were administered.

Early the following morning, on the fifth hospital day, the oxygen saturation decreased to 86%, without shortness of breath. The rate of supplemental oxygen administration was increased to 6 liters per minute, but the oxygen saturation did not increase. The temperature was 37.2°C, the heart rate 81 beats per minute, the blood pressure 126/75 mm Hg, and the respiratory rate 18 breaths per minute. Auscultation of the heart and lungs was normal. Furosemide was administered intravenously, and chest radiography was performed.

Dr. Simeone: An anteroposterior radiograph of the chest showed low lung volumes and otherwise clear lungs (Fig. 1E).

Dr. Allison: Two hours later, high-flow oxygen therapy was administered through a nasal cannula (rate, 60 liters per minute; fraction of inspired oxygen [F_{IO_2}], 1.0); the oxygen saturation remained unchanged. Blood levels of lactate, troponin T, and N-terminal pro–B-type natriuretic

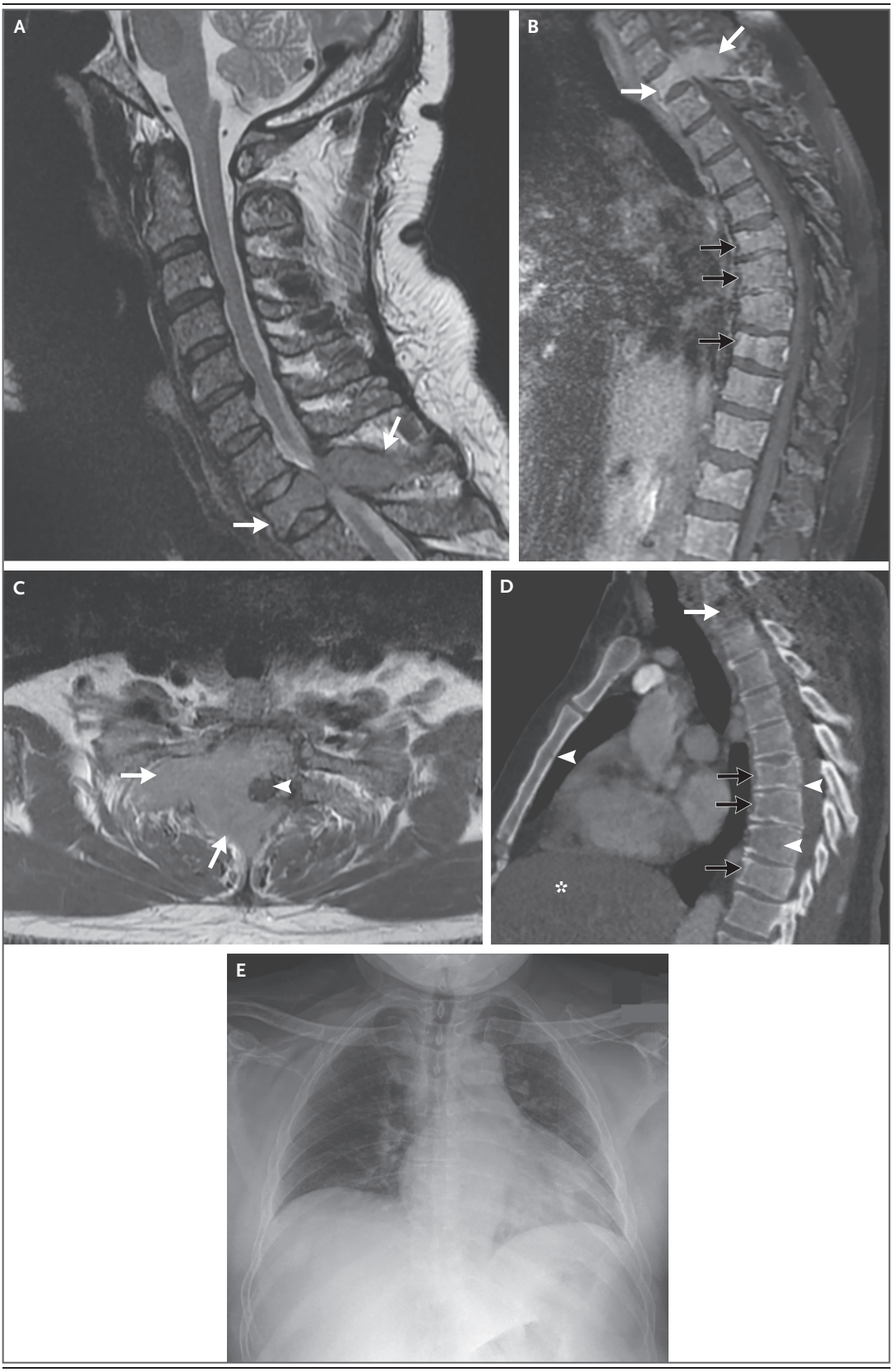

Figure 1 (facing page). Imaging Studies.

Magnetic resonance imaging of the cervical, thoracic, and lumbar spine was performed on the second hospital day. A sagittal T2-weighted image of the cervical spine (Panel A), a sagittal T1-weighted image of the thoracic spine with fat saturation obtained after the administration of intravenous gadolinium (Panel B), and an axial T1-weighted image of the T1 vertebral body obtained after the administration of intravenous gadolinium (Panel C) show a marrow-replacing, destructive lesion involving the T1 vertebral body and posterior elements (white arrows). The bone marrow signal is diffusely heterogeneous, and multiple thoracic vertebral bodies show superior end-plate compression deformities (Panel B, black arrows). There is severe spinal stenosis and leftward displacement of the spinal cord (Panel C, arrowhead) resulting from epidural extension of the mass. Computed tomography of the chest, abdomen, and pelvis was performed on the third hospital day. A coned-down sagittal image of the thoracic spine obtained after the administration of intravenous contrast material (Panel D) shows the destructive lesion involving the T1 vertebral body (white arrow), partial superior end-plate collapse of multiple vertebral bodies (black arrows), and diffuse small, round lytic lesions in multiple vertebral bodies and the sternum (arrowheads), as well as incidental hepatic steatosis (asterisk). Chest radiography was performed on the fifth hospital day, on the day of the current evaluation. The radiograph (Panel E) shows low lung volumes but otherwise clear lungs.

peptide were normal; other laboratory test results are shown in Table 1.

A diagnosis was made.

DIFFERENTIAL DIAGNOSIS

Dr. Lucas X. Marinacci: This 52-year-old man with back pain was admitted to the hospital after a vertebral mass, multiple lytic bone lesions, and severe hypercalcemia were identified and a diagnosis of cancer was suspected. On the fifth hospital day, the oxygen saturation measured by means of pulse oximetry decreased precipitously. I was a member of the team that evaluated this patient during this acute episode, and I am aware of the final diagnosis.

Causes of hypoxemia are typically classified according to the underlying mechanism: decreased F_{IO_2}, hypoventilation, impaired diffusion, ventilation–perfusion mismatch, and shunting. This framework is useful for understanding the pathophysiology, but for two reasons it is often not helpful in the initial evaluation of a patient with acute hypoxemia. First, most possible causes fall into the last two categories. Second, categorization requires knowledge of the difference between the alveolar and the arterial partial pressure of oxygen, known as the alveolar–arterial gradient, a value that is usually not immediately available to the clinician.[1] At the bedside, a step-by-step approach that rapidly identifies findings that alter immediate management and narrows the differential diagnosis is more practical (Fig. 2).

HYPOXEMIA

The first step in the evaluation and treatment of this patient with an acute decrease in oxygen saturation is to determine whether a higher level of care or ventilatory support is needed. Can the patient protect his airway, with intact awareness, reflexes, coordination, and strength to maintain airway patency despite potential or impending obstruction, such as by secretions, vomitus, tissue edema, blood, or a foreign body? Does he have rapidly progressive respiratory fatigue or an increasing oxygen requirement? Does he have an underlying condition, such as severe obstructive lung disease or diffuse parenchymal lung disease, or does he have impaired respiratory mechanics due to massive ascites or neuromuscular weakness — conditions that could be limiting his physiologic reserve?

The patient appeared well and had no preexisting respiratory vulnerability. A caveat to this assessment is that the skin pigmentation may have limited the detection of cyanosis, which can be subtle in patients with dark skin.[2] In such patients, special attention should be paid to the mucous membranes, including the gums, lips, and conjunctivae, where a grayish hue may be present in a cyanotic state.[3]

The next steps are to evaluate for signs of upper airway obstruction — such as stridor, lip or tongue swelling, or the inability to handle secretions — and to assess the thorax by means of physical examination, bedside chest radiography, and point-of-care ultrasonography, if available. This patient had no signs of upper airway obstruction, and he had a normal lung examination and an unremarkable chest radiograph; these findings make primary parenchymal or pleural disease unlikely.

LOW OXYGEN SATURATION AND CLEAR LUNGS

Now that several possible causes of this patient's hypoxemia have been rapidly ruled out, the prob-

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Hospital Day 2	Hospital Day 3	Hospital Day 4	Hospital Day 5, Current Evaluation
Hematocrit (%)	41.0–53.0	37.5	36.9	30.8	28.8
Hemoglobin (g/dl)	13.5–17.5	12.2	12.1	10.1	9.7
White-cell count (per μl)	4500–11,000	10,910	13,920	10,530	11,750
Differential count (per μl)					
Neutrophils	1800–7700	7321			
Lymphocytes	1000–4800	1790			
Monocytes	200–1200	1320			
Eosinophils	0–900	44			
Basophils	0–300	76			
Immature granulocytes	0–100	360			
Sodium (mmol/liter)	135–145	140	143	142	142
Potassium (mmol/liter)	3.4–5.0	4.0	4.0	3.7	4.0
Chloride (mmol/liter)	100–108	96	102	104	106
Carbon dioxide (mmol/liter)	23–32	35	27	28	26
Urea nitrogen (mg/dl)	8–25	18	27	43	52
Creatinine (mg/dl)	0.60–1.50	1.34	1.98	2.38	2.13
Glucose (mg/dl)	70–110	119	119	123	132
Calcium (mg/dl)	8.5–10.5	19.7	15.3	13.4	11.5
Ionized calcium (mmol/liter)	1.14–1.30		1.97	1.75	1.57
Phosphorus (mg/dl)	2.6–4.5	5.4	4.1	2.7	2.4
25-Hydroxyvitamin D (ng/ml)	20–80	11			
Parathyroid hormone, intact (pg/ml)	10–60		10		
Parathyroid hormone–related peptide (pmol/liter)	<2.0		1.0		
β_2-microglobulin (μg/ml)	0.80–2.34		4.40		
Uric acid (mg/dl)	3.6–8.5			11.9	
D-dimer (ng/ml)	<500				2895
Arterial blood gas analysis					
Fraction of inspired oxygen					1.0
pH	7.35–7.45				7.42
Partial pressure of carbon dioxide (mm Hg)	35–42				40
Partial pressure of oxygen (mm Hg)	80–100				200

* 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 phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert the values for uric acid to micromoles per liter, multiply by 59.48.

† 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.

lem representation can be distilled to a patient with low oxygen saturation in the context of clear lung fields. The differential diagnosis can then be further narrowed on the basis of the results of two bedside diagnostic maneuvers: increasing the F_{IO_2} and performing arterial blood gas analysis. Increasing the F_{IO_2} did not affect the patient's readings on pulse oximetry, which

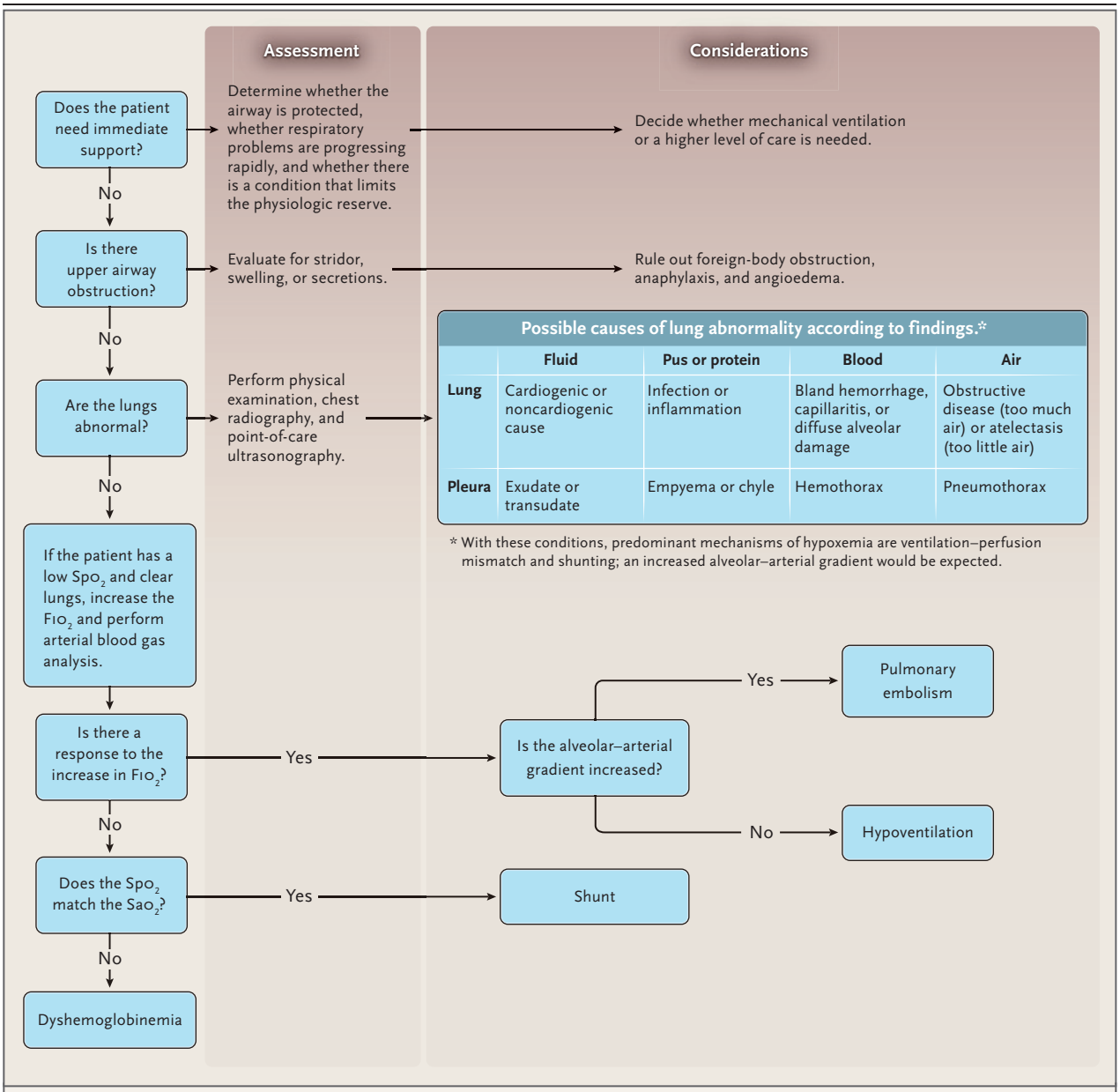

Figure 2. Approach to the Evaluation of a Patient with Decreasing Oxygen Saturation on Pulse Oximetry.

A step-by-step evaluation can assist clinicians in rapidly narrowing the differential diagnosis in hospitalized patients with a new or progressive decrease in the oxygen saturation obtained by means of pulse oximetry (Spo_2). Fio_2 denotes fraction of inspired oxygen, and Sao_2 oxygen saturation obtained by means of arterial blood gas analysis.

were strikingly invariable at 86%. The arterial blood gas measurements are shown in Table 1.

PULMONARY EMBOLISM

Could this patient have pulmonary embolism? He is at an elevated risk because of immobilization due to pathological fracture, suspected cancer, and inpatient status; the last two factors make clinical decision rules less useful and render the elevated D-dimer level nonspecific.[4,5] The patient has anemia, and blood transfusions are incompatible with his religious beliefs; these features increase the risk of harm associated with the empirical initiation of anticoagulation. In addition, he has acute kidney injury, and CT pulmonary angiography is associated with a risk

of contrast-induced nephropathy. Ventilation–perfusion scanning is not available on an emergency basis, and the level of supplemental oxygen being administered would preclude a ventilation–perfusion scan at this hospital. The absence of hypotension, tachycardia, and a change in oxygen saturation in response to increasing the F_{IO_2} argues against, but by no means rules out, venous thromboembolism.[6] Given the potential harms associated with workup and treatment and the uncertainty surrounding the diagnosis, it is reasonable to keep pulmonary embolism on the differential diagnosis while pursuing other possible causes.

HYPOVENTILATION

Hypoventilation is usually clinically apparent on the basis of a low respiratory rate or tidal volume. Furthermore, hypoxemia caused by hypoventilation would abate with the administration of supplemental oxygen and would be associated with a normal alveolar–arterial gradient, and neither of these features was observed in this patient.

OXYGEN SATURATION GAP

The next step in the evaluation of this patient's hypoxemia is to determine whether there is an oxygen saturation gap, defined as a difference of more than 5 percentage points between the oxygen saturation obtained by means of pulse oximetry (Spo_2) and the oxygen saturation obtained by means of arterial blood gas analysis (Sao_2).[7] In this case, the Spo_2 was 86% and the arterial partial pressure of oxygen was 200 mm Hg, which on a standard oxygen–hemoglobin dissociation curve with a temperature of 37°C and a pH of 7.4 correlates with an Sao_2 of 99.2%; the Sao_2 is often reported by the laboratory alongside the arterial blood gas results.[8] Therefore, an oxygen saturation gap is present.

SHUNTING

In the presence of a right-to-left shunt, hypoxemia is caused by blood that does not participate in gas exchange before entering the systemic circulation. Massive atelectasis or processes that lead to alveolar filling, such as acute respiratory distress syndrome, can cause shunting. However, the differential diagnosis of intrapulmonary shunts in the context of clear lungs is limited to conditions associated with anomalous arteriovenous connections, which can be physiological, resulting from vasodilation, as in hepatopulmonary syndrome, or can be anatomical, resulting from arteriovenous malformations, as in hereditary hemorrhagic telangiectasia. However, this patient has no evidence of either of these conditions, and neither would manifest so acutely.

An acute intracardiac right-to-left shunt in an adult without known structural heart disease can occur when there is a previously unrecognized defect, such as a patent foramen ovale, and a cause of newly elevated pressures on the right side of the heart, such as a pulmonary embolism.[9] In this case, there is no reason to suspect elevated pulmonary vascular resistance from underlying lung disease or preexisting pulmonary hypertension. In the absence of markedly elevated pressure gradients, transient intracardiac right-to-left shunt can be due to interatrial anatomical shunt.[10] However, these processes would not cause an oxygen saturation gap, since they are not associated with factors that interfere with the measurement of either Spo_2 or Sao_2.

ARTIFACT

Pulse oximetry involves shining two wavelengths of light, red and infrared, through peripheral tissue that has a pulsating vascular bed, such as the fingertip or earlobe. The two major forms of hemoglobin, deoxyhemoglobin and oxyhemoglobin, absorb light differently at these two wavelengths; deoxyhemoglobin absorbs more red light, and oxyhemoglobin absorbs more infrared light. Measurement of the changes in light absorption over each cardiac cycle allows for generation of a ratio (R) of red light to infrared light absorbed by the arterial compartment. This dimensionless ratio, effectively representing the ratio of deoxyhemoglobin to oxyhemoglobin, is converted into an oxygen saturation measurement with the use of a calibrated curve that has been empirically derived from ratios in healthy volunteers with experimentally induced, independently verified oxygen saturations between 100% and 70%.[11]

If a patient lacks sufficient pulsatile flow at the measurement point, whether because of vasoconstriction or poor perfusion, the Spo_2 may be inaccurate. In addition, the administration of medical dyes that absorb red or infrared light, such as methylene blue, indocyanine green, or

indigo carmine, can interfere with Spo_2 measurements and cause an oxygen saturation gap.[12] This patient's hands were well perfused, and no dyes had been administered; therefore, artifactual results on pulse oximetry can be ruled out.

DYSHEMOGLOBINEMIA

Three abnormal hemoglobin variants — carboxyhemoglobin, sulfhemoglobin, and methemoglobin — absorb both red and infrared light, interfering with Spo_2 measurements and leading to an oxygen saturation gap.[7] Carboxyhemoglobinemia requires exposure to carbon monoxide, which is highly unlikely to occur in the hospital. Sulfhemoglobinemia can be caused by exposure to hydrogenated sulfide in chemicals such as cleaning solutions and, in rare cases, can be a side effect of certain medications, including metoclopramide, sulfonamides, nitrates, and dapsone, many of which would also cause methemoglobinemia. This patient had no known exposure to any of these agents, but he had received rasburicase, a medication that is known to cause methemoglobinemia, particularly in the context of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

METHEMOGLOBINEMIA AND G6PD DEFICIENCY

Although methemoglobinemia can develop after the administration of rasburicase in patients without G6PD deficiency, G6PD-deficient patients are at an elevated risk for both hemolysis and methemoglobinemia resulting from the use of this drug. As such, the Food and Drug Administration recommends that G6PD levels be measured before the administration of rasburicase.[13] The prevalence of G6PD deficiency is high among Black men.[14] Furthermore, the administration of methylene blue in patients with G6PD deficiency can induce hemolysis and paradoxically worsen methemoglobinemia.[15] Therefore, after my colleagues and I evaluated this patient, we considered rasburicase-induced methemoglobinemia in the context of G6PD deficiency to be the most likely diagnosis in this case.

DR. LUCAS X. MARINACCI'S DIAGNOSIS

Rasburicase-induced methemoglobinemia in the context of glucose-6-phosphate dehydrogenase deficiency.

PATHOLOGICAL DISCUSSION

Dr. Grace K. Mahowald: Oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin have characteristic absorbance spectra, and their concentrations can be measured on most blood gas instruments with the use of CO-oximetry. After absorbance is measured at various wavelengths of light, the concentrations of these hemoglobin derivatives can be determined with the use of the Beer–Lambert law; the sum of their concentrations equals the total hemoglobin concentration.

Methemoglobin is a form of hemoglobin in which heme iron is oxidized from the ferrous state to the ferric state and is unable to bind oxygen; in addition, the remaining subunits of hemoglobin bind oxygen more tightly, shifting the oxygen–hemoglobin dissociation curve to the left and further decreasing oxygen delivery to tissues. In this patient, the methemoglobin concentration measured in the sample submitted for arterial blood gas analysis on the fifth hospital day was found to be elevated, accounting for 7.4% (reference range, 0.0 to 1.5) of the total hemoglobin concentration.

Dr. David J. Kuter: Examination of a peripheral-blood smear (Fig. 3) revealed numerous "bite cells," which are formed when oxidized hemoglobin precipitates within red cells and a portion of the cell is removed ("bitten off") by the spleen, eventually resulting in clearance of the entire red cell. A correlated finding on histochemical staining is the presence of Heinz bodies.[16] The most common cause of bite cells is G6PD deficiency.

Dr. Mahowald: Testing for G6PD activity is performed by means of spectrophotometric measurement of NADPH production in red cells when glucose 6-phosphate is provided as a substrate. In this patient, the level was 0.6 U per gram of hemoglobin (reference range, 8.8 to 13.4), confirming the diagnosis of G6PD deficiency. In hindsight, the patient's G6PD level should have been checked before the administration of rasburicase — a central teaching point in this case.

Dr. Kuter: Red-cell hemoglobin is continually subjected to oxidative stress from exposure to high oxygen concentrations and other oxidants. To mitigate the effects of oxidative stress on the iron and protein constituents of hemoglobin, reducing mechanisms have evolved in red cells

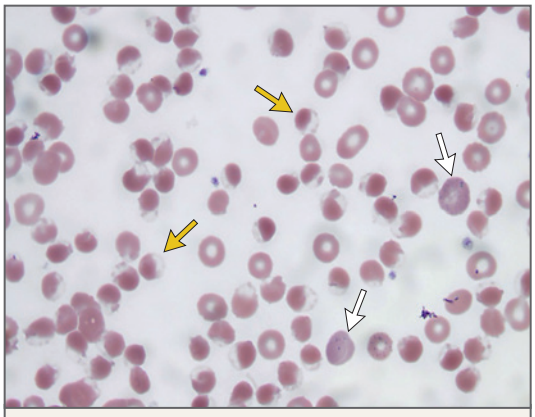

Figure 3. Peripheral-Blood Smear.

A peripheral-blood smear shows "bite cells" (yellow arrows), which are formed when oxidized hemoglobin precipitates within red cells and a portion of the cell is removed ("bitten off") by the spleen, as well as young polychromatophilic red cells with basophilic stippling (white arrows).

(Fig. 4A). G6PD is integral to these reducing mechanisms because it generates NADPH (Fig. 4B), which supports two major antioxidant functions. First, NADPH produces glutathione, the major reducing agent in red cells. Glutathione directly inactivates oxidant molecules such as hydrogen peroxide and reverses oxidative damage to hemoglobin protein. In response to oxidative stress, G6PD can markedly increase the production of glutathione, but this response is diminished in red cells deficient in G6PD.[17,18] Second, NADPH is necessary for the function of NADPH methemoglobin reductase, an enzyme that accounts for approximately 6% of total methemoglobin reduction activity. This enzyme also reduces methylene blue to leukomethylene blue, which serves as an electron donor in the nonenzymatic conversion of ferric iron to ferrous iron; this is the primary mechanism by which methylene blue reduces methemoglobin. Because of the important roles served by G6PD in these antioxidant processes, G6PD deficiency can both modestly increase the severity of methemoglobinemia and limit the ability of methylene blue to treat methemoglobinemia.[19,20]

G6PD deficiency is clinically heterogeneous, and the World Health Organization has created a useful classification scheme.[21] Class III G6PD deficiency, which was present in this patient, is associated with an enzyme half-life of 13 days, enzyme activity that is typically 10 to 60% of the normal level, and intermittent hemolysis; stimuli known to precipitate hemolytic attacks include infection, foods, hypoxemia, inflammation, and certain drugs with high oxidative potential. One such drug is rasburicase, which was administered in this patient. Rasburicase converts uric acid to allantoin and large amounts of hydrogen peroxide. In patients with G6PD deficiency, the oxidative stress from hydrogen peroxide increases iron and protein oxidation, resulting in methemoglobinemia and hemolysis.

PATHOLOGICAL DIAGNOSES

Methemoglobinemia.

Glucose-6-phosphate dehydrogenase deficiency.

DISCUSSION OF MANAGEMENT

Dr. Kuter: Acute management of hemolytic crisis in a G6PD-deficient patient involves discontinuation of the precipitating agent and usually involves transfusion of red cells. However, this patient's religious beliefs precluded transfusion. Alternatives to transfusion include accelerating red-cell production with erythropoiesis-stimulating agents and intravenous iron. Although the use of bovine-derived, hemoglobin-based oxygen carriers remains controversial, a patient-specific investigational new drug application could be submitted. Finally, the new medication luspatercept[22,23] may play a role in future cases.

The management of methemoglobinemia posed an additional challenge in this patient. Because methylene blue is ineffective in patients with G6PD deficiency and may even worsen hemolysis, vitamin C can be administered as a source of reducing activity (albeit a much less active one).

Education of patients and physicians is central to the long-term management of G6PD deficiency. Electronic health record–based clinical decision support systems can alert physicians to potential adverse drug effects,[24] and websites can be referenced when prescribing medications.[25] Availability of rapid tests for G6PD activity would improve the quality and safety of medical care by facilitating the diagnosis of G6PD deficiency when the urgent administration of a drug with high oxidative potential, such as rasburicase, is being considered.

Dr. Andrew L. Lundquist: In addition to having

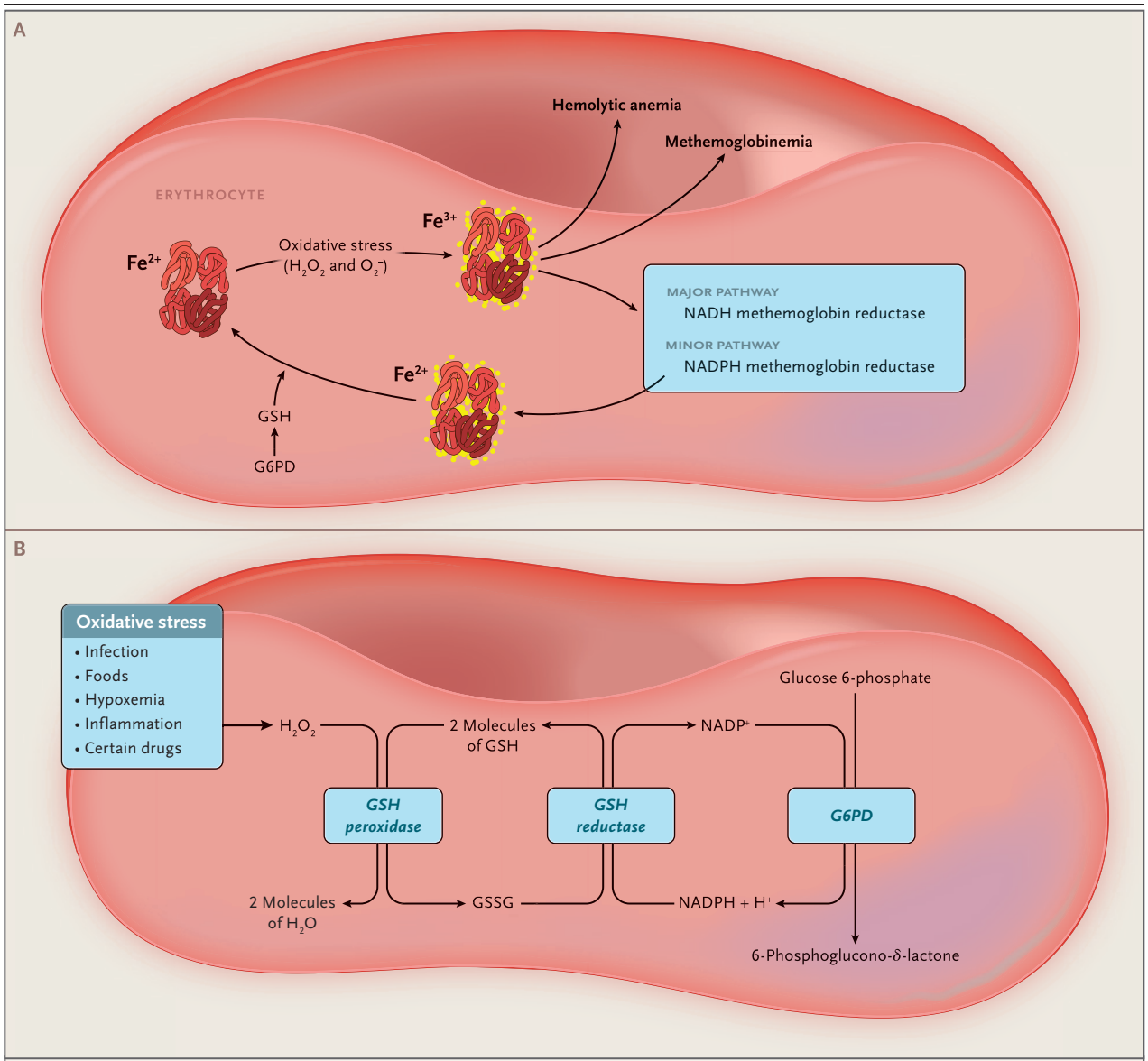

Figure 4. Effect of Oxidative Stress on Hemoglobin and Metabolic Effects of Glucose-6-Phosphate Dehydrogenase.

Panel A shows the effect of oxidative stress on hemoglobin. When the hemoglobin tetramer (four-part red structure) is exposed to oxidative stress, it becomes oxidized (four-part red structure with yellow dots) and its ferrous iron (Fe^{2+}) is oxidized to ferric iron (Fe^{3+}). NADH methemoglobin reductase and NADPH methemoglobin reductase reduce the Fe^{3+} to the Fe^{2+} state, and then glutathione (GSH) reduces the oxidized hemoglobin to the native form. GSH also directly reduces oxidative-stress molecules, such as H_2O_2 and O_2^-. Panel B shows the metabolic effects of glucose-6-phosphate dehydrogenase (G6PD). G6PD transfers two electrons and one hydrogen from glucose 6-phosphate to $NADP^+$, producing 6-phosphoglucono-δ-lactone and NADPH; a free proton (H^+) is also generated. Subsequently, GSH reductase transfers electrons to GSH disulfide (GSSG) to reduce it to GSH. In turn, GSH serves as an electron donor for multiple other reactions, thereby helping to reduce oxidative-stress molecules (as shown for H_2O_2 through GSH peroxidase) or proteins (either directly or through specific reductases, as shown for hemoglobin in Panel A).

hemolysis and methemoglobinemia, this patient had progressive, multifactorial acute kidney injury due to severe hypercalcemia, exposure to intravenous contrast material, recent use of nonsteroidal antiinflammatory drugs, and the presence of what was ultimately shown to be an IgA lambda paraprotein, a finding consistent with multiple myeloma. With multiple osteolytic lesions

on imaging and normal levels of parathyroid hormone, vitamin D, and parathyroid hormone–related peptide, the cancer-related hypercalcemia was due to osteolysis. The hypercalcemia abated with the administration of intravenous fluids to restore extracellular volume, bisphosphonate (with the dose based on the estimated glomerular filtration rate) to inhibit osteoclast activity, and calcitonin to inhibit osteoclast activity and increase urinary calcium excretion.[26,27]

In patients with myeloma, kidney injury can be due to immunoglobulin-mediated glomerular injury (e.g., amyloidosis or monoclonal deposition disease) or to light chain–mediated acute tubular injury or cast nephropathy.[28] The type of proteinuria can signal the mechanism of injury. This patient's 24-hour urine sample contained 5 g of total protein, with minimal albuminuria. The absence of albuminuria argues against glomerular injury, and the marked elevation in total protein suggests the presence of light chains, which increase the risk of tubular injury. Hydration and treatment of the underlying cancer typically lead to improved renal function.[29]

Tumor lysis syndrome with obstruction by uric acid crystals is a possible cause of kidney injury in patients with tumors with a high proliferative rate, a large tumor burden, or high sensitivity to cytotoxic therapy. This patient had a moderately elevated uric acid level and uric acid crystals in urinary sediment, but neither finding would be unusual in the context of acute kidney injury or volume depletion.[30] The normal levels of potassium, phosphorus, and lactate dehydrogenase made tumor lysis syndrome unlikely.[31]

Finally, this patient had severe intravascular hemolysis, a rare cause of kidney injury. Excess free hemoglobin exceeds the binding capacity of haptoglobin, leading to hemoglobin dimers small enough to be filtered by the glomerulus. Kidney injury results from obstruction by hemoglobin casts and direct cytotoxicity of hemoglobin to the proximal tubular cells. The long-term outlook of hemolysis-mediated acute kidney injury is typically favorable with treatment of the underlying cause.[32]

Dr. Allison: Although this patient had severe anemia, his condition ultimately improved after the administration of erythropoietin, intravenous iron, and vitamin C. Hypercalcemia and hemolysis abated, and renal function normalized. Bone marrow biopsy revealed high-risk IgA lambda multiple myeloma, International Staging System stage II. The patient received radiation therapy and chemotherapy with lenalidomide, bortezomib, and dexamethasone. Nine months later, he underwent bloodless autologous stem-cell transplantation and began lenalidomide and bortezomib maintenance therapy. Repeat bone marrow biopsy revealed no evidence of residual disease.

FINAL DIAGNOSES

Rasburicase-induced methemoglobinemia in the context of glucose-6-phosphate dehydrogenase deficiency.

IgA lambda multiple myeloma.

This case was presented at the Medical Case Conference.

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

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