Clinical Problem-Solving

True, True, and Related

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

A 51-year-old woman was admitted to a community hospital with a six-week history of progressive shortness of breath. She had initially noted dyspnea when climbing stairs at work, and by the time of admission it prevented her from walking more than 4.6 m (15 ft).

The rate of progression and the functional impairment imply a serious disorder. Progressive congestive heart failure could explain this picture; bronchiolitis obliterans or hypersensitivity pneumonitis could also proceed at this pace. New-onset asthma or chronic obstructive pulmonary disease is not likely to progress at this rate. Six weeks is too long for typical community-acquired pneumonia, but other infections — such as tuberculosis or histoplasmosis — could proceed at this tempo. I would also consider severe anemia, a gradually accumulating pleural effusion, or pulmonary hypertension.

The patient reported no fever, chills, weight loss, or night sweats. She had not had dizziness, chest pain, cough, orthopnea, paroxysmal nocturnal dyspnea, or lower-extremity edema. She had not traveled recently. Her medical history included mild anxiety and occasional episodes of stress-related headache. She worked as a respiratory therapist in a hospital, and she kept horses on her property in Oregon. She smoked half a pack of cigarettes per day and had done so for the previous 30 years. She reported that she did not use alcohol or illicit drugs. She used no prescription medications but took echinacea, ginseng, glucosamine, and a multivitamin daily. Because of her symptoms, she had begun to take St. John’s wort and valerian two weeks before admission.

The absence of other symptoms and the negative history suggest that the underlying disorder may not be primarily cardiac or pulmonary. As a respiratory therapist, the patient is likely to be exposed to aerosolized medications and air-borne pathogens. Her 15-pack-year history of smoking is unlikely to have caused severe obstructive lung disease. Given that she takes a number of herbal medications, I wonder whether they are causing organ dysfunction or hemolysis. Although anxiety, headache, and palpitations may all be unrelated to her primary disorder, common conditions such as hyperthyroidism and rare conditions such as pheochromocytoma should be considered.

At this point, I am uncertain of the mechanism of the patient’s dyspnea. I wonder whether either an environmental exposure or herbal toxicity might be responsible. Despite the absence of symptoms other than dyspnea, my physical examination would be focused on the cardiovascular system and the lungs.
The patient was a thin woman who appeared fatigued. Her temperature was 36.4°C, her blood pressure was 148/72 mm Hg, her resting heart rate was 108 beats per minute, and her respiratory rate was 20 per minute. The oxygen saturation was 98 percent while she was breathing room air. There were no orthostatic changes in either blood pressure or pulse. Both palpebral conjunctivae were pale. She had no jugular venous distention or lymphadenopathy. Except for tachycardia, the remainder of the physical examination, including the heart and lungs, was normal. A stool sample was negative for occult blood.

Because there is no clear clinical evidence of cardiac or pulmonary disease, anemia is my leading consideration. The pale conjunctivae, resting tachycardia, and dyspnea on exertion are all consistent with a severe anemia that has developed over a period of several weeks. Anemia-related symptoms are determined by the degree of anemia, the rate of development, and the underlying cardiopulmonary fitness of the patient. A remarkably low hemoglobin concentration can be tolerated if there is adequate time for homeostatic mechanisms such as increased cardiac output to compensate for the decreased oxygen delivery to the tissues. There is no jaundice, hepatosplenomegaly, lymphadenopathy, or evidence of other types of cytopenia (e.g., petechiae) — findings that would be clues to a cause, such as hemolysis, toxic effects on bone marrow, or bone marrow infiltration.

I am particularly interested in a complete blood count, red-cell indexes, a reticulocyte count, and a peripheral-blood smear. Although I strongly suspect that the patient has anemia, I would still order chest radiography, electrocardiography, and measurement of arterial blood gases — studies that I routinely order for patients with severe dyspnea.

The results of laboratory tests showed a hemoglobin level of 7.3 g per deciliter and a hematocrit of 20.5 percent. The mean corpuscular volume was 93 µm$^3$. The white-cell count was 6700 per cubic millimeter with a normal differential count. The platelet count was 149,000 per cubic millimeter. Values for electrolytes, serum creatinine, blood urea nitrogen, and protein were normal, as were the results of liver-function tests, coagulation studies, cardiac-enzyme measurements, and urinalysis.

The low hemoglobin level probably accounts for the patient’s exertional dyspnea and compensatory tachycardia. In the evaluation of a normocytic anemia, a crucial piece of laboratory information is the reticulocyte count. An elevated count suggests hemorrhage, which I have no reason to suspect in this case, or hemolysis. A low reticulocyte count suggests a disease that originates in the bone marrow. The mean corpuscular volume may be normal when distinct disease processes simultaneously cause a microcytic and a macrocytic anemia.

Conditions such as anemia of chronic disease or anemia of renal failure are ruled out by the absence of laboratory and clinical evidence (and these conditions usually do not cause anemia of the severity found in this patient). Given that nothing points to a systemic disease, I am focusing on the hematologic system. Acquired severe anemia could be explained by pure red-cell aplasia or myelodysplasia; the low-normal platelet count is consistent with the latter. Although the mean corpuscular volume is frequently elevated in patients with myelodysplasia, normocytic anemia may also occur. I am left wondering about an external factor in this patient, particularly her use of herbal medications. Perhaps one of the herbs has caused hemolysis or has had toxic effects on the bone marrow. I favor the latter possibility because of the borderline platelet count and the normal level of bilirubin, which is often elevated with hemolysis.

The electrocardiogram showed sinus rhythm at 99 beats per minute without evidence of ischemic changes. A chest radiograph (Fig. 1) showed mild hyperinflation and a possible fullness in the anterior mediastinum.

The patient reported no melena, hematochezia, or hemoptysis. She was perimenopausal, having skipped three menstrual periods in the previous six months. Her last menstrual period, two weeks before admission, had very light flow. She did not bruise easily or have bleeding gums. Her family history was negative for bleeding diathesis. She recalled having had a normal hematocrit in tests performed approximately two years before admission.

Can an anterior mediastinal mass account for the patient’s severe dyspnea? Although mediastinal masses can directly compress the trachea and cause dyspnea, I doubt that this is occurring, because the
Rapid progression of her symptoms is not consistent with the slow growth of most such masses. Moreover, there is already a plausible explanation for the dyspnea—severe anemia—that itself requires explanation.

Can the presence of normocytic anemia and of an anterior mediastinal mass be related? The answer is yes, but with a caveat. First, the chest radiograph showed “a possible fullness” (one that would be very easy to miss on casual inspection of the radiograph), rather than a definitive mass; confirmatory imaging with computed tomography (CT) is necessary. Second, this discovery could be incidental and have no bearing on the case; that is to say, the mass and the anemia might be true, true, and unrelated. Many mediastinal masses are incidental findings on radiographs. The common anterior mediastinal masses are thymoma, lymphoma, germ-cell tumor, and substernal goiter. Thymoma merits serious consideration owing to its association with pure red-cell aplasia. A lymphoma could certainly involve the bone marrow or cause an immune-mediated hemolysis. The mass could be a substernal goiter, which is usually a multinodular gland. A very remote possibility would be the combination of Graves’ disease and a coexisting immune disorder such as autoimmune hemolytic anemia or pernicious anemia.

Further evaluation of the normocytic anemia is required, including measurement of the reticulocyte count and a review of the peripheral-blood smear. The evaluation of the anemia should proceed in parallel with the imaging of the mediastinum.

The peripheral-blood smear showed normal red-cell morphologic features. The red-cell distribution width was 12.8 percent (normal range, 11.5 to 15.0), and the other red-cell indexes were normal. The ferritin level was 203 ng per milliliter. The serum haptoglobin, lactate dehydrogenase, vitamin B₁₂, and methylmalonic acid levels were normal. The results of serum protein electrophoresis were also normal. The absolute reticulocyte count was zero (which was confirmed by a subsequent measurement).

The reticulocyte count is the smoking gun. Because the patient has a hypoproliferative anemia, hemolysis and hemorrhage are very unlikely. The normal ferritin and vitamin B₁₂ levels, the normal red-cell distribution width, and the normal peripheral-blood smear confirm that this anemia is not a confluence of microcytic and macrocytic disorders. The low reticulocyte count focuses my attention on disorders of erythropoiesis. These disorders can develop in the presence of a substrate deficiency (e.g., of iron), a lack of erythropoietin, or diseases of the bone mar-
row that encompass primary disorders (aplasia or dysplasia) or the secondary effects of drugs, toxins, infections, and tumors.

The complete absence of reticulocytes is notable among the hypoproliferative anemias and suggests a total arrest in erythropoiesis. This finding is most compatible with pure red-cell aplasia, which is my leading diagnosis. Bone marrow biopsy is essential in order to make this diagnosis and to rule out other causes. The patient’s age and the borderline low platelet count make myelodysplasia a particular concern, although the complete absence of reticulocytes is not characteristic of myelodysplasia.

I would perform a bone marrow biopsy, with the expectation of seeing few or no erythroblasts with normal myeloid cells and megakaryocytes. I would also be very interested to learn whether a thymoma is seen on further imaging of the chest. Given the patient’s severe symptoms, I would also give her a transfusion of packed red cells.

Two units of packed red cells were transfused. A CT scan of the chest obtained without the administration of contrast material (Fig. 2) revealed a lobulated soft-tissue mass, 4 by 5 by 6 cm, in the anterosuperior mediastinum.

It remains conceivable that the mediastinal mass is a lymphoma (which can be associated with pure red-cell aplasia) or that its presence is unrelated to the anemia (which might then be explained by a toxic effect of herbal medication on the bone marrow), but these are remote possibilities. An anterior mediastinal mass in a patient with erythrocyte hypoplasia is a thymoma until proved otherwise.

Surgical resection revealed a hard mass, 9.0 by 5.5 by 4.5 cm, that involved the entire thymus and was adherent to the brachiocephalic vein, the superior vena cava, the right lung, and the pericardium. On pathological examination, it was identified as a thymoma of mixed cell type with extracapsular extension into the pericardium and right pleura. A bone marrow biopsy performed during surgery revealed hypocellularity with rare erythroid precursors, was consistent with pure red-cell aplasia. Adjuvant radiation therapy was administered.

At a follow-up visit one year later, a CT scan of the chest showed no evidence of recurrence. The hematocrit was normal.
confronted with an unexpected finding during the course of a diagnostic evaluation and are forced to decide whether the new information is germane to the chief symptom or is an unrelated finding.

How do physicians handle unanticipated findings? New clinical data are usually interpreted in the context of the working hypothesis at the point in the diagnostic process when the discovery is made. In this case, when the mass was discovered, the discussant was already contemplating the causes of normocytic anemia, suspecting a bone marrow disorder or hemolysis. Among the plausible unifying diagnoses was pure red-cell aplasia due to a thymoma, but autoimmune hemolysis and bone marrow infiltration due to lymphoma were also under consideration. The results of the reticulocyte count further refined the differential diagnosis and supported the discussant’s hypothesis that a thymoma was present.

Physicians frequently seek a unifying diagnosis, in part because we seek parsimony — the simplest possible explanation of all findings — in the working diagnoses that we generate. Additional criteria used in verifying hypotheses are adequacy (the ability to account for all findings and agreement with previous elemental hypotheses) and coherence (consistency with known pathophysiology). Coherence usually requires that a number of common-sense criteria for causality be met (e.g., the cause and effect must be related in time, space, intensity, and magnitude), but often, simply the experience or knowledge of the clinician verifies an association. This was the case in this exercise, in which the discussant had knowledge of the connection between pure red-cell aplasia and thymoma. When unexpected information is presented, we conduct an internal check against these criteria — parsimony, adequacy, and coherence — and if they are satisfied, we incorporate the new findings into our working diagnosis. If the new information fits, we work with it. If a major inconsistency is found, we either revise the working diagnosis or consider the findings to be true, true, and unrelated.

Thymoma is an uncommon condition, with an incidence of approximately 0.13 case per 100,000 population. It is, however, the most common tumor of the anterior mediastinum, accounting for 20 percent of all mediastinal tumors. Thymomas are typically characterized by indolent progression and relatively benign histologic features. However, they often invade local structures and in rare cases can metastasize. About half of thymomas are detected incidentally in asymptomatic patients. Other patients present with symptoms that result from the effect of a thoracic mass or with a paraneoplastic syndrome, such as myasthenia gravis, pure red-cell aplasia, or hypogammaglobulinemia.

This patient presented with dyspnea that was attributable to an acquired normocytic anemia with profound reticulocytopenia. In the presence of a normal leukocyte count and a normal platelet count, this is highly suggestive of pure red-cell aplasia. Acquired pure red-cell aplasia may be a primary hematologic disorder, or it may be due to cancer, infection, autoimmune disease, or the use of prescribed drugs. Typically, the bone marrow shows normal granulocyte maturation and has a normal megakaryocyte count, with a virtual absence of mature erythroid cells. The condition most commonly associated with pure red-cell aplasia is thymoma; 10 to 15 percent of patients with pure red-cell aplasia have an associated thymoma. Although the precise pathogenesis of pure red-cell aplasia in thymoma is unclear, the arrest of erythrocyte maturation appears to occur at several different stages in erythrocyte differentiation, and both cellular and humoral autoimmune mechanisms have been reported.

Surgical resection is the mainstay of treatment for thymoma and leads to the remission of pure red-cell aplasia in 30 percent of patients. This case discussion highlights the importance of not dismissing incidental findings as unrelated without thoughtful consideration of how they may be related to other abnormalities. Although thymoma and pure red-cell aplasia can occur independently, the presence of one should prompt consideration of the other, as conditions that are “true, true, and related.”

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REFERENCES


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