CLINICAL PRACTICE

Exercises in Clinical Reasoning

Look No Further: An Exercise in Clinical Reasoning

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In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (**bold**). Additional commentary on the diagnostic reasoning process (*italics*) is integrated throughout the discussion.

A 64-year-old man presented to the emergency department (ED) with progressive dyspnea on exertion.

Ten days earlier, he was standing near a commercial oven when he began to feel hot, had a sudden loss of consciousness, fell, and struck his nose on a table. There was no shaking or convulsions, tongue biting, or bowel or bladder incontinence. He awoke promptly and presented to the ED, where he denied vertigo, tinnitus, palpitations, or prior syncopal episodes. His vital signs (including orthostatic blood pressure), physical examination, complete blood count, chemistry panel, EKG, and CT of the head were normal. He was discharged from the ED with a diagnosis of vasovagal syncope.

He returned to the ED 10 days after the syncopal episode with exertional dyspnea. He had been experiencing the dyspnea for 3 days. He denied chest discomfort, orthopnea, paroxysmal nocturnal dyspnea, cough, or wheezing. He was able to walk only a few feet before becoming dyspneic. He reported fatigue and a 30-pound unintentional weight loss over the past year, but he denied night sweats or fever. Syncope had not recurred.

The major features of this patient's illness are syncope and dyspnea on exertion. Both symptoms can be explained by conditions that cause hypoperfusion or decreased oxygenation of the coronary and cerebral circulations such as hypotension, vasoconstriction, or anemia. Of these conditions, only anemia

is like to persist over 1 week, but his CBC was normal. A unifying diagnosis for syncope and dyspnea separated in time is not immediately apparent.

Separating the two complaints, categories of diseases that cause dyspnea include pulmonary, cardiac, and other (e.g., anemia and thyroid disease). Dyspnea on exertion in an elderly man warrants consideration of coronary artery disease (CAD), although his fatigue and weight loss suggest that we may be observing an acute manifestation of a chronic systemic illness such as an indolent infection, autoimmune disease, cancer, or chronic obstructive pulmonary disease.

With syncope, considerations include neurocardiogenic, orthostatic, cardiogenic, and neurogenic causes. Vasovagal (neurocardiogenic) syncope is suggested by the prodrome of warmth before loss of consciousness. Orthostatic hypotension is common, although there is no suggestive history such as lightheadedness upon standing. Arrhythmias may be preceded by palpitations but more commonly have no warning signs; this possibility cannot be excluded by a single normal EKG. Careful auscultation to exclude aortic stenosis is warranted, but syncope due to aortic stenosis typically occurs with exertion. There was no report of seizure-like activity or history suggesting a postictal state.

When faced with two distinct complaints (e.g., dyspnea and syncope), clinicians will search for a diagnosis that explains both phenomena or will approach each issue individually in the hope of finding a single unifying explanation. The discussion approaches the differential diagnosis by thinking of physiologic mechanisms that account for dyspnea and syncope. Because a unifying diagnosis is not apparent, he analyzes syncope and dyspnea in a serial manner. Constitutional symptoms like weight loss are discordant for many of the common cardiopulmonary conditions that would easily explain both syncope and dyspnea.

The patient's past medical history included hypertension for which he was prescribed (but was not taking) amlodipine. He had undergone a normal stress echocardiogram 6 months earlier when he experienced chest discomfort. He took ibuprofen and aspirin intermittently for musculoskeletal pain. An uncomplicated cholecystectomy had been performed 4 months earlier for biliary colic. His mother died at age 89 from a myocardial infarction, his

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father died from colon cancer at age 88, and a sister had breast cancer at an unknown age. He worked as a baker and lived alone in an apartment. He consumed one glass of wine weekly and did not use tobacco or illicit drugs. The vital signs were temperature 37 °C, respiratory rate 16 breaths/min, pulse 97 beats/min, blood pressure 145/66 mmHg on the right arm and 143/69 mmHg on the left arm (no orthostatic changes), and oxygen saturation of 93 % on room air. He was alert, oriented, and in no distress. A 1-cm soft, mobile, non-tender lymph node was palpable in both the left anterior cervical chain and the left axilla. The cardiovascular examination was normal. Lungs were clear to auscultation. The abdomen was soft, non-tender, and non-distended without hepatosplenomegaly. A detailed neurologic exam revealed no deficits. There were no rashes, edema, or joint abnormalities.

The heart rate of 97 beats/min is abnormal when resting comfortably. There is also a wide pulse pressure, which can be seen with aortic insufficiency (AI), profound anemia, or atherosclerosis, each of which could account for dyspnea on exertion. The stress test from 6 months ago gives some reassurance that ischemic heart disease is unlikely. AI also appears unlikely, as there were no aortic abnormalities noted on his echocardiogram or his current cardiac examination. There is also no physical evidence of congestive heart failure. Without features of cardiopulmonary disease, anemia remains an important consideration.

The lymphadenopathy increases the likelihood of infection, malignancy (especially given the family history), or autoimmune disease as a cause of the dyspnea. Given the history of fatigue and weight loss, I would consider the possibility of lymphoma, metastatic carcinoma, or human immunodeficiency virus (HIV). Lymphadenopathy could be a harbinger of underlying infections such as tuberculosis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), or disseminated fungal disease. Inflammatory disorders such as sarcoidosis may also present with dyspnea and lymphadenopathy. The syncope appears to remain unrelated and does not explain the current signs and symptoms.

Although the syncope appears to be unrelated, the clinician does not disregard it, but rather leaves it aside to prioritize the readily available data pertinent to the dyspnea and his hypothesis of anemia. A small mobile lymph node may be a relatively normal finding. The clinician however, has interpreted this information as important given the context of the patient's fatigue and weight loss. Two non-contiguous sites of lymphadenopathy likely strengthen his suspicion that the lymphadenopathy is part of the underlying syndrome and not incidental. Given the lack of cardiopulmonary findings, the clinician suspects that anemia could cause the dyspnea and be related to the lymphadenopathy.

The leukocyte count was 10,000/mm³ (47 % neutrophils, 36 % lymphocytes, 11 % monocytes, 2 % eosinophils, 0 % basophils), platelets 259,000/mm³, and hemoglobin 6.7 g/dL (with hemoglobin of 14.3 g/dL 10 days earlier), with a

mean corpuscular volume (MCV) of 129 fL, red cell distribution width (RDW) greater than 30 % (normal: 11–14.5 %), and absolute reticulocyte count 0.40 (normal: 0.02–0.11). Iron was 38 µg/dL, total iron binding capacity 228 µg/dL, iron saturation 17 %, ferritin 614 ng/mL, vitamin B12 212 (normal: 193–986) pg/mL, and a red blood cell folate level of 868 ng/mL (normal: 155–700 ng/mL). The chemistry panel was normal, as were aminotransferases, alkaline phosphatase, albumin, and total protein. Total bilirubin was 4 mg/dL, direct bilirubin 0.5 mg/dL, and indirect bilirubin 3.5 mg/dL. Thyroid-stimulating hormone level was normal. Prothrombin and activated partial thromboplastin times were normal. Fecal occult blood testing was negative.

The profound anemia is the most likely cause of the patient's dyspnea. Acute gastrointestinal bleeding is unlikely because he did not have melena or hematochezia, and testing of his stool for occult blood was negative. The elevated indirect bilirubin, MCV, and RDW favor acute hemolysis. Haptoglobin, lactate dehydrogenase (LDH), reticulocyte count, and peripheral smear would verify the working diagnosis of acute hemolysis.

Hemolysis is caused by congenital and acquired etiologies; given his age, the latter are more likely, and include immune hemolysis, microangiopathic hemolysis (such as disseminated intravascular coagulation [DIC] and thrombotic thrombocytopenic purpura [TTP]), acute infections (like malaria or babesiosis), or medications. TTP and DIC are unlikely because of the absence of thrombocytopenia, although evaluation of a peripheral smear to rule out the presence of schistocytes is required to exclude these diagnoses. The patient is not on any medications commonly associated with hemolysis. More likely possibilities include autoimmune hemolysis and, given the presence of lymphadenopathy and the high-normal white blood cell count, a subacute infection or a lymphoproliferative disorder.

I am uncertain as to how syncope fits into this picture, as the patient was not anemic at the time of the syncopal episode, so I will continue to leave it aside for now, focus on the active issues of anemia and dyspnea, and return to syncope later.

Clinicians often prioritize solving a more specific problem (e.g., dyspnea) in the hope that it will shed light on other problems that have a greater number of possible diagnoses. In order to reduce the cognitive load of two major chief complaints, the clinician has separated the syncope and dyspnea, processing them in a serial manner. Without a clear, unifying diagnosis, the clinician focuses on the anemia while setting the syncope aside.

Pro brain-type natriuretic peptide was 226 pg/mL (normal: 0–125 pg/mL) and troponin 0.024 ng/mL (normal: <0.06 ng/mL). A chest x-ray revealed hypoinflated lungs with a new linear opacity in the right lower lobe. The EKG was normal. LDH was 990 u/L (normal: 117–224 u/L) and haptoglobin was <8 mg/dL (normal: 30–200 mg/dL). Peripheral blood smear revealed a decreased number of erythrocytes, microspherocytes with marked anisopoikilocytosis (Fig. 1), numerous polychromatophilic

Figure 1 Peripheral blood smear shows microspherocytes (red arrowheads) with marked anisopoikilocytosis, numerous polychromatophilic cells, nucleated red blood cells, and red cell agglutination (black arrows). There is also left-shifted myeloid maturation (green star).

cells, nucleated red blood cells, and red cell agglutination. There was left-shifted myeloid maturation and occasional circulating immunoblasts. There were no schistocytes. Anti-nuclear antibody (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Viral hepatitis panel was negative. Serum protein electrophoresis (SPEP) was negative for the presence of a monoclonal gammopathy.

A contrast CT of the neck revealed jugular, parotid, submental, submandibular, subpectoral lymphadenopathy. A contrast CT of the chest revealed axillary lymphadenopathy, with the largest lymph node conglomerate measuring 4.1×1.7 cm in the left axilla (Fig. 2). A subsegmental acute pulmonary embolism was noted in the right lower lobe along with bilateral axillary and subpectoral lymphadenopathy. There was also mild mediastinal lymphadenopathy and a small pulmonary nodule along the posterior pleura of the left lower lobe. A contrast CT of the abdomen revealed splenomegaly and borderline enlargement of the bilateral external iliac lymph nodes.

Figure 2 Arrow: Coronal image of an enlarged homogenous enhancing axillary lymph node measuring 4.1×1.7 cm.

The constellation of laboratory and peripheral smear findings point to hemolysis as the culprit of the patient's anemia. The direct antiglobulin test (DAT) can distinguish immune and non-immune hemolytic anemia; the former often causes microspherocytosis. The leukoerythroblastic (marked left shift plus early erythrocyte precursors) picture on the peripheral smear is consistent with a brisk hemolytic process, although it can also be seen with processes that infiltrate the bone marrow. The red cell agglutination and reticulocytosis likely explain the markedly elevated MCV and RDW (as clumped RBCs and microspherocytes were likely counted as individual RBCs by the CBC analyzer), and typically signifies IgM autoantibodies coating the surface of the RBCs in cold agglutinin disease, a form of autoimmune hemolytic anemia (AIHA).

Diffuse lymphadenopathy with splenomegaly can be caused by malignancy (e.g., lymphoproliferative disorders), infection (e.g., HIV, CMV, EBV, and tuberculosis), and autoimmunity. Lymphoproliferative disorders and certain infections (i.e., EBV, HIV, and *Mycoplasma pneumoniae*) are also associated with the production of cold agglutinins. The hemolytic anemia, diffuse lymphadenopathy, splenomegaly, and pulmonary embolism suggest an underlying lymphoproliferative disorder.

It is unlikely that the subsegmental pulmonary embolism explains the syncopal episode 10 days before, as systemic hypotension is seen with central or more extensive pulmonary emboli. Anemia from acute blood loss could explain the syncope; however, evidence for this hypothesis is lacking. The anemia and pulmonary embolism could explain the dyspnea, but do not account for syncope.

As more specific findings accumulate—hemolysis, unequivocal lymphadenopathy, and pulmonary emboli—the discussant faces the complex task of determining their interconnectedness and the relevance of each to the two main presenting complaints. The discussant now has two potential explanations for dyspnea—anemia and pulmonary embolism—although both are insufficient to explain the syncope.

The patient received a transfusion of two units of packed red blood cells, and intravenous heparin was initiated. A DAT (Coombs test) was positive for both anti-IgG and anti-C3. The cold agglutinin titer was 1:64. *Mycoplasma* IgM was negative. Beta-2 microglobulin was 4.8 mg/dL (normal: 1–2.2 mg/dL), and a glucose-6-phosphate dehydrogenase (G6PD) enzyme level was normal. Lupus anticoagulant was negative. Excisional biopsy of a left axillary lymph node revealed mild follicular hyperplasia without monotypic B-cell or abnormal T-cell populations (Fig. 3). There was no immunophenotypic evidence of lymphoma. Flow cytometry revealed no abnormal immunophenotypes.

AIHA that is associated with both an IgG- and C3-positive DAT is termed mixed AIHA.¹ It is most commonly associated HIV infection, although less common causes include non-

Figure 3 Excisional biopsy of a left axillary lymph node demonstrated mild follicular hyperplasia. Immunohistochemistry revealed no monotypic B-cell or abnormal T-cell populations (i.e., no evidence of a lymphoproliferative disorder).

Hodgkin's lymphoma, systemic lupus erythematosus (SLE), and Evans syndrome.^{1,2} Lymphoma is unlikely given the result of the excisional biopsy, and the pre-test probabilities of both SLE and Evans syndrome are low given the negative ANA and the lack of thrombocytopenia, respectively. In light of the known association between mixed AIHA and HIV, as well as the diffuse lymphadenopathy, an HIV test should be obtained.

The HIV antibody test was positive. The CD4 count was 544/mm³, and the viral load was 441,380 copies/mL. Although risk factors for HIV had been assessed upon admission, the patient later revealed that he had multiple male and female sexual partners for many years. An HIV test 2 years earlier had been negative. Additional testing revealed a positive rapid plasma reagin with a reactive *Treponema pallidum* antibody. QuantiFERON-TB Gold was not detected. The patient was diagnosed with late latent syphilis, pulmonary embolism, and warm and cold agglutinin autoimmune hemolytic anemia (mixed-type AIHA) with HIV. He was treated with penicillin, prednisone, and low molecular weight heparin. Dolutegravir and emtricitabine-tenofovir were started near the end of his hospitalization. At the time of discharge he was asymptomatic. Six months later he felt well; he had no dyspnea, and syncope had not recurred.

The cause of his syncope remains unclear. Because it was an isolated event, and a cause for the dyspnea is evident, the syncope does not mandate further testing. It is possible that it was due to a vasovagal reaction induced by the hot oven.

Now that the cause of the patient's dyspnea has been established, the clinician must decide whether further testing for causes of syncope is warranted. The failure to detect a life-threatening or readily treatable cause of syncope after an extensive evaluation and the knowledge that up to one-third of patients have no diagnosis for isolated syncope may have

dissuaded the discussant from further testing. Vasovagal syncope is plausible, but given the elapsed time, it is an untestable hypothesis.

COMMENTARY

This patient initially presented with syncope of uncertain etiology. When he returned with progressive dyspnea, the clinician faced a new chief complaint and the challenge of correlating syncope and dyspnea. The clinical reasoning literature largely describes the approach to a single complaint, and little has been written about what clinicians do when they are confronted with two major problems. Experienced clinicians instinctively navigate this territory, but may lack a framework for instructing trainees to do the same.^{3,4} Providing the answer to the following three questions may provide guidance:

- 1) **When do I separate the two chief complaints?** If one diagnosis readily explains both chief complaints, then both problems are processed in parallel (simultaneously). If not, the clinician processes each complaint in a serial (sequential) fashion.⁵ For example, if a patient reports cough and fever, these complaints are processed in parallel, leading the clinician to suspect respiratory infection (e.g., pneumonia). In this case, a unifying diagnosis for syncope and dyspnea was not immediately apparent, so the clinician separated them and processed them in a serial manner.
- 2) **Which complaint is prioritized?** Clinicians tend to prioritize the complaint that has more readily available data, has a more limited range of possibilities (e.g., choosing dysphagia over fatigue), or is more life-threatening. The other complaint is then displaced for processing at a later time. In this case, since the dyspnea was acute and could plausibly be explained by life-threatening illnesses (e.g., myocardial infarction), the discussant prioritized it. He briefly considered the differential diagnosis of syncope, but then placed it aside, as it had occurred 1 week earlier and had already been thoroughly evaluated, which made the likelihood of an acutely life-threatening condition low.
- 3) **When do the diagnostic paths cross?** Once an endpoint for one complaint is reached, with either a diagnosis or a roadblock, the clinician returns to the sidelined complaint and determines whether it fits with the established diagnosis or triggers a new line of thought (e.g., a separate diagnosis). Had the CT scan shown a saddle pulmonary embolism, the discussant would have likely attributed the syncope to it and would have merged the two paths at that point. Since the mechanism for the syncope remained unexplained even as other findings—HIV, AIHA, subsegmental pulmonary embolism—emerged, the clinician decided that the syncope likely had an alternative explanation and did not merge the two complaints.

These three questions outline the basic cognitive checkpoints along the road to resolving one of medicine's most familiar dilemmas: will my patient's problems be solved by honoring Occam's Razor (one diagnosis for multiple complaints) or Hickam's dictum (more than one diagnosis for multiple complaints)? The discussant thoughtfully addressed these questions and settled on the latter. In his final synthesis, he also grappled with another of medicine's most universal quandaries: uncertainty.⁶ In the end, he could not explain the presenting complaint of syncope; only a provisional diagnosis could be offered. This concession highlights one of the clinician's most important skills: knowing when to look no further.

KEY LEARNING POINTS

- In autoimmune hemolytic anemia (AIHA), autoantibodies are produced against RBC antigens, resulting in premature destruction.⁷
- Cold AIHA is usually caused by IgM antibodies (cold agglutinins) that bind to erythrocyte antigens and also fix and activate complement (including C3) at temperatures below 37.0 °C (99.0 °F).⁷
- Warm AIHA is caused by IgG antibodies that bind to erythrocyte Rh antigens at 37.0 °C (99.0 °F), usually without complement binding.⁷
- Warm AIHA is characterized by a positive direct antiglobulin test (DAT) due to the presence of anti-IgG and absent or weak anti-C3 on the surface of erythrocytes; the opposite pattern is suggestive of cold AIHA. Spherocytes on the peripheral smear are seen in AIHA of any type, although they are most commonly seen in warm AIHA.⁷

- This patient's studies demonstrated agglutination of erythrocytes with a positive DAT due to both anti-IgG and anti-C3 that was associated with a positive cold agglutinin, indicating a mixed AIHA (which is associated with HIV).^{1, 7}

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Compliance with ethical standards:

Conflict of interest: All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. The authors declare that they do not have a conflict of interest.

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