CLINICAL PRACTICE
Exercises in Clinical Reasoning

Diagnostic Scheming

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J Gen Intern Med 30(12):1874–8
DOI: 10.1007/s11606-015-3478-0

A 27-year-old man presented to urgent care with 6 months of worsening fatigue and dyspnea on exertion.

Six months of progressive dyspnea on exertion (DOE) in a young man is worrisome. I would like to know how this is affecting activities in his life, what he thinks is causing it, and what triggered him to seek care now. DOE raises the prospect of organ-specific maladies as well as systemic diseases. Organ-specific concerns include heart, lung, and blood disorders. I would consider coronary disease due to vasospasm from recreational drugs such as cocaine. Pulmonary parenchymal abnormalities including indolent infection or pulmonary vascular disease could also explain the patient's DOE. Abnormalities in oxygen-carrying capacity such as profound anemia could present this way. Systemic infections such as Epstein–Barr or occult human immunodeficiency virus (HIV) are also possible.

With minimal information the discussant creates a problem representation, a concise summary of the patient's clinical findings, leading him to consider a framework or scheme for DOE (e.g. "heart, lung, and blood disorders"). Using inductive reasoning, a clinician applies a diagnostic scheme to a symptom, physical exam abnormality, laboratory value, or image finding.[1] *A scheme incorporates a decision tree approach that guides clinicians as they incorporate new data to build understanding of the entity. It is helpful, when pattern recognition is insufficient or as additional data emerges, to expand the scope of current diagnostic possibilities.*[2] *Through repeated encounters with an illness or symptom, a clinician's diagnostic scheme grows, particularly if grounded in intentional reflection of the outcomes of past decisions. The diagnostic scheme evokes illness scripts that match the problem representation (see* ***Table below****). When a teaching physician explicitly articulates diagnostic schemes, trainees learn well-developed approaches to common chief complaints such as DOE, enhancing their own diagnostic reasoning skills.*

Term	Definition	Example
Diagnostic Scheme	A conceptual framework or cognitive aid that assists the clinician's approach to an abnormal finding or test result.	When thinking about a patient with vision loss, the first branch point is to determine whether it is monocular or binocular.
Illness Script	A clinician's narrative representation of a disease incorporating epidemiology, clinical presentation, relevant diagnostic tests, prognosis, and treatment. Refined with time, experience, and reflection.	Giant cell arteritis (GCA): *patients over 50 with subacute headache, jaw claudication, proximal muscle weakness, vision loss, and markedly elevated erythrocyte sedimentation rate; steroids must be given promptly to preserve vision.*
Problem Representation	A "one-liner" or concise abstraction of a patient's key clinical findings.	*An elderly woman with subacute headache, myalgias, and vision loss.* This problem representation activates the illness script for GCA.

He reported 6 months of lightheadedness and night sweats, but denied weight loss, fever, and chills. He had previously hiked miles, but was now limited to two blocks, secondary to fatigue and DOE. He denied orthopnea and lower extremity edema. Medications included a daily multivitamin and HH550 (hair growth supplement containing Vitamin A and B complexes). He moved from Arkansas to San Francisco four months earlier and lacked stable housing. He grew up on a cattle farm and had a 10-pack-year history of smoking tobacco but quit four months prior. He rarely drank alcohol but smoked marijuana once per week. He was divorced and not sexually active. He worked as a cook in a grocery store.

This additional history expands my focus from the cardiopulmonary system to more systemic ailments including indolent bacterial, viral, and fungal infections. Being raised on a cattle farm brings to mind pathogens such as *Coxiella* and *Brucella*. Several bacterial infections, including subacute bacterial endocarditis, may present with a chronic progressive picture. Endemic fungi such as *Histoplasma* should be

Received November 25, 2014
Revised March 16, 2015
Accepted July 9, 2015
Published online August 26, 2015

considered in someone from Arkansas. Occult HIV with an opportunistic infection such as pneumocystis pneumonia could present this way. I am unfamiliar with his hair supplement, so I would perform an online search for possible side effects.

The discussant reframes the problem representation to include the patient's exposure to farm animals, which allows him to expand and focus the differential diagnosis. His diagnostic scheme for infection as "bacterial, viral, and fungal" prompts him to list examples and serves as a checklist to ensure common diseases are not overlooked. He recognizes his limitations and the importance of accessing additional online resources.

On physical examination, temperature was 37 °C, blood pressure 137/78 mmHg, heart rate 98 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 100% on room air. He was comfortable and in no apparent distress. Conjunctivae were pale. Lymph node exam was normal. Cardiac exam was normal. Lungs were clear to auscultation. Abdomen was soft without hepatosplenomegaly. Rectal exam revealed brown stool that was hemoccult-negative. No rash was present.

Despite the normal oxygen saturation, I remain concerned about his DOE. He has borderline tachycardia and conjunctival pallor, so anemia is likely and may even be the central cause. With no obvious bleeding source, hemolysis must also be considered. I would order a complete blood count to confirm anemia and assess other cell lines. A urinalysis should be performed to look for evidence of hemolysis or active urine sediment, potential clues to a systemic inflammatory process.

Labs revealed white blood count of 6,100 mm^3 with normal differential, hemoglobin 4.5 g/dL, platelets 324,000/mm^3, and mean corpuscular volume (MCV) 61 fL. Absolute reticulocyte count was 94,000/μL (range 20,000–100,000/μL). Sodium was 139 mmol/L, potassium 4.1 mmol/L, chloride 104 mmol/L, bicarbonate 28 mmol/L, urea nitrogen 23 mg/dL, and creatinine 1.11 mg/dL. Liver and thyroid function tests were normal. Prothrombin time was 15.0 s, activated partial thromboplastic time 24.6 s, and international normalized ratio (INR) 1.2. Chest x-ray was normal.

We have a patient with chronic, progressive DOE and fatigue, few localizing physical findings, and profound hypoproliferative microcytic anemia. I approach anemia by first considering the reticulocyte count. A high reticulocyte count suggests acute blood loss or red blood cell (RBC) destruction, and reflects an appropriate bone marrow response to anemia. This patient has a normal or low reticulocyte count, arguing against acute blood loss or hemolysis, in which the bone marrow typically mounts a compensatory reticulocytosis within days. However, blood loss from a chronic process remains possible. Next I incorporate the MCV, which reveals marked microcytosis, highly suggestive of iron deficiency and, less likely, lead toxicity or thalassemia.

Given concern for iron deficiency, I would search for an occult bleeding source, while still considering processes that affect RBC production. The history did not reveal bloody stools, gross hematuria, hematemesis, hemoptysis, gum bleeding, or bruising. Normal platelet and leukocyte counts with a normal differential argue against bone marrow insufficiency, as does the low MCV. The absence of splenomegaly or abnormalities of other cell lines argues against sequestration.

The high normal creatinine is concerning. Absent history of gross hematuria, he fits the demographic for IgA nephropathy or focal segmental glomerular sclerosis.

The physician updates and revisits the problem representation, incorporating the relatively normal physical exam and profound anemia. After attributing the patient's symptoms to anemia, he explicates his diagnostic scheme for anemia. His first branch point is the reticulocyte count. Next he incorporates the MCV, which implicates iron deficiency as the likely culprit, while considering other causes of anemia to prevent premature closure.

The patient was hospitalized for further work-up of anemia. Serum iron was 14 μg/dL, ferritin 26 ng/mL, transferrin 380 mg/dL, and iron saturation 3%. Erythrocyte sedimentation rate was 20 mm/h and C-reactive protein was 11.5 mg/L. Lactate dehydrogenase was 228 U/L (range 100–190 U/L). Blood smear showed: anisocytosis 1+, microcytes 2+, hypochromatophilia 2+, polychromatophilia 1+, teardrop cells 1+, ovalocytes 1+, and rare schistocytes. Urinalysis showed: 1+ protein, 3+ blood, and 50–100 RBC per HPF. Spot urine protein-to-creatinine ratio was 0.9 and urine microalbumin-to-creatinine ratio was 656.9 mg/g.

The low reticulocyte count, low ferritin, low iron concentration, profound microcytosis, and peripheral smear are classic for iron deficiency anemia. In men, the most common cause is occult gastrointestinal bleeding. However, the urinary tract is a potential source of chronic blood loss given the microscopic hematuria. This could be explained by intrinsic renal disease such as IgA nephropathy, a kidney neoplasm such as renal cell carcinoma, or a structural lesion along the urinary collecting system. The urine protein-to-creatinine ratio indicates non-nephrotic-range proteinuria and suggests glomerular pathology. If the serum creatinine remains stable, I would obtain a computed tomography scan (CT) of the abdomen with contrast to evaluate for renal lesions and spin the urine to look for active urinary sediment.

Now hospitalized, this previously healthy patient is likely experiencing a spectrum of potentially distressing thoughts and feelings. To both establish a therapeutic connection and seek additional diagnostic clues, I would use a relationship-centered communication framework. Specifically, I would utilize the FIFE approach—elicit his **F**eelings (or Fears), ask for **I**deas about the underlying cause, learn how this illness is affecting his ability to **F**unction, and ascertain his **E**xpectations of me and of the care team.[3]

The physician interprets the laboratory results and searches for the source of blood loss. He quickly focuses on the organ system with the most striking abnormality—the kidney. He draws on principles of relationship-centered communication, including the FIFE schema.[3]

CT of abdomen and pelvis was unremarkable but showed irregularities at both lung bases. Spun urine sediment revealed no RBC casts or dysmorphic red cells. Upper endoscopy, colonoscopy, and cystoscopy were unremarkable.

Chest CT showed bilateral patchy ground-glass opacities (GGO), with indistinct central and centrilobular nodules in the upper lobes. Thin-walled cysts were noted in the right middle and lower lobes (Fig. 1).

Structural gastrointestinal and genitourinary abnormalities have been excluded as sources of chronic blood loss. With microscopic hematuria and diffuse GGO with pulmonary nodulosis and cysts, I am concerned about a pulmonary-renal syndrome. Despite the absence of dysmorphic red cells or RBC casts proteinuria and microscopic hematuria increase the probability of glomerulonephritis (GN) due to small-vessel vasculitis and move my thinking away from a systemic infection.

The differential diagnosis for GGO includes pulmonary interstitial hemorrhage, pulmonary edema, and protein or cellular infiltrates due to an infectious, inflammatory, cardiac, or toxic process. In a patient with suspected pulmonary-renal syndrome, the opacities likely represent pulmonary capillaritis and/or diffuse alveolar hemorrhage (DAH). Despite the relatively chronic presentation, DAH can activate suddenly, with dire consequences. Therefore, prompt pulmonary consultation for bronchoscopy is warranted. Kidney biopsy and serologic testing will often be needed to establish the specific etiology for a pulmonary-renal syndrome.

With pulmonary capillaritis and GN, the vasculitis must involve small vessels. Small-vessel vasculitides are typically classified into two categories: anti-neutrophil cytoplasmic antibody (ANCA)-associated and hypersensitivity vasculitides. The three main ANCA-associated vasculitides are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and, less commonly, eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome). Hypersensitivity vasculitides causing pulmonary-renal syndromes include Goodpasture's disease (GD) or secondary vasculitis in the setting of systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). I would query the patient about hemoptysis and other systemic symptoms such as rash, morning stiffness, or joint tenderness.

The discussant is most concerned about a pulmonary-renal syndrome and shares a diagnostic scheme for small-vessel vasculitis. He is very concerned about DAH and recognizes the need for subspecialty consultation to optimize timely diagnosis and treatment. He uses pathophysiologic reasoning to refine the differential diagnosis and direct further history.[4]

Upon further questioning, the patient denied joint or sinus symptoms, but recalled a non-blanching, non-pruritic erythematous rash over the anterior and posterior surfaces of his calves on two occasions within the previous 6 months (Fig. 2). He also reported intermittent frothy, dark urine and occasional specks of blood in his sputum associated with coughing after smoking marijuana.

DAH may present with self-limited episodes of trace hemoptysis. Massive bleeding is somewhat atypical, and roughly one-third of patients have no hemoptysis. The episodic dark

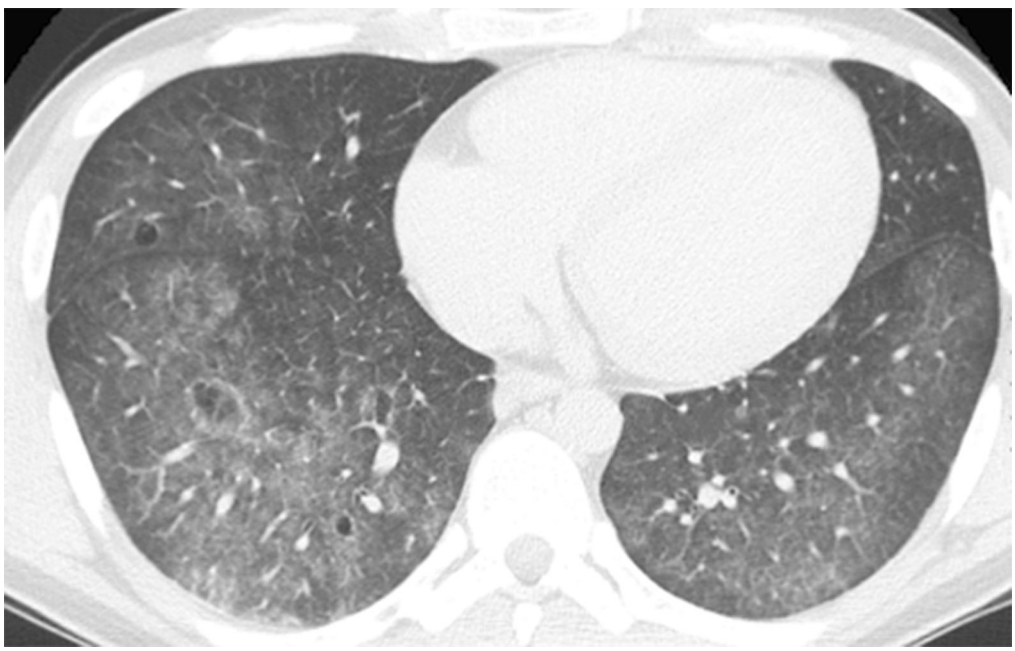

Figure 1. Chest CT showing diffuse patchy ground-glass opacities and cysts

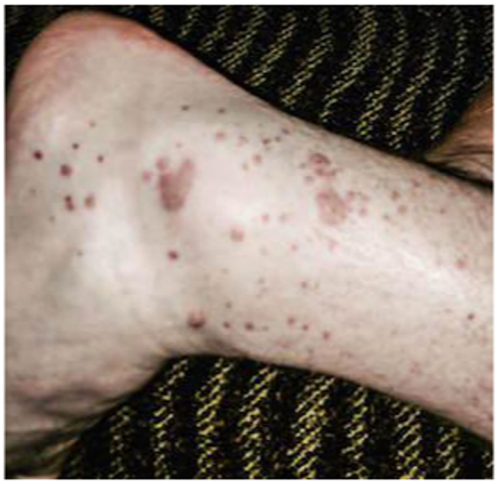

Figure 2. Photograph of the patient's previous rash, most likely representing palpable purpura

frothy urine suggests GN flares manifesting as gross hematuria with accompanying proteinuria. The non-blanching, non-pruritic erythematous rash is consistent with palpable purpura, which reflects extravasation of blood due to leukocytoclastic vasculitis of small cutaneous vessels.

We now have evidence of a chronic, progressive multi-organ process involving small vessels. This picture is most consistent with GD or ANCA-associated vasculitis, although biopsy and serologic testing are required to establish a diagnosis.

The discussant restates and refines the problem representation using knowledge of pathophysiology. This form of analytic reasoning and continuous refinement of the problem representation is a common strategy employed by expert clinical thinkers.

The patient was noted to have erythematous conjunctivae, prompting an ophthalmologic examination, which revealed episcleritis.

Episcleritis is a common complication of GPA. With episcleritis and pulmonary nodulosis, I favor GPA over GD, which is not associated with eye pathology.

Renal biopsy showed pauci-immune GN with 10–15 % focal necrotizing lesions with crescents, minimal interstitial fibrosis, and tubular atrophy. Serial bronchoalveolar lavage (BAL) demonstrated RBC count of 2700, 2850, and 3550 cells/cm^3. Cytology showed increased hemosiderin-laden macrophages. Myeloperoxidase antibody titer returned positive at 255.0 AU/ml. The patient was diagnosed with MPA and treated with pulse steroids followed by rituximab.

BAL confirms DAH, which occurs more commonly in MPA than GPA. Antibodies to myeloperoxidase are strongly associated with MPA and confirm the diagnosis in the setting of pauci-immune GN. I had focused on the pulmonary nodulosis and episcleritis, which nudged me toward GPA. However, chronic sinus pathology is characteristic of GPA, so its absence was a clue that that disorder was less likely.

The clinician performs a post-case cognitive autopsy, a useful way in which experts refine their diagnostic reasoning. By focusing on the impressive eye findings and pulmonary nodules, the discussant may have succumbed to the availability heuristic, which occurs when undue significance is attached to readily available or memorable information.[5] Anchoring on GPA may have led to confirmation bias, the tendency to focus on findings that support that diagnosis (pulmonary nodules and episcleritis), while neglecting findings that refute it (absence of sinus pathology).

Initially, the patient was reluctant to be hospitalized and hesitant about procedures and further testing. Given his uninsured status, he was worried about the cost of hospitalization and therapies. Due to financial concerns and a limited support system, he moved back to Arkansas to live near family. He agreed to receive initial treatment prior to moving.

The patient has a long road ahead. I remain concerned about his access to ongoing rheumatology care and long term health. Given his unstable housing situation and serious illness, I would build upon the FIFE framework to clarify his fears and concerns. To strengthen our partnership for the post-hospitalization phase, I would obtain his cell phone number and arrange close follow-up.

Using a complementary social framework and knowledge of small-vessel vasculitis, the discussant focuses on the challenges to longitudinal care in vulnerable, marginally housed patients. He highlights the importance of establishing follow-up, matching his level of concern for serious illness with sensitivity to the patient's unstable living circumstances.

DISCUSSION

Previous *Exercises in Clinical Reasoning* have emphasized the importance of illness scripts and problem representation.[6,7] Here we illustrate the diagnostic scheme, a cognitive framework that physicians hone over a lifetime with repeated experience of a given clinical problem (e.g. dyspnea).[1] The diagnostic scheme serves as a hierarchical checklist that prompts the clinician to search for illness scripts that fit the patient's problem representation. In this case, the discussant developed diagnostic schemes for DOE, hypoproliferative anemia, pulmonary infection, and small-vessel vasculitis. Experienced clinicians articulate their schema to teach inductive reasoning to housestaff and students.[2]

Unique to this clinician's approach was early recognition of key psychosocial aspects, including housing instability. Such patients often experience delayed diagnostic evaluation because of lack of access to care. Through relationship-centered communication, the clinician established rapport and trust with a patient at high risk of being lost to follow-up.

CLINICAL TEACHING POINTS

1. Relationship-centered communication enhances patient outcomes, adherence to care plans, and care experiences

of patients and providers.[8] In this case, the clinician uses the FIFE framework to set a collaborative agenda, elicit the patient's perspective, and negotiate a shared plan.

2. The clinical presentation of DAH is highly variable, but typical symptoms include cough, dyspnea, chest pain, and transient hemoptysis. Ninety-two percent of patients have pulmonary infiltrates.[9] DAH may cause a hemoglobin drop of 3–4 g/dl; however, up to 33% of patients do not have hemoptysis.[10]
3. MPA and GPA are ANCA-associated vasculitides that commonly present as pulmonary-renal syndromes, including DAH. GPA is characterized by upper respiratory tract (e.g. sinuses, nose, ears) involvement and pulmonary parenchymal abnormalities, along with c-ANCA and proteinase 3 antibody positivity. MPA more often causes DAH with p-ANCA and myeloperoxidase antibody positivity.
4. Historically, 1-year mortality in untreated ANCA-associated vasculitis has approached 90%; current immunosuppressive treatment results in greater than 90% survival.[11]

Conflict of interest: *The authors declare that they do not have a conflict of interest.*

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