CLINICAL PRACTICE

Exercises in Clinical Reasoning

When the Script Doesn't Fit: 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 31-year-old man presented to an urgent care clinic with 1 day of left-sided pleuritic chest pain and cough.

Chest pain is a common problem, and the differential diagnosis is extensive. Life-threatening causes of chest pain, including acute coronary syndrome, aortic dissection, pneumothorax, pulmonary embolism (PE), and esophageal rupture, should be considered early in the evaluation.

The patient's age narrows the differential. A 31-year-old man could have premature coronary artery disease, but is at greater risk for illnesses caused by infection, substance use, or trauma. Certain inherited diseases, such as Marfan and Ehlers-Danlos syndromes, can manifest with chest pain, but these diseases are generally diagnosed earlier in life. In a young man, the presence of acute, unilateral pleuritic chest pain and associated cough are most suggestive of pneumonia, exudative pleural effusion, PE, rib fracture, and spontaneous or traumatic pneumothorax.

Further interview should explore associated infectious symptoms, recent trauma, risk factors for venous thromboembolism (VTE), potential immunosuppression, relevant exposures, and sick contacts.

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The discussant gives early consideration to immediately life-threatening diseases, and emphasizes a key epidemiologic feature—the patient's age—in his problem representation. A problem representation is a one-sentence case summary used to highlight the patient's epidemiology and clinical syndrome.[1,2] To build his differential diagnosis, the discussant searches for illness scripts that match the problem representation. Illness scripts are mental models of disease that summarize risk factors and epidemiology, time course, clinical presentation, and pathophysiology.[1,2] In this case, the discussant uses the patient's age to narrow his focus to illness scripts more likely to fit this demographic.

The patient's cough was non-productive. He had no fever, chills, night sweats, or dyspnea. He had one sick contact with a cough. He reported no recent travel or immobilization. He had no past medical history and was not taking any medications. He lived near San Francisco, CA, and worked in an office setting. He was sexually active with one female partner. He drank alcohol occasionally and did not use tobacco or recreational drugs. There was no significant family history. On examination, temperature was 99.2°F, heart rate 70 beats per minute, blood pressure 117/90 mmHg, respiratory rate 19 breaths per minute, and oxygen saturation 96% on room air. The patient was in no acute distress. There was no palpable lymphadenopathy. Oropharyngeal examination showed no swelling, erythema, or exudates. Lungs were clear to auscultation with normal percussion. Heart sounds were regular with no murmurs, rubs, or gallops. The abdomen was soft and non-tender. No rash was present. Chest radiography (CXR) revealed an airspace opacity in the left lower lobe.

The combination of acute onset, pleuritic chest pain, cough, and lobar infiltrate on CXR is consistent with the syndrome of community-acquired pneumonia (CAP), which is defined as an acute infection of the lung parenchyma acquired in the community. It is important to note that the patient lacks several characteristic features of CAP, including fever and dyspnea. Additionally, his vital signs are all within normal range, and although a respiratory rate of 19 might be considered abnormal in a previously healthy young man, the absence of vital sign abnormalities has been shown to reduce the likelihood of

pneumonia.[3] Given these deviations from the classic presentation, one must continue to consider alternative diagnoses.

Airspace opacities on CXR may be explained by the presence of blood, water (i.e. cardiogenic edema), or pus (i.e. cellular infiltrate due to infection or inflammation). Alveolar hemorrhage is a possibility, but less likely without evidence of hemoptysis or a clear predisposing condition. Cardiogenic pulmonary edema is similarly unlikely given the patient's age, lack of signs or symptoms of heart failure, and asymmetric distribution. PE can cause pulmonary infarction and resultant airspace opacity, but more commonly presents with a normal CXR. Furthermore, the patient's Wells and Geneva scores indicate that the probability of PE was low.

Despite the absence of several classic features, pneumonia remains the most likely diagnosis—particularly when the patient's age is taken into consideration. Indeed, an uncommon presentation of a common disease is still more likely than a common presentation of a rare disease. I would treat the patient for CAP.

The discussant's problem representation activates his illness script for CAP. However, he identifies several features of the case that are atypical for the diagnosis, and the lack of a perfect fit between problem representation and illness script prompts him to consider alternative explanations. He introduces a diagnostic schema for interpreting opacities on CXR. A schema is a conceptual framework that provides a structured approach to a specific clinical problem. When pattern recognition fails to generate a definitive diagnosis, schemas may help expand the differential.[4]

The discussant also acknowledges that common illnesses do not always present in a textbook fashion. Illness scripts that include atypical features may help clinicians avoid prematurely ruling out common diagnoses with a high base rate (e.g. CAP), simply because a patient does not fit the classic pattern. The base rate of disease describes the likelihood of a patient in a given population (e.g. previously healthy young men in the U.S.) having a particular diagnosis in the absence of additional clinical information.[5] *In this case, CAP remains high on the discussant's differential due to its high base rate, despite the absence of several typical findings.*

The patient was diagnosed with CAP and treated with 5 days of doxycycline. One week later, he presented to the emergency department (ED) with worsening cough, fatigue, fevers, and chills, despite taking doxycycline as prescribed.

For an immunocompetent patient receiving outpatient treatment for bacterial CAP, doxycycline was an appropriate choice. There are multiple causes for treatment failure in CAP, including the wrong "bug," wrong "drug," wrong diagnosis, wrong "host," and absence of a true treatment failure (Table 1). In this case, all of these etiologies are possible. In addition to repeating the examination, testing should include a complete blood count (CBC), basic metabolic panel (BMP), d-dimer, and repeat CXR.

The discussant has formed a new problem representation: a patient failing treatment for CAP. Reframing the case allows him to activate a robust diagnostic schema that evokes a checklist of alternative explanations.

In addition to providing a systematic approach for expanding a differential diagnosis, schemas also help clinicians manage cognitive load and maximize problem-solving abilities by providing structure to complex clinical scenarios. For example, a schema for "fever in a returning traveler" might provide a more structured approach to eliciting key diagnostic features (e.g. timing of fever onset, location of exposure, accompanying symptoms). The working memory has capacity for approximately seven items.[6] *Extracted from long-term memory, a well-formed schema can be manipulated in working memory as a single item, providing clinicians with additional bandwidth for reasoning.*[7]

The patient's vitals were unchanged except for a heart rate of 97 beats per minute. Examination revealed decreased breath sounds in the left lower lobe but was otherwise normal. White blood count was 12,400 per cubic millimeter with an absolute eosinophil count of 600 per cubic millimeter. Hemoglobin was 16.1 grams per deciliter and platelet count was 304,000 per cubic millimeter. Electrolytes, serum creatinine, blood urea nitrogen, and albumin were normal. Repeat CXR was unchanged. CT pulmonary angiography revealed scattered ground glass, solid centrilobular nodules in the left lung, consolidation in

Table 1 Causes of treatment failure in community-acquired pneumonia (CAP)

Category	Explanation	Examples
Wrong "bug"	CAP is the correct diagnosis, but the causative organism is unusual	Gram-negative rod, virus, endemic fungus
Wrong "drug"	CAP is the correct diagnosis, but the causative organism is resistant to treatment	Doxycycline-resistant *Streptococcus pneumoniae*
Wrong diagnosis	Patient has an alternative diagnosis, or a complication of CAP	Interstitial lung disease, pulmonary abscess, recurrent aspiration, congestive heart failure
Wrong "host"	CAP is the correct diagnosis, but due to anatomic obstruction, immunocompromised status, or disease severity, the patient is not improving	Malignancy, HIV, empyema
Not a true failure	Patient has not been adherent to treatment, or a drug–drug interaction has lowered therapeutic levels	Fluoroquinolone prescribed with sucralfate

the lingula, a small left-sided pleural effusion, and left hilar adenopathy (Fig. 1). There was no PE.

Laboratory testing reveals leukocytosis with a mild peripheral eosinophilia. In the setting of treatment failure, the presence of peripheral eosinophilia raises my suspicion that the patient's pneumonia is due to an atypical organism (i.e. "wrong bug") or that pneumonia is the wrong diagnosis altogether.

Causes of pulmonary infiltrates with eosinophilia (PIE) can be organized by underlying etiology, including hypersensitivity (e.g. allergic bronchopulmonary aspergillosis [ABPA], drug/toxin-mediated reactions), autoimmune disease (e.g. eosinophilic granulomatosis with polyangiitis [EGPA], other rheumatologic conditions), infection (e.g. parasitic, fungal, mycobacterial), malignancy (e.g. lymphoma, bronchogenic carcinoma), and idiopathic disease (e.g. acute eosinophilic pneumonia). Although the differential diagnosis for PIE is extensive, the clinical presentation and imaging help narrow the possibilities.

Without a history of asthma or bronchiectasis on imaging, ABPA seems unlikely. Similarly, the absence of asthma, wheezing, and more significant peripheral eosinophilia argues against EGPA. Sarcoidosis can present with nodules and lymphadenopathy on imaging and, rarely, peripheral eosinophilia. However, the patient's hilar lymphadenopathy is unilateral, which is almost never seen in sarcoidosis. Given the patient's age, lymphoma must be considered, although the acuity of his illness, absence of peripheral lymphadenopathy, and preserved complete blood count make this diagnosis less likely. Acute eosinophilic pneumonia is typically associated with bilateral peripheral infiltrates (the "photographic negative" of pulmonary edema), which are not seen in this case.

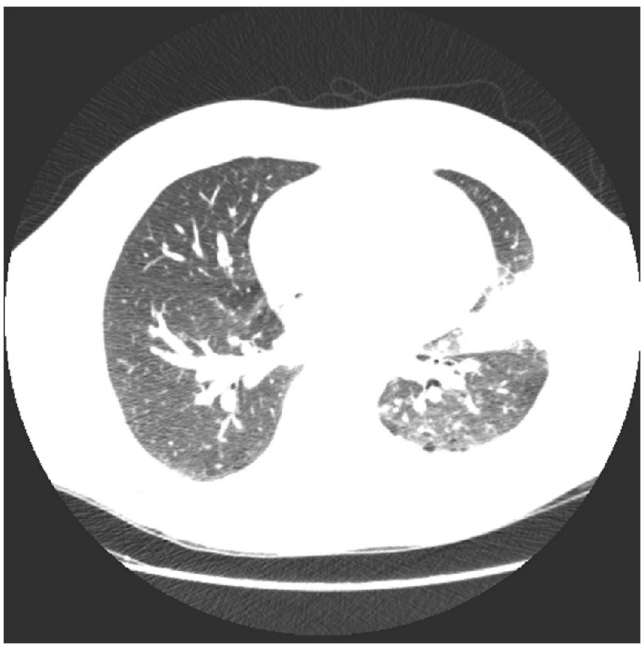

Figure 1 CT pulmonary angiogram showing scattered ground-glass, solid centrilobular nodules in the left lung, consolidation in the lingula, a small left-sided pleural effusion, and left hilar adenopathy.

Atypical infection seems most likely, yet more information is needed to make a diagnosis. Unique exposures are often revealed only with repeated interview, and I would ask the patient specifically about travel to regions endemic for parasitic and fungal infections, tuberculosis (TB) exposure, and inhalational exposure to dust and chemicals. HIV testing should be performed, as a positive test would increase my suspicion for opportunistic infections. Before embarking on an expensive and potentially low-yield serologic evaluation, a review of the imaging with a radiologist may also be helpful. I would be interested to know if the imaging findings are pathognomonic for a particular atypical infection or other PIE syndrome.

Lastly, one must consider the possibility that the patient's mild peripheral eosinophilia is unrelated to his acute illness. If so, bacterial pneumonia—which typically does not cause eosinophilia—may be the correct diagnosis, but with a resistant organism making doxycycline the "wrong drug." The eosinophilia should be followed. In the meantime, the patient should be treated for bacterial CAP with an alternative antimicrobial.

The discussant activates his diagnostic schema for PIE syndromes, which allows him to simultaneously evaluate potential causes of pulmonary opacities and peripheral eosinophilia, thereby easing his cognitive load. He then combines his schemas for PIE and CAP treatment failure in search of shared illness scripts, a technique that enables him to further sharpen his differential diagnosis. Nevertheless, he continues to struggle to find an illness script that closely matches the problem representation.

When unable to match an illness script with the problem representation, experts seek out additional clinical information in order to resolve specific areas of mismatch. New clinical information may change the problem representation in a way that reveals its match with a particular illness script. The search for new information often begins at the bedside with repeat interview and physical examination. The discussant points out that important exposures are often missed on initial interview, as neither the clinician nor the patient may recognize which exposures are relevant.

The discussant also highlights the value of talking with consultants, who may detect subtle clues to specific diseases. Subspecialist consultation can also help clinicians further develop their own illness scripts by layering different or more nuanced details onto their prior knowledge.

The patient was diagnosed with a non-resolving pneumonia and prescribed 5 days of levofloxacin. Four days later, he returned to the ED with worsening pleuritic chest pain, non-productive cough, and night sweats. He had no weight loss, abdominal pain, or rash. Examination revealed a heart rate of 106 beats per minute. The remainder of the vitals, examination, CBC, and BMP were unchanged from his prior presentation. An HIV antibody test was negative. Due to a business obligation, the patient declined hospital admission. He was treated with a single dose of ertapenem and discharged with instructions to return for follow-up the next day.

The patient returned the next day as planned. In addition to persistent cough, pleuritic chest pain, and night sweats, he reported multiple new painful red lesions on his right lower extremity. Vitals were normal except a temperature of 100.9°F and HR of 107 beats per minute. Examination revealed multiple erythematous nodules of various sizes on his shins (Fig. 2). The patient was diagnosed with an allergic reaction to antibiotics, treated with diphenhydramine and ranitidine, and admitted to the hospital.

The patient has developed a rash consistent with erythema nodosum (EN). EN has numerous causes, including rheumatologic (e.g. sarcoidosis, inflammatory bowel disease), infectious (e.g. streptococcal pharyngitis, TB), medication-related, pregnancy-associated, and idiopathic. In the setting of a non-resolving pneumonia and peripheral eosinophilia, the presence of EN narrows the differential significantly.

Acute eosinophilic pneumonia and EGPA are not associated with EN. Sarcoidosis could explain the non-resolving pneumonia, eosinophilia, and EN, but as previously mentioned, remains unlikely in the setting of unilateral hilar lymphadenopathy. EN can be secondary to antibiotics, but doxycycline and levofloxacin have not been associated, and ertapenem is not a common offender. Thus, CAP with a drug reaction is unlikely.

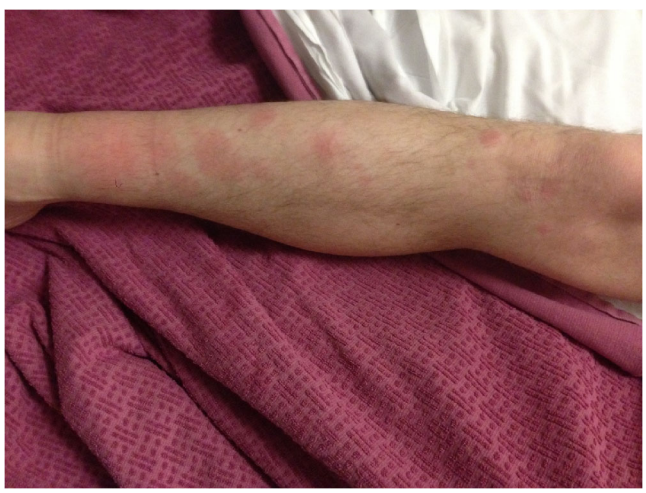

Figure 2 Examination revealed multiple, painful erythematous nodules on the bilateral shins.

Chlamydophila pneumoniae can cause pneumonia with hilar lymphadenopathy and EN, but is reliably sensitive to doxycycline and levofloxacin. Endemic fungi, including coccidioidomycosis, blastomycosis, and histoplasmosis, could explain the presentation. A thorough fungal exposure history should be obtained, including travel to endemic areas, exposure to soil or water, and participation in excavation, construction, or spelunking. Additional consideration should be paid to primary pulmonary TB, which may present with unilateral pulmonary findings (infiltrate, hilar lymphadenopathy, pleural effusion), peripheral eosinophilia, and EN. Repeat examination, laboratory tests (including CBC with differential), and tuberculin skin testing should be performed.

By adding EN to the problem representation, the discussant finds a potential match with his illness scripts for endemic fungal and mycobacterial infections. By using a deliberate, analytic style of reasoning, he was prepared to integrate new clinical findings into his problem representation and avoid anchoring. In contrast, when anchored to a diagnosis, clinicians may unconsciously undervalue or overlook information that does not support their initial hypothesis.[8]

Upon admission, further history was obtained. Two weeks prior to symptom onset, the patient participated in a 10-mile, extreme, outdoor race near San Diego. During the event, participants scramble through an obstacle course of dust, dirt, and mud.

Prolonged exposure to dust in the southwestern United States, combined with the patient's clinical presentation of CAP, peripheral eosinophilia, and EN, is consistent with a diagnosis of acute coccidioidomycosis. *Coccidioides immitis* and *Coccidioides posadasii* are soil fungi endemic to the southwestern United States. Infection occurs from inhalation of spores and is particularly common when dirt is disrupted. The diagnosis of coccidioidomycosis is made by isolation of the organism in culture, identification on histologic specimens, or, more commonly, through serologic testing.

The Coccidioides immunodiffusion test was positive; the complement fixation titer was 1:4. The patient was diagnosed with coccidioidomycosis and started on a 3-month course of fluconazole for his persistent symptoms. His symptoms resolved within a month, and the patient chose to stop the medication. He remained asymptomatic, and further treatment was not pursued.

DISCUSSION

The importance of problem representation and illness scripts in diagnostic reasoning has been well described. However, less has been written about how to proceed when the problem representation fails to match a particular illness script. When a clinical scenario deviates from expected patterns, a more deliberate, analytic style of reasoning becomes necessary.[9] In this case, we describe several tools that may be employed when facing diagnostic uncertainty.

The base rate of disease should always be considered when testing diagnostic hypotheses, but it is particularly important in the absence of a clear diagnosis.[5] Failure to find a close match between a problem representation and illness script should prompt clinicians to recall the truism that "common things are common," and assign additional diagnostic weight to diagnoses with a high base rate. In this case, the discussant recognized that a common syndrome such as CAP may present with atypical features and still be the most likely diagnosis.

The discussant used diagnostic schemas to systematically approach opacities on CXR, CAP treatment failure, and PIE. His introduction of these schemas allowed him to expand his differential in an organized fashion and safeguard against anchoring to an early diagnosis. The discussant's recognition of the problem of "treatment failure" for CAP was pivotal, as it signaled the need to reconsider the diagnosis of bacterial pneumonia and activated a new set of illness scripts. The discussant also used schemas to manage his cognitive load. By manipulating each schema as a single item in his working memory, he was able to consider his approaches to CAP treatment failure and PIE simultaneously, while maintaining the bandwidth to recognize EN and integrate this new finding into his pre-existing diagnostic framework.

Diagnostic uncertainty should trigger a deliberate search for additional clinical information to refine the problem representation. In this case, the discussant's suspicion for atypical infection sent him back to the bedside in search of a detailed exposure history. Ultimately, the discovery of recent dust exposure in an endemic region and the appearance of EN brought the problem representation into alignment with the illness script for coccidioidomycosis.

CLINICAL TEACHING POINTS

1) Coccidioidomycosis is caused by *Coccidioides immitis* and *C. posadasii*, fungi endemic to the southwestern United States.[10] Infection results from inhalation of arthroconidia residing in the soil. High-inoculum exposures such as earthquakes, archeological excavation, and military training exercises are associated with an increased risk of infection and symptomatic disease.[11]
2) The spectrum of disease in coccidioidomycosis is broad, ranging from self-limited "flu-like" illness to disseminated disease. Symptomatic infection commonly presents as CAP 7–21 days after exposure. Other manifestations include fatigue, arthralgias, rash (erythema nodosum, erythema multiforme), and peripheral eosinophilia. Disseminated disease is seen in less than 1% of infections.[11]
3) Symptoms of coccidioidomycosis are often attributed to other causes of pulmonary infection. Lack of familiarity with the disease and failure to obtain a travel history are common reasons for delayed or missed diagnoses.[12]

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