CLINICAL PRACTICE

*Exercises in Clinical Reasoning***A Problematic Palsy: An Exercise in Clinical Reasoning**David J. Einstein, MD^{1,2}, Robert L. Trowbridge, MD³, and Joseph Rencic, MD¹¹Department of Medicine, Tufts Medical Center, Boston, MA, USA; ²Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; ³Departments of Medicine and Medical Education, Maine Medical Center, Portland, ME, USA.**KEY WORDS:** sarcoidosis; Löfgren's; Heerfordt's; problem representation; clinical reasoning.

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A 29-year-old African American woman without significant past medical history presented to her primary care physician complaining of 1 week of fatigue, malaise, and generalized mild abdominal discomfort. She had nausea without vomiting. She denied localizing symptoms, changes in bowel habits, hematemesis, hematochezia, or melena. She denied fevers, chills, or sweats. She had anorexia, with a 2-pound weight loss over that week. She denied eating any unusual or undercooked foods. Her vital signs and exam were unremarkable, including a benign abdominal exam and heme-negative guaiac study.

In formulating the differential diagnosis, my first step is to identify the key features of the presentation while discounting irrelevant information in order to build a problem representation in the hope that a specific recognizable pattern will emerge. Unfortunately, her fatigue, malaise, and generalized abdominal pain are nonspecific.

Secondly, epidemiological factors are critical. Young patients, particularly those without chronic conditions predisposing them to complications, are most prone to infection as a cause of acute illness. Autoimmune disease, especially in a young woman, sarcoidosis in an African American, and malignancy are all considerations, although the acute onset of symptoms and lack of localizing symptoms make these less likely and suggest a viral etiology, especially enteroviruses. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections may present primarily with fatigue and malaise, although both commonly have concomitant pharyngitis. Bacterial infections are more likely to be associated with specific symptoms, and she has no clear risk factors for a fungal or parasitic infection.

At this point, a viral infection appears most likely, and the patient may be followed clinically.

The discussant highlights the critical nature of defining the patient's presentation as a problem representation using clinical findings and epidemiology. A problem representation is a one-sentence summary defining the specific case in abstract terms.¹ Choosing the correct problem to solve is essential to obtaining the correct diagnosis. At this point, the symptoms are nonspecific and the discussant uses epidemiological features to formulate a problem representation. This problem representation triggers diagnostic hypotheses based on the discussant's illness scripts, mental representations of diseases that include predisposing factors, pathophysiology, and clinical findings.¹

One week later, the patient returned feeling no better and complaining of four tender lower extremity "bumps" that had begun spontaneously after the last visit. On exam, 1-cm nodules with a violaceous color were palpable over her shins. The exam was otherwise unchanged.

The two key features now present are the persistent symptoms and the appearance of a rash. The persistent fatigue and malaise for over 2 weeks renders the previous working diagnosis of a nonspecific viral syndrome less likely.

The rash is more useful. The description is most consistent with erythema nodosum. A painful inflammatory reaction usually involving the subcutaneous fat tissue of the shins, erythema nodosum may be associated with several underlying disorders. Most commonly, however, it presents in isolation or in conjunction with a recent streptococcal infection. The low probability of streptococcal infection and the persistent fatigue, however, raise suspicion of another underlying process.

Unfortunately, the differential diagnosis for erythema nodosum is vast. There are over 50 causative infections, including tuberculosis, endemic mycoses, gastroenteritis, and viral infections including EBV and CMV. She has no known risk factors for tuberculosis or fungal infections. Her course is potentially consistent with EBV or CMV infection. A gastrointestinal infection is less likely given the lack of diarrhea and prolonged course. Inflammatory and autoimmune processes such as sarcoidosis and inflammatory bowel disease are also associated with erythema nodosum. However, inflammatory bowel diseases typically have more gastrointestinal manifestations. Lastly, medications, especially oral contraceptives, commonly cause erythema nodosum but would not explain her other symptoms. To investigate the causes of erythema nodosum, I would obtain a complete blood count looking for

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lymphocytosis or lymphopenia associated with viral infections, a chest film looking for the hilar adenopathy common with sarcoidosis, and monospot testing. Supportive care and continued monitoring, however, would also be reasonable.

The discussant updates his problem representation: persistent constitutional symptoms with erythema nodosum. The new problem representation makes his initial consideration of a nonspecific viral syndrome less likely. His recognition of erythema nodosum as a key feature of the presentation triggers an expansive new differential diagnosis.

A diagnostician seeks sensitive and specific features of diseases when performing the history and physical exam, which are most valuable in developing a problem representation. If sensitive features are absent, the disease is likely excluded (e.g., fatigue in adrenal insufficiency), and if specific features are present, the disease is likely diagnosed (e.g., Koplik spots in measles). Practically speaking, few clinical findings have this degree of sensitivity or specificity, as illustrated by the discussant's comments on erythema nodosum. Thus clinicians combine multiple findings to rule in or rule out diseases. They use an intuitive form of serial Bayesian analysis to assess the impact of testing or findings on the likelihood of a diagnosis.² A diagnosis becomes somewhat more likely upon discovering a sensitive finding, but much more likely after a specific finding. An unlikely diagnosis remains unlikely despite a single sensitive finding. However, this analysis relies on correct identification of pertinent and non-pertinent findings. Some may be "red herrings," prominent but distracting features that lead to diagnostic error.³ Others may be incorrectly deemed irrelevant.

Two weeks later, the patient awakened with a left-sided facial droop and presented to the emergency room. She denied any focal weakness or numbness, as well as speech, swallowing, or gait disturbances. She continued to have malaise, nausea, and by this time had lost 10 pounds over the past month due to anorexia. Her review of systems was negative except for her month-long symptoms of fatigue and malaise, and a complaint of long-standing poor vision.

Her mother and father were healthy. She had smoked one pack of cigarettes daily for 13 years and she drank alcohol socially. She denied recreational drug use. She had had three male sexual partners in the past year and did not routinely use condoms. She had no allergies and took an ethinyl estradiol/levonorgestrel contraceptive pill.

Previously, the combination of symptoms of fatigue, malaise, generalized abdominal pain, and erythema nodosum required a very broad differential diagnosis. The appearance of a facial droop, however, substantially narrows the differential.

Unilateral facial droop usually results from seventh nerve palsy, the most common isolated cranial neuropathy. Differentiating upper motor from lower motor neuron lesions is essential. Upper motor neuron lesions usually result in facial hemiplegia that spares the forehead, due to the redundant

bilateral cortical innervation of the facial nuclei. Complete facial hemiparesis suggests a lesion below the level of the facial nucleus.

Viral infections are most frequently postulated to cause acute peripheral seventh nerve palsy. Reactivation of herpes simplex virus infections is considered the most common viral etiology, but vesicles in the outer ear canal, ear pain, and occasional involvement of other cranial nerves may indicate herpes zoster reactivation, the Ramsay Hunt syndrome. In addition, up to one-third of "idiopathic" seventh nerve palsies may be due to *zoster sine herpete*, zoster reactivation without vesicles.⁴ Other viruses, specifically CMV and EBV, remain possibilities, and HIV may also cause seventh nerve palsy, especially in the setting of seroconversion. Lyme disease is a frequent etiology; bacteria, tuberculosis, and syphilis are less frequent causes.

Inflammatory diseases such as sarcoidosis, polyarteritis nodosa, and Sjögren's syndrome can cause peripheral seventh nerve palsy, as can non-inflammatory diseases like diabetes, amyloidosis, and benign intracranial hypertension.

All of this must be considered in the context of the other new piece of information—the visual loss. Assuming that the visual changes are indeed long-standing, however, they are likely unrelated to her current presentation unless they are a manifestation of a chronic disorder that, in turn, predisposes to an acute complication. Optic neuritis due to multiple sclerosis or other central nervous system disorders should be considered, but the chronicity suggests that these are significantly less likely. Furthermore, some systemic disorders such as syphilis can cause ocular inflammation in addition to cranial nerve palsies, but the rest of the presentation is inconsistent.

The new problem representation includes subacute fatigue, malaise, abdominal discomfort, weight loss, erythema nodosum, and seventh nerve palsy. The presence of both erythema nodosum and seventh nerve palsy is helpful in restricting the differential diagnosis. Sarcoidosis can cause both, and is often superimposed on a syndrome of nonspecific symptoms, although it most commonly causes respiratory symptoms, of which she has none. Sjögren's syndrome, polyarteritis nodosa, and granulomatosis with polyangiitis also may cause this constellation of symptoms.

CMV and EBV are common infections in young adults, and her report of several sexual contacts increases the likelihood of both, but the lack of preceding pharyngitis or adenopathy somewhat diminishes the possibility. HIV is also a consideration in light of her sexual history. HIV seroconversion can cause peripheral seventh nerve palsy, and erythema nodosum can occur in HIV, although the latter is usually the result of concomitant tuberculosis.⁵ In this case, erythema nodosum may be the sole initial manifestation of tuberculosis. We must consider Lyme disease if the patient resides in an endemic area and has other signs of infection. Indeed, in endemic areas, a seventh nerve palsy in an otherwise healthy patient could be considered Lyme disease until proven otherwise. Erythema

nodosum, however, is uncommon. Finally, tuberculosis is a frequent cause of erythema nodosum worldwide, and can cause a variety of neurologic manifestations, including cranial nerve palsies.

The discussant further refines his problem representation of a young, healthy woman with subacute fatigue, malaise, generalized abdominal pain, and erythema nodosum with the first specific finding of the case: a seventh nerve palsy. In complex cases, clinicians seek a cognitive “lever”, a clinical finding that elucidates the problem representation in a way that enables them to “crack” the case. The discussant diagnoses a seventh nerve palsy and uses this as a vital piece of the problem representation. This transformation of the problem representation enables him to focus on a manageable differential diagnosis list. From a Bayesian perspective, the added seventh nerve palsy reduces the likelihood of many possible diagnoses, to the point where he can reasonably eliminate them without further testing.

On examination, the patient was an obese young woman who appeared mildly uncomfortable. Vitals were notable for a temperature of 100.1° Fahrenheit, blood pressure of 91/66 mm Hg, pulse of 104 beats per minute, and normal oxygen saturation on room air. Her relevant exam findings included mild diffuse abdominal discomfort and the same nodular, tender rash on her lower extremities seen previously. Her neurological examination demonstrated a significant left-sided facial droop and an inability to close her left eye. It was otherwise unremarkable. Visual acuity was 20/40 in her left eye and 20/400 in her right eye. An ophthalmoscopic exam demonstrated a normal left fundus, but the right fundus was not visible, despite changing the focus of the ophthalmoscope. The remainder of her exam was normal. A diagnostic study was performed.

Her exam largely confirms her history and is most remarkable for the absence of findings. The lack of other neurologic abnormalities, specifically cranial nerve findings, suggests an isolated peripheral seventh nerve palsy; there are no other findings to suggest neurosarcoidosis or brainstem lesion, nor more diffuse neurologic involvement as seen in neurosyphilis and tuberculosis. An enlarged spleen would increase the likelihood of mononucleosis, but its absence, again, does not make it less likely, as is true of the lack of pharyngitis and adenopathy.

Her visual acuity is much more severely compromised in the eye than the history suggested, indicating a likely chronic condition, possibly unrelated to the current presentation. Given the inability to visualize the fundus, a congenital cataract is the most likely diagnosis. Less likely would be an acute process such as vitreous hemorrhage or retinal detachment.

Overall, the combination of erythema nodosum and a peripheral seventh nerve palsy, as well as fatigue, malaise, and fever in an otherwise healthy young woman, is most consistent with a diagnosis of mononucleosis secondary to EBV or CMV infection. The abdominal discomfort, although not a classic

presentation of mononucleosis, may also be seen with this diagnosis, usually because of an associated mesenteric adenitis, hepatitis, or splenomegaly. Lyme disease, simply because of the strength of its association with peripheral seventh nerve palsy, is another strong possibility, as is HIV seroconversion. There are multiple other rare infections that may cause this constellation of findings, but without specific epidemiological risk factors, they are difficult to implicate.

The examination further delineates the problem representation as a young, healthy woman with subacute fatigue, malaise, generalized abdominal pain, erythema nodosum, and a peripheral seventh nerve palsy. However, the discussant now faces a problem representation dilemma: should he include a report of chronic poor vision, with an examination demonstrating severe unilateral vision loss with an inability to visualize the fundus? After careful consideration, he chooses to leave his problem representation unchanged. This dilemma highlights the high-stakes nature of problem representation. The inclusion of a red herring or the exclusion of a critical finding can sabotage the diagnostic process.

A chest x-ray revealed bilateral hilar lymphadenopathy (see Fig. 1). An ophthalmologic consultant’s examination revealed panuveitis, greater on the right side.

The presence of panuveitis on ophthalmological examination is surprising, as most patients would react more vigorously to what is seemingly the rapid onset of visual loss. The differential for uveitis includes CMV and tuberculosis, but one of the most common causes is sarcoidosis.

The hilar adenopathy also entails a broad differential, which includes malignancies such as lymphoma and infections such as tuberculosis and the endemic mycoses. Most clinicians,

Figure 1. Representative image of bilateral hilar adenopathy.

however, immediately associate bilateral hilar adenopathy with sarcoidosis.

The combination of hilar adenopathy, uveitis, erythema nodosum, fever, and unilateral seventh nerve palsy in an otherwise healthy young woman suggests sarcoidosis as the probable diagnosis. While Löfgren's syndrome is characterized by the combination of hilar adenopathy, erythema nodosum, fever, and polyarthralgia, cranial nerve palsies are not present in this syndrome. Tuberculosis is another consideration, although less likely, given the lack of epidemiological risk factors for tubercular infection. Non-Hodgkin lymphoma could also be responsible for such a presentation, but the lack of other evidence of a disseminated malignancy decreases the likelihood. The means of establishing a diagnosis of sarcoidosis is controversial, although many would insist on a tissue biopsy revealing non-caseating granulomata.

The discussion illustrates the power of problem representation. The characterization of the visual disturbance as uveitis immediately triggered the pattern recognition of acute sarcoidosis. Interestingly, although the discussant mentioned sarcoidosis early in his discussion, he did not include uveitis on his differential diagnosis for the highly abnormal eye examination because the patient's presentation did not fit his typical illness script for uveitis (i.e., "acute painful red eye"). Atypical presentations of diseases further complicate the challenge of formulating problem representations. Fortunately, problem representations need not be "perfect" in order to effect an accurate diagnoses. The clinician's problem representation finally contained enough key features to allow a tentative diagnosis, although he avoids premature closure by considering a confirmatory test and keeping other diagnoses in mind.

The patient was clinically diagnosed with acute sarcoidosis and was started on corticosteroid therapy. Biopsy was considered unnecessary in the setting of a syndrome highly suggestive of acute sarcoidosis. All of her symptoms had resolved at a 1-month follow-up visit. Unfortunately, she was subsequently lost to follow-up.

DISCUSSION

Problem representations are one-sentence summaries of a specific case using abstract terms called semantic qualifiers.⁶ To create an accurate problem representation, clinicians must identify key features and discount those that are distracting. The discussion demonstrates the challenge of formulating problem representations in complicated cases. Because few clinical findings are highly sensitive or specific, clinicians often use a constellation of findings to confirm a diagnosis. Our discussant's analytical approach was analogous to a form of serial Bayesian reasoning: each additional piece of information increased or decreased the likelihood of diseases on the differential.

Problem representation is inextricably linked to hypothesis generation and illness script knowledge; that is, experienced clinicians use a hypothesis-driven approach to problem representation. Their diagnostic hypotheses lead to a directed search for new data. However, if the clinicians lack or possess faulty illness scripts (e.g., uveitis manifestations in sarcoidosis), the search may be directed by the wrong diagnostic hypothesis (e.g., CMV, EBV in this case). They may over-value the significance of a given finding—or worse, completely fail to observe it. Hence, one can argue that clinicians' problem representations are only as good as their diagnostic hypotheses, which in turn are only as good as their underlying knowledge (or illness scripts).⁷ This case beautifully illustrates the complex interplay between problem representation, differential diagnosis, and illness script knowledge.

CLINICAL TEACHING POINTS

1. Given its multiple manifestations, diagnosis of sarcoidosis is often delayed, especially when the primary symptoms are pulmonary.⁸ Uveitis in particular may precede other manifestations, and may be asymptomatic in up to one-third of affected patients, unlike typical acute uveitis.⁹ As a general principle, the diagnosis requires demonstration of non-caseating granulomas affecting multiple organ systems, or at least typical pulmonary findings. The pathophysiology of sarcoidosis relates to exposure of genetically susceptible hosts to specific environmental agents.¹⁰ An interaction between HLA-DRB1 polymorphisms and environmental exposures may explain variations in clinical presentation.¹¹
2. The constellation of erythema nodosum, fever, arthralgia, and bilateral hilar adenopathy is known as Löfgren's syndrome. Given its excellent prognosis, biopsy proof may not be required for diagnosis if resolution of the disease is rapid and spontaneous, and it does not necessitate corticosteroid treatment.¹⁰
3. Solitary erythema nodosum is most commonly idiopathic. Among secondary causes, sarcoidosis and non-streptococcal upper respiratory infection are the most common.¹² Approximately 25 % of sarcoidosis patients experience cutaneous manifestations, the most common of which is erythema nodosum.^{10,13}
4. The rare constellation of facial palsy with fever, parotid enlargement, and anterior uveitis is known as Heerfordt's syndrome.¹⁰ Approximately 5–15 % of sarcoidosis patients develop neurologic manifestations, most commonly seventh nerve palsy.¹⁴ Sarcoidosis is the most common cause of bilateral seventh nerve palsy in young adults.¹⁵
5. Expert diagnosticians approach complex scenarios by identifying key findings and assembling them into problem representations, which are updated as the scenario changes, using Bayesian analysis. Illness scripts

allow experts to group clinical memories into a format to which problem representations can be compared.

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