CLINICAL PRACTICE

*Exercises in Clinical Reasoning***The Elusive SIRS Diagnosis**Ivan B. Anderson, MD¹, Shiv Sudhakar, MD², Craig R. Keenan, MD³, and Malathi Srinivasan, MD³¹Division of Cardiovascular Medicine, University of California, Davis Medical Center, Sacramento, CA, USA; ²Division of Infectious Diseases, University of California, Davis Medical Center, Sacramento, CA, USA; ³Division of General Internal Medicine, University of California, Davis Medical Center, Sacramento, CA, USA.**KEY WORDS:** subacute illness; diagnostic reasoning; endocarditis; culture negative endocarditis; Nocardia; brain abscess; diagnostic delays.

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

Clinical Information: A 57-year-old woman presented to an outside hospital (OSH) complaining of clumsiness, falls and confusion. History was obtained primarily through her two sons. Previously, the patient had been working full time as a waitress and living with her sons. One week prior to admission (PTA), she developed dizziness then gait ataxia. Three days PTA, her sons brought her in for evaluation, and a CT head without contrast was normal. She subsequently developed gait instability and was unable to descend her porch stairs as she could not find the stairs with her right foot. She began falling related to her dizziness. She did not fall in any particular direction. One day PTA, she became confused, and did not know the date or her location. She was admitted to the OSH. On presentation, she noted clumsiness in handling her car keys. She had chronic unchanged muscle spasms in her low back only. She denied visual changes, fevers, photophobia, tinnitus, aphasia, muscle wasting, numbness or paresthesias.

Given the alarming nature of her falls, focal apraxia and their progression over 7 days, it seems that the patient has a rapidly progressive multifocal neurologic disorder. I would first evaluate the patient for recurrent embolic strokes, alcoholic ataxia, upper/lower motor neuron disorders or vasculitis. For this patient, the differential diagnosis of acute

falls also includes ischemic or hemorrhagic stroke, demyelinating disorders, medication effect or toxic ingestion, and a variety of other primary and secondary CNS processes. The normal CT head makes a mass lesion or long-standing CNS degenerative process less likely. Of note, the symptoms of ataxia and clumsiness suggest lesions in the brainstem and cerebellum, which are areas poorly visualized on head CT. The next step would be a good physical exam, likely followed by a brain MRI to evaluate the posterior fossa and to look for evidence for the other CNS processes previously mentioned.

An accurate understanding of the nature and timeline of symptoms is crucial to conceptualizing the underlying disease process, correctly identifying the problem presentation, and guiding an efficient workup. A problem representation is an organizational method to categorize the clinical timeline, symptom clustering and rate of disease progression. Initially, broadly categorizing disease presentation as acute (hours to days), sub-acute (days to weeks) and chronic (weeks to months) can help narrow the initial differential diagnosis. Disease progression can be visualized as “the slope of the disease curve”: constant (chronic low back pain); deteriorating linearly (pancreatic CA) or in a stepwise fashion (progressive multiple sclerosis); fluctuating symptoms (hepatic encephalopathy); relapsing with disease progression (congestive heart failure); or intermittent symptoms with disease free intervals (sickle cell disease).

Once clinicians make a problem representation, they reference it against their “illness scripts,” which are organized knowledge structures of conditions they encounter. Clinicians compare and contrast the problem representation and illness scripts rapidly and thus do diagnostic reasoning through pattern matching. Illness scripts have been shown to contain richer detail in experienced clinicians and can be taught.^{1, 2} In this case, the clinician creates a problem representation of “falls, apraxia, and progression over 7 days,” and this matches to “a rapidly progressive multifocal neurological disorder” and then to more specific entities such as embolic strokes.

The patient was relatively healthy, except for intermittent severe low back pain (LBP), and prior domestic abuse with associated anxiety and depression. She had no history of rheumatologic or sexually transmitted diseases. Outpatient medications included aripiprazole,

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paroxetine, hydrocodone/acetaminophen 10/325 mg and dextroamphetamine. She reported using several hydrocodone/acetaminophen tablets for LBP 3 days PTA. Family history was noncontributory. She lived in a rural northern California town. She had smoked one pack per day for 5 years, and quit 15 years ago. She would not quantify her drinking, but reported no alcohol ingestion for 48 h prior to presentation.

This patient's medication profile and unwillingness to quantify her alcohol intake lend to suspicion regarding substance abuse or dependency. Often patients and family do not divulge such information because of concern for pejorative labels and substandard treatment by the patient's care team. In this patient's case, it would be important to consider diseases transmitted by exchange of body fluids (needle sharing, unprotected sexual contact), including viral infections (HIV, hepatitis B or C), spirochetal illnesses (syphilis), or other addictions that can alter the individual's response to standard illnesses. Additionally, abusive alcohol consumption has been clinically and experimentally validated as an immunosuppressant. It is a well-established risk factor for many pulmonary and systemic infections. Pneumonias associated with abusive alcohol consumption include *Streptococcus pneumoniae*, *Legionella* and *Mycobacterial* pneumonias.³ Additionally, alcohol is associated with increased susceptibility to *Listeria* meningitis, *Salmonella* infections, HIV transmission and postoperative infections.⁴ Alcohol impairs the immune response both acutely and chronically by inhibiting T cell proliferation, IL-12 secretion and decreased co-stimulatory molecules in the antigen-presenting complex.³ Alcohol is also implicated in suppression of natural killer cells by reduction of β -endorphin excretion.⁵

Here, the clinician takes the suspiciously evasive alcohol history to postulate alcohol or other substance abuse, which would play an important role in altering the problem representation and expanding the diagnostic possibilities.

On initial presentation, her temperature was 100.4°F, blood pressure 103/70 mmHg, pulse 95, respiration rate 20 and SpO₂ 95 %. She was orientated to name only. Her initial general and neurologic exam was non-focal. Admission WBC was 6,700 cell/mm³, hemoglobin 11 g/dl and platelets 337,000 cells/mm³. Chemistry panel showed sodium 128 mEq/l, potassium 4.5, chloride 91, blood urea nitrogen 66 mg/dl, serum creatinine 3.1 mg/dl, glucose 184 mg/dl, albumin 3.1 g/dl; alanine and aspartate transaminase were 152 and 181 U/l, respectively, and alkaline phosphatase was 135 U/l with an international normalized ratio of 2.1. Tylenol, salicylate and ethanol levels all were undetectable. HIV test was negative. Over several hours, she developed profound hypotension and tachycardia, requiring 5 l of normal saline, then vasopressors. She was subsequently intubated and started on empiric antibiotics (cefepime and

levofloxacin). Three days after presentation, when her clinical picture did not improve, linezolid was added. Lumbar puncture was negative. Blood, urine and sputum cultures showed only yeast in sputum and urine. Bronchoscopy showed alveolar hemorrhage, with negative bacterial cultures. No acid-fast bacilli (AFB) were seen on three sputum stains. CXR and CT chest showed ARDS. CT head, abdomen and pelvis were negative. Except for transient FiO₂ improvement on linezolid, she had poor lung compliance and needed higher fractional inspired oxygen. After 2 weeks of continuous vasopressors and ventilation, she was transferred to our hospital for further evaluation and management.

"Something is not right" is a familiar sensation that all clinicians have experienced. This patient presented with a multisystem disease, with rapid acceleration over a week, with development of delirium, and hypotension. She met the SIRS criteria and was appropriately evaluated for standard bacterial and viral pathogens, presuming an infectious etiology. Yet the patient has not improved on broad-spectrum antibiotics. The differential diagnosis needs to be expanded to include atypical presentation of common diseases (e.g., endocarditis with atypical organism) and diseases that present in an immunocompromised host (e.g., disseminated histoplasmosis). Environmental factors should be explored further by history taking and, potentially, a site visit to her residence or work conducted by public health officials or a home care nurse/physician. Noninfectious etiologies, such as adrenal insufficiency or vasculitis, must also be considered.

The presumptive diagnosis (bacterial sepsis in an immunocompetent patient) as an anchoring heuristic should be changed once common causes of illness are eliminated. When pattern recognition does not immediately lead to the appropriate etiology of illness, another technique is to use the "analytic approach" in which an expanded differential diagnosis is extensively constructed for key symptoms, and the overlap between the symptoms is explored. This is what the clinician does when he expands the differential diagnosis to consider atypical presentations, diseases in an immunocompromised host and environmental factors.

On admission to our facility, her sons noted a 2-month history of exertional dyspnea preceding her initial presentation and revealed a history of alcoholism and alcoholic hepatitis.

This information now changes the problem representation significantly, to a middle-aged alcoholic patient with subacute onset of dyspnea, followed by ataxia, hand clumsiness, confusion and prolonged sepsis-like syndrome. This definitely moves unusual organisms found in immunosuppressed patients higher on the list. It also raises concern for subacute bacterial endocarditis with resultant emboli given the preceding dyspnea. I would also consider conditions that limit antibiotic penetration (such as with an

abscess), resistance to antibiotics or inadequate coverage (not directed at the right range of invasive organisms). The history of alcoholism and her notable coagulopathy make me consider underlying cirrhosis, which is also an immunocompromised state. Her exam as described, however, does not indicate stigmata of cirrhosis.

A common mistake is not to pinpoint when the disease initially presented—thereby constructing an inaccurate problem representation. This is especially true for multi-system diseases in which the underlying disease has a variety of manifestations, such as rheumatologic diseases.

When the patient fails to respond to standard therapy, the clinician should routinely consider re-taking the history and carefully performing a full examination to look for missed features. Similarly, the clinician should consider reasons why appropriate therapy for a correct diagnosis may not be working to its full extent.

The patient was mechanically ventilated and intermittently arousable. Her temperature was 36.9° C, blood pressure 111/70 mmHg (with IV norepinephrine), pulse 88 and regular, and SaPO₂ 96 % on 50 % FiO₂. Soon after transfer, she rapidly required an increase in her FiO₂ to 100 % oxygen. Exam showed equal reactive pupils, normal extraocular movements, poor dentition with missing teeth, regular cardiac rate and rhythm with a grade II/VI mid-peaking systolic ejection murmur noted across her precordium, diffuse crackles, anasarca and cool extremities. When sedation was lifted, she moved all extremities weakly and followed commands. Plantar reflexes were felt to be equivocal bilaterally. Her right first toe was mottled, purple and discolored.

The patient's blue first toe perhaps is related to vasospasm from vasopressors, but alternatively may be an important clue to an embolic phenomenon. In search of a unifying diagnosis to explain this possible embolic phenomenon, malignancy or endocarditis becomes more prominent in the differential diagnosis. Alternatively, endocarditis might have caused subacute valvular insufficiency resulting in heart failure to explain her subacute dyspnea.

Diagnostic reasoning: Combining the expansive history with "pivot points" is a useful technique. Pivot points are conditions or symptoms that have a limited differential diagnosis, around which a clinical team can "pivot" their diagnostic thinking. In this case, the focal skin finding of a potential embolus is a pivot point.

On transfer, her WBC was 27,400 cells/mm³, with neutrophilic predominance with >10 % bands. The platelet count was 40,000 cells/mm³; creatinine was 1.9 mg/dl and rose over the next 48 h to 3.0 mg/dl. Aspartate transaminase was 362 U/l, alanine transferase 92 U/l, alkaline phosphatase 215 U/l, total bilirubin 0.7 mg/dl, activated partial thromboplastin time 40 s and the international normalized ratio 1.25. Fibrinogen was

394 mg/dl. Initial blood gas showed a pH 6.99, pCO₂ 108 and pO₂ 68 on 100 % FiO₂. Chest x-ray and subsequent CT chest at the time of transfer are seen in Figures 1 and 2. These revealed a reticular pattern of lung injury with diffuse nodularity, fibrosis and bilateral pleural effusions. A deep sputum aspirate was sent for AFB stains and for bacterial and mycobacterial culture. The patient continued to deteriorate, becoming progressively more difficult to arouse. An MRI brain was performed and showed hyperintense lesions consistent with subacute emboli in the cerebellum, left postcentral gyrus, the corona radiata bilaterally and the right posterior occipital lobe (Fig. 3).

Culture-negative infective endocarditis is top of the differential diagnosis, given her dyspnea, sepsis and now evidence of multiple embolic phenomena. In addition, non-standard bacterial infections (e.g., bartonella, leptospirosis and typhoidal tularemia) and systemic fungal infections (e.g., disseminated cryptococcosis, histoplasmosis, blastomycosis or coccidioidomycosis) could be considered. Bilateral upper lobe infiltrates on CXR raise concern for tuberculosis or atypical mycobacterial infections, though serial negative acid-fast stains from her sputum argue against these. Pulmonary-renal syndromes may also fit this clinical picture given the fibrosis seen on the CT chest with preceding dyspnea and renal failure. Rheumatologic processes resulting in murmur and endocarditis may also fit given her lower extremity embolic phenomenon and dyspnea. I would request an infectious disease consultation if not yet performed.

Based on the new "pivot point" of multiple CNS emboli, the clinician reorders the differential diagnosis. The clinician here requests the expert opinion of a specialist. Specialists usually have more detailed illness scripts because of their more extensive experience with diseases in their specialty.

Figure 1. Patient portable chest x-ray on day of admission to transfer hospital. A portable chest x-ray obtained on admission showed diffuse, predominantly upper lobe, lacy, reticulonodular opacities.

Figure 2. Patient chest CT, transfer hospital day 2. CT chest without contrast shows diffuse bilateral patchy nodular opacities with significant air trapping in the right middle lobe. Moderate-sized bilateral pleural effusions are noted. There was no significant hilar lymphadenopathy or cardiomegaly. Other cross sections not shown demonstrate fibrosis.

On the day after transfer, a transthoracic echocardiogram showed a normal ejection fraction and a possible mitral vegetation. A subsequent transesophageal echocardiogram demonstrated an 8×7-mm mobile vegetation on the posterior leaflet of the mitral valve (Fig. 4)

The patient had developed culture-negative endocarditis. In the US, *Bartonella* species and *Coxiella burnetii*

Figure 3. MRI brain, T2-weighted images, transfer hospital day 3. T2 MRI with fluid attenuation inversion recovery demonstrates hyperintense cerebellar lesions (arrowheads) consistent with sub-acute embolic phenomena. These lesions were also apparent in the following locations not shown: left postcentral gyrus, the corona radiata bilaterally and the right posterior occipital lobe.

Figure 4. Transesophageal echocardiogram, transfer hospital day 4. Transesophageal echocardiogram done on hospital day 4 showed a 1.0×0.5×0.5-cm vegetation (arrowhead) attached to the P3 (posterior/medial) segment of the mitral valve. The vegetation can be seen as a video clip from the transesophageal echocardiogram available for viewing as an [online appendix](#).

are the most common causes of culture-negative endocarditis, while HACEK organisms and *Corynebacterium* are less common. Rheumatologic processes may cause valvular thickening and mimic infective endocarditis, but in the setting of possible alcohol abuse and no prior history of rheumatologic disease, endocarditis seems more likely. On her initial presentation to our hospital, our working differential diagnosis for her focal weakness included brain emboli, abscess, vasculitis or exacerbation of existing weakness from an undiagnosed prior stroke. Of note, the patient had only had a noncontrast CT of the head at the outside hospital, which did not show any emboli. This illustrates the limitation of noncontrast CT imaging.

The patient's antibiotic spectrum was broadened with the addition of azithromycin, vancomycin and fluconazole to cefepime. A rheumatologic workup was initiated with an antinuclear antibody, antiglomerular basement membrane antibody and cytoplasmic, perinuclear, myeloperoxidase and serine proteinase 3 anti-neutrophil cytoplasmic antibodies—all of which were negative. HIV, hepatitis B and C viral titers were negative. The patient's condition continued to wax and wane. On hospital day 5, the infectious disease consultant called the laboratory contracted by the outside hospital. Although the initial bronchoscopy specimens and sputum cultures from the outside hospital were negative for acid-fast bacilli, a rapidly growing acid-fast organism was isolated and was speciated as *Nocardia cyriacigeorgica*.

Nocardia is a gram-positive, acid-fast bacterium from the order Actinomycetales. It was first described by M.E. Nocard, a French veterinarian.⁶ *Nocardia* is an uncommon pathogen with modern case studies showing associations mostly with impaired cell-mediated immunity such as in HIV, chronic glucocorticoid use or solid organ transplanta-

tion.⁷ However, as many as 15 % of *Nocardia* cases do not have the above-mentioned standard risk factors.⁸ In this patient, alcohol was the presumptive cause of a T cell defect.³

Nocardia is a soil dweller and readily aerosolizes. Its common portal of entry is through the lungs,⁹ and it is associated with chronic lung disease, especially bronchiectasis.¹⁰ It can cause endocarditis and frequently disseminates to the central nervous system, as it did in this patient.¹¹

Subsequent to establishing the diagnosis of *Nocardia*, the patient was prescribed 1 year of high-dose ceftriaxone and bactrim. Her recovery was mostly uneventful with the exception of amputation of her necrotic right first toe. By 6 months after presentation, she was able to again perform activities of daily living, and at the time of this publication she was able to return to work as a waitress.

When a patient fails to respond to standard therapy, the clinician must consider the following scenarios: (1) they have the wrong diagnosis (e.g., not a bacterial endocarditis); (2) the patient does not have a normal host defense (e.g., immunocompromised from alcoholism or malnutrition); (3) the patient has underlying pathologic condition contributing to the presenting illness (e.g., lupus anticoagulant in a patient with recurrent DVTs); (4) the correctly identified process is not responding in a standard manner (e.g., new antibiotic or antifungal resistance); (5) the patient is not receiving the recommended treatment (e.g., drug delivery failure, no insurance).

DISCUSSION

In conclusion, this case of an elusive SIRS diagnosis highlights the differential diagnosis for culture-negative sepsis of unclear etiology. In suspected culture-negative endocarditis, organisms such as *Bartonella*, *Coxiella*, HACEK organisms, atypical *Mycobacteria* and *Corynebacterium* are considered. However, *Nocardia* should also be suspected for clinicians treating such patients, especially with focal neurologic deficit on presentation.

This case highlights potential errors in clinical judgment related to anchoring heuristics. Specifically, an inaccurate problem representation was constructed around the acute presentation of what turned out to have been an acute on subacute disease process. This highlights the difficulty of obtaining a comprehensive and accurate history of present illness in a critically ill patient. Related to a poorly focused differential diagnosis, the search for a systemic illness was misguided. This led to a delay in obtaining a brain MRI until more substantial evidence of systemic emboli became evident (i.e., the foot embolus). In the setting of focal neurologic deficit and in the case of systemic *Nocardia*, an MRI is a better test than a CT.^{12, 13}

CLINICAL TEACHING POINTS

1. The most common causes of culture-negative endocarditis in America are *Bartonella* and *Coxiella*.
2. *Nocardia* frequently disseminates to the central nervous system and can uncommonly cause endocarditis. Thus, it should be considered in the patient with culture-negative endocarditis and focal neurological deficits.
3. Noncontrast head CT imaging can be falsely negative in patients with a brain abscess or malignancy. When these are suspected, contrast CT or MRI imaging should be performed.
4. When illness scripts do not match the problem presentation, the analytic approach should be used. This involves expanding the differential diagnosis around key symptoms, signs and/or test results.

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