Exercises in Clinical Reasoning

A Heart-Breaking Case of Fever and Rash

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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 (italic) is interspersed throughout the discussion.

A healthy 27-year-old Asian-American woman presented with fever and rash.

In a young, healthy person with fever and rash, three disease categories deserve immediate consideration: infectious, non-infectious inflammatory, and environmental or toxin mediated disease. Important elements of the history include epidemiologic clues to severe infection, such as seasonality, geographic setting and recent travel, sexual and dietary habits, and exposure to ill contacts, animals or insects.

Studies demonstrate that physicians form hypotheses within the first 30 seconds of encountering a patient.^{1,2} Here the discussant takes a very limited amount of information and constructs a framework of disease categories that will govern his information search and data interpretation.

The patient was in her usual state of health until 5 days prior to admission, when she developed subjective fever, myalgias, and fatigue. The next day she noted a painless, non-pruritic rash on her abdomen, back, thighs, and antecubital fossae, which spread to her face and neck. Three days prior to admission she developed diffuse abdominal pain, multiple episodes of non-bloody emesis, and watery diarrhea. She denied cough, shortness of breath, or wheeze. She did not have chest pain, palpitations, orthopnea, or paroxysmal nocturnal dyspnea. She denied headache, neck stiffness, or focal neurologic symptoms.

This episode can now be characterized as an acute-to-subacute illness with systemic symptoms, rash, and gastrointestinal

involvement. The initial phase is non-specific and could be compatible with many viral infections, including influenza. The rash is neither pruritic, as is the case with many vesiculobullous eruptions, nor painful, as is the case with conditions such as toxic epidermal necrolysis. The rash spares the distal extremities, which is less typical of infections such as coxsackievirus or secondary syphilis. It does not have a dependent distribution suggestive of petechiae or palpable purpura caused by vasculitis. Facial involvement is unusual for many infectious rashes and may suggest autoimmune and inflammatory conditions, such as systemic lupus erythematosus, and acute febrile neutrophilic dermatosis (Sweet's syndrome).

The onset of abdominal symptoms several days into the illness argues against extraintestinal manifestations of an enteric pathogen (e.g., hemolytic uremic syndrome following enterohemorrhagic *E. coli* infection). Some extraintestinal infections may have prominent gastrointestinal manifestations (e.g., H1N1 influenza or Legionnaire's disease). Toxic shock syndrome secondary to staphylococcal or streptococcal infection is frequently associated with diarrhea, although nausea and vomiting are less common. If she were immunocompromised, the combination of fever, abdominal pain, and truncal rash could suggest disseminated strongyloidiasis. Alternative explanations for her luminal gastrointestinal complaints would be erythema multiforme major (Stevens Johnson syndrome) or small vessel vasculitis, which can involve the skin and other mucosal surfaces (e.g., Henoch-Schonlein purpura).

The discussant takes the key cognitive step of constructing a problem representation using the epidemiology (young, healthy woman), time frame (subacute to acute), and principal clinical features (rash and gastrointestinal symptoms).³ He uses many elements of the rash, including distribution, time course, and symptoms, to trigger or reject potential diagnoses. Similarly, he uses the temporal pattern of her gastrointestinal complaints to consider different infectious and non-infectious syndromes. Finally, he ponders conditions that simultaneously affect the skin and gastrointestinal tract.

The patient's only past medical history was an uncomplicated vaginal delivery 2 years prior. Her only medication was a hormonal intrauterine device (IUD). She did not use any complementary or alternative medicines. She had no known drug allergies. She had received all scheduled childhood and adult vaccinations. She lived with her two-

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year-old son, who attended daycare, and she was employed at a dental office. She had unprotected sex with two male partners, including a new partner in the prior month. She had a pet cat, and swallows nested in the doorway of her urban home. She had no history of international travel, camping or exposure to rural areas. She drank socially, did not smoke, and did not use drugs.

Having a child in daycare increases her risk for childhood viral infections such as parvovirus, and her employment might also increase her risk of aerosolized exposure to viruses. Her sexual history raises concern for a sexually transmitted infection such as acute HIV. The prominent rash would make feline zoonoses such as cat scratch disease or toxoplasmosis less likely. If she had sustained a cat bite, pathogens such as *Pasteurella multocida* and *Capnocytophaga* could cause fever and rash, but severe illness due to those infections is typically seen in patients with other significant comorbidities such as cirrhosis.

*The discussant continues to review a broad differential diagnosis with an emphasis on the defining and discriminating features of each illness. Illness scripts have maximal utility when they contain the defining features of the illness (which allow the clinician to invoke a potential diagnosis) and contain discriminating features that distinguish among similar illnesses under consideration.*⁴

She was ill-appearing, had a temperature of 39.4 °C, blood pressure of 98/69 mmHg, pulse of 145 per minute, respiratory rate of 18 breaths per minute, and a normal oxygen saturation. She had bilateral conjunctival injection with small hemorrhages, moderate oropharyngeal hyperemia, normal tonsils without exudates, and 1–2 cm, tender bilateral anterior cervical and submandibular lymphadenopathy without lymphadenopathy elsewhere. Her neck was supple. Her heart was tachycardic and regular, without murmurs, rubs or gallops. No jugular venous distention was appreciated. Lungs were clear to auscultation. Her abdomen was mildly distended and tender in the epigastrium and right upper quadrant; no rebound, guarding, fluid wave or organomegaly was appreciated. On pelvic exam she had a normal cervix with IUD strings visible at the os and no abnormal discharge or cervical motion tenderness. Extremities were cool with normal distal pulses and no edema. No joint tenderness, effusions or synovitis were noted. She had a diffuse macular, blanching rash on her abdomen, back and groin with areas of non-blanching petechiae and non-palpable purpura, most notably on her thighs (Image 1). Her neurologic exam was normal.

It is most likely that her hypotension is secondary to distributive shock due to sepsis or vasodilatation, but cool extremities raise the question of a cardiogenic or hypovolemic component. Primary or secondary adrenal insufficien-

Image 1. Area of non-blanching petechiae and non-palpable purpura.

cy could be considered as a less common cause for her hypotension. Although the exanthem is most compatible with a viral erythroderma or toxin-mediated disease, her travel history does not indicate risk for a hemorrhagic fever virus that could cause vascular collapse. Furthermore, viruses are less likely to cause this degree of hemodynamic compromise unless there is secondary volume depletion or myocarditis. The conjunctival and pharyngeal findings can be seen with toxic shock syndrome. Although there are small petechial areas, the predominant morphology of the rash is not petechial or purpuric, so I am less concerned about life-threatening infections such as Rocky Mountain spotted fever, meningococemia, and Gram-negative bacteremia with ecthymatous skin lesions. Her vaccination history makes measles unlikely.

The non-infectious differential diagnosis with this degree of illness would include Stevens-Johnson syndrome and, given the duration of illness and presence of lymphadenopathy, Kawasaki disease. If the symptoms continued without a clear diagnosis being established, I would also consider adult Still's disease, despite the absence of joint findings.

White blood cell count was 16,200/uL with 94% neutrophils, 1.4% lymphocytes, and 0.4% eosinophils. Platelet count was 88,000/uL. Renal function was normal. Total bilirubin was 0.9 mg/dL (normal 0.2–1.2 mg/dL), aspartate aminotransferase was 71 U/L (8–48 U/L), alanine aminotransferase was 83 U/L (7–55 U/L), and alkaline phosphatase was 62 U/L (45–115 U/L). International normalized ratio was 1.3, fibrinogen was 748 mg/dL (150–350 mg/dL), and lactate dehydrogenase was 233 U/L (122–222 U/L). Lactate was 4.1 mmol/L (0.5–2.2 mmol/L). Urinalysis was negative for leukocyte esterase and nitrate. Rapid human immunodeficiency virus (HIV) assay was negative. Chest radiograph showed clear lungs with a normal cardiomedial silhouette. Electrocardiogram showed sinus tachycardia without ischemic changes.

She is profoundly lymphopenic, which may be related to acute illness, but also is consistent with acute HIV infection and other viral pathogens. The moderate degree of

thrombocytopenia could represent disseminated intravascular coagulation, bone marrow suppression, or immune-mediated destruction of platelets, and could explain the petechial areas of her rash. While abnormal, the initial routine laboratory results do not alter the diagnostic probabilities, with the exception of increasing the likelihood of acute HIV infection.

The discussant differentiates between the many abnormal tests that are non-specific and the few results (lymphopenia) that are more specific to certain conditions (HIV).

She was admitted to the transitional-care unit. Intravenous fluids and vancomycin, ertapenem, and clindamycin were administered. She remained febrile and tachycardic with blood pressures in the range of 100/60 mmHg over the first 12 h of hospitalization despite receiving 9 L of isotonic intravenous fluids. Her lungs remained clear and her oxygen saturation remained normal on room air. Computed tomography (CT) scan of her abdomen and pelvis showed small bilateral pleural effusions, bibasilar consolidations, and 1–2 cm periportal, portocaval and retroperitoneal lymph nodes.

Twenty-four hours after admission, her blood pressure declined to 63/36 mmHg and she required 2 L of oxygen by nasal cannulae to maintain adequate oxygenation. She was transferred to the intensive care unit. Jugular venous distention and pulmonary crackles were noted. Lactate was 4.6 mmol/L. A transthoracic echocardiogram showed a left ventricular ejection fraction of 20% with global hypokinesis, moderately reduced global right ventricular systolic function, and no valvular disease. The inferior vena cava was dilated and did not collapse with inspiration. Troponin was 0.45 µg/L (normal <0.05 µg/L) and repeat electrocardiogram showed no signs of ischemia. Furosemide and dobutamine infusions were started.

On hospital day three, she required intubation for worsening hypoxia in the setting of pulmonary edema.

New systolic heart failure in a young patient has several potential explanations. Myocardial “stunning” with transient depression of pump function can be seen in the setting of sepsis. Many critical illnesses may result in stress-induced cardiomyopathy, which is attributed to high circulating catecholamine levels. Arguing against this diagnosis is the absence of changes on her electrocardiogram or the characteristic left ventricular apical ballooning on echocardiogram. Myocarditis as a part of a multisystem infectious or inflammatory syndrome is possible, given the mild elevation of troponin. Finally, in a patient at low risk for obstructive atherosclerotic coronary artery disease, other less common etiologies of myocardial infarction need to be considered, such as coronary artery vasculitis. The absence of focal wall motion abnormalities on the echocardiogram

and lack of ischemic changes on the ECG both argue against epicardial coronary artery disease, but do not exclude ischemia on a microvascular basis.

The new data prompts the discussant to modify his working diagnosis (hypothesis refinement⁵) for the patient's refractory hypotension from distributive shock to cardiogenic shock. He elaborates multiple mechanisms for acute myocardial injury in a critically ill patient who is unlikely to have atherosclerotic coronary artery disease, and considers supporting and refuting evidence for each.

Over the next 5 days, bacterial cultures remained negative and viral serologies were non-diagnostic (Table 1). Anti-nuclear antibody (ANA) was negative (<1:40). She remained in critical condition, requiring vasopressor and ventilatory support. Fever continued, white blood cell count increased to 51,000/uL, platelet count increased to 779,000/uL, and C-reactive protein was greater than 200 mg/dL. Given suspicion for parvovirus infection, on hospital day 5 the patient was empirically treated with 1.2 g/kg intravenous immunoglobulin (IVIG) for 2 days. For refractory hypotension, she received 5 days of hydrocortisone 50 mg intravenously every 6 h. Her hemodynamics subsequently stabilized, her oxygenation improved, and she was extubated.

Infectious disease serologic tests done shortly after the onset of illness must be interpreted cautiously, since false negative results may occur. The combination of negative cultures and lack of response to broad-spectrum antibiotics do not suggest a typical pyogenic bacterial etiology. Toxin-mediated infectious disease, such as staphylococcal toxic shock syndrome, is still possible, but non-infectious syndromes, such as adult Still's disease or Kawasaki disease, seem more likely.

It is difficult to determine whether her recovery represented spontaneous resolution of the underlying disease or if her course was ameliorated by corticosteroids or intravenous immunoglobulin. The interpretation of the patient's hemodynamic improvement is also complicated by the question of stress-related cardiomyopathy, which

Table 1. Infectious Disease Tests

Serology	Result
HIV viral load	Not detectable
Respiratory virus panel	Negative
Anti-Streptolysin O titer	Negative
Epstein-Barr Virus IgG	Positive
Epstein-Barr Virus IgM	Negative
Parvovirus IgG	Positive
Parvovirus IgM	Negative
CMV IgG	Positive
CMV IgM	Negative
Coxsackie A & B antibodies	Inconclusive/equivocal
Toxoplasma antibody	Inconclusive/equivocal
Coccidioides immunodiffusion	Inconclusive/equivocal

could resolve over this time frame as the overall condition of the patient improved.

The discussant demonstrates careful consideration of diagnostic tests, which are frequently interpreted as “positive” or “negative.” He avoids this binary characterization of test results by considering how a single factor—time since onset of illness—can affect test characteristics. In addition, the discussant takes care to not automatically assign credit to a particular treatment when multiple therapies have been administered concurrently and when alternative phenomena (e.g., spontaneous resolution of an underlying illness) may account for improvement.

Several days after extubation, the patient developed intermittent chest pain associated with T-wave changes. The troponin level was 0.25 $\mu\text{g/L}$, increased from the most recent value of $< 0.05 \mu\text{g/L}$.

T-wave changes are non-specific and could be associated with myocarditis. However, the dynamic nature of the EKG changes and the association with chest pain and a rising troponin level while her heart failure has improved is more consistent with ischemia. In the context of her fever, rash, lymphadenopathy, and non-diagnostic infectious diseases evaluation, Kawasaki disease with coronary artery aneurysm formation—an otherwise rare disease in young adults—is the likeliest explanation of this patient’s myocardial ischemia.

Cardiac catheterization revealed giant aneurysmal dilatation of the left anterior descending, left circumflex, and right coronary arteries (7–9 mm) (Image 2). Higher dose IVIG (2 g/kg) and aspirin were administered for suspected Kawasaki disease. Three days later, periungual desquamation developed (Image 3). Her heart failure continued to improve. After 16 days of hospitalization, the patient was discharged on aspirin and clopidogrel, doxycycline, simvastatin, and benazepril.

Image 2. Left-heart catheterization showing giant coronary aneurysms.

Image 3. Periungual desquamation on hospital day 14.

One week after discharge, magnetic resonance angiogram showed no aneurysms of the aorta or its major branches. All laboratory abnormalities had resolved. One month after discharge her ejection fraction was 50%. CT angiogram showed that her coronary aneurysms had decreased, and an exercise stress test was negative. She has been able to resume her active lifestyle, including working and caring for her young son.

COMMENTARY

This patient was diagnosed by both the clinical team and the discussant as having an extremely rare syndrome. Rather than emphasizing details about Kawasaki disease, we hope draw attention to the discussant’s orderly reasoning process. Analysis of how the discussant expertly coordinated the elements of problem solving can inform modeling and teaching of this important skill.

The discussant began with a framework of the most basic problem (healthy young patient with fever and rash), which he then refined to a fully formed problem representation (acute-to-subacute illness with systemic symptoms, rash and gastrointestinal symptoms). This problem representation then activated candidate diagnoses in his long-term memory. The richness of the discussant’s mental models (illness scripts) for these conditions was evident from his understanding of typicality (“prominent rash would make feline zoonoses such as cat scratch disease or toxoplas-

mosis less likely” or “It does not have a dependent distribution suggestive of either petechiae or palpable purpura caused by vasculitis”). Armed with detailed characterizations of diseases (developed from years of study, practice, and teaching), he was able to compare and contrast candidate diagnoses with confidence and accuracy, but his shifting of probabilities remained relative, not absolute (“less likely” or “I am less concerned”). He avoided anchoring on a given formulation (distributive shock) when new data arose that suggested an alternative mechanism. When rendering his final (rare) diagnosis, he explained all the elements that collectively justified his conclusion.

Residents report that the teaching they desire most from their instructors is insight into how they think and arrive at their decisions.⁶ This seems like an easy charge, but it requires careful planning and thought. We may know great reasoning when we see it, but it has to be broken down into component steps to make its teaching focused for the instructor, accessible for the learner, and time-efficient for both.⁷ This case discussion demarcates those components—problem representation, illness script content, comparing and contrasting of candidate scripts, and avoidance of cognitive errors⁸—and provides examples of effective language that can be employed when narrating those steps. If teachers learn the components of clinical reasoning they may be better equipped to assess their learners in real time and make an informed choice about what aspect of reasoning they choose to model, discuss, or analyze in the busy clinical setting.

CLINICAL TEACHING POINTS

1. Kawasaki disease is a rare systemic necrotizing vasculitis that occurs most often in children, but rarely can present in young adults.⁹
2. Diagnostic criteria include the presence of fever lasting 5 days or more and at least four of five signs:¹⁰
 - Polymorphic rash
 - Erythema or desquamation of extremities
 - Nonexudative conjunctivitis
 - Injected oropharynx, fissured lips, or “strawberry tongue”
 - Cervical lymphadenopathy
3. Kawasaki disease may be considered in systemically ill patients meeting the diagnostic criteria above, with or without cardiac involvement, in whom viral exanthema, drug reaction, and toxic shock syndrome have been excluded.⁹
4. Cardiac manifestations of Kawasaki disease include pericarditis, myocarditis, and coronary artery aneurysms. Coronary artery aneurysms typically occur after the acute illness has resolved, and are reported much less frequently in adults than in children.
5. Treatment of Kawasaki disease includes intravenous immunoglobulin and aspirin to prevent the development of coronary artery aneurysms. Once aneurysms are present, management consists of anti-platelet therapy to prevent arterial thromboses. Emerging evidence suggests that statins and doxycycline may promote regression of aneurysms.^{11–13}

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