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MORNING REPORT

RASH DECISIONS: AN EXERCISE IN CLINICAL REASONING

Shawna Le; Jared Krainin, MD; Seetha Lakshmi, MD; Shanu Gupta, MD, FACP

(Discussant text in italics.)

Ms. Le (shawnale@health.usf.edu) is a third-year medical student at the University of South Florida Morsani College of Medicine. Dr. Krainin (@Krainin; krainin@health.usf.edu) is an internal medicine resident at the University of South Florida. Dr. Lakshmi (@hmmandwhynot; seetha@health.usf.edu) is an infectious disease faculty at University of South Florida. Dr. Gupta (@shanumeister) is an academic hospitalist at University of South Florida.

A 40-year-old female presents to the emergency department for evaluation of persistent fevers and a rash over one month.

In a young otherwise immunocompetent woman, the subacute onset of rash and fevers raises the possibility of infections, autoimmune conditions, drug induced skin manifestations, or even paraneoplastic conditions. Further history and exam findings will provide additional information to develop the hypothesis.

She described fevers up to 104.5°F for the past five days, noticed a white plaque on her tongue, and a pruritic rash on the face, palms, and soles. Over the last month, she reported generalized fatigue, chills, unintentional weight loss of 12 pounds, and large joint pain in the shoulders and hips that was accompanied by morning stiffness. She denied headache, changes in vision, dyspnea, hemoptysis, abdominal pain, nausea, vomiting, change in bowel movements, back pain, dysuria, and hematuria. She had not been sexually active for several years and had no history of sexually transmitted disease. There was no recent travel. The patient had no family history of autoimmune disorders or cancer. She endorsed a diagnosis of rheumatoid arthritis (RA) in her twenties, although she took no medication and did not follow up for further care. Social history revealed significant intravenous heroin drug use.

The presence of polyarthralgia in the large joints and constitutional symptoms could point towards a serum sickness reaction mediated by toxins from infections, medications or autoimmune conditions, particularly with history of RA. The patient's history of drug use raises the concern for infectious etiologies such as acute hepatitis B, HIV, and infectious endocarditis, all of which produce a serum sickness reaction.

In the emergency department, the patient had a temperature of 102.6°F, a blood pressure of 94/57 mmHg, pulse of 103/minute, respiratory rate of 24/minute, and oxygen saturation of 100% on room air. She appeared uncomfortable on examination. There were white plaques on the posterior tongue and the patient had a pruritic, faint, erythematous macular rash on the face in a malar distribution, on the palmar and dorsal aspects of the hands, and on the soles of the feet that began to exfoliate and spread centripetally. No joint deformities were noted. Heart and lung exams were unremarkable. Initial labs revealed pancytopenia and 200 mg/dL of protein on urinalysis. The patient was given clotrimazole for oral thrush and an empiric dose of vancomycin and piperacillin-tazobactam.

Common but elusive presentations for the internist, rashes can be appraised when categorized by type and distribution. The accompanying table presents a useful framework for evaluating skin manifestations of systemic infections[1]. The macular rash on face, palms and soles, and systemic compromise in this patient lead us to consider early phase staphylococcal scalded skin syndrome (SSS) and streptococcal/staphylococcal toxic shock syndrome.

Although unusual, if the patient had used cocaine contaminated with levamisole a LINES syndrome (Levamisole Induced Necrosis of the Skin), by causing vasospasm of distal blood vessels, could also have this appearance. Normally one would expect ear and nose involvement. Another possibility is systemic lupus erythematosus flare, although a normal joint exam brings into question the diagnosis of RA, and hence autoimmune disorders.

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Table 1: Rashes in Systemic Infections
Can be generalized in immunocompromised patients
** → denotes progression of rash

	Macular	Papular	Vesiculobullous	Pustular	Purpura
Focal	Contact dermatitis →		HSV** →		
			Rickettsial pox	Staph/strep folliculitis	
			Disseminated vibrio	Pseudomonas folliculitis →	
Generalized uncommonly palm and soles	Viral exanthem →			Disseminated gonococcus →	
	Medication →				
	Early Rickettsia →				
	Lupus →				
		Rheumatic fever	Varicella →		
		Stills disease			
Generalized with palms and soles	Syphilis →				Acute meningococcemia
	Late stages of rickettsia →				Purpura fulminans
	Hand foot mouth (Coxsackie) →				Viral Hemorrhagic fevers
	Janeway lesions →				Leucocytoclastic vasculitis
	Staphylococcal scalded skin syndrome →				
	Rat bite fever				

Blood cultures returned with gram positive cocci in clusters, consistent with staphylococcus aureus. The following morning, a new 3/6 holosystolic murmur at the left lower sternal border was appreciated on examination. Echocardiogram revealed a 0.9 x 1.0 cm vegetation on the tricuspid valve with moderate regurgitation. With return of culture sensitivities, the patient was treated for infective endocarditis with cefazolin.

Remaining labs were negative for HIV, syphilis, Hepatitis B, and Hepatitis C. ANA, rheumatoid factor, anti-CCP, anti-dsDNA, ANCA, anti-Jo1, and cardiolipin Ab were negative, and she did not use cocaine.

Infective endocarditis can present with a wide variety of non-specific signs and symptoms. In a large prospective cohort study[2] the most common finding was fever, which was demonstrated in 96% of patients, however no other symptom was present in more than 50% of patients with the diagnosis. Other widely associated findings of endocarditis such as Janeway lesions and Osler's nodes were found in five and three percent of patients, respectively.

Musculoskeletal symptoms of endocarditis, while underappreciated, are a common manifestation of the condition. One retrospective

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study[3] found musculoskeletal manifestations in 44% of cases of bacterial endocarditis. These symptoms included arthralgias (most common) as well as arthritis, low back pain, and diffuse myalgias. In more than 25% of these cases, musculoskeletal complaints were the first manifestations of the infection. Clinicians should be aware of the prevalence of these symptoms in endocarditis due to the potential for delayed diagnosis.

The diagnosis of infective endocarditis is made by the Modified Duke's criteria, which requires two out of three major criteria including: two positive blood cultures of typical microorganisms (or one positive with Coxiella burnetti), a new regurgitant valvular murmur, and evidence of endocardial involvement. Diagnosis can also be made with several "minor" criteria, of which three are needed when one major is present and five minor criteria are needed without presence of a major criterion.

Staphylococcal Scalded Skin syndrome (SSS) results in denudation of the skin caused by exotoxin producing strains of the Staphylococcus species, typically from a distant site.[4] Rarely found in adults, it portends 60% mortality mainly due to underlying disease.[5] The associated rash may progress from localized blisters to a diffuse, markedly erythematous rash with significant tenderness, and flaccid blisters and desquamation with a positive Nikolsky's sign. Patient presentations range from well appearing to fulminant sepsis. A lack of mucous membrane involvement helps differentiate SSS from Toxic Epidermal Necrolysis, which does involve the mucosal surfaces. Early antibiotic therapy is the mainstay of treatment.

After several days of antibiotic therapy, symptoms improved and leukopenia resolved. Her hospital course was complicated by pulmonary septic emboli and a catheter-associated internal jugular vein clot. The patient was discharged with appropriate antibiotics and anticoagulation.

Discussion

Fever and rash as an undifferentiated complaint should be approached as with any other—with a preliminary diagnostic algorithm. In this case, the discussant used semantic qualifiers (*young, immunocompetent* female, *subacute* rash) in the initial problem representation[6] to identify three broad buckets to explore—infection, autoimmune disorder, drug-induced. This process of clinical reasoning is important to note as it is associated with more accurate diagnosis.

As additional information was presented, the discussant deliberated a variety of differentials (e.g., Hep B and C, HIV based on her history, staphylococcus based on her exam findings), noted variance from their illness scripts (e.g., LINES would have ear and nose involvement), and ultimately identified the most likely diagnosis from a framework she uses when evaluating rashes in systemic infections (see the table). The testing confirmed her hypothesis of SSS and infective endocarditis.

The association of SSS with infective endocarditis has been described rarely. Both diagnoses carry significant morbidity and mortality risks, and early diagnosis can result in improved outcomes.

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