CLINICAL PROBLEM-SOLVING

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In Sight and Out of Mind

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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A 21-year-old otherwise healthy man presented to the emergency department with fever and rash. His fever started approximately 1 week before presentation and was associated with chills, myalgia, nausea, and vomiting. He also had a headache without photophobia. On the day of admission, he woke up with a rash on his face, trunk, and extremities but could not recall the pattern of the rash. He also had diarrhea, but he said that he did not have any abdominal pain or urinary symptoms. He reported a mild cough and shortness of breath.

A range of infectious and noninfectious conditions may cause fever and rash. Given the patient's headache, meningococcal meningitis must be considered, but its course is typically fulminant, and fever for a week preceding the rash would be atypical. Autoimmune diseases such as vasculitis, Still's disease, or systemic lupus erythematosus are also possibilities. Finally, neoplastic conditions, including hematologic cancers, should be considered.

The patient lived in the upper midwestern United States, but 1 week before the onset of fever, he was in southern California for 4 days, and he made a short trip to Tijuana, Mexico, at that time. He did not recall being bitten by any insects during that period. He reported being sexually active with multiple female partners, and he used condoms inconsistently. He also had a history of abusing multiple substances, including intravenous heroin, cocaine, lysergic acid diethylamide (LSD), and marijuana, but he said that he had not used illicit drugs recently.

Because of his travel to southern California, I would consider rickettsial infections such as murine typhus and coccidioidomycosis. His history of multiple sexual partners and use of multiple illicit drugs place him at risk for infection with the human immunodeficiency virus (HIV). Acute HIV infection can be manifested as fever and rash; alternatively, he may have undiagnosed chronic HIV infection, which could confer a predisposition to opportunistic pathogens. I would also consider other sexually transmitted infections such as *Neisseria gonorrhoeae* or secondary syphilis.

The patient had no known medical problems and did not take any medications. He smoked about half a pack of cigarettes per day and consumed alcohol rarely. He lived with his mother and two cats and worked in a food-processing factory.

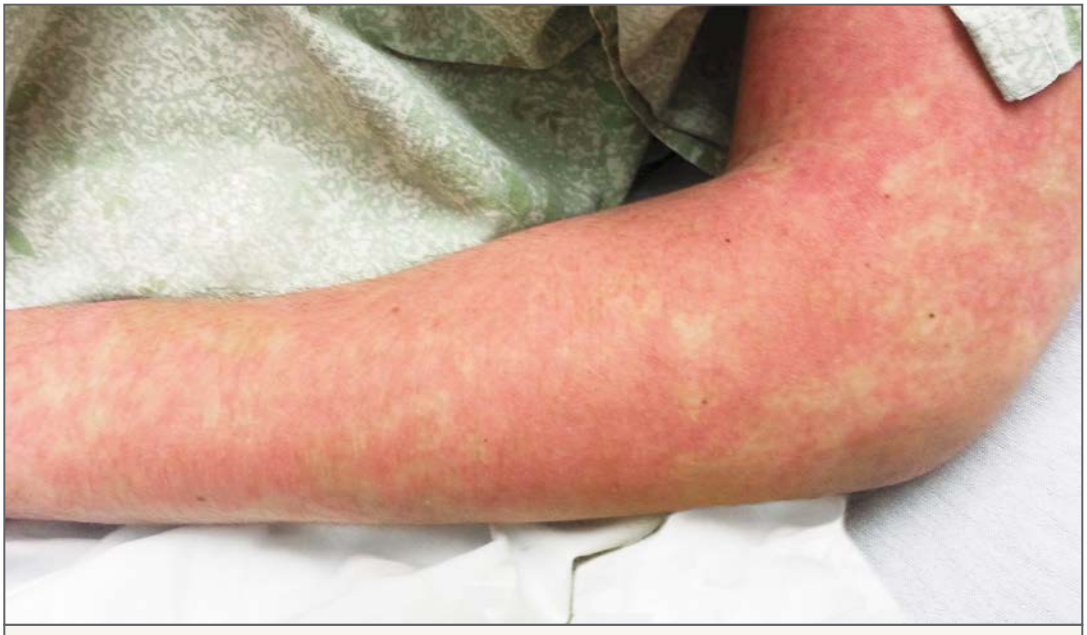

Figure 1. Morbilliform Rash on the Left Arm of the Patient.

Exposure to cats may confer a predisposition to several zoonoses, particularly those caused by bartonella, and inquiry regarding any cat bites or scratches would be prudent, although the patient's current presentation is not typical of cat scratch disease.

On examination, the patient was alert and oriented to place, person, and time. His temperature was 38.4°C, blood pressure 113/50 mm Hg, heart rate 121 beats per minute, and respiratory rate 18 breaths per minute. The oxygen saturation was 92% while the patient was breathing ambient air. He did not appear to be in distress. A generalized, blanching, morbilliform rash was present on his face, neck, trunk, and extremities, including the palms and soles (Fig. 1). The rash was confluent on the trunk and arms; a petechial rash was also noted on his legs. He had tender submental lymphadenopathy. His lungs were clear to auscultation bilaterally, and the heart sounds were normal. His liver and spleen were not enlarged. He did not have any neck rigidity, and a neurologic examination was normal.

The involvement of the palms and soles is an important clue. Numerous bacterial infections can present in this manner, including rickettsial diseases such as Rocky Mountain spotted fever and typhus and neisserial infections such as disseminated gonococcal or meningococcal infections. However, the morbilliform appearance, confluence, widespread nature, and centrifugal spread of the patient's rash are uncommon in neisserial infections and Rocky Mountain spotted fever. Viral exanthems such as measles or rubella or a drug-related reaction are more likely. The absence of nuchal rigidity in the patient and the normal neurologic examination also argue against meningitis. The petechiae, which were noted on his lower extremities and suggest disseminated intravascular coagulation, severe thrombocytopenia, or capillary fragility, may have many causes.

Viral hemorrhagic fevers would be a rare but important class of infections to consider. Dengue fever has been reported in the area of northern Mexico where this patient recently traveled, but it is less likely given the pattern of the rash. Chikungunya has also been reported recently in the United States and in Mexico, but it is extremely rare and classically presents with debilitating arthralgias, which were not prominent in this patient. Noninfectious causes such as vasculitis and hematologic cancers are less likely given the time course and morphologic characteristics of the rash, but they remain important consider-

ations. Chest radiography is warranted given his mild hypoxemia.

The white-cell count was 6400 per cubic millimeter, with 78% neutrophils, 16% lymphocytes, and 5% monocytes. The hemoglobin level was 15.3 g per deciliter, and the platelet count was 99,000 per cubic millimeter. The serum sodium level was 133 mmol per liter, potassium 3.5 mmol per liter, creatinine 1.0 mg per deciliter (88 μmol per liter), and glucose 99 mg per deciliter. The aspartate aminotransferase level was 58 U per liter (normal range, 0 to 50); levels of alanine aminotransferase, total bilirubin, and alkaline phosphatase were normal, as was the urinalysis.

A lumbar puncture was performed. Analysis of the cerebrospinal fluid showed colorless fluid with 15 nucleated cells (75% of which were neutrophils) and 4240 red cells; the glucose level was 54 mg per deciliter (3.0 mmol per liter) (normal range, 50 to 80 mg per deciliter [2.8 to 4.4 mmol per liter]), and protein 49 mg per deciliter (normal range, 15 to 45). Gram's staining of the cerebrospinal fluid did not show any organisms. Chest radiography showed prominent interstitial markings but no consolidation. An HIV antibody test and a rapid plasma reagin test were negative.

The normal glucose level and only mildly elevated protein level in the cerebrospinal fluid, coupled with the negative findings on Gram's staining, argue against bacterial meningitis. Cerebrospinal fluid pleocytosis may occur with many infections, including herpes simplex virus (HSV) infection, Rocky Mountain spotted fever, and West Nile virus infection. The widespread maculopapular rash and normal mental status and neurologic examination make HSV encephalitis unlikely. Syphilis is unlikely given the negative rapid plasma reagin test. Acute HIV infection can be present with a negative HIV antibody test, and a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay to detect HIV should be performed. At this point, viral illnesses such as dengue fever, Epstein–Barr virus (EBV) infection, and other viral exanthems are my main considerations.

Bacterial infections, including rickettsia and neisserial infections, do not usually manifest with a disseminated morbilliform rash and are less likely diagnoses. However, empirical treatment with doxycycline and ceftriaxone would be prudent at this point.

The patient began to receive ceftriaxone and doxycycline empirically for coverage of bacterial and rickettsial infections, respectively. He remained febrile for 1 additional day, but he reported that he felt better. The rash was unchanged. He was discharged while receiving oral doxycycline. Results of serologic testing for viral and rickettsial infections were not available at the time of discharge.

Rickettsial infection, specifically Rocky Mountain spotted fever, could account for the patient's presentation with fever, myalgia, headache, a morbilliform rash involving the trunk, palms, and soles, and mild thrombocytopenia. Rocky Mountain spotted fever is a tickborne illness that is caused by *Rickettsia rickettsii*; because *R. rickettsii* is often not present in large quantities in peripheral blood, PCR is not a sensitive assay for detection of these bacteria. *R. rickettsii* IgG and IgM antibodies are used to confirm the diagnosis; empirical therapy with doxycycline is appropriate while awaiting results regarding titers.

Dengue fever also remains a potential concern, and immunologic testing for dengue-specific IgG and IgM should be performed, although treatment for this infection remains largely supportive. In patients who have had prior dengue infection, diligent monitoring for progression to dengue hemorrhagic fever or dengue shock syndrome is also needed, but these conditions would not be expected in a patient who is exposed to the dengue virus for the first time.

Serologic testing for cytomegalovirus (CMV), hepatitis B surface antigen, and hepatitis C antibody, as well as PCR testing for detection of CMV, were negative. PCR testing of oropharyngeal specimens was negative for influenza and respiratory syncytial virus. Serologic testing for EBV infection showed a positive nuclear antigen, negative early antigen, and positive IgG antibodies to the viral capsid antigen, and the EBV viral load was 13,200 copies per milliliter. Antibodies for Rocky Mountain spotted fever and murine typhus were negative. Blood cultures were sterile. The cerebrospinal fluid culture grew *Propionibacterium acnes*, which was probably a contaminant. Testing for measles-specific IgM antibodies was positive

(15.82 arbitrary units per milliliter; cutoff value for positive infection, 1.21), as was testing for measles-specific IgG antibodies. PCR testing of a nasopharyngeal swab was positive for measles.

The positive IgM results and the positive PCR test of a nasopharyngeal swab confirm the diagnosis of measles. Measles is extremely contagious, and contact tracing is imperative.

The patient recovered with no sequelae. The health care institution and the local health department undertook an extensive infection-control investigation. Although approximately 600 people had been exposed to the patient, no secondary cases of measles occurred.

COMMENTARY

Measles (or rubeola — a term derived from "rubeo," the Latin word for "red") is a highly contagious, acute viral illness that is caused by a single-stranded, enveloped RNA virus. It is classified as a member of the genus morbillivirus in the Paramyxoviridae family. The incidence of this illness is extremely low in developed countries such as the United States. Although in 2000 it was considered to have been eliminated (defined as the interruption of continuous transmission for at least 12 months) in the United States,[1] transmission among persons who travel to areas in which measles persists and occasional local transmission continue to occur.

This patient lived in northeastern Wisconsin but had a history of recent travel to areas in which measles transmission continues to take place, albeit sporadically. In Mexico, the endemic transmission of measles was halted in 1996 after implementation of a national prevention program that included free, mandatory vaccination[2]; however, imported cases of measles still occur. Around the time our patient traveled to California, there was an ongoing outbreak of measles in that state. From January through April 2014, the California Department of Public Health reported 58 confirmed cases of measles, the highest number recorded since 1995.[3]

Measles should be suspected in any patient who presents with fever, rash, a history of travel to endemic areas or areas known to have recent transmission, or exposure to contacts with similar symptoms or a history of exposure to measles. However, the diagnosis can be challenging for physicians and health care staff who may have never seen a patient with this infection. The classic rash in patients with measles develops in a cephalocaudal and centrifugal distribution; if this pattern is described by the patient, it may provide an important clue. Of the prodromal symptoms known as the "3C's" of measles — cough, coryza, and conjunctivitis — our patient reported only cough. Conjunctivitis and Koplik's spots were not observed; however, Koplik's spots are transient and are noted in only 50 to 70% of patients with measles.[4] Headache, mild gastrointestinal symptoms, and mild cerebrospinal fluid pleocytosis are common but nonspecific symptoms.

The patient was treated empirically for rickettsial disease. This was prudent; the triad of fever, petechial rash, and headache is a common manifestation of Rocky Mountain spotted fever, which is a well recognized disease in southern California, and delays in diagnosis and treatment often lead to unfavorable outcomes. However, Rocky Mountain spotted fever was reported in only 15 patients per 100,000 population in 2013,[5] and cases of measles far outnumbered those of Rocky Mountain spotted fever in 2014.

Clinical measles develops in approximately 9 of 10 susceptible persons who have had close contact with a person with measles. The virus is transmitted by direct contact with infectious droplets or by airborne spread when an infected person breathes, coughs, or sneezes.[6] Transmission through aerosolized droplet nuclei has been detected in closed areas for up to 2 hours after a person with measles occupies the area. Patients are infectious for approximately 4 days before and 4 days after the onset of the rash. Given the delay in the diagnosis of the virus and the lack of airborne-infection isolation precautions in this case, contact tracing of health care workers, other patients, and family members was a critical public health function. Fortunately, no secondary transmission of measles occurred in this case.

This patient's presentation also highlights the need to obtain a thorough vaccination history; such a history, although often meticulously detailed in children, is often abbreviated or omitted entirely in adults. The Advisory Committee on Immunization Practices recommends routine

vaccination with two doses of measles–mumps–rubella vaccine for children, with the first dose administered at 12 to 15 months of age and the second dose administered at 4 to 6 years of age, before school entry. Two doses are recommended for unvaccinated adults who are at high risk for exposure and transmission, such as students attending colleges or other educational institutions after high school, health care personnel, and international travelers, and one dose is recommended for other adults who are 18 years of age or older.[7,8] Use of the inactivated vaccine strain between 1963 and 1967 was considered to be ineffective, and persons who were vaccinated during that period should be revaccinated with live vaccine. Vaccination against measles is not necessary if there is evidence of immunity or laboratory confirmation of prior illness.[7]

In the United States, recent declines in the rate of vaccination against measles have led to several outbreaks. The reasons that persons choose not to receive the measles vaccine (or that parents choose not to have their children receive the vaccine) continue to include concerns about an increased risk of autism, despite well-designed studies that refute this claim[9,10] and retraction by the *Lancet* of a study[11] that showed an association between vaccination and developmental delay; that study was found to be based on fraudulent data.

Outbreaks of vaccine-preventable diseases often occur when vaccination rates decrease below a certain threshold, placing the community at risk. This so-called "threshold theorem"[12] underlies the concept of "herd immunity," a concept that explains why it is possible to eradicate an infectious agent even without achieving 100% vaccine coverage. An ongoing multistate outbreak of measles in the United States started with an unvaccinated person with measles at Disneyland in California. As of February 20, 2015, a total of 133 cases of measles with rash connected with this outbreak have been confirmed in U.S. residents.[13] Among 110 patients in California, 49 (45%) had not been vaccinated and another 43% had unknown or undocumented vaccination status. A recent commentary concluded that to prevent measles from reestablishing itself as an endemic disease in the United States, the vaccine must be accessible to all people who need it — especially those traveling to and from countries with circulating disease — and hesitant patients and families must be reassured that the vaccine is safe and effective.[14]

Why did our discussant not pursue the diagnosis of measles despite including it in his initial differential diagnosis? The rarity of measles is the most likely explanation. A rare disease that is generally not at the forefront of a clinician's mind may not be considered seriously or at all, even when several of the cardinal features — in this case, a morbilliform rash preceded by cough in a febrile patient — are in plain sight. Given the resurgence of measles and other vaccine-preventable diseases in the United States, interventions are needed to reintroduce a discussion of these rare conditions into medical education so that clinicians will consider them in differential diagnoses. Otherwise, we run the risk that these reemerging diseases will be in sight, yet out of mind.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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