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Case 13-2015: A 27-Year-Old Woman with Arthralgias and a Rash

Emily P. Hyle, M.D., and Diana Alame, M.D.

PRESENTATION OF CASE

Dr. Anne L. Piantadosi (Infectious Diseases): A 27-year-old woman was seen in the emergency department of this hospital during the summer because of arthralgias and a rash.

The patient had been well until 5 days before this evaluation, when arthralgias in her fingers, hands, and shoulders developed, along with back pain, neck pain, and a retro-orbital headache. Later that day, fever occurred (temperature, 39.0°C) and was accompanied by chills, nausea, decreased appetite, sore throat, and mild redness of her eyes. She also noted a vaginal ulcer, ulcers on the side of her tongue, decreased taste sensation, and enlarged, tender lymph nodes in her neck and groin. The next morning, the patient awoke with a rash on her right forearm. The lesions were pink, pruritic, and nonpainful; some were flat and others were raised, resembling hives. Within 1 hour, the rash spread to her torso and both arms and legs. She presented to the emergency department of another hospital, where a viral illness was diagnosed on the basis of her clinical presentation; she was discharged home.

The following day, the patient's arthralgias persisted and involved not only her fingers, hands, and shoulders but also her elbows, knees, ankles, and toes. Swelling in her wrists and hands led her to remove a bracelet and her wedding ring. Her gums bled easily when she brushed her teeth. By that evening, her fever, headache, and rash had remitted. Over the next 2 days, the arthralgias persisted but all other symptoms continued to abate. On the fifth day of illness, a new pruritic, erythematous rash developed, beginning on her palms and spreading to her arms, chest, abdomen, back, and legs, sparing the soles of her feet. The patient took ibuprofen and diphenhydramine and then presented to the emergency department of this hospital for evaluation.

The patient had a remote history of appendectomy. Her only medication was a daily multivitamin, and she had no known allergies. Immunizations were reportedly current. She lived with her husband in a suburban area of New England, worked as a chemical engineer, and enjoyed running. Three days before the onset of illness, the patient had returned from a 7-day trip to the Turks and Caicos Islands, where she spent time on the beach and received multiple mosquito bites. She was monogamous with her husband, consumed alcohol in moderation, did not smoke or use

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illicit drugs, and had no exposure to sick persons. There was no family history of autoimmune disease.

On examination, the patient appeared well. The temperature was 36.4°C, the pulse 69 beats per minute, the blood pressure 135/87 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. There was subtle swelling of soft tissue in the hands but no joint effusions; movement of the wrists and finger joints caused mild discomfort. There was a diffuse, erythematous, blanching, macular rash involving the abdomen, chest, back, arms, and legs (Fig. 1). There were confluent macules on the palms, but the soles of the feet were spared. The remainder of the physical examination was normal. The application of a tourniquet to an arm for 2.5 minutes did not precipitate the development of petechiae. Results of renal-function tests were normal, as were blood levels of electrolytes, calcium, phosphorus, magnesium, glucose, total protein, albumin, globulin, alkaline phosphatase, total bilirubin, and direct bilirubin; additional test results are shown in Table 1. Urinalysis revealed clear, yellow urine, with a specific gravity of 1.011, a pH of 5.0, and negative results for occult blood, leukocyte esterase, nitrite, albumin, glucose, ketones, bilirubin, and urobilinogen. Testing for urinary human chorionic gonadotropin was negative.

A diagnostic test was performed.

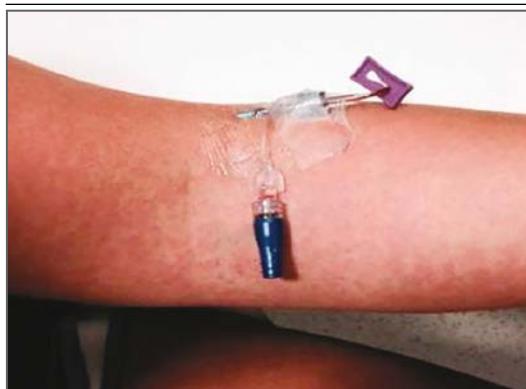


Figure 1. Photograph of Rash.

On presentation to the emergency department, the patient had a diffuse erythematous, blanching, macular rash involving the abdomen, chest, back, arms, and legs.

DIFFERENTIAL DIAGNOSIS

Dr. Emily P. Hyle: This previously healthy 27-year-old woman presented with a sudden onset of fever, rash, and polyarticular, symmetric arthralgias.

RASH

Three distinct rashes were prominent in the patient's presentation. At the time of the initial onset of symptoms, both oral and vaginal mucosal ulcers were present. Shortly after the onset of fever, she noted an erythematous, raised, pruritic rash that spread quickly from her right forearm to her torso, arms, and legs and then resolved within 48 hours; this pattern may be consistent with acute urticaria. Urticaria is common and sometimes associated with viral infections, medications, and foods but has an unknown cause in up to 50% of cases.¹ After resolution of the fever and the initial nonspecific constitutional symptoms, the patient noted a new macular, pruritic rash that started on her palms and spread over her body. In an otherwise healthy person, these rashes would ideally lead to one unifying diagnosis. Before building an initial differential diagnosis, we will consider the other predominant symptom — symmetric, polyarticular arthralgias involving the small and medium joints.

ARTHRALGIAS

The patient reported a variety of nonspecific symptoms that had occurred at the onset of her febrile illness, but her most focal symptoms were musculoskeletal. Back and neck pain and arthralgias in her fingers, hands, and shoulders developed on the first day of illness. Additional arthralgias developed in her elbows, knees, ankles, and toes on the third day of illness.

The first step in evaluating this patient's joint pain is to distinguish between arthralgia and arthritis. Although both terms refer to pain that is localized to the joints, arthritis is associated with the additional specific components of warmth and effusion due to synovitis, leading to decreased range of motion.² Although swelling of the wrists and hands was noted in this patient, the swelling appeared to be in the soft tissue surrounding the joints and not in the joints themselves. Therefore, this patient's presentation is consistent with arthralgias without arthritis, and this distinction helps to narrow the differential diagnosis.

RHEUMATOLOGIC DISEASES

The patient's presentation could represent the initial onset of a rheumatologic disease. Given her fever, rash, and arthralgias, we should consider systemic lupus erythematosus (SLE), acute rheumatic fever, serum sickness, and adult-onset Still's disease.

An early diagnosis of SLE can be challenging because the disease is associated with protean, heterogeneous manifestations. Although several features of this case, including fever, oral ulcers, and arthralgias without arthritis, are consistent with a diagnosis of SLE,³ the patient's current presentation does not fulfill the necessary diagnostic criteria for SLE.

This patient's presentation meets minor criteria for acute rheumatic fever (i.e., fever and arthralgias). However, the patient has no features that fulfill the major Jones criteria (i.e., arthritis involving large joints, carditis, erythema marginatum, subcutaneous nodules, and chorea).⁴

Serum sickness is a type III immunologic drug reaction caused by immune-complex deposition; most patients who receive a diagnosis of serum sickness present with rash, fever, and arthralgias or arthritis. However, serum sickness typically occurs 1 week after exposure to a new medication,² and this patient did not have any exposures to new medications. Furthermore, in patients with serum sickness, arthralgias typically resolve before systemic symptoms improve, and the opposite pattern occurred in this patient.

Adult-onset Still's disease is an important consideration because the majority of affected patients present with high fever, a macular rash, and arthralgias or arthritis early in the presentation. Approximately 70% of patients with Still's disease also note sore throat as part of the initial presentation. However, leukocytosis is typically present, and this patient had a normal white-cell count.⁵ Adult-onset Still's disease is a diagnosis of exclusion; thus, we will continue to look for additional clues to narrow our differential diagnosis.

INFECTION

Many infections are commonly manifested by fever, rash, and arthralgias, and some such infections require prompt diagnosis and treatment. Patients with disseminated gonococcal infection or chronic meningococemia can present with a classic triad of polyarthralgia, tenosynovitis, and dermatitis. However, the rash typically includes

Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On Presentation, This Hospital
Hematocrit (%)	36.0–46.0	41.2
Hemoglobin (g/dl)	12.0–16.0	14.2
White-cell count (per mm ³)	4500–11,000	5600
Differential count (%)		
Neutrophils	40–70	65.6
Lymphocytes	22–44	21.6
Monocytes	4–11	7.3
Eosinophils	0–8	3.9
Basophils	0–3	1.6
Platelet count (per mm ³)	150,000–400,000	107,000
Alanine aminotransferase (U/liter)	7–33	52
Aspartate aminotransferase (U/liter)	9–32	46

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

pustular lesions, and the polyarthralgia usually affects the medium joints and is asymmetric.⁶ Infection with *Streptobacillus moniliformis*, the bacterial pathogen that causes rat-bite fever (also known as Haverhill fever, if the organism has been ingested), should be considered in patients with fever, rash, and polyarthralgia; delays in diagnosis may occur because the pathogen grows slowly in blood cultures. Several different rashes are reportedly associated with *S. moniliformis* infection, but the typical rash is characterized by hemorrhagic vesicles on the arms and legs, which were not present in this case.⁷

Lyme disease should be considered in this patient, given the onset of her symptoms during summer in New England. However, in patients with Lyme disease, arthralgias usually occur during the early disseminated phase, after the disappearance of the initial rash, and Lyme arthritis is a manifestation of late disease that typically is monoarticular or oligoarticular and affects the large joints.⁸ Patients with Rocky Mountain spotted fever present with arthralgias, fevers, headache, and other nonspecific symptoms early in the disease course; a macular rash emerges hours or days later and starts peripherally, spreads centrally, and can involve the palms. Patients with Rocky Mountain spotted fever typically appear

ill by the time the rash occurs,⁹ whereas this patient's symptoms (other than the polyarthralgia) were resolved by the time a macular rash developed.

Another important consideration, especially in a woman of childbearing age, is rubella, which is frequently associated with arthralgias involving the small joints.¹⁰ However, the rash associated with rubella would typically start on the face. Rubella is uncommon among persons in the United States because most have seropositivity after immunization,^{11,12} and this patient reported receiving all childhood vaccinations. Approximately 60% of adults with parvovirus B19 infection have symmetric, polyarticular arthralgias; arthralgias associated with parvovirus B19 infection are twice as common among women as among men. The arthralgias frequently affect the proximal interphalangeal and metacarpophalangeal joints and have been reported to involve the knees, wrists, and ankles.¹³ To rule out these diagnoses, serologic testing should be performed.

Could this patient have acute human immunodeficiency virus (HIV) infection? She reported that she and her husband are monogamous, but acute HIV remains an important consideration because the acute retroviral syndrome can be associated with fever, macular rash, mucosal ulcers, and myalgias or arthralgias.¹⁴

FEVER IN THE RETURNING TRAVELER

When considering any constellation of symptoms, it is essential to clarify whether there are any specific exposures that might put the patient at risk for unusual causes of illness. Although this patient is from New England, she had traveled to the Caribbean shortly before the onset of her symptoms.

The development of fever in returning travelers is relatively common. The specific cause of fever is often not elucidated, but when a diagnosis is confirmed, malaria, dengue, and typhoid are most commonly identified.¹⁵ When considering possible exposures in a returning traveler, it is important to consider the location of travel, food or water consumed, history of insect bites, contact with animals, use of medications or recreational drugs, and sexual contacts. The time elapsed since the potential exposure and onset of symptoms is often helpful to rule out specific causes of fever (Table 2).^{16,17}

Of patients who seek medical attention for

Table 2. Incubation Periods of Common Infectious Diseases among Travelers Returning from the Caribbean or Central America.*

Disease	Mean Incubation Period in Days (Range)
Malaria	6–30†
Dengue	4–8 (3–14)
Typhoid	7–18 (3–56)
Chikungunya virus	2–4 (1–14)
Hepatitis A	28 (15–50)
Leptospirosis	5–14 (2–30)

* Data are from CDC Health Information for International Travel 2014¹⁶ and Manson's Tropical Diseases, 23rd edition.¹⁷

† The incubation period can be up to 3 months for falciparum malaria and can be longer for nonfalciparum species.

travel-related diseases after spending time in the Caribbean or Central America, 17.7% present with fever. No specific diagnosis is made in 40% of cases of fever in persons returning from international travel; when a diagnosis is made, the most common cause is dengue, and malaria, typhoid, and hepatitis A are other common causes.¹⁵ In the Caribbean, malaria has been reported only in Haiti and the Dominican Republic, and this patient did not visit these countries. In addition, this patient returned from the Caribbean just 3 days before the onset of her symptoms and had spent only 1 week there. Because the incubation period for hepatitis A is 28 days (range, 15 to 50), she could not have been infected with hepatitis A while she was on her trip. Although outbreaks of hepatitis A have been reported in the United States¹⁸ and the disease has been associated with arthralgias, it is unlikely to be the diagnosis in this case because of the patient's nearly normal hepatic aminotransferase levels. Leptospirosis is important to consider in any returning traveler, since this illness can be missed on routine testing.¹⁹ Arthralgias can be associated with leptospirosis,²⁰ but this patient did not have any of the typical symptoms associated with severe leptospirosis, such as jaundice and acute kidney injury, and she did not report any exposures to water other than swimming in the ocean. Typhoid is a common diagnosis among returning travelers, and arthralgias have been reported in up to 80% of affected patients²¹; however, the

onset of typhoid is usually subacute, especially during the first week, whereas this patient had a sudden onset of new symptoms, including high fevers.¹⁷

Given that this patient returned from the Caribbean less than 14 days before the sudden onset of illness, either dengue or chikungunya virus infection is the most likely cause of her illness. The incubation periods of both viral diseases are short (Table 2), so either infection is possible; the patient noted receiving numerous mosquito bites while she was in the Caribbean, which puts her at further risk for these vectorborne diseases.

The clinical presentations of dengue and chikungunya virus infection overlap considerably. Both diseases are typically manifested by fevers and myalgias; headache, rash, nausea, and vomiting are also commonly associated with both diseases (Table 3).^{22,23} Abnormal laboratory findings, especially thrombocytopenia, are typically more pronounced in patients with dengue than in those with chikungunya virus infection. Hypocalcemia and an elevated creatine kinase level sometimes occur in patients with chikungunya virus infection, although we are told that this patient had a normal calcium level. This patient had bleeding gums, which is a mild form of the hemorrhagic manifestations that can be associated with both viral diseases but are more commonly associated with dengue. Such symptoms can herald the onset of severe dengue, especially in patients with the capillary leak syndrome, which this patient did not have.²⁴ The three specific rashes described in the patient's presentation — the mucosal ulcers, the urticaria, and the macular, pruritic rash — have all been reported in patients with chikungunya virus infection.²⁵ It is important to note that symmetric polyarthralgia involving the small and medium joints is the hallmark of chikungunya virus infection^{22,23,26,27} and is less commonly reported in patients with dengue.²⁸

Distinguishing between dengue and chikungunya virus infection is challenging but clinically important. Dengue can cause rapid deterioration after the initial febrile phase,²⁴ and some patients with dengue require hospitalization for observation or supportive care if they meet specific criteria.^{29,30} In contrast, the fatality rate associated with chikungunya virus infection is low and deaths are usually due to coexisting conditions,^{23,26,27} although longer-term sequelae with

Table 3. Clinical Features of Chikungunya Virus Infection.

Clinical Feature	Prevalence among Patients with Chikungunya Virus Infection		Present in This Patient
	Returning Travelers (N=20)*	On Reunion Island during Outbreak (N=157)†	
	<i>percent</i>		
Fever	100	96	Yes
Rash	75	40	Yes
Arthralgias	100	96	Yes
Palpable swelling	95	32	Yes
Headache	20	47	Yes
Nausea, vomiting, or diarrhea	15–30	47	Yes
Conjunctivitis	20		Yes
Pruritus	25		Yes
Hemorrhagic manifestations	5	6	Yes (bleeding gums)
Leukopenia	25	79	No
Thrombocytopenia	25	44	Yes (mild)
Elevated aminotransferase level	25	2× upper limit of normal in <10	Yes (mild)
Elevated creatine kinase level		10	Not assessed
Hypocalcemia		55	No

* Data are from Taubitz et al.²²

† Data are from Borgherini et al.²³

arthritis can be extremely painful. The tourniquet test is a clinical tool that has long been in use to aid in the diagnosis of dengue, but it has low sensitivity (52 to 56%) and specificity (58 to 68%) in a region with high prevalence.³¹ Therefore, the negative tourniquet test in this case points us away from the diagnosis of dengue but does not rule it out.

The last piece of critical information is the date when this patient traveled to the Caribbean. Before October 2013, chikungunya virus had never been reported in the Western Hemisphere, and outbreaks were limited to Africa and Asia.³² However, since December 2013, more than 1 million suspected cases of chikungunya virus infection have been reported in the Americas, with cases reported in the United States, the Caribbean, Central America, and South American countries north of the Andes.³³

In summary, this patient's constellation of

symptoms would be most consistent with acute chikungunya virus infection since she had traveled to the Caribbean after December 2013. Because she presented on the fifth day of her acute illness, serologic testing for chikungunya virus–specific IgM antibodies is likely to be diagnostic; acute-phase and convalescent-phase serologic testing could be used to confirm the diagnosis if the test for IgM antibodies is nondiagnostic.²⁶

Dr. Virginia M. Pierce (Pathology): Dr. Piantadosi, what was your impression when you initially evaluated this patient?

Dr. Piantadosi: Given that this patient presented with fever, headache, arthralgias, rash, mildly elevated results of liver-function tests, and thrombocytopenia shortly after returning from a trip to the Caribbean in the summer of 2014, we thought that her illness was most likely due to either dengue or chikungunya virus infection.

CLINICAL DIAGNOSIS

Dengue or chikungunya virus infection.

DR. EMILY P. HYLE'S DIAGNOSIS

Chikungunya virus infection.

PATHOLOGICAL DISCUSSION

Dr. Diana Alame: Serologic testing of blood specimens for parvovirus B19, dengue, and chikungunya virus was performed. Titers for parvovirus B19–specific IgG antibodies were elevated and titers for the IgM antibodies were normal; these findings are indicative of previous exposure to parvovirus B19. Acute-phase and convalescent-phase testing for dengue-specific IgG and IgM antibodies was negative, ruling out this diagnosis.

Several diagnostic tests are available for chikungunya virus infection. Serologic testing by means of an enzyme-linked immunosorbent assay can aid in the diagnosis, and depending on the timing of the patient's presentation, detection of viral nucleic acids may also be possible.³³ High-level viremia is detectable during the first week after illness onset, IgM antibodies are typically present within 5 to 7 days after illness onset and persist for several months, and IgG antibodies are present soon after IgM antibodies become present and persist for life.^{34,35} In this case, a blood specimen was sent to a reference

laboratory for serologic testing. Screening for chikungunya virus–specific IgM antibodies was positive, and the IgG antibodies were not detected; these results indicate recent infection with chikungunya virus.

Dr. Pierce: Dr. Piantadosi, would you tell us what happened with the patient?

Dr. Piantadosi: We saw the patient for follow-up 2 weeks after her initial presentation. She reported ongoing arthralgias in her hands, as well as new low back pain and stiffness for which she was taking acetaminophen and ibuprofen intermittently. She also noted worsening fatigue but had no further fevers, and the rash had resolved after a few days. At that follow-up visit, results of liver-function tests and the platelet count were normal. She was encouraged to take antiinflammatory medications regularly, along with a proton-pump inhibitor. During the next month, she had a waxing and waning course of symptoms. Two months after her initial presentation, she returned to the clinic with severe arthralgias in her wrists, elbows, ankles, and knees. She also noted feeling depressed, with decreased enjoyment of social activities and difficulty focusing. Because of these symptoms, she had taken a medical leave of absence from work. At that visit, therapy with meloxicam was initiated for her joint symptoms, and she was referred for psychiatric evaluation.

Dr. Pierce: Dr. Freudenreich, would you tell us your impression when you evaluated this patient for depression?

Dr. Oliver Freudenreich (Psychiatry): When I initially saw this patient, she had been ill with chikungunya virus infection for several months and had characteristic symptoms of major depression, including low energy, anhedonia, difficulty concentrating, crying spells, self-dislike, and no hope about her future. Her depression was complicated by headaches and joint pain.

When evaluating a patient with a medical illness and depression, I first look at the pathophysiological features of the medical disease and consider possible direct effects on the brain. Infections can cause depression through an increase in proinflammatory cytokines such as tumor necrosis factor α and interleukin-6. Their presence causes a behavioral syndrome called sickness behavior, which is characterized by feeling poorly, staying in bed, and not seeking out the company of other people; these are all features

of depression. Another cytokine, interferon- γ , can activate a key enzyme of tryptophan metabolism called indoleamine 2,3-dioxygenase, causing tryptophan depletion, which is associated with depressive symptoms.

Second, I look at specific symptoms and their relevance. Chikungunya virus infection is known to cause debilitating, clinically significant musculoskeletal pain. Pain and depression are intricately linked, and this patient's depression improved as her pain lessened with treatment and time.

Finally, there is an existential aspect to becoming and being sick. This patient had always been well, so her illness led to a crisis of meaning, and she had to psychologically work through it. With time, the symptoms of her infection were likely to become reduced. I thought that an antidepressant might make her feel better more quickly, but she elected for psychotherapy, so I followed along, encouraging her to stay active despite her pain and supporting her by looking at her illness experience and trying to convey hope.

Dr. Pierce: We are privileged to have the patient in attendance. She would like to make a few comments regarding her illness.

The Patient: I had a great vacation in the Turks and Caicos Islands. When I returned, I had mosquito bites, and then I had the rash and all these other crazy symptoms. The first time I went to the emergency department, I was handed a pamphlet that said "Chikungunya" across the top and my first reaction was, "This can't happen to me! I'm young. I'm healthy. I exercise five or six times a week. I eat healthily. I floss every day. I'm a pretty happy person." But it's interesting: the ini-

tial phases of illness come on like the seven plagues. I first had pain behind the eyes, then bleeding gums, then joint pain and headache. It was the gift that kept on giving.

The joint pain definitely affected my daily activities. I take the train to work and it was really hard for me to make my train. Things like showering were really painful — even turning on the shower. Getting dressed in the morning, putting on pants, and putting on shoes were all very painful. After a few months, I was still having pain in my wrists, ankles, and all my joints, and then depression and mood disturbance developed. I was a newlywed, my husband and I had just bought our own house, and I had a job that I took a lot of pride in, and then all of a sudden I was miserable. I had no history of depression. I wasn't looking forward to weekends or spending time with friends or family, and I was hit pretty hard with it.

Seven months into the illness, I'm now feeling better and I definitely feel like some remedies and psychotherapy worked pretty well. I'm also spending time with friends and family, and that is really making a difference. Having people to laugh with and shoulders to cry on has really helped.

FINAL DIAGNOSIS

Chikungunya virus infection.

Presented at the Medical Case Conference.

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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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LANTERN SLIDES UPDATED: COMPLETE POWERPOINT SLIDE SETS FROM THE CLINICOPATHOLOGICAL CONFERENCES

Any reader of the *Journal* who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is now eligible to receive a complete set of PowerPoint slides, including digital images, with identifying legends, shown at the live Clinicopathological Conference (CPC) that is the basis of the Case Record. This slide set contains all of the images from the CPC, not only those published in the *Journal*. Radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs, as well as unpublished text slides, tables, and diagrams, are included. Every year 40 sets are produced, averaging 50-60 slides per set. Each set is supplied on a compact disc and is mailed to coincide with the publication of the Case Record.

The cost of an annual subscription is \$600, or individual sets may be purchased for \$50 each. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or e-mail Pathphotoslides@partners.org.