CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 19-2007: A 19-Year-Old College Student with Fever and Joint Pain

Benjamin T. Davis, M.D., and Mark S. Pasternack, M.D.

PRESENTATION OF CASE

Dr. Maxwell T. Vergo (Department of Medicine): A 19-year-old woman was transferred to this hospital because of joint pain, fever, and hypotension.

The patient, a freshman student at a local university, had been in good health until the late spring, approximately 11 days before admission, when sore throat and fatigue developed. She was evaluated at the university health service. A Monospot test was positive, and a rapid screening test for group A streptococcus was negative; a diagnosis of infectious mononucleosis was made. The results of laboratory tests are shown in Table 1. One week before admission, nasal congestion and oral ulcers developed, and she returned to the health service; aphthous ulcers and enlarged, tender, bilateral anterior cervical lymph nodes were present on examination. Viscous xylocaine and pseudoephedrine were prescribed. Four days before admission, she returned to the health service with increasing pain in her throat and ear and difficulty swallowing. The tonsils were enlarged and red. The nasal mucosa was congested, and bilateral, tender, cervical lymphadenopathy was present. A 5-day course of prednisone at a dose of 60 mg per day in divided doses was started, and the next day, her symptoms had improved.

During the next 24 hours, nausea, vomiting, shaking chills, and lower abdominal pain developed, and she vomited the medications. She returned to the health service. On examination, she appeared ill. The temperature was 37.6°C; while the patient was supine, the pulse was 129 beats per minute and the blood pressure 86/64 mm Hg. When she was standing, the pulse was 144 beats per minute and the blood pressure 100/72 mm Hg. Examination revealed large tonsils without exudate; the tonsils were less red than they had been the day before. The findings from the remainder of the examination were unchanged from those of the day before. The results of laboratory tests are shown in Table 1. Three liters of normal saline were infused, and acetaminophen and ondansetron were administered. The symptoms improved, and she was sent home with instructions to return the next day. At that time, her symptoms had improved, and examination showed a decrease in the pharyngeal swelling and cervical lymphadenopathy.

On the day of admission, the patient awoke in the early morning with pain in the right elbow and left ankle. She returned to the health service. On examination, the temperature was 37.4°C and the pulse 92 beats per minute; the respirations were 18 per minute and the blood pressure was 104/64 mm Hg. The right elbow and left

From the Division of Infectious Diseases (B.T.D., M.S.P.), and the Department of Pediatrics (M.S.P.), Massachusetts General Hospital; and the Departments of Medicine (B.T.D.) and Pediatrics (M.S.P.), Harvard Medical School.

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Table 1. Results of Laboratory Tests.*

Variable	Reference Range at This Hospital†	11 Days before Admission	2 Days before Admission	6 Hr before Admission (to University Health Service)	3.0–4.5 Hr before Admission (to Other Hospital)	On Admission
Hematocrit (%)	36.0–46.0 (in females)	48.9	41.7	41.4	37.6	30.2
Hemoglobin (g/dl)	12.0–16.0 (in females)	16.5	13.4	13.8	12.4	10.5
White-cell count (per mm^3)	4500–11,000	9,300	20,900	23,200	20,400	22,200
Differential count (%)						
Neutrophils	40–70	36	86	79	74	
Band forms				6	6.0	
Lymphocytes	22–44	41	6	7	11	
Atypical lymphocytes		19	3	3	6.0	
Monocytes	4–11	4	5	5	3.0	
Platelet count (per mm^3)	150,000–350,000	146,000	296,000	334,000		247,000
Mean corpuscular volume (μm^3)	80–100			90.0	89.6	88.0
Erythrocyte sedimentation rate (mm/hr)					62	36
Prothrombin time (sec)	11.1–13.1					12.8
Partial-thromboplastin time (sec)	22.1–35.1					21.7
Glucose (mg/dl)	75–115				95	130
Sodium (mmol/liter)	136–145				141	136
Potassium (mmol/liter)	3.5–5.0				3.5	2.8
Chloride (mmol/liter)	98–106				104	111
Urea nitrogen (mg/dl)	10–20				14	14
Creatinine (mg/dl)	<1.5				0.8	0.9
Bilirubin (mg/dl)						
Total	0.3–1.0		0.6		0.3	0.3
Direct	0.1–0.3		0.3			0.1
Protein (g/dl)						
Total	5.5–8.0		6.9		7.0	5.4
Albumin	3.5–5.5		3.7		3.8	2.4
Globulin	2.0–3.5		3.2			3.0
Phosphorus (mg/dl)	2.6–4.5					0.9
Magnesium (mmol/liter)	1.8–3.0					1.1
Calcium (mg/dl)	9.0–10.5				9.5	7.0
Alkaline phosphatase (U/liter)	30–120		107		101	72
Aspartate aminotransferase (U/liter)			35 (reference range, 7–40)‡		16	16
Alanine aminotransferase (U/liter)	0–31		80 (reference range, 5–40)‡		47	38
Lipase (U/dl)	0.0–160.0					2.0
Amylase (U/liter)	60–180					16
C-reactive protein, high-sensitivity (mg/liter)	0.02–8.00					51.10

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229.

† 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. These ranges may therefore not be appropriate for all patients.

‡ Reference ranges are for the outside hospital.

ankle were tender on palpation, and there was pain on deep palpation in the middle portion and right lower quadrant of the abdomen. No rash was present. A rapid screening test for group A streptococcus was negative; the results of other laboratory tests are shown in Table 1. She was transferred to another hospital by ambulance.

On arrival, she described symptoms including headache, cough, malaise, sore throat that had improved since the previous day, diffuse myalgias, and pain in the right elbow and left leg extending from the lower leg to the ankle. She rated this pain as 10 on a scale of 1 to 10, with 10 being the most severe pain. There was no history of trauma. On examination, the patient appeared alert and uncomfortable; the temperature was 38.3°C and the pulse 108 beats per minute; the respirations were 22 per minute and the blood pressure was 109/71 mm Hg. Oxygen saturation was 100% while she was breathing ambient air. The neck was supple, with tender lymphadenopathy on the right side. The right elbow was swollen and painful, and there was tenderness over the left Achilles' tendon. The remainder of the examination was normal. Laboratory test results are shown in Table 1. Lumbar puncture revealed clear, colorless cerebrospinal fluid, with protein 17 mg per deciliter (reference range, 15 to 45) and glucose 79 mg per deciliter (reference range, 50 to 80). Staining of the fluid showed no organisms or white cells. Specimens of the blood and cerebrospinal fluid were sent for culture. The results of radiography of the chest and elbow were normal.

Within 2 hours of her arrival, the temperature was 38.6°C, the pulse 108 beats per minute, and the blood pressure 76/38 mm Hg. Normal saline was infused. Urinalysis was normal, except for trace protein; a specimen was sent for culture. Ceftriaxone at a dose of 1 g was administered intravenously. Ten minutes after the antibiotic infusion, pruritus developed, and urticaria was noted on the neck and abdomen; there were no respiratory symptoms. Diphenhydramine, at a dose of 25 mg, and methylprednisolone, at a dose of 125 mg, were given intravenously. Electrocardiography showed sinus tachycardia. The blood pressure decreased to 61/39 mm Hg despite the infusion of 3 liters of saline, and a continuous infusion of dopamine hydrochloride was started through a peripheral intravenous line. Vancomycin at a dose of 1 g and oxygen by nasal cannula were given. The patient was transferred by ambulance to the emergency department of this hospital after the start of the infusion of a fourth liter of normal saline.

The patient had been in good health except for allergic rhinitis and acne. She lived in a dormitory and was sexually active with a single partner, always with the use of condoms. She had received meningococcal vaccine at the age of 18 years before entering college; her only medication was an oral contraceptive. Azithromycin had caused nausea and vomiting, and meclizine led to breathing problems and mental-status changes. She drank alcohol socially and did not smoke tobacco or use intravenous drugs. She was physically active, and 2 months previously she had been in a wilderness area of Maryland. She had traveled throughout the United States, Cuba, and the Mediterranean years earlier. There was no family history of immunodeficiency.

On examination, the patient was alert and she appeared to be comfortable. The temperature was 37.1°C, the pulse was 105 beats per minute, the respirations were 14 per minute, and the blood pressure was 84/48 mm Hg while she was receiving dopamine hydrochloride at a dose of 5 μg per kilogram per minute intravenously. The oxygen saturation was 98% while she was breathing 2 liters of oxygen per minute by nasal cannula. Examination revealed ulcerated lesions on the left oral mucous membranes, petechiae on the posterior oropharynx and buccal mucosa, tender cervical lymphadenopathy, mild neck stiffness without meningismus, and tenderness in the right upper abdominal quadrant with a palpable liver edge at the costal margin. The right elbow was painful with passive motion; swelling and an effusion were present. There was no erythema over the joint. An urticarial rash was present on the arms, chest, and legs. The remainder of the examination, including a gynecologic examination, was normal. Laboratory test results are shown in Table 1. A chest radiograph was normal, and a test of urine for pregnancy was negative.

An internal jugular central venous line was placed, and boluses of normal saline with potassium chloride were infused. The dopamine infusion was discontinued; the vital signs remained stable. Arthrocentesis of the right elbow joint was performed in the emergency department; the aspirate was orange-tinted, with 17,250 white cells per cubic millimeter (94% leukocytes, 2% lymphocytes, and 4% monocytes). A Gram's stain revealed abundant polymorphonuclear leukocytes, few mononuclear cells, and red cells; no organisms

were seen. The joint was immobilized with a splint. Specimens of blood were sent for serologic testing for Epstein–Barr virus (EBV) and Lyme antibodies; specimens of synovial fluid, blood, and secretions from the nares, cervix, rectum, and urethra were sent for cultures. The patient was admitted to the medical intensive care unit.

The next day, the temperature was 37.3°C, and the pulse and blood pressure were normal. The rash had resolved, movement in the right elbow was less painful, the liver was palpable 3 cm below the costal margin, the spleen tip was palpable, and the results of the remainder of the examination were unchanged from those of the previous day. Tests for adenovirus, influenza A, and influenza B, parainfluenza types 1, 2, and 3, and respiratory syncytial virus (direct fluorescent antibody) antigens were negative. The result of a diagnostic test was reported.

DIFFERENTIAL DIAGNOSIS

Dr. Benjamin T. Davis: This young woman presented initially with a constellation of symptoms that will be readily recognized by any primary care physician. In a college student with sore throat, cervical lymphadenopathy, and fatigue, infectious mononucleosis caused by EBV can be confidently diagnosed by a heterophil antibody test, particularly if the symptoms have lasted longer than 1 week. However, mononucleosis may have a bumpy course, and patients frequently return for care because of worsening or changing symptoms. The trick in this case is to determine which of the patient's subsequent problems are due to EBV and which are sufficiently unlikely to be due to EBV that a new diagnostic evaluation is indicated.

ORAL ULCERS

Four days after diagnosis, the patient returned with nasal congestion and oral ulcers. The differential diagnosis of oral ulcerations includes infectious causes such as herpes simplex virus (HSV), coxsackievirus, and acute human immunodeficiency virus (HIV) infection and noninfectious causes such as neutropenic ulcers, iron deficiency, and Behçet's disease. Ulcerations caused by HSV are anterior, around the gums and lips, whereas those due to coxsackievirus are typically more posterior and are associated with cutaneous lesions on the palms and soles. Classic aphthous stomatitis, shallow painful ulcers in the posterior pharynx with a fine, sharp, yellowish rim, may be triggered by other infections, such as HIV and HSV, or it may be idiopathic. Aphthous stomatitis, however, is not commonly associated with EBV infection.

PAIN IN THE EAR

The patient returned 3 days later with increasing throat and ear pain, difficulty swallowing, and enlarged tonsils and cervical lymph nodes. These symptoms are consistent with mononucleosis; the ear pain is probably caused by pharyngeal swelling and eustachian-tube blockage. Primary care physicians are often confronted with the dilemma of whether to prescribe corticosteroids for severe throat pain, as were given in this case. In controlled trials, the benefit of corticosteroids in mononucleosis has not been proved.[1] Nevertheless, acute airway obstruction caused by tonsillar enlargement is a known complication of mononucleosis, and impending obstruction may be a reasonable cause for administering corticosteroids.

GASTROINTESTINAL SYMPTOMS

One day after the patient received prednisone, she returned again, this time with nausea, vomiting, chills, low abdominal pain, and dehydration. Hepatitis is a complication of mononucleosis that might have explained these symptoms, but her aminotransferase levels were only mildly elevated, and her symptoms resolved quickly.

ARTHRALGIAS, FEVER, AND HYPOTENSION

Until this point, the progression of the patient's symptoms has been characteristic of mononucleosis, albeit with some atypical features such as aphthous ulcers. On the day of admission, however, her condition changed dramatically, with the sudden onset of fever, hypotension, myalgias, joint pain, and abdominal pain.

Could these symptoms be related to another uncommon complication of mononucleosis? Acute monoarthritis due to EBV has only rarely been reported in the literature,[2] and in only one case has EBV DNA been isolated from synovium.[3] Patients with mononucleosis may become hemodynamically unstable, most commonly after splenic rupture, but this patient's abdominal findings were not characteristic of splenic rupture. The hemophagocytic syndrome or development of B-cell lymphoma may occur in rare cases of mononucleosis. These complications, however, are unlikely in a nonimmunosuppressed patient; therefore, we are compelled to consider illnesses other than EBV infection.

Differential Diagnosis of Acute Joint Inflammation

Joint pain, as experienced by this patient, may be caused by an actual infection or inflammation of a joint capsule (arthritis), infection or inflammation of periarticular structures (tenosynovitis), or inflammation at the tendinous insertion of a bone (enthesitis). Several of these anatomic compartments may be involved in a given illness; for example, septic arthritis may begin with an infection of the tendon sheath and progress over time to involve the actual joint space. This patient has a joint effusion of the elbow and tenderness of her left Achilles' tendon, indicating pauciarticular inflammation with arthritis of the elbow and probably enthesitis of the ankle.

The differential diagnosis of acute-onset monoarticular or pauciarticular arthritis includes bacterial infections such as *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, reactive arthritis, sarcoidosis, fracture, hemarthrosis, gout, pseudogout, and monoarticular rheumatoid arthritis. The differential diagnosis of acute polyarticular arthritis — involvement of more than just a few joints — includes endocarditis, serum sickness, acute HBV infection, HIV infection, parvovirus infection, rheumatic fever, rheumatoid arthritis, and systemic lupus erythematosus. Lyme arthritis may be pauciarticular or polyarticular, but there is usually less severe pain, more stiffness, and larger effusions than were seen in this patient. In a young person such as this patient with pauciarticular arthritis without coexisting conditions, the differential diagnosis may be rapidly narrowed to septic arthritis and reactive arthritis.

Reactive Arthritis

Reactive arthritis is an acute, asymmetric arthritis that typically follows chlamydial urethritis or infectious gastroenteritis within 6 weeks. It mainly affects joints of the legs, most commonly the knees, ankles, and feet. Enthesitis, particularly at the Achilles' tendon, as seen in this patient, is characteristic. Although this patient had recently had nausea and vomiting, she did not have diarrhea, which would have suggested infectious gastroenteritis; although she had no symptoms of urethritis, it is not uncommon for chlamydial urethritis in women to be asymptomatic. Reiter's syndrome is associated with urethritis and conjunctivitis, and so it is not likely in this case. Although this patient's presentation is consistent with reactive arthritis, the involvement of her elbow, the absence of any gastrointestinal or urethral symptoms, and, most important, her hemodynamic instability make septic arthritis more likely. Finally, a diagnosis of reactive arthritis cannot be made without first excluding septic arthritis.

Septic Arthritis

The two most likely causes of septic arthritis in young people are *N. gonorrhoeae* and *S. aureus*. Other causes such as pneumococcus, gram-negative bacilli, and candida occur far less commonly, are often associated with antecedent joint disease such as rheumatoid arthritis, and occur more often in the elderly. Distinguishing gonococcal and staphylococcal arthritis can be done reliably only by joint aspiration and culture. *S. aureus* is typically seen on Gram's stain and is often associated with an exuberant neutrophilic reaction in joint fluid (more than 100,000 neutrophils per cubic millimeter). Joint culture is positive in 90% of cases, and bacteremia is common. The results of this patient's joint-fluid analysis, with only 17,000 neutrophils and a negative Gram's stain, would be unusual for *S. aureus* infection.

Gonococcal Arthritis

Disseminated gonococcal infection due to *N. gonorrhoeae* may cause two distinct musculoskeletal syndromes: localized septic arthritis and a syndrome of arthralgias, skin lesions, and tenosynovitis called arthritis–dermatitis syndrome. The latter syndrome is associated with positive blood cultures and characteristic skin lesions, which may include macules, petechiae, and purulent vesicles.[4,5] Septic arthritis is rarely found at the same time as bacteremia, a feature that distinguishes this infection from that of *S. aureus*.

Strains of *N. gonorrhoeae* that cause disseminated infection differ biochemically from more common strains that cause urethral symptoms[6-8]; they are less potent stimulators of inflammatory responses and are less likely to cause symptomatic urethral infection.[9-13] Deficiencies of the terminal components of the complement cascade are found in 10% of patients with disseminated gonococcal infection.[14] Disseminated gonococcal infection has been increasingly identified in women. Menstruation appears to be an important risk factor in dissemination, since most cases of this infection occur within 1 week after the onset of menses; thus, details of this patient's menstrual history would have been pertinent.

The diagnosis of disseminated gonococcal infection is established by culturing the blood, cer-

vix, urethra, rectum, pharynx, and synovial fluid. As with all sexually transmitted infections, testing patients and their sexual partners for both gonorrhea and chlamydia is critical.

Treatment for disseminated gonococcal infection is rapidly effective, and the prognosis for both the joint and the patient is excellent. Intravenous ceftriaxone is the mainstay of therapy. Treatment in this case would be a challenge, because the patient had a serious reaction to ceftriaxone in the emergency room. An alternative for patients with cephalosporin allergies had been intravenous quinolone, typically ciprofloxacin, but the Centers for Disease Control and Prevention has recently recommended against the use of fluoroquinolone therapy because of the emergence of widespread resistance in the United States.[15]

In summary, the most likely diagnosis in this case is septic arthritis due to disseminated gonococcal infection in a patient with coincidental EBV-associated infectious mononucleosis.

Dr. Nancy Lee Harris (Pathology): Dr. Davis, the case history rather conspicuously mentions that this patient is a college freshman whose illness occurred in the spring. Do these facts prompt you to consider additional diagnoses?

Dr. Davis: The emphasis on these clues suggests that consideration of an uncommon diagnosis may be warranted. Invasive meningococcal infections are common in nonimmune adolescents and young adults who are exposed to the organism in settings such as college dormitories. College freshmen are particularly at risk, so this patient received vaccination. Invasive infections are thought to be facilitated by the presence of upper airway irritation and may follow upper respiratory infections or influenza. Infection is often acquired in the winter months, so the fact that her presentation was in the spring may be relevant. This patient did not have a typical syndrome of invasive meningococcal infection such as meningitis, fulminant sepsis, and purpuric skin lesions. Chronic meningococcemia is a rare complication associated with characteristic skin lesions; it can be converted into a more acute form by corticosteroids, which this patient did receive shortly before presentation.

Septic arthritis is an uncommon complication of meningococcal infection, but it has been reported.[16,17] This patient may have acquired an infection with a strain of meningococcus that is not covered by the usual vaccine, her upper airway irritation because of infection with EBV may have led to invasive meningococcal infection, and the treatment with corticosteroids for symptoms of mononucleosis may have converted what might have been transient, asymptomatic bacteremia into symptomatic septic arthritis. The one clinical feature of her presentation at her admission to the other hospital that might have suggested the diagnosis of meningococcal sepsis is the presence of profound hypotension, which was only partially relieved by fluids and pressors.

Dr. Harris: Dr. Vergo, will you tell us about the clinical thinking at the time of her admission and the result of the diagnostic test?

Dr. Vergo: Our thinking was similar to that of Dr. Davis. We believed that the patient had septic arthritis, and we strongly favored the diagnosis of disseminated gonococcal infection.

Dr. Harris: Did anyone ascertain the date of her last menstrual period?

Dr. Vergo: No.

CLINICAL DIAGNOSIS

Disseminated gonococcal infection with septic arthritis.

DR. BENJAMIN T. DAVIS'S DIAGNOSIS

Disseminated gonococcal infection with septic arthritis.

PATHOLOGICAL DISCUSSION

Dr. Vergo: On the second hospital day, the first hospital notified us that four of four specimens obtained for blood culture had grown gram-negative diplococci. We then assumed that our clinical diagnosis of disseminated gonococcal infection was correct. We began treatment with ciprofloxacin at a dose of 400 mg intravenously twice daily because of her allergy to ceftriaxone. The next day, the gram-negative cocci were identified as *N. meningitidis.* The specimen was sent to the Massachusetts State Laboratory Institute, which identified the organism as group B *N. meningitidis*.

There was no bacterial growth from cultures of the blood, synovial fluid, throat, cervix, and urethra performed at this hospital. EBV-specific antibody testing confirmed the concurrent diagnosis of acute mononucleosis. The patient was desensitized to ceftriaxone and completed a 2-week course of ceftriaxone at a dose of 1 g intravenously daily. All her close contacts were treated with a single dose of ciprofloxacin by mouth for prophylaxis.

Dr. Harris: Dr. Pasternack, this patient had received meningococcal vaccination before starting college, yet became ill with meningococcal sepsis. Can you discuss the reason for its apparent lack of effectiveness?

Dr. Mark S. Pasternack: Although invasive meningococcal infection is caused by a pathogen with limited antigenic diversity, the currently available vaccines do not prevent all meningococcal infections. There are 13 serologically distinct groups of meningococci, but the vast majority of clinical illness is associated with only 5: A, B, C, Y, and W-135.[18] Unfortunately, the polysialic acid structure of the group B polysaccharide is homologous to human neural glycolipid surface antigens[19]; thus, vaccines against group B may lack immunogenicity or elicit immune reactions against self-antigens and potential immune injury. Therefore, currently available vaccines do not include group B antigens.[20] Not surprisingly, this patient was infected with a group B meningococcal strain, which is not covered by any currently available vaccine.

ANATOMICAL DIAGNOSES

Meningococcal arthritis.
Infectious mononucleosis.

Dr. Davis reports receiving consulting fees from Gilead Pharmaceuticals and having equity ownership in Merck. Dr. Pasternack reports receiving consulting fees from Indevus Pharmaceuticals and having equity ownership in Merck. No other potential conflict of interest relevant to this article was reported.

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