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Case 29-2017: A 59-Year-Old Woman with Pain and Swelling in the Right Hand and Ankles

Lee Park, M.D., Sandra B. Nelson, M.D., and Sarah E. Turbett, M.D.

PRESENTATION OF CASE

Dr. Miranda Theodore (Medicine): A 59-year-old woman was admitted to this hospital because of stiffness, swelling, and severe pain in her right thumb and both ankles.

The patient had been well until 9 days before admission, when stiffness, swelling, and pain developed in the metacarpophalangeal joint of the right thumb that limited her ability to perform tasks such as dressing. The stiffness was not worse in the morning than during the rest of the day, and it did not improve throughout the day. The patient presented to another hospital for evaluation. Radiographs of the hand and wrist were reportedly normal.

Six days before admission, swelling and pain in both ankles developed. The patient was evaluated by her primary care physician, and a 6-day tapering course of oral methylprednisolone was prescribed. After 4 days of methylprednisolone therapy, the joint pain had progressively worsened, and the patient had difficulty walking. She presented to this hospital for evaluation.

On evaluation in the emergency department, the patient reported progressive pain in the right thumb and both ankles. She had no associated fever, chills, night sweats, or preceding trauma. There was also no nausea, vomiting, abdominal pain, diarrhea, cough, rhinorrhea, or dysuria. She had no history of rashes, dry mouth, dry eyes, oral or nasal lesions, or other joint pain. She had a history of stroke and glaucoma, and 7 years before presentation, she had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy for menorrhagia. The patient lived in New England, worked in health care, and was widowed. She was sexually active with one male partner and had had unprotected vaginal intercourse 2 weeks before presentation. She had no pets and did not often spend time outdoors. She did not drink alcohol or use tobacco or illicit drugs. Medications included aspirin and atorvastatin.

On examination, the temperature was 36.6°C, the blood pressure 117/58 mm Hg, the pulse 73 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. She was in no distress and appeared well. The mouth and nose were normal, with no ulcers, and the parotid glands were not enlarged. The first and second heart sounds were

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normal, with no murmurs. The breath sounds were normal bilaterally, with no wheezing or rhonchi. Bowel sounds were present, and the abdomen was soft, nondistended, and nontender on palpation. The edge of the liver was not palpable, and the spleen was not enlarged. The patient had no rash or telangiectasias. The metacarpophalangeal joint of the right thumb was erythematous and warm, and movement and palpation of the joint caused pain. Effusion of both ankle joints was present, with associated warmth but no erythema. There was pain with dorsiflexion, plantar flexion, eversion, and inversion and on palpation of the ankle joints. The remainder of the examination of the joints was normal.

Blood levels of electrolytes and glucose were normal, as were the results of liver- and renal-function tests. The white-cell count was 13,300 per cubic millimeter (reference range, 4500 to 11,000); the remainder of the complete blood count, including a differential count, was normal. An assay for antinuclear antibodies was positive at a titer of 1:40 with a speckled pattern. Urinalysis by dipstick was normal; examination of the sediment revealed no red cells, no bacteria, and 5 to 10 white cells per high-power field (reference range, 0 to 2). The C-reactive protein level was 47.7 mg per liter (reference range, <8.0), and the erythrocyte sedimentation rate was 62 mm per hour (reference range, 0 to 20).

Radiographs of the ankles and feet showed mild, scattered degenerative changes, with no displaced fractures or dislocations. Radiographs of the right hand showed no fractures or dislocations. A radiograph of the chest showed normal lung volumes, with a normal cardiac silhouette and no focal consolidation, pulmonary edema, or pleural effusions.

The patient was admitted to the hospital, and a diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Lee Park: This 59-year-old woman had a sudden onset of erythema, pain, and swelling in the metacarpophalangeal joint of the right thumb, with no associated symptoms or preceding illnesses. Three days later, pain, warmth, and swelling developed in both ankles and progressed despite empirical treatment with glucocorticoids. In developing a differential diagnosis, I will con-

sider the tempo of her illness, the distribution of joint involvement, associated symptoms, and patient-specific risk factors.

MUSCULOSKELETAL INJURY

When the patient initially presented with isolated symptoms involving the metacarpophalangeal joint, I would have had a high suspicion for musculoskeletal injury, which is a common cause of acute joint pain. However, the patient did not recall having an injury, and radiographs did not show a fracture or other abnormalities. Furthermore, the development of symptoms in both ankles 3 days later makes a musculoskeletal process unlikely.

OSTEOARTHRITIS

Osteoarthritis is a common cause of pain in middle-aged and older patients and may involve multiple joints. However, I would expect the symptoms of osteoarthritis to have a gradual onset, to be exacerbated by activity, and to be relieved by rest. The sudden onset, rapid progression, and constant nature of the joint pain seen in this case make osteoarthritis an unlikely diagnosis.

RHEUMATOID ARTHRITIS AND SYSTEMIC RHEUMATIC DISEASES

Rheumatoid arthritis typically involves multiple joints and commonly affects the small joints of the hand. Systemic lupus erythematosus and Sjögren's syndrome can be associated with an inflammatory arthritis that is similar to rheumatoid arthritis, but this patient did not have any associated symptoms (e.g., rash, dry eyes, or dry mouth) that would suggest these diagnoses. Although this patient did not have the rash that is characteristic of psoriasis, psoriatic arthritis precedes the skin manifestations of psoriasis in 15% of patients.¹ Rheumatoid arthritis and arthritis that is associated with other systemic rheumatic diseases classically cause joint stiffness in the morning that lasts for more than 30 minutes. This patient reported joint stiffness, but it was not worse in the morning than during the rest of the day and did not improve throughout the day. In addition, her joint symptoms did not improve after empirical treatment with glucocorticoids. Although early-stage rheumatoid arthritis and psoriatic arthritis remain possible diagnoses in this case, I do not think that either of these

conditions fully accounts for the features of this patient's presentation.

CRYSTAL-INDUCED ARTHRITIS

Gout and calcium pyrophosphate deposition disease are important considerations in a patient with acute joint pain. However, several features of this patient's presentation argue against a diagnosis of crystal-induced arthritis. The incidence of gout is four times as high in men as in women,² although this disparity decreases with age. Gout can affect multiple joints, but most patients with gout initially present with monoarticular disease, classically in the big toe.³ In addition, this patient had not taken medications that are known to confer a predisposition to gout and had not had a provoking event, such as alcohol ingestion or infection.⁴ Calcium pyrophosphate deposition disease generally occurs in patients older than 65 years of age and often begins in the knee, not in the metacarpophalangeal joint or ankles.⁵ Finally, I would expect both gout and calcium pyrophosphate deposition disease to dissipate with glucocorticoid treatment. Overall, this patient's sex, age, distribution of joint involvement, and lack of clinical response to glucocorticoids make gout and calcium pyrophosphate deposition disease unlikely diagnoses in this case.

REACTIVE ARTHRITIS

Reactive arthritis may develop days to weeks after infection with either a gastrointestinal or genitourinary pathogen. During the inciting infection, patients may have diarrheal illness (e.g., due to salmonella, shigella, or campylobacter infection), urethritis (e.g., due to *Chlamydia trachomatis* infection), or no symptoms.⁶ Reactive arthritis is generally monoarticular, although patients may have asymmetric oligoarthritis, dactylitis, or enthesitis.⁶ Patients may have associated extraarticular symptoms, such as uveitis, urethritis, or oral lesions. This patient had not had a recent diarrheal illness or urethritis. She did not report any exposures to new foods, raw foods, or sick contacts. She was sexually active but did not have multiple sexual partners, and she is in an age group associated with a low incidence of *C. trachomatis* infection; in 2015, less than 1% of chlamydial infections in the United States occurred in patients older than 55 years of age.⁷ Although a diagnosis of reactive arthritis associated with an asymptomatic infection with a gastrointestinal or

genitourinary pathogen is possible, it seems unlikely in this case.

INFECTIOUS ARTHRITIS

A key consideration in this case is the apparent involvement of multiple joints, which may suggest a systemic infection with hematogenous spread to the affected joints rather than direct infection or inoculation of a single joint space. Although virtually any systemic infectious process can involve multiple joints, the diseases that are most likely to cause this patient's presentation include certain viral infections, Lyme disease, and disseminated bacterial infections.

Could a viral infection explain this patient's presentation? She had no associated rash or fever and therefore was unlikely to have parvovirus or rubella virus infection. Infection with dengue virus or chikungunya virus is unlikely in the absence of travel outside of New England. Infection with hepatitis B virus (HBV) can cause arthritis during the prodromal phase of illness, when patients may not have any other symptoms.⁸ The patient was sexually active and worked in health care, and these are both risk factors for HBV transmission, but she did not have a known history of needlestick injury at work and did not use injection drugs. I would also expect that, as a health care worker, she most likely had received an HBV vaccine. Hepatitis C virus (HCV) infection can also be associated with arthritis,⁹ and this patient was born between 1945 and 1965, a time period associated with a known high prevalence of HCV infection. Although she had normal results of liver-function tests and no other risk factors for HCV infection, arthritis related to HBV or HCV infection remains a possible diagnosis in this case.

Could this patient have Lyme arthritis? Arthritis is a common manifestation during the late stage of Lyme disease, which is endemic in New England, where this patient lives. Lyme arthritis is typically a monoarticular disease that affects the knee, but it may involve multiple joints.¹⁰ Patients with Lyme arthritis typically appear well and do not have the systemic symptoms that accompany early-stage localized Lyme disease.¹⁰ Although this patient did not have pets or spend time outdoors, patients with Lyme arthritis often do not remember having a tick bite or rash, and the exposure may have occurred months before the onset of arthritis.¹⁰ Without specific serologic

testing, it is not possible to definitively rule out the diagnosis of Lyme arthritis in this patient.

Septic arthritis due to bacterial infection is most commonly caused by gram-positive organisms.¹¹ This patient did not have a history of joint disease, injection-drug use, or direct trauma, but 20% of patients with septic arthritis due to bacterial infection do not have any known risk factors.¹¹ Septic arthritis due to bacterial infection is typically monoarticular, but it is polyarticular in 10 to 20% of cases,¹¹ particularly in patients with preexisting joint disease or overwhelming sepsis. If this patient's polyarticular joint symptoms were due to bacterial infection, I would expect her to have an ill appearance, unless the infection were due to *Neisseria gonorrhoeae*.

Could this patient have disseminated gonococcal infection? This infection can cause either purulent arthritis or a combination of rash, tenosynovitis, and migratory arthralgias.¹² The majority of patients with purulent arthritis due to disseminated gonococcal infection have polyarticular joint involvement, and the knee is the most commonly affected joint.¹¹ Disseminated gonococcal infection is more common in women than in men. However, gonococcal infection is rare among patients in this patient's age group; in 2015, less than 2% of cases of gonococcal infection in the United States occurred in patients older than 55 years of age.⁷ Although this patient is not in a high-risk age group for gonococcal infection, she had unprotected sexual intercourse 2 weeks before her presentation, which fits with the expected time course of disease onset in a person with disseminated gonococcal infection.

ADDITIONAL DATA

Are there any clues in the laboratory data that can help to further narrow the differential diagnosis? Leukocytosis is not unexpected in a person who has recently received glucocorticoids. The elevated C-reactive protein level and erythrocyte sedimentation rate suggest inflammation or infection but are nonspecific. A low positive titer of antinuclear antibodies is unhelpful in the absence of other symptoms that are suggestive of systemic lupus erythematosus or other systemic rheumatic diseases; up to one third of healthy patients have a positive titer.¹³ Urinalysis revealed 5 to 10 white cells per high-power field and no bacteria. Although the results of a urine culture are not available, the absence of bacteria in the urinalysis suggests sterile pyuria (defined as the

presence of >3 white cells per high-power field and a negative urine culture).¹⁴ Sterile pyuria occurs in approximately 14% of women¹⁴ and has a broad differential diagnosis that includes recently treated urinary tract infection, genitourinary tuberculosis, and gonococcal or chlamydial infection.

SUMMARY

This patient presented with acute oligoarthritis, sterile pyuria, and a history of recent unprotected vaginal intercourse. Although this patient's age does not place her at high risk for a sexually transmitted infection, the history of recent unprotected vaginal intercourse 2 weeks before the onset of her joint symptoms and the presence of sterile pyuria on presentation suggest a sexually transmitted infection. Reactive arthritis is a possibility, but it is commonly a monoarticular disease, and the patient did not have any of the characteristic symptoms. Overall, I think disseminated gonococcal infection with purulent arthritis is the most likely diagnosis.

I suspect the diagnostic test was analysis of synovial fluid, obtained by means of arthrocentesis, to further assess for septic arthritis due to gonococcal infection. Nucleic-acid amplification testing of a urine specimen for gonococcal and chlamydial infection may have also been performed.

Dr. Meridale V. Baggett (Medicine): Dr. Nasrallah, what was your impression when you evaluated this patient?

Dr. Mazen N. Nasrallah (Medicine): The rheumatology team was asked to evaluate this patient in the emergency department. When evaluating a patient with joint pain, we ask four important questions. First, has the patient's illness lasted for less than 6 weeks or more than 6 weeks? This patient had had symptoms for 9 days. Second, is the process primarily articular or periarticular? An examination of this patient confirmed the presence of an articular process. Third, is the process inflammatory or noninflammatory? The history and an examination of this patient suggested an inflammatory process. Fourth, what is the pattern of involvement and how many joints are involved? This patient had involvement of three joints in an asymmetric pattern.

In considering these features together, our assessment was that this 59-year-old woman had acute asymmetric oligoarticular inflammatory arthritis. We considered crystal-induced arthritis, early rheumatoid arthritis, seronegative spondy-

loarthropathies, sarcoidosis, and infectious arthritis. We thought that bacterial infectious arthritis was unlikely, since she appeared well.

Arthrocentesis of the tibiotalar joint was performed, and analysis of synovial fluid revealed a nucleated-cell count of 96,000 per cubic millimeter with neutrophil predominance. Given the patient's history of unprotected vaginal intercourse, we thought disseminated gonococcal infection was the most likely diagnosis. We notified the microbiology laboratory that we suspected a diagnosis of gonococcal infection and recommended that a blood specimen be obtained for culture and a urine specimen be obtained for nucleic-acid amplification testing for gonorrhea and chlamydia.

CLINICAL DIAGNOSIS

Septic arthritis due to disseminated gonococcal infection.

DR. LEE PARK'S DIAGNOSIS

Disseminated gonococcal infection with purulent arthritis.

PATHOLOGICAL DISCUSSION

Dr. Sarah E. Turbett: Culture of synovial fluid, which had been obtained by means of arthrocentesis of the right tibiotalar joint, was positive for *N. gonorrhoeae*. Bacterial growth was noted on the blood agar plate and chocolate agar plate and in the thioglycollate broth after 24 hours of incubation (Fig. 1). Gram's staining of a bacterial colony revealed gram-negative diplococci, a finding suggestive of *N. gonorrhoeae*. Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) analysis resulted in the preliminary identification of *N. gonorrhoeae*, which was confirmed with the use of a rapid nucleic-acid hybridization probe specific for *N. gonorrhoeae*. Antimicrobial susceptibility testing with the use of disk diffusion revealed that the isolate was resistant to penicillin and tetracycline but susceptible to ceftriaxone, ciprofloxacin, and spectinomycin. A chromogenic cephalosporin test for β -lactamase revealed that the isolate was positive for penicillinase production, a finding that confirmed resistance to penicillin, ampicillin, and amoxicillin. Finally, on the 15th day of illness, one of four bottles of blood (which had been drawn around

the time that arthrocentesis had been performed) was positive for growth of gram-negative diplococci. A blood workup similar to the synovial-fluid workup confirmed the isolation of *N. gonorrhoeae*, and results of antimicrobial susceptibility testing of this isolate were identical to results of synovial-fluid testing.

DISCUSSION OF MANAGEMENT

Dr. Sandra B. Nelson: The infectious diseases service was consulted on hospital day 5, after the diagnosis of disseminated gonococcal infection had been made. Several subtle features of this patient's presentation highlight the challenge of making a diagnosis of disseminated gonococcal infection. Patients with polyarticular bacterial septic arthritis often have bacteremia and an ill appearance. Thus, in a patient who appears well, such as this patient, inflammatory arthropathies may be more likely to be considered. It is important to note that patients with polyarticular arthritis due to disseminated gonococcal infection may not appear to have generalized sepsis.

Furthermore, the cell count in synovial fluid may be lower in patients with septic arthritis due to gonococcus than in those with septic arthritis caused by other organisms, and the diagnosis can sometimes be overlooked because of the relatively low count. Although there is no threshold at which infection is confirmed, the likelihood of an infectious explanation is lower when the white-cell count in synovial fluid is less than 50,000 per cubic millimeter in a native joint.¹⁵ However, patients with gonococcal septic arthritis often present with a white-cell count in synovial fluid that is within this range.¹⁶ Finally, it is not unusual for patients who present with sexually transmitted infections to have a delay in diagnosis when they are not perceived to be at high risk.

At the time of our evaluation of this patient, we considered strategies for antimicrobial management, the role of surgical débridement, and the potential for coinfection with other sexually transmitted pathogens, as well as public health issues, including the need for reporting. Before the culture results were known, antimicrobial therapy was withheld, because the patient appeared to be clinically and systemically well. After the culture of synovial fluid grew gram-negative diplococci, therapy with intravenous ceftriaxone was begun and a dose of azithromycin was administered. In most cases, the diagnosis of gonococcal

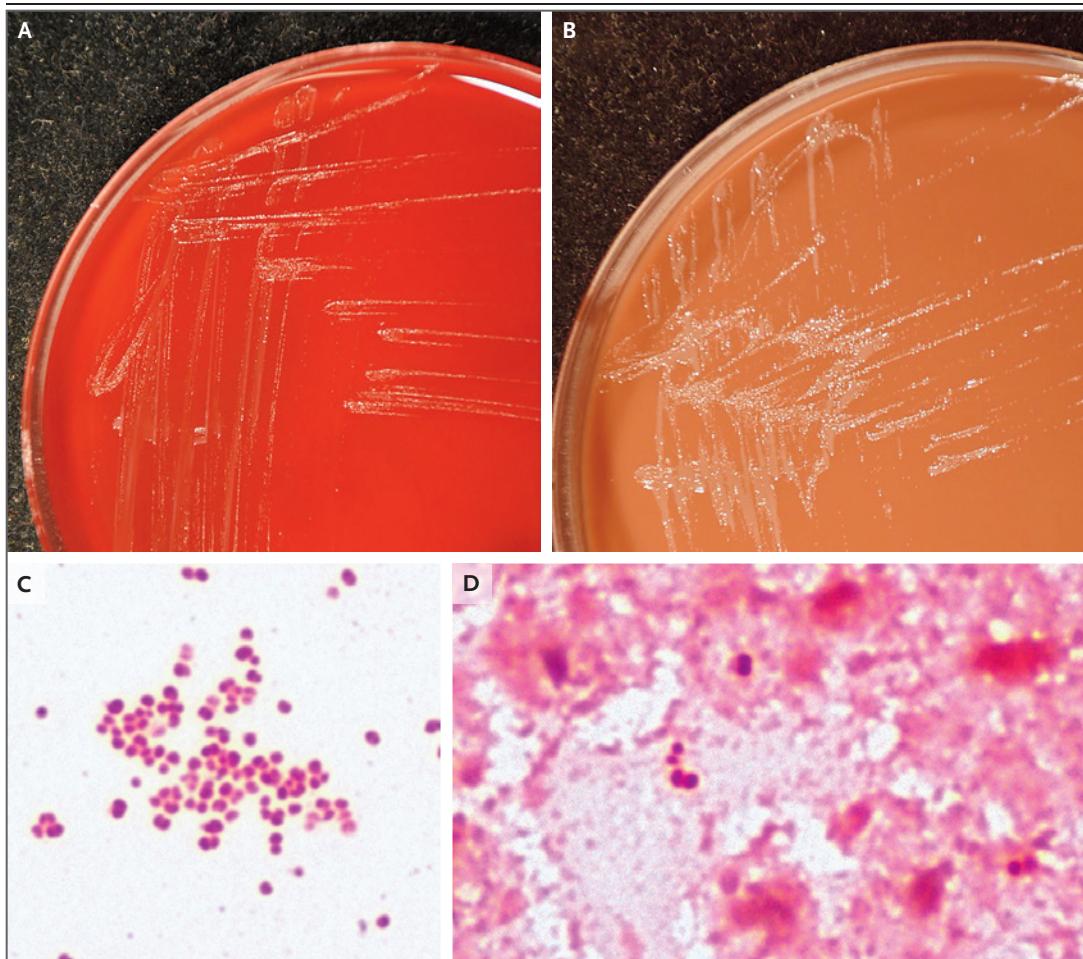


Figure 1. Specimens of Synovial Fluid from the Right Tibiotalar Joint and of Blood.

Culture of the synovial fluid on a blood agar plate (Panel A) and on a chocolate agar plate (Panel B) showed a small, wet-appearing colony after 24 hours of incubation. Gram's staining of the colony (Panel C) revealed gram-negative diplococci. Gram's staining of a bottle of blood (Panel D) also revealed gram-negative diplococci. Molecular testing confirmed that both isolates were *Neisseria gonorrhoeae*.

infection is based on clinical findings or results of nucleic-acid testing, and an organism is not available for antimicrobial susceptibility testing. Therefore, decisions regarding antimicrobial treatment are based on guideline recommendations that have been established as a result of national surveillance. Because there is an increasing rate of antimicrobial resistance among gonococci,¹⁷ the only recommended treatment for disseminated gonococcal infection is intravenous ceftriaxone (with oral azithromycin).¹⁸ However, depending on the clinical context, when the results of susceptibility testing are known, there may be additional treatment options for step-down therapy, provided that the patient has had appropriate

clinical improvement with the use of parenteral therapy. This patient received intravenous ceftriaxone during hospitalization, but fortunately, an organism grew in the culture, which enabled susceptibility testing. Her treatment was subsequently transitioned to ciprofloxacin, which has high bioavailability when administered orally.

Although the standard approach for the treatment of septic arthritis is surgical débridement, this procedure may be avoided in some patients with early-stage gonococcal arthritis. However, the threshold for performing the surgery is lower with the involvement of weight-bearing joints, because such involvement would be associated with functional risks if clinically significant post-

infectious arthritis were to develop. This patient had the progressive inability to walk (despite treatment with intravenous ceftriaxone), bilateral involvement of weight-bearing joints, and a high white-cell count in synovial fluid obtained from the left ankle, a finding consistent with purulent arthritis; all these features contributed to the decision to pursue surgical débridement. On hospital day 4, she underwent arthroscopic irrigation and débridement of both ankles; serosanguineous fluid was noted on the right ankle, and purulent fluid on the left ankle. Because she had previously received antibiotic treatment, operative cultures were negative.

The patient also underwent serial examination of the right thumb, and progressive limitations in flexion of the right thumb developed that were consistent with flexor tenosynovitis. Although gonococcal tenosynovitis often involves the extensor tendons and may not be an indication for surgical débridement, flexor tenosynovitis represents a closed-space infection in which clinically

significant tendon injury can occur. Because this patient's infection involved her dominant thumb, surgical débridement was performed. On hospital day 7, she underwent débridement of the right thumb and flexor tenosynovectomy. The tenosynovium was inflamed but no gross purulence was encountered; operative cultures were negative.

The patient's case was reported to the Massachusetts Department of Public Health, as required by law. An evaluation for other sexually transmitted infections was negative. She reported ongoing symptomatic improvement after the procedures and was discharged to a rehabilitation facility for additional therapy.

FINAL DIAGNOSIS

Septic arthritis due to disseminated infection with *Neisseria gonorrhoeae*.

This case was presented at the Medical Case Conference.

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

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