Disseminated Gonococcal Infection of Pharyngeal Origin: Test All Anatomic Sites

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PRACTICE **POINTS**

- *Neisseria gonorrhoeae* infections of the genitourinary system, rectum, and pharynx can disseminate and cause fever, joint pain, and hemorrhagic papulovesicles that can mimic other serious conditions and require dermatologic expertise to confirm.
- Patients with suspected disseminated gonococcal infection (DGI) as well as patients who are asymptomatic and at increased risk should have all possible anatomic sites of infection—the genitourinary system, rectum, and pharynx—tested with the appropriate molecular assays and culture when appropriate.
- Appropriate recognition and treatment of DGI is vital, as undertreatment can result in serious complications and contribute to the increasing global public health threat of antimicrobial-resistant gonococcal infections.

To the Editor:

Gonococcal infections, which are caused by the sexually transmitted, gram-negative diplococcus *Neisseria gonorrhoeae*, are a current and increasing threat to public health. Between 2012 and 2021, the rate of gonococcal infection in the United States increased 137.8% in men and 64.9% in women,[1] with an estimated 1.5 million new gonococcal infections occurring each year in the United States as of 2021.[2] *Neisseria gonorrhoeae* is the second most common bacterial sexually transmitted infection (STI), and patients with gonococcal infection frequently are coinfected with *Chlamydia trachomatis*, which is the most common bacterial STI. Uncomplicated gonococcal infection (also known as gonorrhea) most commonly causes asymptomatic cervicovaginal infection in women and symptomatic urethral infection in men.[2] Other uncomplicated manifestations include rectal infection, which can be asymptomatic or manifest with anal pruritus, anal discharge, or tenesmus, and oropharyngeal infection, which can be asymptomatic or manifest with throat pain. If uncomplicated gonococcal infections are left untreated or are incompletely treated, serious complications including septic arthritis, myositis, osteomyelitis, myocarditis, endocarditis, and meningitis might occur.[2-5] Ascending, locally invasive infections can cause epididymitis or pelvic inflammatory disease, which is an important cause of infertility in women.[2,3] Gonococcal conjunctivitis also can occur, particularly when neonates are exposed to bacteria during vaginal delivery. Although rare, gonococcal bacteria can disseminate widely, with an estimated 0.5% to 3% of uncomplicated gonococcal infections progressing to disseminated gonococcal infection (DGI).[3-6] Because DGI can mimic other systemic conditions, including a variety of bacterial and viral infections as well as inflammatory conditions, it can be difficult to diagnose without a high index of clinical suspicion. We present a case of DGI diagnosed based on dermatologic expertise and pharyngeal molecular testing.

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A 30-year-old man presented to the emergency department with a rash on the extremeities as well as emesis, fever, sore throat, and severe arthralgia in the wrists, hands, knees, and feet of 2 days' duration. The patient also had experienced several months of dysuria. He reported daily use of the recreational drug ketamine, multiple new male sexual partners, and unprotected oral and receptive anal sex in recent months. He denied any history of STIs. Physical examination demonstrated tender edematous wrists and fingers, papulovesicles on erythematous bases on the palms, and purpuric macules scattered on the legs (Figure 1). The patient also had tonsillar edema with notable white tonsillar exudate.

A shave biopsy performed on a papulovesicular lesion on the right thigh showed an intact epidermis with minimal spongiosis and no viral cytopathic changes. There was dermal edema with a moderate superficial and deep neutrophilic infiltrate, mild karyorrhexis, and focal dermal necrosis (Figure 2). Rare acute vasculitis with intravascular fibrin was seen. Periodic acid-Schiff stain for fungi, Gram stain for bacteria, and immunostains for human herpesviruses 1 and 2 were negative.

Laboratory studies revealed neutrophil-predominant leukocytosis (white blood cell count, 13.89×10^9/L [reference range, $4.5–11.0\times10^9$/L] with 78.2% neutrophils [reference range, 40.0%–70.0%]) as well as an elevated C-reactive protein level and erythrocyte sedimentation rate (19.98 mg/dL [reference range, <0.05 mg/dL] and 38 mm/h [reference range, 0–15 mm/h], respectively). His liver enzymes, kidney function, prothrombin time, and international normalized ratio were all normal. Urinalysis showed trace amounts of blood and protein, and urine culture was negative for pathogenic bacteria. A rapid plasma reagin test and a fifth-generation HIV antibody test were nonreactive, and bacterial blood cultures were negative for other infectious diseases. Nucleic acid amplification testing (NAAT) performed on a swab from a papulovesicular lesion was negative for human herpesviruses 1 and 2, varicella-zoster virus, orthopoxvirus, and mpox (monkeypox) virus. Based on recommendations from dermatology, NAATs for *C trachomatis* and *N gonorrhoeae* were performed on urine and on swabs from the patient's rectum and pharynx; *N gonorrhoeae* was detected at the pharynx, but the other sites were negative for both bacteria. A diagnosis of DGI was made based on these results as well as the patient's clinical presentation of fever, arthralgia, and papulovesicular skin lesions. The patient was treated with 1 g of intravenous ceftriaxone while in the hospital, but unfortunately, he was lost to follow-up and did not complete the full 1-week treatment course.

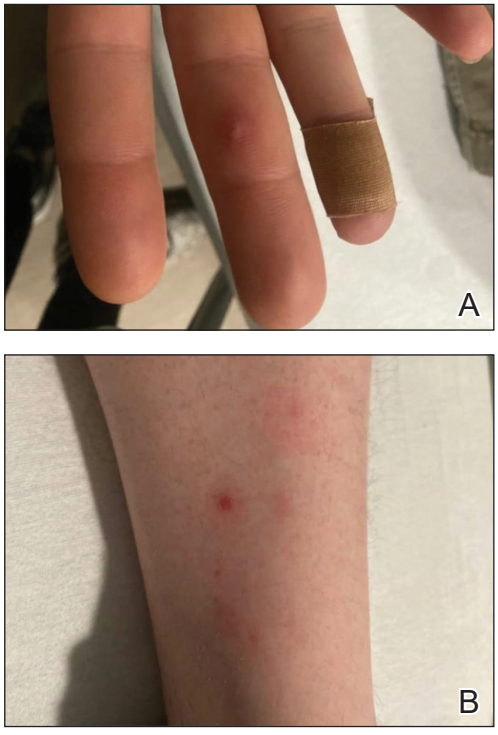

FIGURE 1. A and B, Papulovesicular rash on erythematous bases on the palms and purpuric macules scattered on the legs, respectively, diagnosed as a disseminated gonococcal infection.

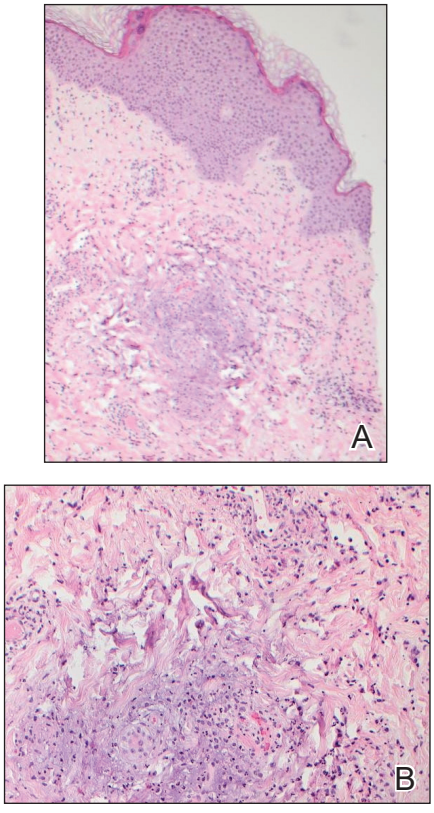

FIGURE 2. A and B, Histopathology from a biopsy of the right thigh revealed an intact epidermis with minimal spongiosis, no viral cytopathic changes, and dermal edema with a moderate superficial and deep neutrophilic infiltrate (H&E, original magnification ×10) as well as mild karyorrhexis and focal dermal necrosis (H&E, original magnification ×40).

Disseminated gonococcal infection (also known as arthritis-dermatitis syndrome) is characterized by the abrupt onset of fever, skin lesions, and arthralgia in a symmetric and migratory distribution. Tenosynovitis involving the extensor tendons of the wrists, fingers, knees, and ankles (particularly the Achilles tendon) is characteristic. Skin manifestations usually include hemorrhagic vesicles and papulovesicles limited to the extremities, often with an acral distribution,[2-5] though other cutaneous lesions have been described in DGI, including macules, purpura, periurethral abscesses, multifocal cellulitis, and necrotizing fasciitis.[7] It is important to consider DGI in a patient who presents with acute systemic symptoms and any of these cutaneous manifestations, even in the absence of joint pain.

The differential diagnosis for a patient with acute fever, joint pain, and hemorrhagic macules, pustules, or vesicopustules includes neutrophilic dermatoses; endocarditis; and infections with other Gram-negative bacteria, such as rat bite fever, *Rickettsia* species, enteroviruses, human herpesviruses, and mpox virus. Evaluation of a patient with suspected DGI includes skin biopsies for histopathology and tissue culture to rule out other conditions, NAATs for gonococcus and chlamydia, and *N gonorrhoeae*–specific cultures at all possible sites of infection, as well as possible disseminated sites such as joint aspirates, blood, or cerebrospinal fluid when appropriate.

Diagnosis of DGI can be difficult, and surveillance is limited in the United States; therefore, the risk factors are somewhat unclear and might be changing. Traditional risk factors for DGI have included immunosuppression due to terminal complement deficiency, female sex, recent menstruation, and pregnancy, but recent data have shown that male sex, HIV infection, use of methamphetamines and other drugs, and use of the monoclonal antibody eculizumab for treatment of complement disorders have been associated with DGI.[2,6-8] In the past decade, uncomplicated gonococcal infections have disproportionately affected Black patients, men who have sex with men, adults aged 20 to 25 years, and individuals living in the southern United States.[1] It is unclear if the changing demographics of patients with DGI represent true risk factors for dissemination or simply reflect the changing demographics of patients at risk for uncomplicated gonococcal infection.[6]

Dermatologic expertise in the recognition of cutaneous manifestations of DGI is particularly important due to the limitations of diagnostic tools. The organism is fastidious and difficult to grow in vitro, thus cultures for *N gonorrhoeae* are not sensitive and require specialized media (eg, Thayer-Martin, modified New York City, or chocolate agar medium with additional antimicrobial agents).[3] Molecular assays such as NAATs are more sensitive and specific than culture but are not 100% accurate.[2,3,5] Finally, sterile sites such as joints, blood, or cerebrospinal fluid can be difficult to access, and specimens are not always available for specific microbial diagnosis; therefore, even when a gonococcal infection is identified at a mucosal source, physicians must use their clinical judgment to determine whether the mucosal infection is the cause of DGI or if the patient has a separate additional illness.

Once a diagnosis of gonococcal infection is made, any isolated gonococcal bacteria should be tested for antimicrobial susceptibility due to rising rates of drug resistance. Since at least the 1980s, *N gonorrhoeae* has steadily evolved to have some degree of resistance to most antimicrobials, and epidemiologic evidence indicates that this evolution is continuing.[2] Current Centers for Disease Control and Prevention (CDC) recommendations are to treat uncomplicated gonococcal infections with 1 dose of ceftriaxone 500 mg intramuscularly in individuals weighing less than 150 kg (increase to 1 g in those ≥150 kg). Disseminated gonococcal infection requires more aggressive treatment with ceftriaxone 1 g intravenously or intramuscularly every 24 hours for at least 7 days and at a higher dose and for longer duration for patients with endocarditis or meningitis.[2] If there is notable clinical improvement after 24 to 48 hours and antimicrobial susceptibility testing confirms an oral agent is appropriate, the patient can be switched to that oral agent to complete treatment. Also, if chlamydia has not been excluded in patients with any type of gonococcal infection, they also should be treated for chlamydia with doxycycline 100 mg twice daily, per CDC guidelines.[2] Dermatologists should advocate for patients to be treated for DGI even if the diagnosis is clinical because of the potential for untreated or undertreated patients to progress, to develop additional antimicrobial resistant bacteria, and/or to transmit the infection to others.

This case highlights 2 important points about gonococcal infections and DGI. First, it is important to test and screen patients for gonococcal infection at genitourinary, rectal, and pharyngeal sites. Despite our patient's report of dysuria, gonococcal infection was only detected via NAAT at the pharynx. As of 2021, CDC guidelines recommend not only testing for gonococcal infection in symptomatic patients at all mucosal sites but also screening all mucosal sites in asymptomatic individuals at high risk.[2] Second, dermatologists' specialized knowledge of cutaneous manifestations provides a valuable tool in the clinical diagnosis of DGI. In this patient, it was the dermatology team's high index of concern for DGI that led to NAAT testing at all mucosal sites and resulted in an accurate diagnosis. Ultimately, dermatologists play an important role in the diagnosis and management of DGI.

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