Disseminated Gonococcal Infection in Japan: A Case Report and Literature Review

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Abstract

Disseminated gonococcal infection (DGI) is quite a rare condition, especially in the Japanese population; only 10 cases have been reported in case notes and minutes. We describe a man in which Neisseria gonorrhoeae was suspected to have infected the patient through his pharynx. He developed chills, fever, tonsillitis, papules, tenosynovitis and migratory polyarthritis without genitourinary symptoms. After conducting a literature review, we suggest that being male is a possible risk factor and that blood culture can be used for diagnosing DGI in Japan. DGI should be considered as a diagnosis for patients with fever, dermatitis and joint pain in Japan.

Key words: disseminated gonococcal infection, Neisseria gonorrhoeae, gonococcal arthritis, gonococcal pharyngitis

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Introduction

Disseminated gonococcal infection (DGI) is a rare but important complication of mucosal infection with Neisseria gonorrhoeae. Classic DGI typically manifests as a combination of dermatitis, tenosynovitis and migratory polyarthritis, or as purulent arthritis without skin lesions (1). Endocarditis, meningitis and osteomyelitis may also occur. However, these complications are considered rare. DGI is reported to develop in 1 to 3% of the 600,000 Americans infected with N. gonorrhoeae each year (2). It is most common in young women, but may develop in sexually active persons of any age.

In the Japanese population, GDI is quite rare; only 10 cases have been ever reported. However the incidence of gonococcal infection in men is as frequent as 33-199 per 1,000,000 people per year (3, 4). Herein, we report a male case of DGI. N. gonorrhoeae is thought to have infected the patient through his pharynx and developed into systemic infection without genitourinary symptoms. In addition, we describe a literature review of Japanese patients with DGI.

Case Report

A 29-year-old healthy, heterosexual, unmarried man was admitted to Nihon University Itabashi hospital because of high fever, sore throat and bilateral arthritis of the wrists. He had been well until 4 days before admission, when he developed chills, fever (40°C) and sore throat. Two days before admission, painful swelling of the right wrist and a rash appeared. He had no history of urethral symptoms or travel abroad. He disclosed unprotected sexual contact including oral sex, 7 days before the onset of symptoms with a Japanese woman (non-commercial sex worker). He denied being homosexual or bisexual.

Physical examination revealed a temperature of 39.4°C. The posterior wall of the pharynx was reddened. Both tonsils were enlarged and reddened, and the crypts were covered with white exudate. A bilateral cervical lymphadenopathy was also noted. Multiple rashes were composed of tender erythematous papules, partly pustular, on both of the forearms and both hands (Fig. 1). Both wrists had painful swelling, and the right wrist had associated flexor tenosyno-
vitis. There were no signs of meningeal, ocular, genitourinary or rectal involvement.

The patient was admitted to our hospital with suspected bacterial endocarditis. On admission, his white blood cell count was 22,400 cells/μL (88.2% polymorphonuclear leukocytes, 5.7% lymphocytes). His C-reactive protein level was 25.1 mg/dL, and his procalcitonin level was 2.4 ng/mL (<0.5). The result of routine biochemical tests and analysis of his urine were normal. Serological tests for syphilis, hepatitis B and human immunodeficiency virus -1 and -2 of his urine were normal. Serological tests for syphilis, hepatitis B and human immunodeficiency virus -1 and -2 were negative. Terminal complement factor and immunoglobulin were normal. Chest X rays and a transthoracic echocardiography showed no abnormalities. Radiographs of the hands and knees were normal.

He was started on 0.5 g of intravenous meropenem four times daily for two days. On the second day of admission, his temperature decreased, but he developed another rash on the inferior limb and asymmetrical painful arthritis involving the jaw, elbows and knees (Fig. 2).

*Neisseria gonorrhoeae* was identified in a blood culture. Gram-negative diplococci from the pustular lesion (Fig. 3) were identified as *Neisseria gonorrhoeae* by a nucleic acid amplification test (NAAT). An arthrocentesis of the right knee showed purulent synovial fluid containing 18,800 white blood cells/mL. NAAT of *Neisseria gonorrhoeae* in the synovial fluid was positive, though the cultures remained sterile. In the urine specimen, cultures and NAATs for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were negative. A group A streptococcus antigen immunochromatographic detection kit was negative when used on a swab of the pharyngeal membranes. Only resident oral flora was cultured from the throat specimens. The NAAT was not performed on the throat swabs, because false-positive results can potentially occur on throat specimens due to cross-reactivity with non-pathogenic Neisseriae, such as *Neisseria lactamica* (5). Based on these findings, the patient was diagnosed with DGI. The strain from this patient was sensitive to ceftriaxone and fluoroquinolones and did not produce β-lactamase. The minimum inhibitory concentration (MIC) of ceftriaxone was 0.03 μg/mL and 0.08 μg/mL for ciprofloxacin. Benzylpenicillin had intermediate resistance with an MIC of 0.12 μg/mL.

The patient was started on intravenous ceftriaxone at a dose of 1 g twice a day, on the fourth admission day. His symptoms and laboratory abnormalities were normalized on the tenth day, and the patient was discharged on the twelfth day after admission.

### Discussion

DGI results from bacteremic dissemination of *N. gonorrhoeae* and typically develops within 2 to 3 weeks of the primary infection (6). Patients with DGI usually have no urogenital symptoms but do have a history of past venereal infection (1). *N. gonorrhoeae* is transmitted by sexual or perinatal contact with the mucous membranes of the urethra, cervix, rectum, oropharynx or conjunctivae.

Pharyngitis caused by *N. gonorrhoeae* infection has increased recently because of changes in sexual behavior (7). However, it is uncommon for Japanese internists to treat patients with an oral infection for *N. gonorrhoeae*. Oral gonococcal infection is difficult to diagnose because symptoms are often lacking or are nonspecific. Also, it can occur in the absence of genital infection (8). The prevalence of symptoms is higher in tonsillitis than in pharyngitis, and the tonsils were invariably enlarged and had whitish-yellow exudates with anterior cervical lymphadenopathy (9). The present patient was predicted to have been infected through the oropharyngeal mucosa because he had pharyngitis, bilateral purulent tonsillitis and bilateral cervical lymphadenopathy without genitourinary symptoms or laboratory abnormalities.

In patients with severe DGI symptoms, approximately 60% develop dermatitis, 60% develop tenosynovitis (10) and 85% have arthralgia (6). Septic emboli can cause polyarticular tenosynovitis and dermatitis. Immunological mechanisms may contribute in some cases, which are demonstrated by frequent negative cultures (1). The skin lesions are typically few, limited to the extremities and start as papules, which then progress into hemorrhagic pustules (11). Tenosynovitis can usually be confirmed by eliciting pain along the tendon sheath with active or passive joint movement. Often multiple tendons are simultaneously inflamed, particularly in the wrist, fingers, ankle and toes. However, symmetric joint involvement is uncommon. Typically, the initial aspiration of the synovial fluid is negative when cultured. If arthritis caused by DGI is untreated, it may develop into septic arthritis (12).

Generally, DGI is difficult to diagnose. A history of recent symptomatic genital infection is rare (1). In most cases, cultures of the synovial fluid and skin lesions were negative (12, 13), but positive blood cultures are found in 50% of DGI cases that present with dermatitis, tenosynovitis or
polyarthralgia syndrome (6, 14, 15). After the development of purulent arthritis, \textit{N. gonorrhoeae} is recovered from fewer than 50 percent of purulent synovial effusions (11, 14, 16). The percentage of positive mucosal surface cultures on Thayer-Martin media from urethral, cervical and rectal samples from patients with DGI ranges from 25% to 100% (14-16). The NAAT offers greater sensitivity than bacterial culture. However, relying on the NAAT for diagnosis has two problems. First, cross-reaction with related \textit{Neisseria} species can cause false-positive results (5, 17). Second, NAAT does not provide data on antibiotic resistance. Thus, culture remains the gold standard. In the present case, the diagnosis of DGI was made because of the clinical picture: a positive blood culture and a positive NAAT concurrent with synovial fluid and skin lesions.

DGI is approximately four times more common in women than men in the United States (6), and many of the men with DGI are homosexual or bisexual. Dissemination is more likely following menstruation and during the postpartum period (2) because of alterations in vaginal pH and the nature of cervical mucus, which enables bacteria to more easily enter the bloodstream through the endometrium (5, 13). A reduced local inflammatory response to gonococcal strains may also occur when DGI is combined with congenital or acquired complement deficiencies or systemic lupus erythematosus (16, 18).

A summary of the 11 reported cases of DGI in Japan is shown in Table 1 (19-28). Ten cases were reported to the Japana Centra Revuo Medicina between 1983 and 2010, including three that presented with very rare conditions: two with endocarditis and one with meningitis. Most of the cases were in young to middle-aged men (male-female ratio 9 to 2, age range 15 to 57 years old, average age 39.8 years old, n=11). All ten patients developed a fever, eight developed polyarthralgia, and eight had dermatitis. Of the eleven cases, four were immunodeficient: two had hypocomplementemia (cases 4 and 5), one was infected with HIV and one had short bowel syndrome with pulmonary tuberculosis. Of the immunocompetent patients, two had been traveling to Southeast Asia (case 6 and 10). In the present case (case 11), the patient had no risk factors and no history of overseas travel. Only two cases, cases 1 and 5, had urogenital symptoms. Of the cases in women, two were younger than the male patients, 15 and 21 years old. Of the two cases, one had trichomonal vaginitis, herpes simplex and hepatitis B infection and had had frequent sexual intercourse with multiple partners.
partners. The other had severe systemic lupus erythematosus. Neither infection was related to menstruation or the postpartum period. Unlike in the United States, we found DGI to be less common in women. Three out of the eleven cases in Japan had very rare conditions, such as endocarditis or meningitis. Eight patients had positive blood cultures. Therefore, we find that blood cultures are useful for the diagnosis of DGI in Japan. Therefore, we advocate the importance of timely diagnosis and therapeutic intervention for DGI patients with fever and dermatitis in conjunction with joint swelling and pain, even if the patient has no genitourinary symptoms.

The authors state that they have no Conflict of Interest (COI).

References