Disseminated Gonococcal Infection in an Immunocompetent Patient Caused by an Imported Neisseria gonorrhoeae Multidrug-Resistant Strain

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We herein report the microbiological features of a Neisseria gonorrhoeae strain isolated from an immunocompetent patient with disseminated gonococcal infection (DGI). The strain expressed the IA/IB serovar; was resistant to penicillin, tetracycline, and ciprofloxacin; and had presumably been acquired in Southeast Asia. To date, this is the first case reported in our country of DGI due to an imported multidrug-resistant strain.

CASE REPORT

A 48-year-old man reported to the emergency department of Turin General Hospital with generalized malaise, pyrexia, nausea, and vomiting. His past medical history revealed hypertension and a recent trip to Thailand where he had engaged several times in sexual intercourse with local sex workers. Physical examination revealed a temperature of 39.8°C, a blood pressure of 190/100 mm Hg, a faint mitral holosystolic murmur, and diffuse hemorrhagic skin rash. There were no signs of meningeal involvement. The patient was admitted to the general medicine ward with suspected bacterial endocarditis. Upon admission, biochemistry was normal, and the white blood cell count was 14,100 (83.9% polymorphonuclear leukocytes, 7.3% lymphocytes, and 8.5% monocytes). The erythrocyte sedimentation rate was 78 mm/h, and the C-reactive protein level was 5.9 mg/dl. Chest X rays and transthoracic echocardiography were normal. Gram-negative diplococci were observed. The gonococcal strain was sent to the laboratory of the Istituto Superiore di Sanità for complete phenotypic and genotypic characterization. After growth on GC agar plates supplemented with 2% Isovitalex (Oxoid) and incubated at 37°C in 5% CO2 for 18 to 20 h, a serological assay by coagglutination reaction was performed using two monoclonal antibodies (Phadebact GC serovar test; Boule Diagnostic AB, Sweden) directed against epitopes of the IA and IB porin proteins. The isolate showed a reactivity against both porin proteins, thus resulting in a hybrid serovar (IA/IB).

Antimicrobial susceptibility testing was carried out using a panel of 5 antibiotics (penicillin, tetracycline, spectinomycin, ciprofloxacin [Cip], and ceftriaxone) by the E test method (ABbiodisk, Sweden) and by the CLSI (3). A nitrocefin chromogenic test (Oxoid) according to the manufacturer's instructions was performed. The antimicrobial susceptibility breakpoints were those defined by the CLSI (3). A nitrocefin chromogenic test (Oxoid) was used to detect the presence of β-lactamase production. The strain was resistant to three of the five antibiotics tested. In particular, the MICs were >32 μg/ml for penicillin, 24 μg/ml for tetracycline, and 4 μg/ml for Cip. MICs for ceftriaxone and spectinomycin were 0.002 and 6 μg/ml, respectively.

Molecular analysis of the target genes involved in each antibiotic resistance mechanism was performed. In particular, after total bacterial DNA extraction with a QIAGEN DNA extraction kit, a multiplex PCR assay was used to differentiate β-lactamase plasmids using the following primers: BL1 (5'-TACTCAATCCTGTAATTGGCT), BL2 (5'-CACCATAAAATCTCGCAAGC), BL3 (5'-CCATAGTGTTGAGTATTGCG) (10, 11, 12), BL4 (5'-TCATCGTGCTTCTAGGA) (10, 11, 16). Detection of a plasmid named “Toronto/Rio” confirmed the presence of a penicillinase-producing N. gonorrhoeae isolate, a common feature of most gonococci responsible for disseminated gonococcal infection (DGI) (8, 9).

The tetracycline resistance mobile elements were detected by PCR using three primers, UF (5'-CTCGGACAAAGGAGAAAC), AR (5'-GCATTCACCTTCACAC), and DR (5'-TGCAAGAGGAAC), which previously described (10, 11, 16). The high level of tetracycline resistance (MIC of 24 μg/ml) was due to a plasmid defined as an “American type plasmid,” the most frequently detected plasmid in tetracycline-resistant N. gonorrhoeae isolates (16).

To investigate the presence of amino acid substitutions on the two target genes (gyrA and parC) known to be involved in resistance to ciprofloxacin (2), sequence analyses of the quinolone resistance determinant regions were performed after amplification with primers gyrA1 (5'-CGGCGCTACTGTACGCGGATC) and gyrA2 (5'-ATGTCGCCAGCTTCTCAGTGAA), parC1 (5'-ATGCAGATGTGGGTTTACG), and parC2 (5'-GGACACACGGAATTCGCAG) (15). The anal-
ysis of sequences revealed the presence of amino acid substitutions Asp$_{96}$→Asn in the parC gene and Ser$_{91}$→Phe and Asp$_{95}$→Gly in the gyrA gene. These changes have already been described in the literature as being correlated to the Cip-resistant phenotype (1).

*N. gonorrhoeae*, the causative agent of the homonymous sexually transmitted disease, has the human genital tract as its reservoir. However, it has also numerous other presentations both inside and outside the genitourinary tract (14). In recent years, despite the worldwide increase in genital gonococcal infections, complicated cases such as DGI have rarely been reported (6, 9, 14). The clinical manifestations of DGI include skin disorders, arthritis, endocarditis (rarely occurring in 1 or 2% of cases), or other localized infections (1, 7–9, 13, 14). The pathogenesis of DGI has been associated with both microbial and host factors. The patient’s complement deficiency is considered one of the most important causes favoring the course of disease (12). In this report, we investigated a case of DGI in an immunocompetent patient with suspected bacterial endocarditis. The *N. gonorrhoeae* isolate was completely characterized for its microbiological features.

Considering the history of the patient, infection very likely occurred in Southeast Asia; the isolated strain showed multiple-antibiotic resistance, and this is particularly significant occurred in Southeast Asia; the isolated strain showed multiple-antibiotic resistance, and this is particularly significant. The spread of gonococci with multiple-antibiotic resistance could partially explain the occurrence of DGI without any particularly altered host factor. The characterization of molecular changes associated with gonococcal resistance in DGI is essential to provide rapid advice for clinical management of cases. In fact, multidrug-resistant DGI can be fatal if not recognized and treated correctly. Moreover, the sporadic occurrence of DGI highlights the need for a reconsideration of diagnostic and epidemiologic criteria to include the search for *N. gonorrhoeae* in clinical samples in order to avoid misidentification and thus a delay in appropriate treatment.

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**REFERENCES**