New microbial and host factors in disseminated gonococcal infection: case report

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SUMMARY Disseminated gonococcal infection was diagnosed in an immunocompromised patient who presented with oligoarthritis and tenosynovitis. The gonococcal isolate was prototrophic, showed intermediate resistance to penicillin, and belonged to serogroup WII/III. An isolate from the patient's sexual contact showed similar characteristics. The patient had a *Saccharomyces* opsonin defect, which is associated with childhood infections and has not been reported previously in association with disseminated gonococcal infection. The pathogenetic importance of the unusual isolate and the underlying host defence defect is considered.

Introduction

Disseminated gonococcal infection is a rare but important complication of mucosal infection with *Neisseria gonorrhoeae*.¹¹ Most strains recovered from systemic disease require arginine, hypoxanthine, and uracil for growth,^{2,3} and show pronounced sensitivity to penicillin.⁴ We report, however, on a patient with disseminated gonococcal infection whose gonococcal isolate was atypical and whose complement pathway was defective.

Patient and methods

A West Indian girl aged 17, who was constitutionally well, presented on the first day of her menses with asymmetric oligoarthritis and tenosynovitis of four day's duration. She had developed the nephrotic syndrome four years earlier, had required haemodialysis after two years, and was currently receiving azathioprine 150 mg and prednisolone 17.5 mg a day three months after undergoing cadaveric renal transplant, the underlying pathology being mesangial proliferation.

N gonorrhoeae was isolated from a high vaginal swab. Cultures for gonococci from the urethra, throat, and blood gave negative results.

She was treated with high doses of penicillin for nine days; benzyl penicillin 600 mg intravenously four times a day for 48 hours followed by a week's course of amoxycillin 500 mg orally three times a day. Her symptoms resolved within two days. Follow up gonococcal cultures were reported as giving negative results on two occasions.

Her male sexual partner and his two additional female sexual contacts were culture positive for *N gonorrhoeae*; none had evidence of disseminated gonococcal infection.

MICROBIOLOGY

N gonorrhoeae was isolated on neisserial medium containing 36 g/l GC base agar (Difco), 1% IsoVitalax (BBL), and vancomycin, colistin, trimethoprim, and amphotericin incubated at 36°C for 48 hours in 6% carbon dioxide. Colonies of oxidase positive Gram negative cocci were confirmed as being *N gonorrhoeae* by their ability to produce acid from glucose, but not from maltose or sucrose, and their inability to produce β galactosidase.

Auxotyping was performed by the method described by Catlin *et al.*⁵ Susceptibility to penicillin was assessed by incorporating penicillin (range 0.015 mg/l to 2 mg/l) into agar plates by methods previously described.⁶ The serogroup and serovar were identified by a coagglutination test using a panel of monoclonal antibodies⁷ raised to the outer membrane protein (PI), which were provided by Dr S Bygdeman, Stockholm, Sweden. The presence of serum IgG and IgA antibodies to a cell envelope extract of *N gonorrhoeae* was verified using an enzyme linked assay.⁸

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TABLE I Characteristics of typical isolates of *Neisseria gonorrhoeae* and those from patient with disseminated gonococcal infection and her sexual contact

	Patient	Contact	Typical
Auxotype	Prototrophic	Prototrophic	Arg ⁻ Hyx ⁻ Ura ⁻
MIC (mg/l) of penicillin	0.12	0.12	0.03
Serogroups	WII	WII	WI
Serovar	Bajk	Bajk	Not known

MIC = minimum inhibitory concentration.

Arg⁻ = arginine requiring, Hyx⁻ = hypoxanthine requiring, Ura⁻ = uracil requiring.

IMMUNOLOGY

Saccharomyces opsonins were tested using the radiometric method of Bridges *et al.*⁹ modified for use with *Saccharomyces cerevisiae*. In brief, 4×10^4 normal neutrophils were incubated in a microtitre plate for 40 minutes with 2% patient serum and 2×10^5 *Saccharomyces*. Tritiated uridine was added, and incubation proceeded for a further hour. Cells were harvested and beta counted giving counts per minute (cpm). An opsonin index was calculated by comparison with a well free from neutrophils using the following equation:

$$\frac{(1\text{-cpm with neutrophils})}{(\text{cpm without neutrophils})} \times \frac{\text{Saccharomyces concentration}}{\text{polymorph concentration}}$$

Results

BACTERIAL FACTORS

Table I shows characteristics of the isolates of *N gonorrhoeae* from our patient and her male sexual partner compared with the gonococcal isolates typically associated with disseminated gonococcal infection.

HOST FACTORS

A reduced *Saccharomyces* opsonin index of 1.8 (normal more than 2.8) was recorded in the acute and convalescent phases, which represented an underlying defect of the complement pathway. *Candida* opsonins were normal. Circulating C₁ binding immune complexes were present at the onset of the acute infection (table II).

Discussion

Strains of *N gonorrhoeae* isolated from disseminated gonococcal infection all have similar characteristics; they require arginine, hypoxanthine, and uracil for growth, are very susceptible to penicillin, and generally belong to serogroup WI. These organisms are also able to resist killing by normal human serum.¹⁰ The bactericidal action of human serum is thought to protect the host from systemic infection by strains sensitive to serum. The isolates of *N gonorrhoeae* from this patient and her sexual contact were prototrophic (wild type), showed increased levels of resistance to penicillin, and belonged to serogroup WII/WIII. These characteristics are more commonly associated with organisms sensitive to serum.

The absence of IgG and IgA antibodies in three consecutive serum samples from our patient was also unusual. Our experience is that patients with disseminated gonococcal infection produce high concentrations of antibody in this test.

The role of opsonisation in mucosal and disseminated gonococcal infection is not defined. A reduced *Saccharomyces* opsonin index has been associated with various pyogenic infections, especially in childhood, but not with disseminated gonococcal infection.¹¹

The abnormal handling of *N gonorrhoeae* in this patient may also have been due to the defect in opsonisation, though disseminated gonococcal infec-

TABLE II Underlying defects in defence mechanism of patient with disseminated gonococcal infection

Complement profile	Date tests performed			Normal range
	8.8.84	20.8.84	1.10.84	
Total haemolytic C(%)	115	120	125	60-140
C4 (%)	190	110	105	60-140
C3 (%)	180	135	100	75-125
C3d (mg/l)	Not done	117	89	40-130
C reactive protein (mg/l)	27	< 5	< 5	< 5
C ₁ binding immune complexes (IgG and IgM)	Present	Not done	Not done	
<i>Saccharomyces</i> opsonin index*	Not done	1.8	1.85	> 2.8
<i>Candida</i> opsonins or procidins	Normal	Normal	Normal	
Antibody (IgG and IgA) to <i>N gonorrhoeae</i>	Absent	Absent	Absent	Present

* $\frac{(1\text{-cpm with neutrophils})}{(\text{cpm without neutrophils})} \times \frac{\text{Saccharomyces concentration}}{\text{polymorph concentration}}$

tion has only been associated previously with defects of the late complement components.¹² The *Saccharomyces* opsonin defect may affect both classic and alternative complement pathways.^{13 14} Alternative pathway complement activation may be necessary to initiate the lytic pathway as part of non-specific defence against the gonococcus, pending a specific antibody response that would utilise classic pathway activation as a means of promoting lytic pathway activation.

Since presenting this case report, a second patient with disseminated gonococcal infection has been found to have a reduced *Saccharomyces* opsonin index, and an associated defect of *Candida* opsonisation (Lacey C, personal communication). This additional case lends further support to the idea that this type of complement pathway defect is indeed an important background to disseminated gonococcal infection. It also seems unlikely that the immunosuppressive treatment given to our patient was a major factor in predisposing to disseminated gonococcal infection.

In conclusion, disseminated gonococcal infection was caused by an atypical strain of *N gonorrhoeae* in a patient who had a defect of the complement pathway not previously associated with disseminated gonococcal infection.

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