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# CIRCULATING IMMUNE COMPLEXES IN A PATIENT WITH PROLONGED GONOCOCCAL SEPTICEMIA

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*Abstract.* A case of prolonged gonococcal septicemia is presented. Lack of genital symptoms, of demonstrable gonococcal antibodies in whole serum, and initially also of skin lesions contributed to a delayed diagnosis that was finally confirmed by positive blood culture. Evidence of circulating immune complexes was obtained by the demonstration of gonococcal IgG antibodies after dissociation of serum by gradient centrifugation at pH 4.0. The possibility that circulating immune complexes may contribute to the symptomatology of gonococcal septicemia is pointed out.

*Key words:* N. gonorrhoeae; Arthritis; Septicemia; Immune complexes

Intermittent fever, migratory arthralgia, arthritis with or without effusion, muscular pain and characteristic papulopustules or cutaneous manifestations resembling urticaria or erythema nodosum have been described as typical of gonococcal septicemia in a number of reports, both from the pre-antibiotic era (9) and during the last decade (1, 3, 13). Gonococci have been isolated in these patients from the blood and joint effusion (3, 7) and they have been demonstrated in smears and biopsies of skin lesions by immunofluorescence techniques (4, 8). Genito-urinary symptoms are often absent but cultures from these sites demonstrate growth of gonococci in most of the patients (2, 3, 13).

The main symptoms in patients with this syndrome are clearly related to an active infection by *N. gonorrhoeae* and there is much evidence indicating that joint effusions and skin lesions are manifestations of gonococcemia (1, 3, 7, 13). Other inflammatory reactions, for example migratory arthralgia, "sterile" arthritis, muscular pain, perimyocarditis and erythema nodosum-like manifestations might be the result of a direct toxic effect of the potent endotoxin of the gonococcus. They might, however, also be consistent with the expressions of an immune complex disease, as was suggested by Holmes et al. (7), although they did not present any evidence for this hypothesis.

To our knowledge, no data have been reported on the existence of circulating immune complexes in gonococcal septicemia. We therefore found it worthwile to present a case of prolonged gonococcemia in which evidence for circulating immune complexes was obtained by the demonstration of gonococcal antibodies after dissociation of serum at low pH.

## MATERIAL AND METHODS

### *Case Report*

The patient was a 38-year-old male, who in 1964 was splenectomized because of essential thrombocytopenia. In Dec. 1972, his heels were affected by pain and tenderness and he had slight and transient fever. He was admitted to the Roslagstull Hospital for Infectious Diseases, Jan. 16, 1973 on account of persistent symptoms. He was in good general condition but subfebrile and had moderate swelling and slight warmth of the ankles. No skin lesions were found. ESR was 34 mm/1 hr, WBC 9 600/mm³ with 55 % polymorphonuclear cells and 14 % eosinophils. Urine analysis, serum-creatinine, and liver function tests were normal. Nose and throat cultures were normal. Blood cultures were not performed. Tests for rheumatoid factor were negative. IgG in serum was 520 mg/100 ml, IgM 45 mg/100 ml, IgA 250 mg/100 ml. The symptoms disappeared without specific therapy and he was discharged on Feb. 1, afebrile but with WBC 11 000 cells/mm³ and ESR 20 mm/1 hr. In May 1973 he had a period of shivery chills and fever spikes up to 40.3°C, without any other concomitant symtoms. The fever subsided within a week and he was free from symptoms for the next 2 months. On Aug. 19, he had a chill with a fever spike up to 39.6°C, accompanied by aches in hands, knees and ankles. On the following day he was still febrile and he noticed a small pustular lesion in the left thumb-grip. He was hospitalized on Aug. 21. Temperature was then 37.3°C but during the following 2 weeks he got fever spikes every second to

Table I. *Gonococcal antibody titres demonstrated with the GCFT in serum specimens*

| Day of serum sampling | Antibody titre with the GCFT |
|---|---|
| August 23 | < 1:2 |
| September 5 | < 1:2 |
| September 13 | 1:2 |
| October 8 | 1:8 |

fourth day. No signs of arthritis or symptoms from the genito-urinary tract were noted. ESR 17 mm/hr, WBC 8000–14 900/mm³. Urine analysis and liver function tests were normal. Widal tests were negative in spite of TAB-vaccination a few months previously. Two blood cultures (Aug. 23 and Sept. 5) yielded growth of gonococci, fully sensitive to penicillin. Culture of specimens from urethra and rectum were negative for gonococci. Aspirates from scattered skin efflorescences that developed in connection with a fever spike on the 16th day of hospitalization gave no growth but numerous gonococci were demonstrated by IF technique. Histopathological examination of a biopsy from an erythema of the hand that appeared 10 days after admission, revealed small perivascular cell infiltrates with lymphocytes and some eosinophils. Benzylpenicillin, 6 mega-units daily, was given for 7 days, and oral penicillin V for another 7 days. The lesions disappeared and the patient promptly became asymptomatic. He was discharged on Sept. 15.

*Gonococcal complement fixation test (GCFT)*

The micromodification of the Laboratory Branch Complement Fixation (LBCF) test was used as described elsewhere (5) for tests of gonococcal antibodies in serum specimens and in serum fractions obtained by preparative ultracentrifugation. Whole cells of the gonococcal strain isolated from the patient's blood were used for the preparation of gonococcal antigen, prepared as previously described (5). A polyvalent antigen prepared from six randomly selected gonococcal strains was also used. This antigen is used in the laboratory in the routine GCFT. Each test was done in duplicate and appropriate controls were included.

*Preparative ultracentrifugation*

0.5 ml of serum diluted 1:2 was layered over gradients of sucrose ranging from 10 to 27%, with a final volume of 5 ml.

Table II. *Gonococcal antibody titres demonstrated with the GCFT in fractions from preparative ultracentrifugation at pH 7.2 and pH 4.0 of serum specimen from August 23*

| Fractions from preparative ultracentrifugation | Antibody titre with the GCFT |
|---|---|
| IgM-fraction, pH 7.2 | < 1:2 |
| IgG-fraction, pH 7.2 | < 1:2 |
| IgM-fraction, pH 4.0 | < 1:2 |
| IgG-fraction, pH 4.0 | 1:8 |

The pH of the gradients was 7.2 and 4.0 respectively. The gradients were centrifuged in a Spinco SW 50 rotor at 35000 rpm for 18 hours at 4°C. Serial fractions were collected from the bottom of the tubes. IgM and IgG levels of the fractions were determined by single radial immunodiffusion (10).

*Platelet aggregation (pl.a.) test*

The test was carried out as described by Myllylä et al. (12).

## RESULTS

The results of GCFT are summarized in Tables I and II. It will be seen that serum specimens from Aug. 23 and Sept. 5 were negative with both antigens. A third serum specimen, obtained on Sept. 13, during treatment, had a titre of 1:2. A fourth specimen obtained 4 weeks after commencement of therapy, had a titre of 1:8. The same results were obtained both with antigen from the patient's own strain and with the polyvalent antigen.

Serum from Aug. 23 was subjected to gradient centrifugation at pH 7.2 and pH 4.0. Table II shows that after centrifugation at pH 7.2 all fractions were negative in the GCFT, whereas after centrifugation at pH 4.0 the fraction corresponding to IgG (Fig. 1) gave a titre of 1:8, whereas that corresponding to IgM was negative.

Pl. a. tests on sera from Aug. 23 and Sept. 5 were both negative.

## DISCUSSION

The findings of the present study indicated the presence of circulating immune complexes in a patient with prolonged gonococcemia that was confirmed by positive blood cultures and by the demonstration of gonococci in skin lesions.

During the clinical phase of the patient's disease, gonococcal antibodies were not demonstrated, either in whole serum or within the 7S IgG fraction after gradient centrifugation at neutral pH. Antibodies were demonstrated, however, after such centrifugation at pH 4.0. Antigen–antibody complexes will dissociate at the low pH, thus revealing the gonococcal antibody which at neutral pH is blocked by inhibiting antigens. It might be presumed that the immune complexes in this patient had a molecular size corresponding to a sedimentation constant < 19 S as the platelet agglutination test was negative. This test is considered very sensitive (14) but reveals only complexes with a sedimentation constant > 19 S.

Mannick & Arend (11) have shown that the RES removes circulating immune complexes very rapidly but that small complexes are removed slowly from the circulation. Our patient was splenectomized 10 years earlier and it is possible that the RES function could have been influenced by this event, thus promoting the persistence of immune complexes within the circulation.

Using the GCFT, Danielsson et al. (5) reported the occurrence of an active immune response to gonococcal antigens in about 90% of the patients with gonococcal septicemia, and 2 to 3 weeks after treatment the titres were usually relatively high. The low gonococcal antibody titres found after adequate treatment of the patient in this report, his negative Widal test despite a booster dose of TAB vaccine a few months earlier, and his low serum levels of IgG (5.2 mg/ml) and IgM (0.4 mg/ml) might indicate a decreased capacity for antibody formation. These circumstances may have contributed to the formation of soluble immune complexes, as has been suggested that individuals producing antibody responses less than equivalent to the antigenic stimulation may be most susceptible to immune complex diseases (6). This view is consistent with an increased incidence of immune complex diseases in hypoimmunoglobulinemic individuals (6).

These mechanisms might have been operating in this patient. It should be mentioned in this connection that large numbers of gonococci were demonstrated in his skin lesions by immunofluorescence and that two consecutive blood cultures showed growth of gonococci. It is our experience that gonococci occur sparsely in the skin lesions (3, 4) and in a series of 23 patients with gonococcal septicemia, Barr & Danielsson (3) obtained positive blood cultures in only 15% of them.

We consider that our findings in this patient should draw attention to the possibility of circulating immune complexes contributing to the symptomatology of gonococcal septicemia. Using the GCFT, Danielsson et al. (5) reported that during the early phase of gonococcemia only 30–40% of the patients have demonstrable antigonococcal antibodies and usually of low titres even though many of these patients have had the gonococcal infection for a long time. Search for gonococcal antibodies after dissociation of immune complexes at low pH may be profitable in cases without gonococcal antibodies demonstrable in whole serum by conventional methods.

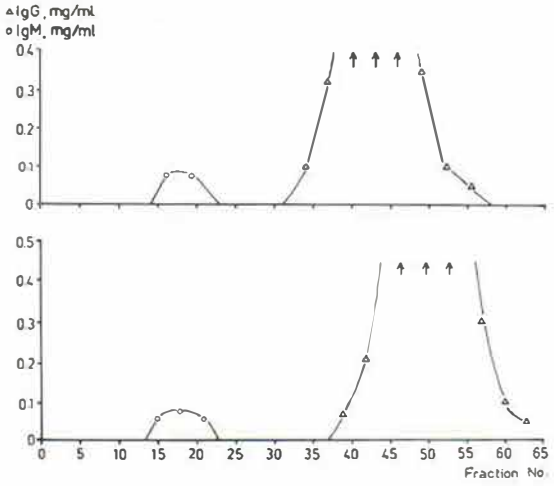


*Fig. 1.* Gradient centrifugation of serum from Aug. 23 at pH 7.2 (upper diagram) and at pH 4.0 (lower diagram). Fractions 15–23 (IgM of both pH 7.2 and 4.0), 33–55 (IgG of pH 7.2), and 37–60 (IgG of pH 4.0) were collected and subjected to GCFT.

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