

Aseptic arthritis after gonorrhoea

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SUMMARY Sixteen patients with aseptic arthritis developing after gonorrhoea and 14 patients with arthritis after nongonococcal urogenital infection have been analysed with respect to clinical course, roentgenological signs, and humoral as well as cellular immune responses to *Neisseria gonorrhoeae* antigen. Fifty-eight healthy blood donors were used as controls. The clinical pattern did not differ significantly between the 2 groups. Eye or skin lesions indicative of Reiter's syndrome were found in 5 patients of both groups. Signs of sacroiliac arthritis were found in 8 and 6 patients respectively. Gonococcal complement fixation was positive in 9 of 16 patients in the postgonorrhoeal arthritis group and in 0 of 14 patients in the arthritis group with nongonococcal urogenital infection. The lymphocyte stimulation induced by gonococcal antigen was significantly greater in patients with postgonorrhoeal arthritis than in healthy controls. When reference was made to the results of stimulation of the lymphocytes with PPD, there was also a significant difference in the lymphocyte reactivity to gonococcal antigen between the group of patients with postgonorrhoeal arthritis and that of patients with arthritis after non-gonococcal urogenital infection. No such difference was noted between the latter group and the healthy controls. The clinical and immunologic data argue in favour of the hypothesis that *Neisseria gonorrhoeae* may induce an aseptic arthritis which sometimes presents as a complete Reiter's syndrome.

Most authors have accepted a gonococcal aetiology of joint complications associated with urethral discharge only when *Neisseria gonorrhoeae* are found in the synovial fluid and/or in the peripheral blood or when there is a dramatic improvement within 2-3 days of penicillin administration (Harkness, 1949; Ford, 1953; Czonka, 1959; Wright, 1963; Brandt *et al.*, 1974). Aseptic penicillin-insensitive arthritis after gonorrhoea has, especially in the Anglo-American literature, been interpreted as a Reiter variant (Ford, 1961). However, as pointed out by Ford (1953) and Olhagen (1960), from a clinical point of view the aseptic arthritis following gonorrhoea is identical with that following 'non-specific' urethritis and it is an entity with a recognisable clinical course.

On the basis of clinical studies Olhagen (1960) has proposed the term uroarthritis as a common designation for aseptic ('reactive') arthritides which develop in association with urogenital infection. The joint manifestations may appear after gonococcal as well as after a nongonococcal urethritis. The term includes also abortive forms of Reiter's

disease, i.e., polyarthritis with urogenital disease alone, without eye or skin lesions. It covers both acute and chronic forms of arthritis as well as extra-articular equivalents.

In an immunological study of uroarthritis Rosenthal (1976) found that lymphocyte stimulation induced by gonococcal antigen was significantly greater in cells from uroarthritis patients with known gonococcal infection than in cells from healthy controls. The purposes of the present study was to analyse further these observations and, if possible, to establish whether gonococcal infection would play a role in the pathogenesis of uroarthritis, including Reiter's syndrome, by comparing the clinical course and the immunological reactions to gonococcal antigen in patients with arthritis developing after gonorrhoea and in patients with arthritis after nongonococcal urogenital infection.

Material and methods

Postgonorrhoeal arthritis: 12 males, 4 females, mean age 30.8 years. In 12 cases the arthritis or severe arthralgia developed within 3 weeks of a gonococcal urethritis; in 2 cases gonococci were found in the urethra or in the cervix uteri when the patients

came to the emergency ward for acute exudative synovitis. Only in 1 case did a nonspecific ('sterile') urethritis develop directly after the gonococci had disappeared from the urethra.

In 2 cases strongly positive gonococcal complement fixation tests (GCFT) were considered to be sufficient reason for inclusion in the group.

One male patient (case 2, 53 years old) had had a very severe gonorrhoea with urethral secretion lasting for 7-8 months in the preantibiotic era. A chronic prostatitis and a pelvospondylitis developed later. When he first visited the rheumatology department in 1955 for recent exudative gonitis, cultures from urethral smear and prostatic fluid were negative. The GCFT was strongly positive but became negative after antibiotic treatment and remained so for many years. When the patient was admitted in 1971 to the hospital with relapsing exudate in both knee joints and acute uveitis, it was found that the GCFT had become positive again. Cultures on urethral smear and prostatic fluid were negative. Before these tests he had, however, been treated with tetracycline during 4 months for a chronic prostatitis. After ampicillin treatment there was a slow regression of the GCFT titre. During a relapse of the arthritis in 1974 the GCFT was positive again.

Case 5, female, 52 years old, was referred to the rheumatology department for a swollen painful wrist on the left side. She had been treated in the surgical outpatient department for a superficial abscess in the right wrist 1 week before. Culture of the pus yielded no growth. She had no urogenital symptoms but a history of a sore throat, so she was given penicillin. Later on the GCFT was positive. The joint swelling disappeared after 3 months, and the GCFT became negative at the same time (Table 1).

For comparison 14 cases of arthritis after non-gonococcal urogenital infection, e.g., with *Staphylococcus aureus*, group B streptococci, anaerobic streptococci, chlamydia, and *Mycobacterium tuberculosis*, were analysed. Eleven were males, 3 females, and the mean age was 31.4 years. The diagnoses included acute Reiter's disease of venereal origin, chronic uroarthritis, and pelvospondylitis. Most of the male patients had prostatovesiculitis (Table 2).

Fifty-eight healthy blood donors were used as controls in the lymphocyte studies but they were not examined for gonococcal infection.

Clinical examinations. Synovitis, tendinitis, and tendoperiostitis, eye involvement, skin changes, and mucosal lesions were recorded. Urological and gynaecological examinations were generally also performed.

Laboratory investigations. ESR, ordinary blood

Table 1 Patients with postgonorrhoeal arthritis: clinical data

Patient	Sex	Age yr	Interval between gonorrhoea and rheumatic symptoms	Number of gonococcal infections	Prostatitis (P) Salpingitis (S)	Conjunctivitis	Keratoderma blennorrhagica	Periphereal arthritis Monoarthritis (gonitis)	Polyarthritis Small joints	Polyarthritis Big joints	Sacroiliac arthritis	Duration of arthritis (at lymphocyte reactivity test)	GCFT
1	F	23	11 days	1	-	-	-	+	+	+	+	6 wk	-
2 ^a	M	53	?	1 + ?	P	-	-	-	+	+	+	19 and 22 yr resp. ^a	+
3 ^b	M	27	3 wk	2	-	+	-	+	+	+	+	1 mo	-
4	M	24	2 wk	1	P	-	-	+	+	+	+	3 mo	-
5	F	52	?	?	-	-	-	+	+	+	+	5 mo	+
6	M	32	2 wk	1	-	-	-	+	+	+	+	2 mo	+
7	M	23	1 wk	1	P	-	-	+	+	+	+	9 mo	+
8	M	28	2 wk	1	-	-	+	+	+	+	+	18 mo	+
9 ^b	M	25	2 wk	1	P	-	-	+	+	+	+	6 mo	+
10 ^b	M	41	1 wk	1	-	+	-	+	+	+	+	3 yr	+
11	M	21	4 wk	1	P	-	-	+	+	+	+	14 mo	+
12	M	25	1 wk	>3	P	-	-	-	+	+	+	6 mo	+
13 ^c	M	41	5 days	2	P	-	-	+	+	+	+	5 mo	+
14	F	26	7 ^a	2	-	-	-	+	+	+	+	3 mo	+
15	F	20	7 ^a	2	S	-	-	+	+	+	+	2 wk	+
16	M	32	3 wk	1	-	+	-	+	+	+	+	3 mo	+

(+) = Tender joints (arthritis). ^a Asymptomatic gonorrhoea. ^b Complete Reiter's triad. ^c Chronic polyarthritis + ankylosing spondylitis. ^d Examined twice: 1971 and 1974.

Table 2. Patients with nongonococcal uroarthritis; clinical data

Patient	Sex	Age yr	Diagnosis	Interval between nongonococcal urethritis and rheumatic symptoms (weeks)	Previous history of gonorrhoea	Prostatitis (P) Salpingitis (S)	Conjunctivitis	Peripheral arthritis Monoarthritis (gonitis)	Polyarthritis small joints	Polyarthritis big joints	Sacroiliac arthritis	Duration of arthritis ^c	GCFT
17	F	30	Uroarthritis	2	—	—	—	—	—	—	—	2 mo	—
18	M	57	Uroarthritis ^a	?	—	—	—	—	—	—	—	8 mo	—
19	M	25	Uroarthritis	6	—	—	—	—	—	—	—	2 mo	—
20	M	48	Uroarthritis	?	20 yr earlier	P	—	—	—	—	—	11 mo	—
21	F	24	Pelvispondylitis	?	6 yr earlier	P	—	—	—	—	—	6 mo	—
22	M	27	Uroarthritis	?	'Several yr earlier'	P	—	—	—	—	—	12 mo	—
23	M	26	Uroarthritis	1	—	—	—	—	—	—	—	1 mo	—
24	M	28	Uroarthritis ^b	?	6 yr earlier	P	+	—	—	—	—	3 mo	—
25	F	22	Sacroiliitis	?	—	—	—	—	—	—	—	8 yr	—
26	M	29	Uroarthritis ^b	2	—	—	—	—	—	—	—	3 mo	—
27	M	25	Uroarthritis ^b	1	—	—	+	—	—	—	—	3 mo	—
28	M	35	Uroarthritis	2	—	—	—	—	—	—	—	3 mo	—
29	M	36	Uroarthritis ^b	2	—	—	—	—	—	—	—	2 mo	—
30	M	29	Uroarthritis ^b	3	—	—	+	—	—	—	—	10 mo	—

^a Chlamydia in conjunctivae and urethra, asymptomatic. ^b Complete Reiter's triad. ^c At lymphocyte reactivity test.

counts as well as synovial fluid examination including culture (when sufficient specimens were available). Routine gonococcal complement fixation test, rheumatoid factor test (sheep red cell agglutination by the Svartz-Schlossman technique). A search for *Chlamydia* in the smear could not be carried out before 1977.

X-ray of the peripheral joints was performed in cases of chronic synovitis and of sacroiliac joints in patients with backache.

In vitro lymphocyte reactivity to *Neisseria gonorrhoeae* and tuberculin was studied as follows:

Bacterial antigens. In the early period of our studies (1971) the antigen used was a commercial gonococcal antigen from the National Swedish Bacteriological Laboratory. A dilution of 1:500 of this antigen was found to be optimal in pilot tests. Later on, one strain of *Neisseria gonorrhoeae* of colony morphology type T₂ whole cells was prepared as described elsewhere (Rosenthal and Danielsson, 1978), at a concentration of approximately 2 × 10⁶ per culture.

Purified protein derivative of tuberculin (PPD) was obtained from the Statens Seruminstitut, Copenhagen, and used at a concentration of 0.01 mg/ml.

Preparation of lymphocytes and measurement of DNA synthesis. During the first part of the present study lymphocytes were isolated from defibrinated blood by gelatin separation and set in cell cultures with and without antigen. 0.2 µCi of ¹⁴C-thymidine (Radiochemical Centre, Amersham, England) was added to the cultures on the fifth day of the experiment. The activity (¹⁴C-thymidine uptake) was measured in a gas-flow Geiger detector (Nuclear, Chicago) as described in detail elsewhere (Rosenthal, 1976). From 1973 the cells were separated on Ficoll-Isopaque density gradient. The cells were resuspended in medium as described by Mishell and Dutton (1967), supplemented with 10% human AB serum. Triplicate cell cultures containing 3 × 10⁵ cells/tube with and without antigen were set up. 0.1 µCi of ¹⁴C-thymidine in 0.05 ml of phosphate buffered saline was added to each culture on day 5, and the radioactivity was measured in an Inter-technique (Nano teknik, Sweden) liquid scintillation counter (Rosenthal and Danielsson, 1978).

In the last part of our study (1977) the lymphocytes were cultured in microtitre plates (Falcon 3040) in a cell concentration of 5 × 10⁶/ml. 0.1 ml of antigens was added to the cell cultures. 2 µCi of ³H-thymidine in 0.05 ml of PBS were added on day 5 to the cultures, and the uptake of ³H-thymidine into cells was measured in the Inter-technique scintillation counter.

For statistical methods see Appendix.

Results

The *clinical pattern* of the postgonorrhoeal arthritis group had no characteristic features that would make it possible to differentiate it from other forms of uoarthritis (Tables 1 and 2). Conjunctivitis was found in 4 patients and keratoderma blennorrhagica in 1 patient in the postgonorrhoeal group; in the comparative nongonococcal group there were 5 cases with symptoms of conjunctivitis and 1 patient in whom *Chlamydia trachomatis* was isolated from the conjunctiva and the urethra. Signs of sacroiliitis arthritis were found in 8 and 6 patients respectively.

Evidence of septic gonococcal arthritis in the form of positive synovial-fluid culture was lacking, nor was there any dramatic effect of penicillin or other antibiotics on the articular symptoms. There was no blood leucocytosis, and the number of leucocytes in specimens of synovial fluid varied between 0.6 and $19 \times 10^9/l$. The GCFT was positive in 9 out of 16 of the postgonorrhoeal arthritis patients and in none of the patients with arthritis after nongonococcal urogenital infection. The rheumatoid factor test showed a transitory weakly positive reaction in one case (case 4).

The differences in lymphocyte reactivity to gonococcal antigen (GC) between the 3 tested groups, i.e. postgonorrhoeal arthritis (PGA), nongonococcal uoarthritis (NGU), and healthy controls (C), are set out in Table 3, as are the quotients (q) between the net cpm for GC and PPD expressed as the function $A=200 + 100 \log q$ as described in the Appendix. The results are recorded separately for the years 1971, 1973-74, and 1977.

It is obvious that if the results for the GC stimulation are expressed in relation to those for the PPD there is a considerable gain in discrimination. The results can be expressed in this way: (1) There is a

highly significant difference between PGA and C in 1971 as well as in 1973 ($P < 0.001$). (2) There is a significant difference in the lymphocyte reactivity to GC between PGA and NGU ($0.001 < P < 0.01$). (3) There is no significant difference between NGU and C.

Discussion

This is a retrospective study of the clinical course, laboratory data, x-ray changes, and immunological parameters in patients with postgonorrhoeal aseptic arthritis and in patients with arthritis associated with nongonococcal urogenital infection. It is evident from the clinical data that postgonorrhoeal arthritis may present as a complete Reiter's syndrome.

Chlamydia trachomatis is nowadays held responsible for perhaps half the nonspecific urethritides (Holmes, 1974) and consequently is also incriminated as an aetiological factor of Reiter's syndrome (Kinsella *et al.*, 1968; Delbarre and Amor, 1976; Schachter, 1976). The evidence put forward in favour of chlamydial infection as a cause of Reiter's syndrome is the demonstration of *C. trachomatis* in urethral or cervical smears, a positive complement-fixation test (Kinsella *et al.*, 1968), and a positive lymphoblast transformation test in the presence of chlamydial antigen (Amor *et al.*, 1972). The same argument is, however, valid with respect to a gonococcal aetiology, namely, cultural evidence of *N. gonorrhoeae* and serological and cellular immune responses to gonococcal antigen.

The fact that penicillin clears the gonococcus from the urethra without preventing the subsequent development of Reiter's disease or without influencing the established condition has been taken as an argument against a gonococcal aetiology of the syndrome (Czonka, 1959). However, recent investigations have shown that the accessory genital glands are invaded by gonococci in at least 40% of male patients with uncomplicated gonococcal urethritis and also that the gonococci remain in these glands for up to at least 3 weeks after cure of the urethritis (Danielsson and Molin, 1971). It has formerly been shown that the penetration of penicillin into the prostate is rather low (Winningham *et al.*, 1970).

We suggest that in many patients with gonorrhoea who are treated with penicillin early and in adequate dosage the gonococci may survive in the accessory glands or the oviducts, thereby being capable of inducing an aseptic postinfectious ('reactive') arthritis in susceptible patients, i.e., in HLA B27 positive individuals.

In all probability this is an immunological reaction in the joint similar to rheumatic fever and the other

Table 3 Differences in lymphocyte reactivity to gonococcal antigen between patients with postgonorrhoeal arthritis (PGA), nongonococcal uoarthritis (NGU), and healthy controls (C)

Year	Groups	Method of calculation ^a	Mean	SE	DF	t
1971	PGA-C	100 log x_1/x_2	75.6	30.5	20	2.48*
	(n=7) (n=15)	100 log q_1/q_2	80.0	16.0	20	4.99***
	PGA-NGU	100 log x_1/x_2	47.9	23.9	12	2.00
	(n=7) (n=7)	100 log q_1/q_2	60.0	17.7	12	3.38**
1973-74	NGU-C	100 log x_1/x_2	27.7	29.2	20	0.95
	(n=7) (n=15)	100 log q_1/q_2	20.0	17.8	20	1.12
1974	PGA-C	100 log x_1/x_2	53.4	17.2	26	3.10**
1977	(n=10) (n=18)	100 log q_1/q_2	58.8	14.2	26	4.13***
	NGU-C	100 log x_1/x_2	17.9	14.5	30	1.23
	(n=7) (n=25)	100 log q_1/q_2	24.2	15.7	30	1.54

^a See Appendix. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

postinfectious arthritides, for instance, yersinia arthritis. Our cases showed evidence of such reaction, especially a cellular immune response, but also often humoral antibodies to the gonococcus, i.e., positive GCFT.

Serial analyses in a few patients show that the cellular immune response, i.e., the lymphocyte reactivity, to GC-antigen lasts definitely longer than the humoral antibody response, even after disappearance of the arthritis (Rosenthal and Olhagen, unpublished observations). Molin and Danielsson (1970) have studied male patients with repeatedly negative urethral smears and cultures but named as sources of gonorrhoeal infection. These patients had a history of gonorrhoeal and/or 'nongonorrhoeal' urethritis within the previous 1 to 2 years. Cultures of prostatic secretions were positive in only 1 of the cases, but direct microscopy and immunofluorescence test were positive for gonococci in all. The prostate is thus considered to be a reservoir of gonococci, with strong antigen stimulation as a result (Molin and Danielsson, 1970). There are also the observations by others and ourselves that a long-standing GCFT may disappear after proper antibiotic and urological treatment of the chronic prostatitis (Romanus, 1953; Olhagen, 1975).

To be claimed as the cause of an aseptic joint reaction a bacterium should be shown to have elicited an immunological response in the host. As to gonococcal infection, the many reports, recently summarised by Holmes (1974), are mainly concerned with the humoral response. The value of the GCFT has been under debate and there are contradictory experiences. Many rheumatologists think that this test has 'no diagnostic value' (Sharp 1972). This opinion is not in accordance with the experience of Swedish investigators (Danielsson *et al.*, 1972), who found a much higher frequency of positive GCFT in complicated gonorrhoea, including postgonorrhoeal arthritis, than in single gonococcal urethritis in the male. In the present study out of 16, or 56%, of the patients with postgonorrhoeal arthritis had a positive reaction, which is in accordance with the findings of Hess *et al.* (1965).

In a series of experiments Rosenthal (1976) has demonstrated the presence of a cellular immune response to the gonococcus in leucocytes from some patients with uroarthritis. However, the lymphocyte stimulation induced by virulent gonococcal antigen in cell cultures from patients with single or multiple gonococcal urethritis with urogenital complications, and from controls showed no differences in the ^{14}C -thymidine uptake (Rosenthal and Sandström, 1978).

It will be seen from Table 2 that 4 of the 14 patients

who were classified as having nongonococcal uroarthritis had a history of gonorrhoea for 'several' to 20 years before the development of the articular symptoms. Three of them showed virtually the same low response to gonococcal antigen in the lymphocyte stimulation test as the controls; only one displayed a moderate reactivity. Two patients (cases 18 and 30) showed high stimulation without a *known* history of gonorrhoea. It is at present difficult to give a satisfactory interpretation of this phenomenon. These patients might of course be asymptomatic carriers of gonococcal infection; another possibility is an immune response developing as a result of a past infection in which cross-reacting antigens are involved.

Table 3 shows the differences in lymphocyte reactivity to GC-antigen between the groups and their significance based both upon the net cpm values and on the quotient values between the net cpm for GC and PPD. The *q* values give more clear-cut results. The efficiency of this method of calculation is also evident from the higher significances obtained.

A strong indication that this method effectively compensates for even very large systematic differences in the experimental results is evident from Table 4. Cells from healthy controls studied in 1973 and 1977 show a very great difference in net cpm between the groups, because quite different experimental methods were used. The *A* values, on the other hand, give nearly the same results in both groups. Thus, comparison based upon the cpm for an antigen *relative to* a suitable 'reference antigen' can yield relevant results even when the experimental conditions vary greatly between the groups.

The increased cellular immune response to *N. gonorrhoeae* in patients with postgonorrhoeal arthritis is in strong contrast to the poor lymphocyte reactivity to this antigen in patients with true septic gonococcal arthritis (Rosenthal, 1976). This difference in lymphocyte reactivity signals a discrepancy in immune reactivity which has a possible immunogenetic background, namely, the presence or absence of the HLA-B27 antigen in these 2 disorders (Möller and Olhagen, 1975; Wagner, 1975).

Table 4 *Difference in lymphocyte reactivity to gonococcal antigen between 2 groups of healthy controls, studied in 1973 and 1977. Comparison between different methods of calculation*

	Method of calculation ^a	Mean	SE	DF	<i>t</i>
C71-C73 (n=25) (n=18)	100 log x^1/x^2	82.1	12.0	41	6.85***
	100 log q^1/q^2	4.7	12.2	41	0.38

^a See text. *** $P < 0.001$.

Appendix: Statistical methods

The evaluation of the results is based upon the net cpm (counts per minute in a test *with* antigen, minus counts per minute in a test *without* antigen). In each of the groups of patients and controls these net cpm values had a definitely skew distribution. In logarithmic terms, however, the values had a nearly normal distribution.

To get satisfactory results the calculations were therefore made on logarithmically rendered values. The function $100 \log x$ was used, where x stands for the net cpm value.

The significance of a difference between groups of persons was tested in the usual way by the t test (Snedecor and Cochran, 1974). The significances are given as * for $0.01 < P < 0.05$, ** for $0.001 < P < 0.01$ and *** for $P < 0.001$. The difference between 2 groups is

$$100 (\log x_1 - \log x_2) \text{ or } 100 \log x_1/x_2.$$

Differences in lymphocyte reactivity between individuals might to some extent be compensated for by using the results of stimulation of the lymphocytes with PPD as a reference.

Analyses using the *quotient* between the net cpm for GC and PPD antigen were therefore performed. If we call this quotient q , the function we used is $A = 200 + 100 \log q$. The term 200 was added to avoid negative values.

The quotients in the 2 compared groups are called q_1 and q_2 , whence the difference between the A values for the two groups is $100 \log q_1/q_2$. By subtracting 100 from this value and taking the antilogarithm, the quotient between the q measures for the 2 groups will be obtained.

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