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ERYTHEMA NODOSUM IN CHLAMYDIAL INFECTIONS

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Abstract. Twelve patients suffering from erythema nodosum who had diagnostic titres or seroconversions in chlamydial complement fixation test are described. Eleven had respiratory infections. The twelfth had sterile pyuria, symptoms of pelvic inflammatory disease and exceptionally high antibody titres against *Chlamydia trachomatis* in an immunofluorescence test. The simple chlamydial complement fixation test is recommended for the screening of cases of erythema nodosum.

Key words: Erythema nodosum; Chlamydia psittaci; Chlamydia trachomatis

Although the list of aetiological agents provoking erythema nodosum (EN) is lengthy, the cause remains unknown in many cases. In a Finnish study of 343 patients, no triggering factor was found in 22% of the cases (6). In recent years chlamydiae have aroused considerable interest as important human pathogens (22, 23, 24). Both known species, *Chlamydia psittaci* and *C. trachomatis*, have been reported to be associated with EN (20, 10). However, no systematic study has been carried out.

We describe here 12 cases of erythema nodosum collected in a single virus diagnostic unit from among patients with suspected viral illnesses and with serological evidence of recent chlamydiosis.

MATERIAL AND METHODS

The patients were selected from among persons with suspected viral illnesses, whose samples were sent to the Department of Virology for serological screening during the 3½ year period January 1975 to June 1978. The serological screening was performed using complement fixation (CF) in a microtest with 16 to 18 different antigens, including the chlamydial group antigen from *C. trachomatis*, serotype E (acetone–ether extract, kindly provided by Dr C. Mordhorst, State Serum Institute, Copenhagen, Denmark). Fourfold changing titres or stable titres ≥64 were regarded as indicative of recent chlamydial infection. High-titred sera from 4 patients with EN were further tested in a single-antigen immunofluorescence antibody test (IFAT) using *C. trachomatis* serotype L2 inclusions in tissue culture as antigen (19).

The hospital records of patients who had chlamydial CF antibodies in significant titres were retrieved and reviewed. After June 1978, 3 more patients with EN were found to have had a recent chlamydial infection and were added to this series.

RESULTS

During the 3½ year period from January 1975 to June 1978, chlamydial CF antibodies in titres of ≥64 or fourfold seroconversion were detected in sera of 177 of about 10000 patients. Hospital records of 133 of these cases were available and were reviewed. Sixty-four (48%) of the patients had acute respiratory symptoms as their main complaint. Pneumonia was found in 51 cases (38%). Patients without respiratory complaints were clinically much more heterogeneous (to be published).

EN was present in 9 cases (7%). After the series had been collected, 3 further patients with EN were found to have had a recent chlamydial infection and were added to the series. The main clinical and laboratory data of these 12 patients were pooled and are set out in Table I. There were 4 males and 8 females. Their mean age was 35 years, ranging from 17 to 58 years. A respiratory infection had preceded EN by one or two weeks in 11 patients. Six patients had had pneumonia and 5 an upper respiratory infection. One patient (case 7), a 17-year-old woman, had a pelvic inflammatory disease and pyuria. Three patients (case 1, 8 and 11) had had EN previously. Patient no. 1 had had this skin eruption 4 years earlier, associated with *Yersinia enterocolitica* infection, whereas in the others the cause of the previous EN had remained obscure.

All patients had typical nodular, warm, painful, non-ulcerating erythematous eruption on the extensor aspects of the legs. Two patients also had similar lesions on the arms, and 3 patients had erythema multiforme lesions on the upper trunk and on the arms. Eye symptoms were observed in 3 patients.

Table I. *Main clinical and laboratory data of 12 patients with erythema nodosum*

Pat.	Age	Sex	Type of infection	Other symptoms	ESR/h	Leukocyte count $\times 10^9$/l	S-ALAT (U/l)	AST
1	58	M	Upper resp. illness	–	104	8.0	35	125
2	50	F	Upper resp. illness	Myalgia	40	10.0	13	1 600
3	48	F	Upper resp. illness	–	58	10.0	ND	200
4	43	F	Pneumonia	Erythema multiforme, episcleritis	113	5.4	56	100
5	24	F	Pneumonia	–	120	7.0	ND	200
6	44	M	Upper resp. illness	Arthralgia	116	13.6	58	50
7	17	F	Pelvic inf. disease	Pyuria	101	7.0	40	ND
8	43	M	Pneumonia	Arthralgia, conjunctivitis	87	12.3	17	200
9	32	F	Upper resp. illness	Erythema multiforme	77	8.2	40	200
10	18	M	Pneumonia	–	56	11.2	21	100
11	48	F	Pneumonia	Erythema multiforme episcleritis	122	9.4	123	250
12	31	F	Pneumonia	–	88	11.3	ND	ND

Two patients had episcleritis (cases 4 and 11) and one patient had conjunctivitis (case 8).

Erythrocyte sedimentation rate (ESR) was elevated in all patients, the average being 88 mm/h. Mild peripheral blood leukocytosis with a normal differential count was found in 7 patients. The alanine aminotransferase (ALAT) was transiently elevated in 3 of the 9 patients examined. One patient (case 11) had cryoagglutinins in titres of 32. Two patients had an elevated antistreptolysin titre (AST). Yersinia agglutinins were not measured in significant titres. Sarcoidosis, tuberculosis and inflammatory bowel disease were not detected in any of the patients. None of the patients had received sulphonamides. Two patients were pregnant, however.

Chlamydial CF antibodies were measured in titres of ≥ 64 in all patients except one, who was among the 5 patients showing a fourfold seroconversion. No diagnostic titres were detected with other CF antigens (mostly viral) used in screening. The woman (case 7) with a pelvic inflammatory disease had a high chlamydial IFAT antibody titre against *C. trachomatis*, serotype L2.

Skin biopsy specimens were taken both from the erythema nodosum and from the erythema multiforme lesions of patients 4 and 11 for histopathological and immunohistological studies. The histological picture of the erythema nodosum lesions was deep septal panniculitis. In erythema multiforme lesions there were subepidermal oedema and cell infiltration around small subpapillary vessels. The cell infiltration consisted of small lymphocytes in case 4. Case 11 had features of allergic vasculitis with polymorphonuclears, nuclear dust and degenerative changes in vascular walls. The immunohistology of the erythema multiforme lesions examined with a polyvalent immunoglobin conjugate was negative in both cases.

The skin lesions disappeared in 1–5 weeks without scarring. Patient 12 was 13 weeks pregnant at the onset of the illness. Six months later she gave birth to a healthy baby. The other pregnant woman, patient No. 9, had an IUD and underwent a therapeutic abortion.

DISCUSSION

Erythema nodosum has been considered an immunopathological process arising in response to various triggering factors. The pathogenesis of EN is still unresolved. It has been suggested that EN is an Arthus-type reaction or a delayed hypersensitive reaction, or both (6). Hannuksela found among his 157 unselected cases of EN that 33% of the patients had sarcoidosis, 27% had probable or possible streptococcal infection and 10% had yersiniosis. The rate of tuberculosis as a cause has decreased in recent decades (6, 14). There are geographical differences among triggering infections. For instance, fungi are of importance in the USA (25). Pregnancy and oral contraceptives have also been found to provoke EN (6, 29).

In one patient in this series a streptococcal infec-

Yersinia antibody titre	Chlamydia CF antibody titre	Chlamydia IFAT antibody titre
<10	128–64	ND
80–80	32–128	ND
<8	128–64	ND
<8	8–32	256
<8	256–64	64
<8	64–32	ND
<8	64–32	2 048
<8	256–64	64
<8	500–256	ND
<8	500–500	ND
80–80	64–128–256	ND
<8	512	ND

tion could not be excluded as the triggering infection, and 2 patients were pregnant. All, however, had evidence of a recent chlamydial infection, and in a further 8 patients no distinct clinical or laboratory proof of other alleged causes could be found.

Chlamydial group CF antibodies of low titre are commonly found in adults. In 885 Finnish blood donors, antibodies in titres of 10 were demonstrated in 21.6% (11), and 22% of 2679 patients over 20 years of age, screened at the Department of Virology in 1978, had a titre of ≥8 (30). High titres are rare, however, in the general population and ≥64 in CF is suggestive of a recent chlamydial infection, although fourfold seroconversions are even more confirmatory (21). Refvem et al. reported (1976) that sarcoidosis patients tend to have more and higher chlamyidal CF titres than normal controls (18). However, none of our patients showed signs of sarcoidosis.

The spectrum of diseases caused by chlamydial agents is very wide (for review, see Schachter 1978) (22, 23, 24). Of the two species, *C. psittaci* is thought to be transmitted to humans from birds and causes respiratory infections, which may vary from mild respiratory disease (5) to fulminant psittacosis with high mortality (4), and *C. trachomatis*, causing trachoma, inclusion conjunctivitis, genito-urinary infections and lymphogranuloma venereum, from humans. Although lymphogranuloma venereum (10, 27) and cat scratch disease, which is suggested to be caused by chlamydia (for review, see Warwick 1967) (32), are well known causes of EN, we have found only eleven documented cases of erythema nodosum suggested to be associated with *C. psittaci* (3, 28, 20, 9, 26).

In the present study it was not determined whether the infections were due to *C. psittaci* or to *C. trachomatis*, since no isolation attempts were made and the microimmunofluorescence test capable of differentiating between these species was not available. Eleven of the patients complained of respiratory symptoms commonly thought to reflect an infection caused by *C. psittaci*. However, *C. trachomatis* has recently emerged as a respiratory pathogen. Published reports have so far described infections only in newborns (2) and children (30); the reliability of the CF test in these cases has been questioned (1). The results of single-antigen IFAT in our respiratory cases tested do not speak in favour of *C. trachomatis*, either. This test is said to be just as sensitive as CF for measuring group-specific antibodies, but far more sensitive for measuring species-specific antibodies (18). Results of this test speak in favour of *C. trachomatis* infection in the patient with pelvic inflammatory disease and pyuria. Moreover, the symptoms in this case are consistent with recent descriptions of generalized *C. trachomatis* genito-urinary infection in females (15, 16, 17).

EN associated with yersiniosis and chlamydiosis have certain clinical features in common. EN in yersiniosis has been reported to be more acute, more widespread and of a shorter duration than the eruptions triggered by other factors (7). This was also true in the present series. The combination of EN and erythema multiforme is more common with yersiniosis than with other underlying causes (8). Three out of 12 in the present series and 2 out of 6 patients described by Sarner & Wilson (1965) (20) had this combination of skin eruptions. Both of these organisms seem to be capable of triggering not only EN but also another type of reaction in certain individuals, namely Reiter's disease (13, 12).

Though this survey of patients with suspected viral illnesses does not provide exact data on the prevalence of chlamydiosis in association with erythema nodosum, its incidence may well be higher than suspected. It may be worth screening the cases of EN with chlamydial group antigen. Whether or not the commonest chlamydial infections, which are superficial and do not reliably induce CF antibody (21), are capable of provoking EN, remains an unanswered question.

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