STREPTOCOCCAL PHARYNGITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

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The aetiology of systemic lupus erythematosus (SLE) remains unknown and it is thus conceivable that the cause may differ from case to case. It has been suggested that there may be an inherent host abnormality, possibly genetic, predisposing to abnormal immunological reactivity, and that extrinsic factors might precipitate the onset of clinical features.[1,2] The disease has a tendency to acute exacerbations and Marian W. Ropes[3] in the Walter Bauer Memorial Issue of *Medicine* in 1964, considers it imperative 'to determine the regime which will lessen the tendency to acute exacerbation and hasten remission'.

A 17-year-old girl, with a family history of rheumatoid arthritis, developed chronic polyarthritis followed by florid SLE. There was concomitant clinical and bacteriological evidence of streptococcal pharyngitis. This association might be coincidental and irrelevant but alternatively it could be the clue to an important precipitating factor in this particular case of SLE. The purpose of this paper is to report the association, and draw attention to the possible therapeutic implication of prophylactic penicillin therapy.

CASE REPORT

A 17-year-old schoolgirl, while studying for her matriculation examination, developed chronic polyarthritis in September 1965. She did not complain of a sore throat, but in December 1965 her throat and tonsils were noted as 'red' and 'inflamed' by her general practitioner and also at the medical outpatient department.

Owing to interest in the possible role of streptococci in rheumatology, the investigations included a throat swab, which was negative, and the *serum antistreptolysin-O-titre which was found raised to 333 Todd units.* The haemoglobin was 10 G/100 ml., ESR 40 mm./hr. (Westergren), and the LE screening test was negative. Salicylates improved the arthritis, but she began to feel tired, listless, and ill. On 26 January 1966 she was given phenoxymethyl penicillin, 250 mg. 6-hourly for 10 days, in view of the raised ASO titre. However, her general health continued to deteriorate with severe tiredness and weakness, anorexia, loss of weight, and the appearance of an erythematous rash on her face. On 9 February left-sided pleurisy developed and she was admitted on 17 February. Her mother has chronic rheumatoid arthritis and is known to one of us (M.H.).

She looked ill and her temperature was 100°F. An erythematous rash was present on the 'butterfly' area of her face. The proximal interphalangeal and wrist joints were slightly swollen. The tonsils were enlarged and slightly inflamed. A left pleural effusion was present. The pulse rate was 100/min. No other clinical abnormalities were noted. The blood pressure was 110/65 mm.Hg. Urinalysis showed a 1+ proteinuria.

Chest X-ray confirmed the presence of a left pleural effusion, with some cardiac displacement to the right. On aspiration, it was a serous exudate with protein 3·6 G/100 ml., scanty polymorphs, but no growth on culture. An electrocardiograph showed non-specific T-wave flattening. The ESR was 113 mm./hr. (Westergren), haemoglobin 9 G/100 ml., PCV 28%, WBC 2,300/cu.mm. with 62% neutrophils, 32% lymphocytes, 2% eosinophils, and 4% monocytes. Platelets were 44,000/cu.mm. Blood urea was 75 mg./100 ml., serum albumin 4·4 G/100 ml., serum globulin 2·5 G/100 ml., thymol turbidity 4 units, zinc turbidity 10 units, and gammaglobulins were raised on the electrophoretogram. Blood culture yielded no growth and sputa were normal. The latex fixation test and the SLE latex agglutination test were negative. *Throat swab yielded a poor growth of beta-haemolytic streptococci,* sensitive to penicillin, streptomycin, erythromycin, novobiocin, and tetracycline. *The antistreptolysin-O titre was 100 Todd units.*

Management of SLE. On 18 February she was very ill with a temperature of 104°F, and prednisone therapy was commenced with a dose of 60 mg. daily. Her response and improvement were prompt, dramatic, and progressive and all

the clinical abnormalities disappeared. Proteinuria was no longer detectable after a few days. The pleural effusion was absorbed and the ECG became normal. The haemoglobin rose to 11·2 G/100 ml., WBC to 13,900/cu.mm., and platelets to 204,000/cu.mm. The ESR fell to 7 mm./hr. (Westergren).

Prednisone was reduced to 40 mg. daily from 20 February, to 30 mg. daily from 29 March when she was discharged, then to 20 mg. daily on 28 April, and to 15 mg. daily on 23 June. She has remained well as an outpatient with a repeatedly normal ESR. Haemoglobin rose to 14·5 G/100 ml., and there was no proteinuria. There were no important side-effects from prednisone therapy, except a transitory abdominal discomfort in March, which ceased after the addition of antacids. The improvement in renal involvement was particularly gratifying. The blood urea remained slightly elevated for 2 months, but finally became normal (45 mg./100 ml. on 23 February, 62 mg./100 ml. on 3 March, 54 mg./100 ml. on 15 March, 51 mg./100 ml. on 22 March, 49 mg./100 ml. on 7 April, 40 mg./100 ml. on 21 April, and 29 mg./100 ml. on 9 June).

Management of beta-haemolytic streptococcal pharyngitis. Erythromycin, 250 mg. 6-hourly, was given on 24 February for 10 days, but throat culture on 1 March and 7 March yielded a growth of beta-haemolytic streptococci again, still sensitive to penicillin, streptomycin, chloramphenicol, tetracycline, erythromycin and novobiocin. Phenoxymethyl penicillin was accordingly given, 500 mg. 6-hourly from 11 March for 10 days. As an outpatient she continues to receive 250 mg. phenoxymethyl penicillin *b.i.d.* in an attempt at prophylaxis against recurrence of streptococcal pharyngitis (and subsequent possible exacerbations of SLE). There have been no signs of any 'drug reaction' and a subsequent throat swab was negative. Antistreptolysin-O titre in June was 100 Todd units.

DISCUSSION

Although LE cells were not demonstrated, the clinical and laboratory features were typical of SLE, including high pyrexia, polyarthritis, pleurisy with effusion, erythematous rash on the 'butterfly' area of the face, abnormal electrocardiogram, renal involvement with proteinuria and slight azotaemia, anaemia, leucopenia, thrombocytopenia, and very high ESR. Prednisone therapy led to a rapid and complete clinical and laboratory remission and the maintenance dose in June was 15 mg. daily.

When first seen at medical outpatient department in December 1965, 3 months after the onset of chronic polyarthritis, which resembled early rheumatoid arthritis, she did not complain of a sore throat. However, observers noted redness of the pharynx and tonsils and the antistreptolysin-O titre was raised to 333 Todd units. In February 1966 when she was admitted with florid SLE, the antistreptolysin-O titre had fallen to 100 Todd units. There was thus proof of recent infection by beta-haemolytic streptococci. The throat swab at medical outpatient department was negative, but on and after admission cultures yielded beta-haemolytic streptococci on 3 occasions. Combining these clinical and bacteriological observations, the presumptive site of the streptococcal infection which raised the antistreptolysin-O titre was the pharynx.

The suggestion is being propounded that the streptococcal pharyngitis and the development of SLE were neither coincidental nor fortuitous in this case, but that the streptococcal pharyngitis was the actual initiator of the SLE. She has a potential genetic 'soil', as her mother has rheumatoid arthritis, and perhaps the streptococcal pharyngitis acted as the 'seed', the situation being analogous to that in rheumatic fever, and this possibly initiated the clinical manifestations of SLE.

Textbooks of medicine contain statements such as 'patients may relate the onset of SLE to a local infection',[2] and 'upper respiratory infections sometimes precede the initial appearance of symptoms',[4] but give no more specific details. Moore and Lutz,[5] in a review of SLE in 1955, mentioned that 'an ordinary sore throat may have precipitated the illness', but also provide no further details. Ropes[3] accepts 'infections' as one of the major factors which can precipitate the onset of the initial attack of SLE. On the other hand, authorities such as Dubois and Tuffanelli,[6] Talbott and Moleres Ferrandis,[7] and McGee Harvey *et al.*[8] are either unconvinced or unimpressed by the possible role of infections as initiators of SLE.

In this case, it is not being suggested that the streptococcal pharyngitis acted as a non-specific 'infective stress'. It is rather postulated that the streptococcal pharyngitis acted as a specific initiator of SLE just as it is the specific initiator of rheumatic fever in other patients. Rheumatic fever and SLE have pathological relationships and are sometimes classified together as 'connective tissue diseases' or 'collagen diseases'. Rantz *et al.*[9] did investigate antistreptolysin-O titres in 6 cases of SLE in 1952, and found them normal, but they do not state at what stage of the disease the investigations were done. If the first antistreptolysin-O titre had not been requested in this case when she was still an outpatient before her admission, then its evanescent rise would have been missed.

In 1953[10] LE cells were found in concentrated heparinized marrow preparations from 3 patients with severe penicillin reactions, and Kark and Pollak[11] include penicillin among the drugs best avoided in SLE. In this case, chronic polyarthritis and impaired general health were already present before the first course of oral penicillin was given at medical outpatient department, so it is unnecessary to incriminate penicillin in the pathogenesis of the SLE. When she was an inpatient, the second course of penicillin therapy was only undertaken after much consideration, but was considered justifiable as the streptococcus was persisting in the pharynx in spite of erythromycin therapy. It did not cause any drug reaction or exacerbation of SLE, which continued to improve and remit during prednisone therapy.

These considerations are not merely of theoretical interest. If streptococcal pharyngitis recurs in patients who have had rheumatic fever, it is well known that there is a high incidence of recurrence of rheumatic fever, and hence the value of prophylactic penicillin therapy in such cases. So, by analogy, phenoxymethyl penicillin is being continued indefinitely in this case as an attempted prophylaxis against recurrences of streptococcal pharyngitis and the possible serious exacerbations of SLE. This procedure might constitute a major beneficial factor in her unknown prognosis.

CONCLUSION

Streptococcal pharyngitis was detected in close relationship to the onset of a case of SLE. The antistreptolysin-O titre was significantly raised to 333 Todd units. There was prompt and complete response to prednisone therapy which is being maintained. It is postulated that the association is not merely coincidental, but of significance, analogous to the role of streptococcal pharyngitis in rheumatic fever. The beta-haemolytic streptococcus may have been the 'seed' on a genetically-determined 'soil' with a family history of rheumatoid arthritis.

So little is known of the aetiology of SLE that it is worth drawing attention to a possible initiating factor in a particular case.

The suggestion is not merely of theoretic interest, but has practical therapeutic implications. Oral phenoxymethyl penicillin therapy is being continued as attempted prophylaxis against recurrences of streptococcal pharyngitis. It is hoped that this may improve the prognosis in this particular case of SLE.

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