Systemic lupus erythematosus in *Staphylococcus aureus* hyperimmunoglobulinaemia E syndrome

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Abstract

The prevalence of autoimmune diseases, including systemic lupus erythematosus, is increased in failure of certain host defence mechanisms. Systemic lupus erythematosus, however, has not been recorded as a late complication of the *Staphylococcus aureus* hyperimmunoglobulinaemia E (hyper-IgE) syndrome. Such a case was investigated in a man suffering from a classic example of the syndrome. Antinuclear antibodies were analysed on a molecular basis.

The emergence of immunological and clinical features of systemic lupus erythematosus in patients with defective host defence mechanisms against staphylococcal infections is unlikely to be fortuitous and may help elucidate the pathogenesis of systemic lupus erythematosus. The observations will also aid the long term management of patients with *S aureus* hyper-IgE syndrome.

Introduction

Patients with the *Staphylococcus aureus* hyperimmunoglobulinaemia E (hyper-IgE) syndrome suffer life threatening bacterial infections beginning in early infancy. The infections are usually manifested by recurrent subcutaneous abscesses and pneumonia, but other sites may also be affected. Chronic eczematoid dermatitis, blood eosinophilia, and raised serum IgE concentrations are additional characteristics; mucocutaneous candidiasis may be observed in some patients. The first clinical description of the disorder was by Davis *et al* (Job's syndrome)¹; later Buckley *et al* analysed the disease in more detail,² and since then many further cases have been reported.³

The clinical findings suggest failure of host defence mechanisms, but the propensity to widespread abscess formation (mainly due to *S aureus*) remains unexplained. Defective chemotaxis of polymorphonuclear leucocytes in vitro has been reported but not in all cases.⁴⁻⁶ The pathogenetic implication of IgE antibodies against staphylococcal antigens detectable in the serum of these patients remains speculative.⁷⁻⁹ Clinical and laboratory evidence of impaired cell mediated immunity was first presented by Buckley *et al*.²⁻⁹ More recently Geha *et al* have reported defective suppressor cell function,¹⁰ which may be related to the genesis of hyperimmunoglobulinaemia E.

Strict control of infections, mainly with antibiotics, is the only treatment available and the long term prognosis is un-

known; two patients have developed neoplastic disease.^{3,11} In this paper we report the development of systemic lupus erythematosus in a patient with classic hyper-IgE syndrome and examine the pathophysiological implications.

Case report and immunological findings

A 20 year old man had begun to have a history of serious infections within the first weeks of life, when he suffered severe staphylococcal pyoderma and generalised eczematoid dermatitis. He had been admitted to hospital on 35 occasions for major surgical treatments of staphylococcal abscesses. Staphylococcal bullous pneumonia had required thoracotomy when he was 6, and two years later he had been admitted because of meningoencephalitis due to *Cryptococcus neoformans*.¹² Between admissions he had had many abscesses incised, cultures of which invariably grew *S aureus*. Conjunctivitis and ear infection were particularly frequent. Control of infections had been tried with long term flucloxacillin, oral cephalosporins, and, more recently, co-trimoxazole. He was still suffering from chronic dermatitis and candidal onychomycosis. Blood eosinophilia, hyperimmunoglobulinaemia E (varying from 4000 to 30 000 IU/ml), and anti-staphylococcal IgE antibodies⁷ had persisted throughout. Repeated intradermal testing with recall antigens (Multitest IMC, Institut Mérieux, Lyon, France) invariably showed complete anergy.

This patient with hyperimmunoglobulinaemia E and recurrent staphylococcal infections subsequently developed clinical and immunological features of systemic lupus erythematosus, including arthralgias, pleurisy, a necrotic skin lesion in the left temporal region, alopecia areata, and pronounced fatigue. A positive Coombs test result (anti-IgG), slight anaemia (haemoglobin concentration 11.3 g/dl), mild reticulocytosis (2.7%), leucopenia (3.0 g/l), and cold reactive antilymphocytic antibodies were first noted in late 1981.

Serum samples stored at -70°C since 1976 were tested by standard techniques for autoantibodies, immunoglobulins, and complement components. The table summarises the results. Concentrations of C3 and C4 had been decreasing since July 1979, but the first pronounced drop in these values occurred in February 1981 and coincided with a rise in antinuclear antibody titres and anti-dsDNA values. At the time there were no symptoms of systemic lupus erythematosus. Circulating immune complexes in the serum were detectable in February 1982 (measured by C1q fixation¹³). Hyperimmunoglobulinaemia of the IgG type was a constant feature. Leucopenia in February 1982 was mainly due to neutropenia (polymorphonuclear leucocytes 0.9 g/l, lymphocytes 1.8 g/l).

Further to characterise the antinuclear antibodies serum samples were processed as described.¹⁴ Briefly, after absorption of serum IgG with Protein-A Sepharose beads (Pharmacia Chemicals, Uppsala, Sweden) and incubation with ³²P-HeLa cell extracts, ribonucleic acids were purified from ribonucleoprotein antigens bound to IgG antibodies, separated by polyacrylamide gel electrophoresis, and visualised by autoradiography (figure).

Discussion

The diagnosis of systemic lupus erythematosus in this patient suffering from classic hyper-IgE syndrome was based on clinical and laboratory findings. Analysis of serum samples stored since 1976 showed that immunological changes of systemic lupus erythematosus had been developing over several years. Concomitantly with the first clinical symptoms there was a sharp fall in serum C3 and C4 values as well as an impressive rise of antinuclear antibody titres in late 1981 (table). Drug induced lupus has not been reported with the agents used and can

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Laboratory findings in patient with hyperimmunoglobulinaemia E syndrome developing systemic lupus erythematosus

Sample No	Date	C1q fixation (normal <5%)	C3 (normal 1.0-2.0 g/l)	C4 (normal 0.13-0.25 g/l)	Antinuclear antibody titre* (normal <1/10)	Anti-dsDNA antibodies† (normal <20 U/ml)	IgG (normal 7.0-14.0 g/l)	White blood cells (normal 5.0-10.0 g/l)
1	July 73		1.75					
2	Dec 76						14.50	7.0
3	July 77		1.20	0.14	<1/10	47	18.00	5.4
4	July 78		1.51	0.17	<1/10	44	16.97	6.0
5	Nov 78				1/40	54		6.8
6	July 79	<5	1.04	0.08	1/80	62	19.50	
7	May 80	<5	0.90	0.09	1/80	75	19.20	5.4
8	Nov 80	<5	0.90	0.10	1/80	66	23.50	
9	Feb 81	<5	0.66	0.08	1/320	88	16.30	4.2
10	July 81	<5	0.90	0.11	1/80	69		
11	Dec 81	<5	0.60	0.04	>1/1280	>100		3.0
12	Feb 82	22	0.64	0.05	>1/1280	>100	19.20	2.9
13	May 82	<5	0.30	0.04	1/1280	>100		
14	Sept 82	<5	0.66	0.04	1/640	>100		

*Measured by indirect immunofluorescence.

†Measured by Farr technique using commercially available kits (Amersham, Buckinghamshire, England).

Ribonucleic acid polyacrylamide gel electrophoretic pattern visualised by autoradiography.

A= Ribonucleic acids extracted from ³²P labelled HeLa cells used as antigens for immunoprecipitation.

B= Ribonucleic acids precipitated by IgG antibodies in serum sample from another patient with systemic lupus erythematosus.

C and D= Negative control sera.

Numbered samples are from patient with hyperimmunoglobulinaemia E syndrome (numbers correspond to those in table).

Anti-(U1)-ribonucleoprotein antibodies are observed in 30-50% of patients with systemic lupus erythematosus.²⁰U1= Small nuclear ribonucleoprotein antigen containing about 171 nucleotides; U1* is breakdown product of U1.¹⁴

probably be excluded.¹⁵ Antibodies binding to (U1)-ribonucleoproteins are characteristic in mixed connective tissue disease and are apparently associated with a benign type of renal disease in systemic lupus erythematosus if there are no anti-Sm antibodies.¹⁶

Systemic lupus erythematosus is predominantly a disease of young women and rarely occurs in men (average male to female

ratio 1:9—if only young patients are considered the ratio is probably even more in favour of women),¹⁵ and the hyper-IgE syndrome is probably even rarer; hence we think that the occurrence of both conditions in our patient was not fortuitous. That specific infectious agents might cause systemic lupus erythematosus has been shown conclusively only in an animal model.¹⁷ But it is well known that patients with various defective host defence mechanisms do have an increased incidence of autoimmune phenomena including systemic lupus erythematosus.^{18,19} Development of systemic lupus erythematosus has not been observed in patients with the hyper-IgE syndrome. Conceivably in all these disorders impaired handling of several microbial pathogens rather than a single agent may be associated with the development of autoimmune phenomena. Lifelong exposure to inappropriately processed or presented microbial agents may ultimately trigger the development of systemic lupus erythematosus.

We conclude that the onset of features of idiopathic systemic lupus erythematosus in the hyper-IgE syndrome may be taken as further evidence of a link between hyperimmunisation by defined micro-organisms and the pathogenesis of the disease. Finally, the possibility of various late onset complications must be considered in the management of long term survivors suffering from the *S aureus* hyper-IgE syndrome despite adequate control of infections.

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Abnormal cervical smears: are we in for an epidemic?

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Abstract

A retrospective study was conducted to examine the pattern of a disturbing increase in abnormal cervical smears in one health district. Past records over fifteen years (1965-79) were analysed to produce pick up rates according to age, screening state, severity of lesion, and area of residence. Main findings included an increased pick up rate in unscreened (5.8 to 12.9/1000 smears) and screened (0.9 to 3.6/1000 smears) women. The order of increase was proportionately much higher in women under 40 years. The only significant epidemiological variable in the catchment area was a substantial population increase, overweighted by the younger age groups.

The principal conclusion of the study was that the increased pick up rates of abnormal cervical smears in the district reflected a true increase in the incidence of premalignant lesions of the cervix. Screening efforts aided by computerisation should be examined nationwide in order to reach high risk groups and thus try to prevent an increase in carcinoma of the cervix.

Introduction

During the past seven years the Department of Health and Social Security annual returns from the cytology laboratory at this hospital (form SBH 40) have shown a sudden, pronounced increase in the number of cervical smears reported as "suspicious of severe dysplasia, carcinoma in situ, or worse." This increase has not been so dramatically paralleled in the total DHSS figures for England and Wales.¹ Concern was magnified by the fact that no special effort had been made to screen high

risk women in the area. Despite a large increase in the local population, the impression was that most of the smears examined came from previously screened women.

The returns made to the DHSS may be misleading for various reasons. The number of positive smears is not broken down by histological diagnosis and may include smears from patients with genital tract carcinomas other than cervical. They also include cytological false positive smears and cases of recurrent or residual neoplastic lesions of the cervix. The total number of smears examined gives no indication of the age groups or screening state of the women concerned. We therefore decided to analyse retrospectively the work done by the laboratory and to look for factors that might have contributed to an approximate doubling of the pick up rate of abnormal smears in the DHSS returns between 1975 and 1979 (8.9/1000 smears examined) compared with the previous 10 years (4.7/1000 smears examined). These included alterations in reporting by the laboratory, differences in screening practices, and changes in the population served.

Methods

A 10% sample was taken of all smears examined during the 15 years 1965-79. For each smear a record was made of the age of the woman, the year the smear was taken, and whether or not the woman had had a previous smear examined at the laboratory. These results were used to estimate the total number of smears taken from previously screened and unscreened women in each of the four age groups <30, 30-39, 40-49, and ≥50 during the three five year periods 1965-9, 1970-4, and 1975-9. Women who had had a previous smear examined at the hospital were classified as "screened." Information on smears taken elsewhere was unreliable, and for records where the only indication of a previous smear related to some other laboratory the smears were classified as screened or unscreened in the same proportions as for the other women in the appropriate subgroup.

The estimated total numbers of smears taken in each category were used as denominators in calculating the rates of positive smears. The numerators of these rates were calculated by extracting records relating to all women with positive smears over the same 15 year period. The few women who had positive smears taken elsewhere were classified as screened or unscreened proportionately, using the same procedure as for the denominators. Those who were found to have a histologically confirmed dysplasia, carcinoma in situ, or invasive carcinoma were classified according to the year of their

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