

Case report

Systemic lupus erythematosus and Klinefelter's syndrome

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SUMMARY A case of Klinefelter's syndrome presenting with systemic lupus erythematosus while receiving androgen replacement therapy is described. The association of systemic lupus erythematosus with Klinefelter's syndrome is discussed, particularly in terms of the effect of sex hormones.

Klinefelter's syndrome (XXY karyotype, gynaecomastia, hypogonadism, aspermatogenesis, and increased gonadotrophin secretion) has been described in association with systemic lupus erythematosus (SLE) in a total of 15 patients since the first description in 1969.¹ This association has evoked interest because of the increasingly evident effect of sex hormones on the pathogenesis of SLE. Sex hormone effects may be a common factor linking SLE in females and in males with Klinefelter's syndrome.³

A further case of Klinefelter's syndrome is presented in whom active SLE developed during and despite adequate androgen replacement therapy.

Materials and methods

Serum antinuclear antibodies (ANA) were detected by indirect immunofluorescence, deoxyribonucleic acid (DNA) antibodies by passive haemagglutination (Fujizoki Pharm., Tokyo) and antibodies to extractable nuclear antigen (ENA) by counterimmunoelectrophoresis with an extract of rabbit thymus (Pelfreeze Biol., Rogers, Arkansas) as antigen.³ Plasma C3 conversion was measured by serum immunoelectrophoresis.⁴ Serum immune complex concentrations were measured by Clq binding, K-cell inhibition, and Raji cell radioimmune assays.⁵

Case report

This 42-year-old male had presented in 1971 and 1973 with abdominal pain of unknown cause. On the

second occasion the ESR was 40 mm/h and the peripheral blood white cell count was $4.0 \times 10^9/l$.

In 1978 Klinefelter's syndrome was suspected and confirmed by chromosome analysis. Subsequent analysis showed both X chromosomes to have normal banding patterns. The plasma testosterone concentration was 3.6 nmol/l (normal range 2-19). The 24-hour urinary luteinising hormone concentration was 97 IU (4-45) and the follicular stimulating hormone concentration was 43 IU (2-22). In addition the ESR was elevated at 72 mm/h and there was a leucopenia of $2.7 \times 10^9/l$. Androgen replacement therapy was begun, initially with oral fluoxymestron and later changed to parenteral Sustanon (testosterone esters in oil). Subsequently, plasma testosterone concentrations were repeatedly normal. A raised ESR and leucopenia were present on 3 occasions during the ensuing 3 years of androgen replacement therapy, and at the end of this time serum ANA were detected at a titre of 1/200 and DNA antibodies at a titre of 1/640.

Three months later he was admitted to hospital with acute pleuritic chest pain, multiple haemoptyses, and a persistent fever of at least 38.6°C. A chest x-ray showed bilateral pleural effusions and a linear infarct at the right lung base. An elevated ESR to a maximum of 116 mm/h, a leucopenia, and serum ANA and DNA antibodies were again present. Antibodies to extractable nuclear antigen (ENA) were not detected. Serum immunoglobulin concentrations were normal and there was no cryoglobulinaemia. Plasma C3 and C4 concentrations were normal, and there was no plasma C3 conversion. Circulating immune complexes were detected by the Clq binding assay (41.86% binding, normal <20%). A direct Coombs test and serological tests for syphilis were negative. Proteinuria was not present.

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Anticoagulation with heparin was begun and prednisolone 40 mg daily was started 2 days later. After this there was symptomatic improvement, the pyrexia resolved, the ESR fell, and the white cell count became normal. Heparin therapy was stopped because of difficulties in obtaining adequate anticoagulation and the dose of prednisolone was gradually reduced to 20 mg daily. However, a subsequent episode of chest pain was found to be due to a pulmonary embolus from a deep venous thrombosis, and long term anticoagulation with warfarin was started. Further reductions of the dose of prednisolone to 7.5 mg daily were followed by the development of arthritis in both knees associated with a rise in the DNA antibody titre to 1/1280 and low plasma C3 and C4 concentrations but without evidence of C3 conversion.

Discussion

The association of SLE with Klinefelter's syndrome has been reported on a sufficient number of occasions for a relationship between the 2 conditions to be suspected.⁶⁻¹⁴ However, most reports have consisted of only one or 2 cases, and it has been argued that the prevalence of SLE in males with Klinefelter's syndrome is no greater than in males without the syndrome.⁹ None of the epidemiological studies of the prevalence of SLE or ANA in a chromatin-positive male population have included either adequate clinical assessment or serological investigations,^{9 15 16} and it is possible, therefore, that the SLE may not have been recognised in the patients in these studies. Most of the previously reported cases were not found to have Klinefelter's syndrome until they had presented with SLE,^{9 10 12-14} while in others with known Klinefelter's syndrome SLE was only diagnosed at post-mortem.⁸ The association of the 2 conditions has been found with such frequency that a relationship must be strongly suspected, but there is nevertheless still a need for an adequate epidemiological survey.

The effect of sex on the incidence of SLE is striking, and it is not surprising therefore that the concurrence of SLE and Klinefelter's syndrome has attracted attention.

It is well established from studies in the NZB/NZW mouse model of SLE that sex hormones can influence the development of autoimmune disease.¹⁷ Oestrogens enhance the autoimmune process, whereas androgens exert a protective effect. Oestrogens also appear to have an effect in human SLE. Abnormalities of oestrogen metabolism have been described^{12 18} in females, males without Klinefelter's syndrome, and males with Klinefelter's syndrome who have SLE. It is suggested that such abnormalities cause a hyperoestrogenic state which affects the

immune system. In animal models oestrogens enhance humoral immunity while depressing cell mediated immunity.¹⁹ Impaired clearance of immune complexes by the reticuloendothelial system has also been shown to be related to oestrogens in NZB/NZW mice.²

An alternative view of the effect of sex hormones in SLE in both the NZB/NZW mouse and Klinefelter's syndrome is that lack of testosterone rather than a hyperoestrogenic state is the important factor.¹⁰ There have been reports of androgen therapy improving SLE in females.²⁰ However, the present case had persistent evidence of SLE and an acute presentation while receiving adequate androgen replacement therapy with normal plasma testosterone concentrations, while other cases have also had normal testosterone concentrations during disease activity.¹⁴

The effect of sex hormones on the immune system, which is manifest in some patients with Klinefelter's syndrome, is clearly only one factor in the pathogenesis of SLE, but further study of this effect is important because of the possibility of additional therapeutic measures.

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