Case Report

A Male Lupus Patient with Klinefelter's Syndrome

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Abstract: A Chinese male systemic lupus erythematosus patient was coincidentally found to have hypergonadotrophic hypogonadism and subsequently diagnosed to be Klinefelter's syndrome. His lupus remained active despite androgen replacement therapy. The association between systemic lupus erythematosus and Klinefelter's syndrome is discussed.

Keywords: Klinefelter's syndrome, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune inflammatory disease with remarkable predominance of female during childbearing age, and female to male ratio is estimated to be 9.3 to 1 in Hong Kong.1 This observation strongly implies a significant role for hormonal influence in the multi-step pathogenesis. Klinefelter's syndrome (47 XXY) is the most common sex chromosomal disorder. Search in English language literature did not yield any previous report on the coexistence of SLE and Klinefelter's syndrome in Chinese patients.

We report a Chinese male systemic lupus erythematosus patient who was coincidentally diagnosed to have Klinefelter's syndrome. His lupus activity did not improve with androgen replacement therapy. The association between systemic lupus erythematosus and Klinefelter's syndrome is discussed.

Case Report

A 40-year-old man was first admitted to Queen Elizabeth Hospital in 1998 for culture negative fever despite empirical antibiotic treatment. In addition, he was found to have malar rash, polyarthritis in small joints of fingers, leucopenia 2.0 x 10⁹/L (neutrophil 1.0 x 10⁹/L and lymphocyte 0.8 x 10⁹/L), thrombocytopenia (119 x 10⁹/L), Coomb's positive autoimmune haemolytic anaemia (Hb 7.8 g/dL normochromic normocytic and haptoglobin <0.06 g/L), positive ANA (1:640; homogenous), anti-DNA 1017 IU/mL (normal <60), anti-Ro and depressed C3 level (0.39 g/L; NR 0.90-1.80). A diagnosis of SLE was made and he was treated with oral and later intravenous corticosteroids, hydroxychloroquine and azathioprine.

In the subsequent two years he had another two febrile episodes with leucopenia, and as a result azathioprine was stopped. He complained of back pain, subjective limbs weakness, myalgia and tremor which caused him a few trip-over injuries. Muscle enzymes were within normal and electromyogram showed myopathy but no active myositis. In view of these, hydroxychloroquine was also stopped for the remote possibility of drug-associated neuromyopathy.

Further questioning revealed that the patient had been investigated for primary infertility and a very low sperm count had been confirmed. He had normal erection and libido though he did not require frequent shaving. On physical examination, he did not have definitely abnormal facial feature though his voice pitch was slightly high. He had no beard, dubious gynaecomastia, normal height and arm span and testicular volume reduced to around one ml only.

Hormonal profile showed hypergonadotrophic hypogonadism. Testosterone (<0.2 nmol/l) and oestradiol levels (<73 pmol/l)
were undetectable while follicular stimulating hormone (22.5 IU/L) and lutenising hormone (8.0 IU/L) levels were elevated. Thyroid stimulating hormone was normal (1.55 mIU/L), and so were free T4 (14.8 pmol/l), prolactin (two spot samples 547 and 288 mIU/L) and spot growth hormone (<2.4 mIU/L) levels. Adrenocortical axis was hard to assess while he was on prednisolone. Testicular biopsy might be able to differentiate primary atrophy from testicular infarct which might occur consequent to lupus vasculitis. However it was not considered at that juncture as the histological result would not affect further management strategies. Osteopenia, both pre-existed due to hypogonadal state and chronic corticosteroid treatment, was revealed by DEXA scan which showed a T score of -1.5 in the lumbar region and -1.7 in the femoral neck. He was referred to geneticist and chromosomal analysis eventually confirmed Klinefelter's syndrome (47 XXY). Meanwhile testosterone replacement therapy was commenced (Sustanon 250 mg intramuscularly every three weeks). Daily oral prednisolone was maintained at a range of 5 to 15 mg daily.

Six years after initial presentation, the patient was admitted three times within half a year because of fever and leucopenia. Microbiologic workup was negative. Chest radiograph was clear. As he also complained of breathlessness, the following investigations were subsequently performed. Ventilation/perfusion scan showed normal finding; echocardiogram showed normal left ventricular function, no pulmonary hypertension, mild mitral regurgitation; spirometry and diffusion study were normal. Coincidentally, proximal myopathy was demonstrated (power grade 4+/5) and creatine kinase was elevated to 600 IU/L. Electromyogram and muscle biopsy showed non-specific myopathic changes. Anti-HIV was negative. Empirically oral prednisolone was stepped up to 60 mg daily to cover the possibility of lupus associated inflammatory myositis, and his muscle power slowly improved. Few months later high resolution computed tomogram of thorax revealed subpleural interstitial shadows in lung bases, suggestive of interstitial lung disease.

In the following year, he was admitted twice for fever with negative sepsis workup. Anti-DNA was elevated to >300 IU/ml and C3 depressed to 0.47 g/L. Total white cell count was 2.9 x 10^9/L (neutrophil 1.7 x 10^9/L and lymphocyte 0.5 x 10^9/L). Contrast computed tomogram of thorax revealed a small area of consolidation at right lower lobe of the lung, a small (<1 cm) cavitating lesion at the left lung apex, and old changes of interstitial lung disease. Gallium scan showed mild diffusely increased uptake in mid and lower parts of right lung field. Bronchoscopy and bronchoalveolar lavage were all negative. DLCO and spirometry on lung function tests were within normal range. However his muscle power again deteriorated to grade 3/5 and he needed major assistance to get up from bed. At the same time, a new onset of significant proteinuria of 2.2 g/day with bland sediment was detected. Renal biopsy confirmed class IIIA lupus nephritis.

The patient eventually agreed for intravenous cyclophosphamide therapy to control his active lupus disease which was refractory to high dose steroid and cyclosporine therapy. In view of low white cell count, mini-pulse every 2-4 weeks regime was adopted. In total 11 doses of cumulative dose 2875 mg were administered.

Just after the third dose of intravenous cyclophosphamide injection, the patient developed acute pulmonary oedema and required mechanical ventilation for three days. Echocardiogram showed global hypokinesia and left ventricular ejection fraction was only 25%. He was subsequently tided over with three courses of intravenous immunoglobulin. Half a year later, coronary angiogram showed normal coronary vessels, grade 2/4 mitral regurgitation, no pulmonary hypertension or intracardiac shunting, and left ventricular ejection fraction restored to 57%. Currently the patient was in New York Heart Association functional class I status, maintained on prednisolone 9 mg daily, hydroxychloroquine 200 mg daily and azathioprine 50 mg alternate day.

In summary, this is a 40-year-old man was diagnosed to have SLE in 1998 and had been followed up for nine years in our unit since then. He had the following organ involvement: malar rash, arthritis, cytopenia, WHO class IIIA lupus nephritis, interstitial pneumonitis, myositis, myocarditis, fever and active serology. Throughout the course of disease, he had been treated with various agents including oral and intravenous corticosteroid, azathioprine, hydroxychloroquine, cyclosporine, intravenous cyclophosphamide and intravenous immunoglobulin for lupus activity and flares. Klinefelter's syndrome was diagnosed one year after the diagnosis of SLE based on noted clinical features of hypogonadism and his hormonal profile. Many of the above major lupus flares occurred while he was put on testosterone replacement.

**Discussion**

Klinefelter's syndrome is the most common sex chromosome...
disorder in male, affecting approximately 1 in 660 live male births. Typical clinical signs of Klinefelter's syndrome are: absent frontal baldness, tendency to grow fewer chest hairs, breast development, female type pubic hair pattern, small testicular size, poor beard growth, narrow shoulders, wide hips and long legs (eunuchoid body habitus). On the other hand, the striking female predominance in SLE, especially during the child-bearing age, strongly reflects the influence of hormonal factors. The coexistence of SLE and Klinefelter's syndrome in the same patient was first reported in 1969, and so far around 30 cases appeared in English literature. The obvious interest in these patients, males with 47 XXY karyotype, is that they may increase our understanding of the role of hormonal influence in patients with SLE.

Are Lupus Patients with Klinefelter's Syndrome Different from Lupus in General?

Sex Hormones Profile

Sex steroid metabolisms in lupus patients with Klinefelter's syndrome were similar to lupus female patients. Elevated levels of oestrogens and oestrogen metabolites, decreased testosterone, increased follicle stimulating hormone and increased luteinizing hormone can all be expected with testicular failure in all patients with Klinefelter's syndrome. However, it was not clear whether the hyperoestrogenic state or lack of testosterone, or both, are responsible for the autoimmunity. Androgens seem to act as natural immunosuppressors and their deficiency has been observed in lupus and rheumatoid arthritis male patients.

Clinical Manifestations

According to a review of 23 lupus patients with Klinefelter's syndrome reported in English literature, the clinical manifestations of lupus patients with Klinefelter's syndrome are similar to other lupus patients except perhaps for the low frequency of cutaneous symptoms. Age of onset ranged from 12 to 73 years. Many of these patients still had active lupus activity despite testosterone replacement. In Asian Pacific region, only two reports of Japanese patients were available: one with co-existence of anti-cardiolipin antibodies, and another one with autoimmune hepatitis.

Autoimmunity phenomena had well been reported to be associated with Klinefelter's syndrome. Increased number of autoantibodies like rheumatoid factors, antinuclear antibodies and other organ-specific antibodies had been reported. Klinefelter's syndrome had also been reported to be associated with autoimmune diseases other than lupus, e.g. myasthenia gravis, scleroderma and antiphospholipid antibody syndrome.

Is Lupus and Klinefelter's Syndrome a Mere Coincidence?

Dubois and Kaplan performed buccal smears on 22 male lupus patients but failed to identify any cases of Klinefelter's syndrome. The following is a rough estimation of SLE risk in Klinefelter's syndrome basing on available local data: assuming that the reported patient is the only one with Klinefelter's syndrome among 74 male lupus patients in our cohort in Queen Elizabeth Hospital, given that the estimated point prevalence of male lupus in Hong Kong being 11.7 per 100,000 and background prevalence of Klinefelter's syndrome being quoted to be around 1 per 660 live male birth (risks of chromosomal abnormalities is similar across different ethnic groups). By Bayes' Theorem, the SLE risk in Klinefelter's syndrome is calculated to be 104 per 100,000, similar to the estimated point prevalence of female lupus in Hong Kong, i.e. 104 per 100,000. Therefore, the above epidemiological estimation suggests that Klinefelter's syndrome poses SLE risk in male at a magnitude that only approximates that in female in general population. Taking this further, as the hormonal and physiological differences between 47 XXY (Klinefelter's syndrome) and 46 XX (female), if any at all, do not confer a higher SLE risk, and XX (female) has ten-fold risk of XY (male), it might be inferred that Y chromosome does not play a major role in the pathogenesis of SLE.

It is prudent to maintain clinical suspicion of Klinefelter's syndrome in male lupus patients. Recognition can lead to awareness of the effect of hypogonadism, e.g. osteoporosis (on top of that arises from side effects of steroid which is often used to control lupus activities) and myopathy (inflammatory myositis being a differential diagnosis). Replacing testosterone may ameliorate some of these manifestations, but on its own is at best an adjunct therapy to conventional immunosuppressive strategies that are still the mainstay treatment for major lupus flare. In fact, lupus can still be active even when testosterone is replaced, as in our reported case in which active myositis, lupus nephritis, interstitial lung disease and myocarditis occurred during Sustanon maintenance therapy. This illustrates that hormonal
influence contributes only a part among other multiple etiological factors in the pathogenesis of SLE.

The other relevant clinical implication is on the well recognised association of malignancy with lupus, with a recent international cohort study showing an overall 15% increase in standardised incidence ratio of all cancers.14 Although the standardised incidence ratio for breast cancer was 0.76 (95% confidence interval 0.60-0.95) and the stage-adjusted disease survival was similar between female and male patients, male breast cancers were more likely to have lymph node involvement and a more advanced stage.15 Conversely, in an unselected retrospective series of 93 male breast cancer patients, the prevalence of Klinefelter's syndrome was determined to be as high as 7.3% using fluorescence in-situ hybridization technique on archival tissue sample.16 It is therefore intuitively sound to ask this specific group of male lupus patients to self notice any new breast mass and to offer regular breast examination. Nearly all cancers had been reported to occur coincidentally with lupus, except prostate cancer, and this can be readily explainable by hormonal factors. However, with testosterone replacement using Sustanon intramuscular injection, a cyclical androgen surge might have led to the potential of stimulating prostate neoplasm. As pre-emptive precaution in any patient put on long term testosterone replacement, prostatism symptoms enquiry and regular monitoring of prostate specific antigen level are certainly warranted. Hence, clinicians should be alert of breast and prostate cancers in this particular group of lupus patients with Klinefelter's syndrome. And one must bear in mind that such recommendation does not always prevent major lupus flares. During testosterone replacement, one should still be vigilant in surveillance of prostate cancer.

Summary

The hormonal profile of Klinefelter's syndrome is essentially that of women and this probably poses the same risk of SLE as in female general population. The clinical manifestations of lupus in this specific group of male patients are similar to those of female lupus patients, except perhaps less cutaneous symptoms. Androgen is a natural immunosuppressing hormone. There are scattered reports of Klinefelter's syndrome associated with other autoimmune diseases and occurrence of autoantibodies. As in all patients with Klinefelter's syndrome, once diagnosed, testosterone should be replaced life-long. In addition, it has another role in these lupus patients in tackling the problem of pre-existing osteopenia due to hypogonadal state. On the other hand, replacing androgen is at best an adjunctive therapy to immunosuppressive strategies in managing lupus in this specific group of patients, as it does not always prevent major lupus flares. During testosterone replacement, one should still be vigilant in surveillance of prostate cancer.

References