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CASE REPORT

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# Klinefelter's syndrome associated with systemic lupus erythematosus and autoimmune hepatitis

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**Abstract** Klinefelter's syndrome (KFS) tends to be associated with immunological disorders. We describe a 37-year-old man who presented signs of testicular atrophy and decreased body hair. He showed pancytopenia and elevated levels of liver enzymes. Chromosome analysis revealed 47XXY karyotype; therefore, he was diagnosed with KFS, with systemic lupus erythematosus and autoimmune hepatitis. Treatment with a high dose of methylprednisolone and methyltestosterone improved thrombocytopenia and symptoms, suggesting that methyltestosterone may have a clinical benefit in the treatment of KFS with a low level of testosterone accompanying immunological disorders.

**Key words** Autoimmune hepatitis · Klinefelter's syndrome · Systemic lupus erythematosus · Testosterone

## Introduction

Klinefelter's syndrome (KFS) is primary male hypogonadism caused by developmental testicular defects related to an underlying chromosomal abnormality. Klinefelter's syndrome tends to accompany autoimmune diseases, leukemia, malignant lymphoma, or malignant tumors.[1–3] In particular, the association of KFS with systemic lupus erythematosus (SLE) has been recognized.[4,5] Here we describe the first case of KFS accompanied by both SLE and autoimmune hepatitis (AIH).

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## Case report

A 37-year-old Japanese man visited a local hospital in February 2003 complaining of fever, weakness, and polyarthralgia. After a laboratory examination, he was referred to our hospital due to thrombocytopenia and high level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). He had no previous history of disease or hospitalization. However, he has had repeated tubercle-related maculoerythematous eruption in the neck from childhood, and he had fever and systemic erythema in particular after ocean bathing. Since then, he never went ocean bathing again. His elder sister was diagnosed with Sjögren's syndrome and his niece with neonatal lupus syndrome.

His height was 175 cm, body weight 105 kg and arm span 88 cm. Body temperature was 37.6°C. He exhibited signs of testicular atrophy and decreased body hair. Alopecia was recognized, as well as gynecomastia and indolent mouth ulcers.

Laboratory findings are shown in Table 1. Complete blood cell count indicated anemia (Hb 9.1 g/dl), leukocytopenia (1720/mm$^3$) and thrombocytopenia (60000 μl). Blood chemistry analysis revealed increased levels of AST (161 IU/l, normal 10–32 IU/l), ALT (182 IU/l, normal 7–27 IU/l) and lactate dehydrogenase (LDH) (471 IU/l, normal 118–257 IU/l). The level of total bilirubin was normal. Laboratory data showed positive inflammatory reactions including erythrocyte sedimentation rate (ESR, 64 mm/h, normal 3–11 mm/h), C-reactive protein (CRP, 1.2 mg/dl, normal value less than 0.1 mg/dl) and γ-globulin (2828 mg/dl, normal 793–1846 mg/dl). Antinuclear antibodies (ANA) were positive (titer 1:2560, with homogeneous and speckled pattern) and anti-dsDNA antibody was high (over 400 IU/ml). Anti-smooth muscle antibody (ASM) was positive (titer 1:40). The serum level of complement 50 and complement 3 were reduced to 11.4 IU/ml and 42 mg/dl, respectively. The urine was negative for protein. Serum HBs antigen (Ag), anti-HBs, HBe Ag, anti-HBc, and anti-HCV were negative. HLA-DR was 2 and 4.

**Table 1.** Laboratory findings

| Complete blood cell count | | Blood biochemistry | | Hormone | |
|---|---|---|---|---|---|
| WBC | 1720/mm$^3$ | TP | 7.1 g/dl | Testosterone | 140 ng/dl (male: 250–1100 ng/dl) |
| Hb | 9.1 g/dl | Alb | 2.6 g/dl | | |
| Platelet | 60 000/mm$^3$ | Na | 139 mEq/l | LH | 10.4 mIU/ml (male: 1.5–5 mIU/ml) |
| | | K | 4.1 mEq/l | | |
| Immunological and serological tests | | Cl | 109 mEq/l | FSH | 16.8 mIU/ml (male: 4–15 mIU/ml) |
| ANA (homogeneous, speckled) | 1 : 2560 | BUN | 10.3 mg/dl | | |
| | | Cre | 0.6 mg/dl | | |
| Anti-ds-DNA Ab | >400 IU/ml | AST | 161 IU/l | | |
| Anti-ss-DNA Ab | >800 IU/ml | ALT | 131 IU/l | | |
| Anti-sm Ab | (–) | LDH | 478 IU/l | | |
| Anti-SS-A Ab | 118.9 U/ml | γ-GTP | 52 IU/l | | |
| Anti-SS-B Ab | 31.8 U/ml | ALP | 233 IU/l | | |
| Anti-liver kidney microsome Ab | 1 : 32 | ChE | 126 IU/l | | |
| Anti-smooth muscle Ab | 1 : 40 | T-bil | 1.0 mg/dl | | |
| $CH_{50}$ | 11.4 IU/ml | IgG | 2282 mg/dl | | |
| C3 | 42 mg/dl | CRP | 1.2 mg/dl | | |
| C4 | 4 mg/dl | ESR | 64 (1 h)/128 (2 h) | | |
| Urine analysis | | | | | |
| Protein | (–) | | | | |
| Glucose | (–) | | | | |
| Ketone bodies | (–) | | | | |

**Table 2.** Diagnosis of autoimmune hepatitis in our patient according to a scoring system by the International Autoimmune Hepatitis Group

| Parameters/features | | |
|---|---|---|
| Male | | 0 |
| ALP/AST (or ALT) ratio | <3 | +2 |
| Serum globulins or IgG | >2 | +3 |
| ANA, SMA, or LKM-1 | >1 : 80 | +3 |
| Hepatitis viral markers | Negative | +3 |
| Drug history | Negative | +2 |
| Average alcohol intake | 35–50 g/day | 0 |
| Liver histology | Predominantly plasma cell infiltrate, with lobular involvement and bridging necrosis; rosetting of liver cells | +5 |
| Other autoimmune diseases | Positive | +2 |
| HLA | DR4 | +1 |
| Response to therapy | Partial response | 0 |
| Aggregate score | | |
| Before treatment | | 21 (>15 definite AIH) |
| After treatment | | 21 (>15 definite AIH) |

Laparoscopic observation revealed multiple small nodules on the surface of the liver, suggesting cirrhosis. Histological appearance of the liver biopsy specimen showed fibrosis and enlargement of the portal tract with marked lymphocytic infiltration. These findings were compatible with those of AIH.

The patient was diagnosed as having autoimmune hepatitis according to Diagnostic Criteria for Type I AIH (Table 2). His symptoms and data of the examination fulfilled the American College of Rheumatology (ACR) SLE diagnosis criteria (photosensitivity, antinuclear antibody and leukopenia, immunologic disorder, indolent mouth ulcers, central nervous system lupus). Despite positive anti-SSA and anti-SSB antibody, Schilmer's test was negative and the salivary flow rate by chewing a sugar-free gum for 10 min was within the normal limit. These results did fulfill the Japanese criteria of Sjögren syndrome.

We initiated treatment with prednisolone 60 mg/day. After liver function returned to the normal range, we then reduced administration of the steroid by 5 mg every 2

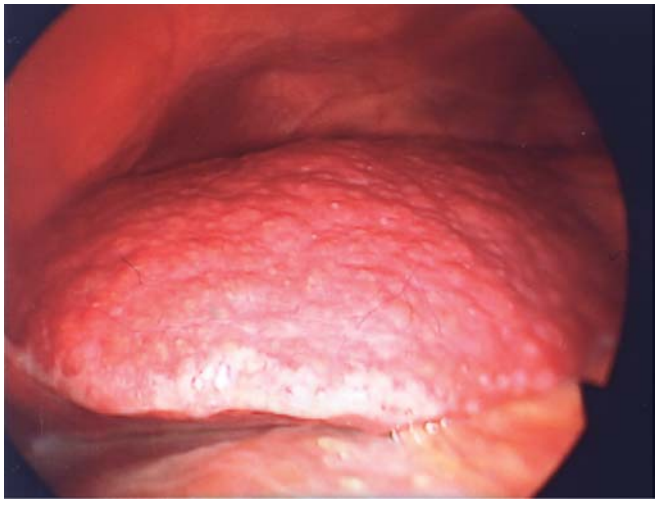

**Fig. 1.** Laparoscopic observation shows that liver surface is irregular, suggesting cirrhosis

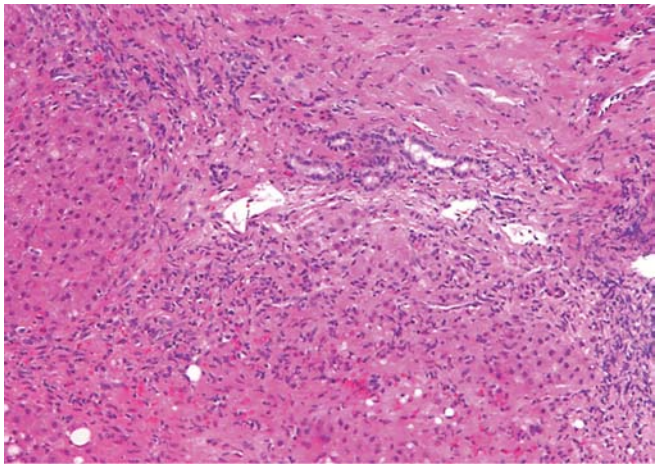

**Fig. 2.** Histological appearance of the liver biopsy specimen, showing fibrosis and enlargement of the portal tract with marked lymphocytic infiltration (HE staining, ×100)

weeks. In the course of prednisolone reduction, the patient complained of headache, delirium, tremor, restlessness, and agrypnia. In addition, a high level of interleukin-6 (IL-6) was evaluated in the cerebrospinal fluid (IL-6: 89.4 pg/ml, the cell number was 3/μl, the total protein concentration was 40 mg/dl). He showed a high signal in brain cortex bottom via T2 emphasis image on the brain magnetic resonance imaging (MRI; Fig. 3). These symptoms and the findings suggested occurrence of central nervous system lupus. We therefore initiated a high dose of methylprednisolone (1 g/day) for 3 days. Headache, delirium, restlessness, and agrypnia disappeared with reduction of IL-6 level in the cerebrospinal fluid; however, tremor was not improved. We performed examination of cerebrospinal fluid again, but IL-6 levels were not high (3.4 pg/ml), suggesting that the activity of central nervous system lupus was suppressed by methylprednisolone.

Since the improvement in his platelet number was slow, we performed a bone marrow examination. Bone marrow was found to be normal and we did not detect phagocytosis of blood cells by macrophages. Chromosome analysis revealed 47XXY karyotype; therefore, we confirmed KFS with a low level of serum testosterone. Since the patient was then treated with methyltestosterone, thrombocytopenia and tremor were improved, and the serum level of anti-dsDNA antibody (18 IU/ml) was reduced. (Fig. 4).

## Discussion

Klinefelter's syndrome tends to accompany autoimmune diseases, leukemia, malignant lymphoma, or malignant tumors, presumably due to the excessive X chromosome.[1–4] Among the autoimmune diseases, SLE has been well known to be associated with this syndrome.[4,5] We diagnosed SLE according to ACR criteria; however, pancytopenia might have been due to liver cirrhosis. Despite that, the other findings fulfilled the criteria of SLE. We also diagnosed our patient as having autoimmune hepatitis accord-

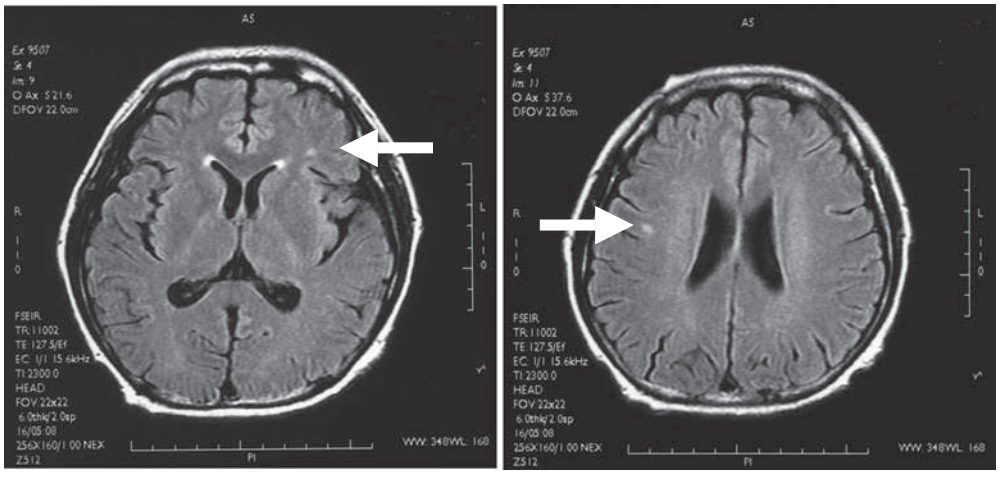


**Fig. 3.** Brain magnetic resonance imaging T2 emphasis image. *Arrow*, high signal

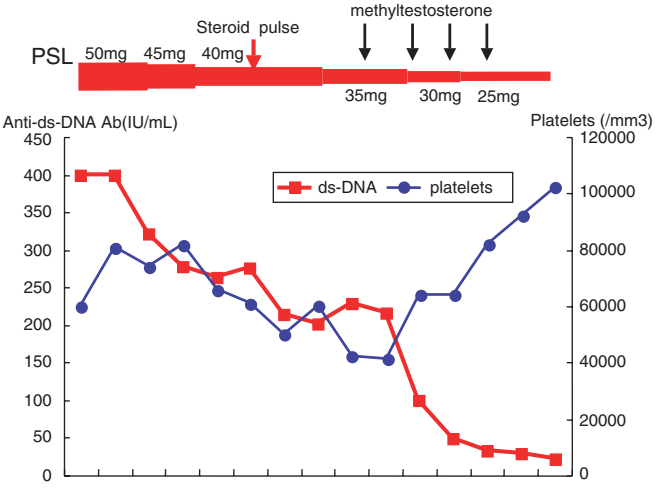


**Fig. 4.** Clinical course of the patient. *PSL*, prednisolone

ing to Diagnostic Criteria for AIH (Table 2). We diagnosed Type I AIH due to positive results for ANA and ASM.

This predilection is ascribed to the fact that each sex steroid hormone exerts its specific action on the immune system. To date, many researchers have investigated the effects of sex steroid hormones on the immune system and their role in autoimmune diseases.[8–10]

Testosterone, the immediate precursor of estradiol, is found in both men and women, and is generally accepted as being immunosuppressive. While testosterone decreased significantly in female patients with SLE compared with controls,[10,11] many studies reported that there was no significant decrease of testosterone in male patients with SLE.[9,10]

Bizzarro et al. demonstrated that testosterone replacement therapy induced clinical improvement of SLE, suggesting that testosterone may play a critical role in immunoregulation in those patients with KFS.[12] We also confirmed the clinical improvement of this case after testosterone replacement therapy.

As to the other sex steroids used for therapy, Petri et al. reported that SLE patients receiving oral prasterone 200 mg/day had improvement in disease activity and symptoms in a multicenter randomized trial.[13] Prasterone is the United States Adopted Names generic designation for dehydroepiandrosterone. Dehydroepiandrosterone (DHEA) is a naturally occurring steroid produced by the adrenal glands. It is secreted primarily as its metabolite, DHEA sulfate (DHEAS), which is the most abundant circulating adrenal steroid in humans. Both DHEA and DHEAS are subsequently converted into androgenic and estrogenic steroids in peripheral tissues. Decreases of 50% in circulating levels of DHEA and DHEAS have been observed in female patients with SLE.[14] Previous studies in animal models of SLE have demonstrated improvement with androgen administration, including DHEA.[15] In addition, there is evidence that DHEA has an immunomodulatory role, including upregulation of interleukin-2 (IL-2) and downregulation of IL-6 expression, both of which have been reported to be abnormal in SLE.[16,17]

To date, there have been reports of AIH patients with KFS; yet this is the first report of KFS with SLE and AIH. We had experienced some difficulties in evaluating and discerning central nervous system symptoms caused by SLE from those caused by KFS; however, it was useful to measure IL-6 in cerebrospinal fluid for this differential diagnosis. Since a male SLE patient with KFS is not so rare, it is important to measure serum testosterone level for the diagnosis, and this may help in the treatment of SLE patients with KFS.

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