

## Rheumatic Diseases and Klinefelter's Syndrome

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Klinefelter's syndrome, which occurs in males, is not a rare gonosomal aberration. The disorder is characterized by microorchidism. Another typical although not constant symptom of this disorder is gynecomastia, with almost normal male secondary sex characteristics. The etiology of this disease remains unknown. Previous studies have shown that this disorder is a genetic chromosomal abnormality associated with the presence of one additional chromosome due to abnormal division. Thus, the affected individual has 47 chromosomes with the resulting chromosomal constellation of XXY (classical form) or 46,XY/47,XXX (mosaic form).

Large population studies have estimated the incidence of Klinefelter's syndrome at 1:1000 live-born male babies [1]. The locomotor apparatus of persons affected by the syndrome is characterized by acromicria, clinodactyly, conrescence of thoracic vertebral bodies, and spinal osteoporosis not only in older individuals but also in younger persons.

In the 1960s and 1970s, reports were published on the concurrence of Klinefelter's syndrome with autoimmune diseases. In this article we discuss case reports published by authors from our institute, and present an overview of the reports published so far, mainly from abroad.

### With rheumatoid arthritis

Bošmanský and Kopecký [2] described the development of rheumatoid arthritis in a 61 year old patient with Klinefelter's syndrome; the patient had been diagnosed with rheumatoid arthritis at age 55. This disease had a clearly benign development, slow progression, mild aggressiveness and minimal exudative manifestations that may be attributed to the presence of Klinefelter's syndrome, and the patient concurrently developed diabetes mellitus. The erythrocyte sedimentation rate was moderately elevated. Rheumatoid factors gave positive results (LFT 1280, HT 112). Electrophoresis demonstrated elevated alpha-2 and gammaglobulins. Diffuse ischemic changes could be identified on the electrocardiogram. The patient died after suffering a myocardial infarction.

In their report, Bošmanský and Kopecký [2] pointed to the relatively rare coincidence of Klinefelter's syndrome and rheumatoid arthritis. The cases reported in the available pre-1979 literature included a case of rheumatoid arthritis, type II insulin-resistant diabetes mellitus and Klinefelter's in a 41 year old patient [3]; MacSween's [4] report of a patient with malignant lymphoma, rheumatoid arthritis and Klinefelter's; and the de-

scription by Tsung et al. [5] of a 46 year old patient with Klinefelter's, high titers of rheumatoid factors, malignant lymphoma and Osler-Weber-Rendu's syndrome (hereditary hemorrhagic telangiectasia).

Kobayashi et al. [6] described a patient with Klinefelter's syndrome associated with rheumatoid arthritis. Low testosterone levels are considered a contributing factor in males with the latter disorder, in particular during the active phases of the disease. The question remains open whether hypogonadism is a predisposing factor or an actual consequence of the disease. Those investigators [6] contend that low testosterone levels do not necessarily represent a predisposition for rheumatoid arthritis activity. The course of the disease in their patient was benign, as in the case reported by Bošmanský and Kopecký [2].

### With polymyositis and dermatomyositis

Rovensky et al. [7] reported the case of a patient with Klinefelter's syndrome associated with antisynthetase syndrome (Raynaud's phenomenon, acrosclerosis, 'mechanic's hands', mild weakness of proximal muscles of the hands, presence of interstitial pulmonary fibrosis, tendency to recurrent infections, and secondary Sjögren's syndrome). The presence of anti-Jo-1 antibody along with anti-Ro and anti-La antibodies was detected upon repeated tests. Two cases of a similar association were reported from South Africa by Nielsen et al. [8] and Murakami et al. [9]. These cases involved the concurrence of classical polymyositis with Klinefelter's syndrome.

### With systemic lupus erythematosus

Among the other rheumatic diseases, several cases of SLE have been reported. The coincidence was reported by Ortiz-Neu and LeRoy in 1969 [10]. The authors presented two patients with Klinefelter's syndrome and SLE. In their third patient with Klinefelter's they found glomerulonephritis with antinuclear antibody positivity. Later on, Vitori and Desaegher [11] mentioned several other reports, such as those by Landwirth and Berger [12] and Saeed Uz Zafer et al. [13]. The latter group even described a case of Klinefelter's syndrome, SLE and porphyria cutanea tarda. Folomeev and collaborators in 1991 [14] described the case of a 2 year old male in whom SLE was characterized by Raynaud's phenomenon with necrosis of the fingers, dyspnea and chest pain due to pleuritis. In the laboratory workup an-

SLE = systemic lupus erythematosus

tinuclear antibodies were detected, and the Bordet-Wasserman reaction gave false positive results. Some 10 years later, the patient was again admitted for skin rash, sensitivity to the sun, and ulcers in the oral cavity. Moreover, Raynaud's phenomenon was present, with necroses of fingertips and lymphadenopathy. Laboratory workup revealed leukopenia, high ESR values, LE cell positivity, elevated antinuclear antibody titer, presence of anti-dsDNA antibodies, anticardiolipin antibodies and lupus anticoagulants, mild proteinuria and pulmonary infiltrates. The patient's androgen levels were decreased and his estrogen levels elevated. Klinefelter's syndrome was unambiguously proven by endocrinologic and genetic tests.

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### *Klinefelter's syndrome may occur concurrently with inflammatory rheumatic diseases*

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Stern and colleagues [15] studied urinary estrogen levels in patients with Klinefelter's syndrome and SLE. In one patient the levels of all three urine estrogens were elevated (estrone, estradiol, estriol), with the estriol levels being markedly high. No such findings could be identified in another patient, who had altered estrogen metabolism detected by labeled estradiol, i.e., disturbed estradiol to estrone conversion. Subsequent conversion to estriol increased in both patients. These results suggested excessive estradiol transformation into estriol and reduced metabolism of 2-OH estrone. Lahita [16] pointed to the fact that estradiol levels are frequently high in Klinefelter's syndrome, reaching values of a normal menstrual cycle, whereas androgen levels are similar to those found in prepubertal males. Estrogens seem to play a role in the modulation of the immune system and a significant role in the pathogenesis of SLE itself. Other studies showed that plasma androgen levels, including those of testosterone, androstendione, dehydroepiandrosterone and dehydroepiandrosterone sulfate, are reduced in SLE. Michalski and team [17] described a patient with testicular insufficiency, reduced testosterone and increased follicle stimulating and luteinizing hormone levels, as may be expected in patients with Klinefelter's syndrome. Lahita and Bradlow [18] studied several patients with Klinefelter's and SLE and concluded that their metabolism of sex steroids was similar to that observed in women with SLE. French and Hughes [19] pointed also to testicular insufficiency in patients with SLE. The above-mentioned cases, however, failed to clarify whether it is hyperestrogenism or the lack of testosterone, or both, that is responsible for the development of autoimmunity in these individuals. Androgens seem to be natural immunosuppressors, and their

deficiency was observed in SLE and in males with rheumatoid arthritis.

The list of reports on patients with SLE and Klinefelter's syndrome concludes with a paper by Gilliland and Stashower [20], who described the case of a 12 year old boy in whom epileptic episodes had been occurring since he was 4 years old. Initially, he experienced skin manifestations on his face and shoulders as well as in the auricular region. Biopsy suggested discoid lupus erythematosus. Weakness and arthritis of the small joints of the hands and feet developed after several months. Antinuclear antibodies, anti-dsDNA antibodies, hypocomplementemia, mild lymphopenia and elevated ESR values were present. The disease was controlled by antimalaria medication and prednisone. A follow-up examination at age 16 revealed that the patient had small testes. Hormone and chromosome analysis confirmed the presence of Klinefelter's syndrome. The patient was subsequently treated with 200 mg testosterone at 3 week intervals. The skin symptoms worsened at age 19, accompanied by hair loss and arthritis, with the only positive laboratory parameter being antinuclear antibody.

### **With systemic sclerosis**

Nowlin et al. in 1985 [21] described the concurrence of Klinefelter's syndrome with systemic sclerosis. A short description had been published earlier by O'Donoghue [22]. In one of the two patients described by Nowlin and team, hypogonadism had been present prior to the development of the sclerosis. The authors discussed the role of testicular failure as a disease-modifying factor in systemic sclerosis. In the other patient, Raynaud's

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### *Early diagnosis of the syndrome, when occurring simultaneously with autoimmune diseases, is important*

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phenomenon appeared with lack of androgens. Testicular fibrosis along with vasculopathy is believed to contribute to gonadal failure in systemic sclerosis. DeKeyser et al. [23] reported a case of systemic sclerosis and Klinefelter's, with the clinical picture being dominated by sclerodactyly and bilateral basillary pulmonary fibrosis, and synovitis of the metacarpophalangeal joints. Again, the authors speculated about the potential effects of Klinefelter's syndrome on the development of the autoimmune syndromes. This mainly concerns the effects of the doubling of the X chromosome and the low androgen-to-estrogen ratio. And finally, Kobayashi et al. [24] reported systemic sclerosis in a patient with Klinefelter's who had been infertile for 20 years; both disorders were diagnosed when she was 43 years old. The authors mentioned five cases of systemic sclerosis in persons aged 41–61, and speculated about the association between the two diseases.

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ESR = erythrocyte sedimentation rate

LE = lupus erythematosus

### With mixed connective tissue disease

Takeuchi and co-workers [25] described a patient with Klinefelter's syndrome presenting with mixed connective tissue disease, diabetes mellitus and some other endocrinologic disturbances. On admission, the 57 year old man had polyarthritis, sausage-shaped fingers and Raynaud's phenomenon. Restrictive disturbance of the diffuse pulmonary capacity, and myogenic lesion were demonstrated on electromyography, along with anti-RNP antibodies positivity and diabetes mellitus, hyperprolactinemia, hypothyroidism and hypocorticism.

### Conclusions

With regard to the pathogenesis of Klinefelter's syndrome and autoimmune diseases, opinions converge that a doubled chromosome X and a low androgens-to-estrogens ratio, which is a typical feature of Klinefelter's, may play an important role in the pathogenesis of autoimmune diseases. Low testosterone levels in patients with Klinefelter's might suggest a predisposition for the development of autoimmune diseases. It may therefore be appropriate to continuously monitor testosterone levels in patients with an autoimmune disease and to compare them with the progression and outcome. Also, it appears that Klinefelter's syndrome should be monitored from the aspect of the development of autoimmune diseases, since it is associated with hypogonadism. It appears that the syndrome may be a conducive setting for the development of autoimmune diseases.

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*I was never less alone than when by myself*

Edward Gibbon (1737-94), British historian known mostly for his monumental *The History of the Decline and Fall of the Roman Empire*. The work's epic scope and dignity of style have ensured its survival.