Rheumatic diseases and Klinefelter’s syndrome

This review summarizes reports on the concurrence of Klinefelter’s syndrome with inflammatory rheumatic diseases, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, the antiphospholipid syndrome and ankylosing spondylitis. This article includes two case reports of patients with Klinefelter’s syndrome that is concurrently associated with rheumatoid arthritis or antisynthetase syndrome, respectively, and were previously reported by the author and his coworkers. Attention is paid to the pathogenesis and the course of disease in patients with Klinefelter’s syndrome. The importance of early diagnosis of the syndrome when occurring simultaneously with other diseases of the connective tissue is emphasized.

Keywords: ankylosing spondylitis, Klinefelter’s syndrome, polymyositis, dermatomyositis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis.

Results

Klinefelter’s syndrome & rheumatoid arthritis

Bošanský and Kopecký described the development of rheumatoid arthritis (RA) in a 61-year-old patient with KS; the patient was diagnosed with RA at the age of 55 [1]. The RA demonstrated a clearly benign development, slow progression and mild aggressiveness, and minimal exudative manifestations may be attributed to the presence of KS and concurrently developed diabetes mellitus. Erythrocyte sedimentation rate (ESR) values were moderately elevated. Rheumatoid factors gave positive results (rheumatoid factor latex test: 1280; Coombs hemagglutination test: 112) and electrophoresis (ELFO) of serum protein levels demonstrated elevated α2 and γ globulin. Diffuse ischemic changes could be identified on the electrocardiography (ECG). The patient died after suffering a myocardial infarction.

In their report, Bošanský and Kopecký pointed to the relatively rare coincidence of KS occurring with RA [3]. The cases reported in the available pre-1979 literature include a case of RA, Type II insulin-resistant diabetes mellitus and KS in a 41-year-old patient [4]; Mac Sween reported on a patient with malignant lymphoma, RA and KS [5] – Tsung et al. described a 46-year-old patient with KS and the presence of high titers of rheumatoid factors, malignant lymphoma and Osler-Weber-Rendu syndrome [6]. Kobayashi et al. also described a patient with KS associated with RA [7].
Both RA and KS are diseases in which perturbations of the gonadal axis have been reported. Low testosterone levels or an increased ratio of estradiol:testosterone have been considered contributing factors in the development of RA in males \([8,9]\). In RA males, estradiol was found to be correlated with the degree of inflammation \([10]\).

In addition, the local action of gonadal steroids, determined by factors such as conversion to active metabolites or receptor sensitivity in tissues affected with inflammation, may also play an important role in RA pathogenesis \([11]\). Although the underlying mechanism of the gonadal axis perturbations in RA is likely to be different from that in KS, the hypoandrogenic status found in both diseases on a systemic level might explain the concurrence of KS with autoimmune disorders. Furthermore, genetic abnormalities in androgen receptor-coding genes, such as polyglutamine repeat length, were found to contribute to phenotypic variability in KS, suggesting alterations in androgen action and that they may indeed play a role in the development of autoimmunity in KS as well \([12]\). On the other hand, Kobayashi et al. are inclined to believe that low testosterone levels need not represent a predisposition factor to RA activity \([7]\). The course of the disease in their patient was benign, as it was in the case report by Bošmanský and Kopecký \([3]\).

### Klinefelter’s syndrome & juvenile idiopathic arthritis

Mirkinson et al. published a case of KS and juvenile idiopathic arthritis (JIA) \([13]\). The patient, a 16-year-old Caucasian male, was referred for evaluation after a 3-year history of bilateral ‘claw hand’ and of diffuse morning stiffness of the proximal and distal phalanges of both hands. At the time of his initial visit, his morning stiffness lasted for 60 min. He denied having symptoms of pain or swelling of other joints or the back, with the exception of suffering decreased lateral flexion of his neck. The patient was diagnosed with KS and a 47,XXY karyotype at the age of 6 years. Evaluation was prompted by concerns of developmental delay and attention deficit disorder. Consistent with this diagnosis, transdermal testosterone therapy was started at age 14 years. At the start, supplemental testosterone therapy was initiated; the patient’s testosterone level was 0.1 ng/dl (normal is 3.0–10.0 ng/dl) and the luteinizing hormone level was below 0.09 mIU/ml (normal is 2.4–9.4 mIU/ml). At the time of his initial evaluation for arthritis, his only medication was a testosterone patch that was applied daily.

At the time of the patient’s initial evaluation, a diagnosis of polyarticular JIA was made. The patient was initially started on NSAID therapy. A total of 3 months later, oral methotrexate (MTX) at a dose of 10 mg/week (0.18 mg/kg/week) was added to his regimen owing to continued evidence of active inflammation manifested by joint swelling and morning stiffness. A marked improvement was noted in morning stiffness and joint swelling when the MTX dose was increased to 0.3 mg/kg/week. A loss of clinical signs of active inflammation was achieved 9 months after the initiation of MTX therapy. NSAID therapy was later discontinued and the patient was treated with a maintenance dose of 0.2 mg/kg/week of MTX. Although the observed association of JIA with KS could support the hypothesis of hypogonadism being a predisposing factor in autoimmunity development, a causal relationship between autoimmunity and androgen/estrogen balance cannot be established. Whether or not KS predisposes to autoimmune disease because of its associated reduction in androgens remains unclear.

### Klinefelter’s syndrome & psoriatic arthritis

Melillo et al. reported on a 52-year-old Caucasian man with KS and psoriatic arthritis (PsA) \([14]\). This case report emphasizes the role played by sex hormones and chromosomal abnormalities in the pathogenesis of autoimmune disorders, and to our knowledge, this is an uncommon case of a patient with KS who developed PsA.

### Klinefelter’s syndrome polymyositis G-protein/dermatomyositis

Rovenský et al. reported a case of a 47-year-old man with KS associated with the 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) \([15]\). The presence of anti-Jo-1 antibody together with anti-Ro and anti-La antibodies was detected in repeated tests. Two cases of a similar association have been reported from South Africa by Nielsen et al. \([16]\) and Murakami et al. \([17]\). The latter cases concern the concurrence of classical polymyositis with KS.

### Klinefelter’s syndrome & systemic lupus erythematosus

Among other rheumatic diseases, several cases of systemic lupus erythematosus (SLE) have been reported. Ortiz-Neu and LeRoy reported the coincidence in 1969 \([18]\). The authors presented...
two patients with KS and SLE. In the third patient with KS the authors identified glomerulonephritis with a positive antinuclear antibody test. Ensuingly, Vittori and Desaegher referred to other papers [19] such as those by Landwirth and Berger [20] and Saeed Uz Zafer et al. [21]. The latter group described a case of KS, SLE and porphyria cutanea tarda. In 1991, Folomeev et al. described the case of a 22-year-old male in whom SLE appeared to be characterized by Raynaud’s phenomenon with necrosis of the fingers, dyspnoea and chest pain owing to pleuritis [22]. Among the laboratory parameters analyzed, the presence of antinuclear antibodies (ANA) was detected and the Bordet–Wasserman reaction gave false positive results. Some 10 years later, the patient was admitted again for skin rash, sensitivity to sunrays and ulcers in the oral cavity. Moreover, Raynaud’s phenomenon was present with necroses of the fingertips and lymphadenopathy. The laboratory parameters showed leucopenia, high ESR values and positive LE cells, elevated ANA titers, the presence of anti-dsDNA antibodies, antiphospholipid antibodies and lupus anticoagulants, mild proteinuria and pulmonary infiltrates were detected. The patient’s androgen plasma levels were decreased and estrogen levels were elevated. KS was unambiguously proved by endocrinology and genetic tests.

Stern et al. studied urinary estrogen levels in KS and SLE. One patient had elevated levels of all three urine estrogens studied (estrone, estradiol and estriol), with the estriol levels being markedly elevated. However, no such findings could be identified in another patient who had an altered estrogen metabolism detected by labeled estradiol, that is, disturbed estradiol to estrone conversion [23]. Subsequent conversion to estriol was enhanced in both patients. These results suggest excessive estradiol transformation into estriol and a reduced metabolism of 2-OH estrone. Lahita highlighted the fact that estradiol levels are frequently elevated in KS, reaching values of those measured in women with a normal menstrual cycle, whereas androgen levels are similar to those found in prepubertal-age males [24]. 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 demonstrated that plasma androgen levels, including those of testosterone, androstenedione, dehydroepiandrosterone and dehydroepiandrosterone sulphate, are reduced in SLE. Michalski et al. described a patient with testicular insufficiency, reduced testosterone and increased follicle stimulation and luteinizing hormone levels, as may be expected in patients with KS [25]. Lahita and Bradlow studied several patients with KS and SLE and concluded that their metabolism of sex steroids was similar to that observed in women suffering from SLE [26]. French and Hughes also pointed to testicular insufficiency in patients with SLE [27]. However, the above-mentioned cases failed to clarify whether it is hyperestrogenism, a lack of testosterone or both that are responsible for the development of autoimmunity in these individuals. Androgens seem to be natural immunosuppressors and their deficiency was observed in SLE and in RA males.

Gilliland and Stashower described a case of a boy with a history of epileptic episodes. At the age of 12 years, the patient developed discoid lupus erythematosus with arthritis of small joints in the hands and feet, ANA, anti-dsDNA antibodies, hypocomplementemia, mild lymphopenia and elevated ESR values. Hypogonadism was diagnosed at the age of 16 and genetic testing confirmed KS [Table 1]. Testosterone supplementation was added to SLE therapy in the latter case; however, no significant improvement was observed [28]. Jiménez-Balderas et al. studied the presence of rheumatic diseases in subjects with untreated male hypogonadism with low testosterone levels. In this latter study, two out of four KS cases also had SLE and one KS case had ankylosing spondylitis [29].

It is known from epidemiological surveys in our region that for SLE, the female: male ratio is 9:1. The incidence of KS has been estimated to be 1.7/1000 males born and the occurrence of both syndromes simultaneously may be coincidental. On the other hand, there have been attempts to screen male patients with SLE for the presence of KS. Dubois and Kaplan attempted to detect the presence of KS in 22 male patients with SLE using swabs from buccal mucosa; however, no KS case was identified. Upon physical examination of young males with diagnosed SLE, it is important to look for hypogonadism and gynecomastia and to pay attention to secondary sexual characteristics [30].

So far, there have been only two studies published that focus on the effects of testosterone therapy on clinical manifestations in SLE. Bizzarro et al. demonstrated that testosterone administration in two patients with SLE was followed by clinical and immunological remission in both of them [31]. In their patient, Olsen and Kovacs administered testosterone replacement therapy and increased the patient’s testosterone levels to normal [32]. These authors described both a clinical improvement and an improvement in hematological and serological parameters.
Table 1. List of publications on Klinefelter’s syndrome and SLE.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age of onset of SLE</th>
<th>Skin symptoms</th>
<th>Discoid exantema</th>
<th>Photosensitivity</th>
<th>Mouth mucus defects</th>
<th>Arthritis</th>
<th>Serositis</th>
<th>Kidney impairment</th>
<th>Neurologic disorders</th>
<th>Immunol. disorders</th>
<th>Hematol. disorders</th>
<th>ANA</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oritz-Neu et al. (1969)</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[18]</td>
</tr>
<tr>
<td>Landwirth et al. (1973)</td>
<td>12</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>[20]</td>
</tr>
<tr>
<td>Duboa et al. (1976)</td>
<td>UA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[30]</td>
</tr>
<tr>
<td>Price et al. (1976)</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>[2]</td>
</tr>
<tr>
<td>Stern et al. (1977)</td>
<td>24</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>[23]</td>
</tr>
<tr>
<td>Segami and Alarcón-Segovia (1977)</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>[54]</td>
</tr>
<tr>
<td>Michalski et al. (1978)</td>
<td>47</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>[25]</td>
</tr>
<tr>
<td>Fam et al. (1980)</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>[55]</td>
</tr>
<tr>
<td>French and Hughes (1983)</td>
<td>42</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>[27]</td>
</tr>
<tr>
<td>Schlegelberger et al. (1986)</td>
<td>UA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>[56]</td>
</tr>
<tr>
<td>Bizzarro et al. (1987)</td>
<td>UA</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>[31]</td>
</tr>
<tr>
<td>Dugernier et al. (1987)</td>
<td>28</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>[37]</td>
</tr>
<tr>
<td>Marshall (1988)</td>
<td>54</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>[58]</td>
</tr>
<tr>
<td>Schattner and Berrebi (1989)</td>
<td>73</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>[59]</td>
</tr>
<tr>
<td>Folomeev et al. (1991)</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>[22]</td>
</tr>
<tr>
<td>Miyagawa et al. (1995)</td>
<td>24</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>[60]</td>
</tr>
<tr>
<td>Olsen and Kovacs (1995)</td>
<td>31</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>[32]</td>
</tr>
<tr>
<td>Gilliland and Stashower (2000)</td>
<td>12</td>
<td>x</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>–</td>
<td>x</td>
<td>x</td>
<td>[28]</td>
</tr>
</tbody>
</table>

Data taken from [27] and expanded by the authors.

during a 9-month therapy. A similar clinical and laboratory improvement was observed during testosterone replacement therapy in males suffering from RA [33].

The paper by Strand suggested that dehydroepiandrosterone replacement treatment is a possibility for SLE [34]. It is mainly used in the treatment of corticosteroid dose-dependent SLE and it improves bone density and the lipid spectrum. In other words, progress in hormonal therapy for SLE is suggested to take this direction and it cannot be ruled out that this method of treatment will also be used in other autoimmune diseases or to treat concurrent KS and SLE and/or other nosological entities.

Recently, a large genotyping study in SLE patients revealed that of 213 SLE men, five had KS (47,XXY genotype) [35]. The risk of SLE in men with the 47,XXY genotype has been calculated to be approximately 14-times higher than in men with the 46,XY genotype, which is consistent with the notion that SLE susceptibility is partially explained by an X chromosome gene–dose effect [35].

Klinefelter’s syndrome & systemic sclerosis
In 1985, Nowlin et al. described the occurrence of KS with systemic sclerosis (SSc) [36]. A short description was published earlier by O’Donoghue [37]. In one of the two patients described by Nowlin, hypogonadism had been presented prior to the development of SSc. The authors discussed the role of testicular failure as a disease-modifying factor in SSc. In the other patient, Raynaud’s phenomenon appeared with a lack of androgens. Testicular fibrosis along with vasculopathy are believed to contribute to gonadal failure in SSc. DeKeyser et al. reported on a case of SSc with KS, with the clinical picture being dominated by sclerodactyly and bilateral basal pulmonary fibrosis as well as synovitis of the metacarpophalangeal (MCP) joints [38]. Again, the authors speculated about the potential effects of KS on the development of the autoimmune syndromes. This mainly concerns the effects of the doubling of the X chromosome and the low androgen:estrogen ratio. Kobayashi et al. described SSc in a patient with KS who had been infertile for 20 years of marriage; SSc and KS were diagnosed at the age of 43 years [39]. The authors mentioned a total of five cases of SSc in individuals of 41–61 years of age and speculated about the association between KS and SSc. Finally, Bargagli et al. detected an association of pericentromeric inversion of chromosome 5 with KS in two siblings – a male with SSc and a female with RA (Table 2) [40].

Klinefelter’s syndrome & mixed connective tissue disease
Takeuchi et al. published a report of a 57-year-old man with KS, presenting with mixed connective tissue disease (MCTD), diabetes mellitus and other endocrine disturbances. Approximately 40 years before admission, he was diagnosed with SLE and was treated with prednisolone from 1971 to 1991. In 1986 he complained of thirst and dry eyes and was admitted to the hospital where the diagnosis of Sjögren’s syndrome was suspected; later, the disease was compatible with the diagnosis of Sjögren’s syndrome. Upon admission, the 57-year-old male demonstrated polyarthritis, sausage fingers and Raynaud’s phenomenon in his clinical picture. Restrictive disturbance of the diffuse pulmonary capacity and a myogenic lesion were demonstrated upon EMG, along with a positive test for anti-RNA/protein (RNP) antibody, diabetes mellitus, hyperprolactinemia, hypothyreosis and hypocorticism [41].

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Symptoms &amp; complications</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Donoghue (1982)</td>
<td>41</td>
<td>Raynaud’s phenomenon, systemic sclerosis, telangiectasia, lungs fibrosis, testicles like in a child, gynecomastia, low intensity of body hair growth and claw-like hands</td>
<td>[37]</td>
</tr>
<tr>
<td>Nowlin et al. (1985)</td>
<td>51</td>
<td>Raynaud’s phenomenon, localized scleroderma, calcinosis in finger ball, telangiectasia, gynecomastia, small fibrous testicles, Raynaud’s phenomenon, diffusive scleroderma, lung fibrosis, telangiectasia, finger-ball ulceration and small fibrous testicles</td>
<td>[36]</td>
</tr>
<tr>
<td>Kobayashi et al. (1991)</td>
<td>49</td>
<td>Raynaud’s phenomenon, systemic sclerosis, ulcerous finger defects, lungs fibrosis, right arm calcinosis, esophagus motility disorder, small fibrous testicles and low intensity of body hair growth</td>
<td>[61]</td>
</tr>
<tr>
<td>Bargagli et al. (2008)</td>
<td>44</td>
<td>Raynaud’s phenomenon, systemic sclerosis and lung fibrosis</td>
<td>[40]</td>
</tr>
</tbody>
</table>

Data from [61].
Kasten et al. described a 43-year-old male with euunochoid body proportions and a history of deep venous thromboses in the right leg who presented with recurrent ulcers in the right perimalleolar region that he had experienced for 6 years. Karyotyping revealed a 47,XXY KS, while serological testing demonstrated a protein S deficiency, hyperhomocysteinemia and a positive lupus anticoagulant. He also had mixed connective tissue disease (Sharp’s syndrome) with acrosclerosis, proximal finger edema, Raynaud’s phenomenon and high titers of ANA and U1RNP-antibodies, as well as osteoporosis [42].

Ishihara et al. reported a case of a 28-year-old Japanese patient with KS who developed MCTD and Sjögren’s syndrome and presented with Raynaud’s phenomenon, dry eye, fever and polyarthralgia. Anti-nRNP antibodies, leucopenia and lung fibrosis were revealed upon clinical examination and KS was diagnosed. A relative increase in peripheral CD8⁺ T cells carrying either MHC class II antigen (HLA-DR) or CD57 was observed in the patient. In vitro concavalin-stimulated IL-2 production was decreased [43].

Klinefelter’s syndrome & antiphospholipid syndrome
Miyagawa et al. described the occurrence of KS in a patient with SLE, presenting with ulcerous formations on the lower extremities. The patient was found to produce anticardiolipin antibodies, which may play a role in the development of occlusive alterations in peripheral arteries [44]. The association of antiphospholipid syndrome with KS was first described in 1993. Later, two cases of SLE with secondary antiphospholipid syndrome in KS were reported by Folomeev et al. [22] and Bajocchi et al. [45]. Miyagawa et al. highlighted the fact that the immune mechanism including the β2-GPI cofactor may contribute to the reasons underlying the vascular alterations in KS [44].

Klinefelter’s syndrome & ankylosing spondylitis
Armstrong et al. described the presence of KS with ankylosing spondylitis (AS). The authors suggested that the development of AS in their patient was clinically, substantially milder [46]. The course of the disease in the patient seemed to be similar to the course of the disease in females: previous authors, such as Resnick et al. [47], suggested that the cervical spine of female patients suffering from AS usually demonstrates syndesmophytic formations and ankylosis of apophyseal joints. Such alterations were observed by Resnick et al. in five out of 16 female patients with AS diagnosis [47]. Upon a similar examination of 55 males, isolated abnormalities were observed in the cervical spine. Hart and Robinson also observed more frequent clinical involvement of the cervical spine in females affected by AS [48]. Armstrong et al. speculated that the karyotype 47,XXX, and thus, the X chromosome may play an important role in the expression of the disease [46]. Some later references can be found in the literature to three cases of coincidented AS and KS – papers by Couloumer et al. [49] and Pages et al. [50], who were the first to describe the association of the peripheral form of AS with KS, and Atabek et al. [51] reported a 14-year-old boy with KS who developed severe acne fulminans and bilateral sacroiliitis after testosterone and isotretinoin administration.

Future perspective
This review summarizes evidence for the possible association of KS with several rheumatic and autoimmune diseases, including RA, JIA, PsA, polymyositis/dermatomyositis, SLE, MCTD, SSc and AS. Anecdotal reports also suggest a coexistence of KS and some other rare autoimmune syndromes, such as primary biliary cirrhosis [52].

With respect to the pathogenesis of autoimmune diseases, the described episodic findings may suggest that KS can be considered a contributing factor to autoimmunity development. So far, the recent findings by Scofield et al. provide the strongest evidence for an association between SLE and KS [35]. Owing to a lack of other studies with relatively larger cohorts, it is difficult to draw any conclusions regarding the association between KS and other autoimmune disorders. Furthermore, data reviewed from the available literature do not provide evidence for any causal link between KS and autoimmunity.

Research into the neuroendocrine mechanism in autoimmune diseases provides some important clues for the short- and long-term effects of steroid hormones, including estrogens and androgens, on immune function. A long-term activation or perturbation of the neuroendocrine immune system can predispose to autoimmunity development. In support of the latter assumption, multiple hormonal and cytokine correlations were found before the clinical onset of RA in men [53]. Thus, the hypoandrogenic status of KS could potentially be the major candidate for the ‘missing link’ between KS and autoimmunity. However, further studies are necessary to support the latter hypothesis.
From the routine clinical point of view, based on the present data, a genetic screening for KS in male patients with an autoimmune disorder cannot be advisable. However, from a research point of view, estimating the frequency of KS among male patients with autoimmune disorders would lay the groundwork for exploring the X chromosome effects in autoimmunity development. As such, this kind of research could provide new insights into fundamental questions including female gender as a risk factor for autoimmunity.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary
- A diagnosis of infertility in a male with an autoimmune disease is suggestive of chromosomal abnormalities.
- Micro-orchidism and gynecomastia are usually the leading symptoms of the Klinefelter's syndrome and the diagnosis can be confirmed by chromosomal analyses.
- Klinefelter's syndrome is characterized by a chromosomal constellation of XXY (classical form) or 46,XY/47,XXY (mosaic form).
- There have been reports on the concurrence of Klinefelter’s syndrome with several inflammatory rheumatic diseases including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, the antiphospholipid syndrome and ankylosing spondylitis.
- Early diagnosis of the syndrome, when occurring simultaneously with autoimmune diseases, is important.

Bibliography
Papers of special note have been highlighted as:

**The concurrent development of various clinical diagnoses with Klinefelter’s syndrome, as well as reduced testosterone levels and increased follicle-stimulating hormone and luteinizing hormone may be expected in Klinefelter’s syndrome patients, is interesting for clinical rheumatologists.**


**It is important to look for hypogonadism and gynecomastia and to pay attention to secondary sexual characteristics for diagnosis of Klinefelter’s syndrome.**


**Detection of an association of pericentromeric inversion of chromosome 5 with Klinefelter’s syndrome in two siblings – a male with systemic sclerosis and female with rheumatoid arthritis.**


**Discusses Interesting connections between Klinefelter’s syndrome, autoimmune diseases (mixed connective tissue disease) and endocrine disorders (diabetes mellitus).**


