Klinefelter's syndrome and systemic lupus erythematosus

Sir,

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with multisystem involvement of unknown etiology. With its striking female predominance, especially during the child-bearing age, hormonal factors most likely play a role. In 1969 Oritz-Neu and LeRoy (1) first reported SLE and Klinefelter's syndrome occurring in the same patient. They reported 3 cases of this association. Since their initial report, 20 other cases of this association have been reported in the English language medical literature (1-17). Another article alludes to a few other patients with this association, but there is little clinical data about these patients (18). The obvious interest in these patients, males with an XXY karyotype, is that they represent a group of individuals who may increase our understanding of the role of hormonal influence in patients with SLE.

Herein we report another case of SLE occurring in a Klinefelter's syndrome patient and review the clinical features of patients with Klinefelter's syndrome as well as pertinent hormonal studies and the role of testosterone replacement.

A 12-year-old male with a history of a seizure disorder since the age of 4 presented initially with an erythematous malar rash and scaly, erythematous plaques on his pre-auricular areas and upper arms. A biopsy displayed the features of discoid lupus erythematosus including a thinned epidermis with hyperkeratosis, follicular plugging, vacuolar degeneration of the basal layer and a dermal inflammatory infiltrate of lymphocytes and histiocytes were present in a superficial and deep perivascular, perifollicular, and periecrine distribution.

Several months later, he developed fatigue and arthritis in the small joints of his hands and feet. Laboratory data revealed a positive ANA (1:320), positive anti-dsdna, hypocomplementemia, mild lymphopenia, and an elevated erythrocyte sedimentation rate (ESR). Symptoms remained well-controlled over the next several years with hydroxychloroquine (200 mg p.o. q.d.) and prednisone (5 mg p.o. q.d.). However, a routine evaluation at the age of 16 revealed that he had small testes. Hormonal and chromosomal analysis were consistent with Klinefelter's syndrome (XXY karyotype). Treatment with intramuscular testosterone (200 mg testosterone IM every 3 weeks) was initiated.

When first seen in our clinic at the age of 19, he complained of worsening red facial lesions, patchy hair loss, and arthritis. Physical examination revealed scaly, indurated plaques on his face, patchy alopecia, prominent periungual erythema, and tender microinfarct-like papules on his fingertips. Chronic synovial thickening of the proximal interphalangeal joints was apparent.

The only notable laboratory result was his ANA which was positive with a titer of 1:640, diffuse pattern. Complete blood count, chemistry panel, urinalysis, ESR, anti-dsDNA, anticardiolipin, and anti-ENA were normal or negative. Biopsies of the temporal area and scalp were again consistent with discoid lupus.

We asked whether the clinical features of SLE in association with Klinefelter's syndrome are different from those of the general population with SLE. We searched the literature by PubMed using the terms lupus, systemic lupus erythematosus, and Klinefelter's syndrome. We found 17 articles that described the clinical features of 23 patients with both diseases. The ages of the patients ranged from 12-73 years old.

The clinical data which support the diagnosis are listed in Table I. It should be noted that several patients do not satisfy 4 ACR criteria for the diagnosis of SLE (19), although clinical features of these case reports were not always complete. Clinical manifestations are similar to other patients with SLE although cutaneous findings, especially discoid lesions, photosensitivity, and oral ulcers apparently occur at lower frequency in SLE patients with Klinefelter's syndrome.

All patients demonstrated one or several features of Klinefelter's syndrome with hypogonadism, eunuchoid body habitus, gynecomastia, and female distribution of hair being the most common features noted. All chromosomal analyses if reported revealed a classic Klinefelter's karyotype (47XXY), except for one who displayed a mosaic karyotype (XXY/XXXY) (13).

Hormonal studies were not reported in most of these cases. Stern *et al*. (5) measured the levels of estrogens and estrogen metabolites in their 2 patients. They found elevated levels of estrogens in a 24-hour urinary collection in one patient and evidence of abnormalities of estrogen metabolism in both. Michalski *et al*. (7) reported that one patient had testicular failure based on decreased testosterone, increased follicle stimulating hormone, and increased luteinizing hormone as expected in patients with Klinefelter's syndrome. While not discussing the clinical characteristics of the patients in their study, Lahita and Bradlow (18) studied several patients with Klinefelter's and SLE and concluded that sex steroid metabolism of Klinefelter's patients with SLE were similar to that of women with SLE. French and Hughes (8) also found testicular failure in their patient. The above cases do not clarify whether the hyperestrongenic state or lack of testosterone or both are responsible for the autoimmunity in these individuals. Androgens seem to act as natural immunosuppressors and their deficiency has been observed in SLE and rheumatoid arthritis male patients. (20)

Only two studies addressed the effects of testosterone therapy on the clinical manifestations of the patient's SLE. Bizzarro *et al.* (11) reported that after initiating testosterone therapy in 2 patients, both had a clinical and serologic (ANA and rheumatoid factor titers, ESR, and complement levels) remission of their SLE. More recently, Olsen and Kovacs (17) treated a patient with testosterone replacement in doses sufficient to normalize the serum level of testosterone, and found not only clinical improvement, but improvement in hematologic and serologic parameters within 9 months of therapy. Similar clinical and laboratory improvement during testosterone replacement therapy was previously observed in male rheumatoid arthritis patients. (21)

SLE is a disease of unknown etiology which throughout all ethnic and geographical regions affects women more frequently than men. The prevalence of SLE in males remains fairly stable across all age ranges (22). Reported prevalence of SLE in men range from 3-9/100,000 in white and 3-53/100,000 in black males (23-25). The incidence of Klinefelter's syndrome has been estimated at 1.7/1000 male births (26). With these figures in mind, the occurrence of these two syndromes may indeed be coincidental. With nearly 30 years of reports of this association, only 25 cases have been clearly described in the medical literature. Certainly, other cases may not have been reported so that the number of patients with both diseases is underreported.

Dubois and Kaplan performed buccal smears on male patients with SLE in an attempt to identify patients with Klinefelter's syndrome. They analyzed chromosomes and buccal smears from 22 male patients but failed to identify any cases of Klinefelter's syndrome (3). This emphasizes the importance of doing a thorough physical examination looking for the presence of hypogonadism, gynecomastia, or lack of secondary sex characteristics, especially in a young male who presents with SLE.

The clinical manifestations of SLE in these patients are similar to others with SLE except for the seemingly low frequency of cutaneous symptoms. It is especially interesting that one investigator who compared the clinical differences between males and females found that males tended to have more

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Table I. Review of reports of Klinefelter's syndrome and SLE in the literature.

Reports of Klinefelter's syndrome and SLE	Age at SLE onset	Malar rash	Discoid rash	Photosen-sitivitiy	Oral ulcers	Arth-ritis	Sero-sitis	Renal disorder	Neurologic disorder	Hematologic disorder	Immunologic disorder	ANA
Oritz-Neu & LeRoy (1969) [1]	23					X	X	X			X	
	18					X			X	X	X	
	39							X				X
Landwith & Berger (1973) [2]	12	X					X			X	X	
Dubois & Kaplan (1976) [3]	NS											
Price et al. (1976) [4]	30					X		X			X	X
	32					X		X				X
Stern et al. (1977) [5]	24	X				X		X			X	
	39			X		X	X			X	X	
Segami & Alarcon-Senovia	22					X	X			X		
(1978) [6]	33						XX		X		X	X
Michalski et al. (1978) [7]	47					X	X		X	X	X	X
Fam et al. (1980) [8]	17					X	X	X		X	X	X
French & Hughes (1983) [9]	42						X			X	X	X
Scleyelberger et al. (1986) [10]						X	X				X	X
Bizzarro et al. (1987) [11]	NS	X				X	X	X			X	X
	NS	X		X		X	X	X	X		X	X
DuGenier et al. (1987) [12]	28	X				X					X	X
Marshall (1988) [13]	54					X		X		X	X	X
Schattnen & Berrebi (1989) [14]	73					X				X		X
Folomeev et al. (1991) [15]	22					X			X	X	X	X
Miyagawa et al. (1994) [16]	24	X	X			X		X			X	X
Olsen & Kovacs (1995) [17]	31					X				X	X	X
Current Patient (1998)	12	X	X			X			x ?		x	x

NS - None stated

discoid and subacute cutaneous lupus and less arthritis (27). That does not appear to be the case in this group of patients.

In addition to SLE, other autoimmune phenomena have been found in patients with Klinefelter's syndrome. Increased number of autoantibodies (rheumatoid factors; antinuclear antibodies, and organspecific) (28-30), myasthenia gravis (7), progressive systemic sclerosis (31), and antiphospholipid antibody syndrome (16, 32) have also been reported in patients with Klinefelter's.

While the number of cases of this interesting association remains small and may indeed be coincidental, it is worth noting. Further study of these patients may provide additional clues about the pathogenesis of SLE and other autoimmune diseases.

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Acute arthritis associated with acute Q fever

Sirs,

In clinical practice rheumatologists often see patients with undifferentiated arthritis. In many of these cases synovitis remains unclassified after an adequate period of follow-up (1). Acute Q fever is known to be a cause of acute pneumonia, hepatitis or self-limited fever. In addition, a variable degree of arthralgia and myalgia is also common. However, acute arthritis as the predominant and presenting manifestation of acute Q fever is exceptional (2). In this report, we describe a patient presenting with acute arthritis with serological evidence of acute Q fever which was successfully treated with doxycycline.

A 33-year-old female farm worker presented at our outpatient clinic because of pain and swelling in her right knee that had begun 6 days earlier. She denied other symptoms and, apart from the presence of severe synovitis in the right knee, the rest of the physical examination was unremarkable. Full blood cell count and hepatic and renal functions tests were normal. The erythrocyte sedimentation rate was 14 mm/hr. C reactive protein was increased (37.5 mg/L; normal < 5 mg/L). Antinuclear antibodies and rheumatoid factor were negative. Interestingly, arthrocentesis yielded an inflammatory synovial fluid (SF) (7,446 leucocytes/mm^3) with 70% macrophages, 20% lymphocytes and 10% polymorphonuclear cells (Fig. 1). The glucose level in the synovial fluid was normal (61 mg/dl; serum glucose level 87 mg/dl) and no microcrystals were seen. Cultures of the SF were also negative. Tuberculin skin test and serological tests for syphilis, brucella, yersinia, salmonella, cytomegalovirus, mononucleosis, rubella, toxoplasma, mycoplasma, and hepatitis B and C were negative. Chest radiograph was normal.

However, serology for *Coxiella burnetii* (immunofluorescence) was positive; phase II IgG positive at 1/640 and IgM positive. Antibiotic therapy with doxycycline (100 mg/bid) was given for 14 days. The patient experienced a rapid improvement of the synovitis within the first 72 hours after the onset of the antibiotic therapy. In a further study performed 3 months later, the serology for *C. burnetii* showed the following results: phase II IgG positive at 1/80 and IgM negative. Six months after the diagnosis of acute Q fever she remained asymptomatic.

This report describes a case of Q fever presenting with acute arthritis which often is not diagnosed at the right time if serological tests are not considered for early diagnosis.

Q fever is caused by an obligate intracellular parasite, *C. burnetii*, acquired through inhalation of infected dust or ingestion of unpasteurized milk from subclinically infected farm animals. A definite diagnosis of acute Q fever depends on the demonstration of an IgM antibody response. Chronic osteoarticular infections associated with Q fever have been reported (3). In acute Q fever, arthralgia is common. However, acute arthritis as presenting manifestation of acute Q fever has not been commonly reported (2, 4-7).

To the best of our knowledge, there are only 6 cases described in the literature (2, 4-7). Three of them presented as monoarthritis (2 hip, 1 knee), and the other 3 as polyarthritis. In only one of these patients were the characteristics of the SF described (5). As in our case, a predominance of macrophages was observed. Direct infection was confirmed by immunofluorescence in the SF in only one patient presenting with acute arthritis (5). In this regard, although it is not a definitive criterion, in our case the rapid response to antibiotic therapy might be supportive evidence of an infectious arthritis. However, the rarity of macrophagic synovial effusions make it difficult to determine whether this feature may be a useful indicator of the diagnosis of Q fever arthritis. Descriptions of further cases will be required to confirm whether the predominance of macrophages in the synovial fluid might be a clue for this particular infectious arthritis. Finally, we do not know whether HLA determination would have given additional information concerning the possible immunogenetic predisposition toward such a type of articular reaction to the infection.

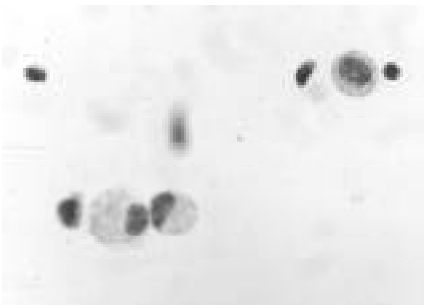

Fig. 1. Presence of histiocytes with eccentric nuclei and clear and microvacuolated cytoplasms along with some lymphocytes and polymorphonuclear cells in the synovial fluid of our patient (Giemsa x 400).

In summary, the present case may be a good example of the necessity of using serological tests in those patients presenting with acute arthritis of unclear etiology from endemic areas for Q fever. Indeed, even in atypical cases like this one, where pulmonary and hepatic findings were absent, a positive test for Q fever might allow us to make a diagnosis of this condition.

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