Seminars in Arthritis and Rheumatism 43 (2014) 508–512

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Female polysomy-X and systemic lupus erythematosus

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ARTICLE INFO

Keywords:
Gene dosage
Lupus genetics
Polysomy-X
Sex differences
SLE
X-chromosome

ABSTRACT

Objectives: Systemic lupus erythematosus (SLE) occurs more commonly in females than in males. Recent evidence suggests that genetic factors transmitted by the X-chromosome may confer increased risk for autoimmune disease in general, and for SLE in particular. It is therefore possible that X-chromosome polysomy might confer further increased risk for lupus. In addition to describing the clinical and immunologic features of a young woman with polysomy-X and SLE, we sought to review all other published cases associating female or male polysomy-X with SLE or other forms of autoimmunity.
Methods: We report a case of a prepubertal girl with polysomy-X and SLE. We performed a systemic literature review for cases of polysomy-X and SLE and summarize previously published cases. In addition, we reviewed reports concerning the possible association between SLE and other connective tissue diseases and male polysomy-X.
Results: An 11-year-old girl with tetrasomy-X (48 XXXX karyotype) presented with prolonged fever. Workup led to the diagnosis of SLE, and subsequent renal biopsy revealed mild diffuse mesangial proliferative glomerulonephritis. Two additional cases of SLE in women with 47 XXX and one of 48 XXXX karyotype were found in a literature review and compared to the present case. We identified studies that found X-chromosome polysomy to be over-represented in male patients with SLE and case descriptions of connective tissue diseases occurring in patients with polysomy-X.
Conclusion: No consistent pattern of disease was observed in female polysomy patients with SLE. Taken together with the data concerning the frequency of polysomy-X among males with SLE, our findings provide additional support for the hypothesis that X-chromosome polysomy may confer increased susceptibility to SLE. Molecular mechanisms that might account for this phenomenon are discussed.
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Systemic lupus erythematosus (SLE) occurs more commonly in females than in males. Although hormonal influences may partially account for this discrepancy, pre-adolescent girls are also at an increased risk for SLE [1], suggesting the involvement of non-endocrine factors.

There are very few descriptions of SLE in females with X-chromosome polysomy [2–4]. Herein we describe an 11-year-old girl with polysomy-X (48 XXXX karyotype) diagnosed with SLE, including Class II glomerulonephritis, and review published reports concerning this association. In addition, we review the published literature concerning SLE and other autoimmune and connective tissue diseases occurring in the context of female and male polysomy-X. Finally, we discuss possible mechanisms by which X-chromosome polysomy might confer increased susceptibility to SLE.

Methods

In addition to the presented case, we searched MEDLINE (using pubMed), EBSCO, and Scopus search engines. Search terms included the following: polysomy-X; 47, XXX; 47 XXX; triple X; trisomy X; 48, XXXX; 48 XXXX; tetrasomy-X; 49, XXXXX; 49 XXXXX; pentasomy X; sex chromosome polysomy; sex chromosome trisomy; sex chromosome tetrasomy; sex chromosome pentasomy; Klinefelter syndrome; 47, XXY; 47 XXY; 48, XXXY; 48 XXXY; 49, XXXXY; 49 XXXXY; AND SLE OR lupus OR autoimmune. Additional articles were identified from the list of references in the reports found by computerized search. All case report articles were reviewed. In addition, we review and discuss possible evidence for X-chromosome dosage effect in the pathogenesis of lupus.

Results

Case report

An 11-year-old Caucasian girl with known tetrasomy-X was hospitalized for investigation of prolonged fever (8 weeks) and

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http://dx.doi.org/10.1016/j.semarthrit.2013.07.014

Table 1
Polysomy-X females with SLE, characteristics of reported patients[a]

Clinical characteristics and karyotype	Patient 1 48, XXXX (present report)	Patient 2 48, XXXX [2]	Patient 3 47, XXX [3]	Patient 4 47, XXX [4]
Age at diagnosis	11 years	19 years	21 years	26 years
Hormonal phenotype	Prepubertal	Irregular menses, underdeveloped genitalia, and normal hormonal profile	Normal menstrual cycles and normal hormonal profile	Primary amenorrhea, underdeveloped secondary sex signs, and low estradiol and testosterone
		Lupus criteria		
Mucocutaneous features	Malar rash and oral ulcers	Oral ulcers		
Arthritis	Arthralgia	Arthralgia		Polyarthritis
Serositis	Pleurisy			
Renal disorder	Proteinuria of 5.4 g/d and mesangioproliferative glomerulonephritis		Proteinuria > 0.5 g/d and mesangioproliferative glomerulonephritis	
Neurologic disorder			Epilepsy	
Hematologic disorder	Anemia and lymphopenia	Hemolytic anemia and thrombocytopenia	Hemolytic anemia	Hemolytic anemia and lymphopenia
Autoantibodies	ANA, anti-DNA, and anti-Sm	ANA and anti-DNA	ANA, anti-DNA, and VDRL	ANA, anti-SSA, anti-SSB, and anti-RNP
Other symptoms	Alopecia	Alopecia		Myalgia and Sjorgen's syndrome, Raynaud's phenomenon
C3, C4	Low	Low	C3 normal and C4 low	Normal

[a] A fifth case of a hypogonadotropic female patient with SLE and 45 X0/46 XX/47 XXX mosaicism has also been reported; however, the details of her SLE features have not been fully provided [7].

fatigue. Her chromosomal abnormality was detected during the first year of life, as a part of an investigation for dysmorphic physical features and developmental delay. She reported recent weight loss, alopecia, and a photosensitive rash on her cheeks. Upon admission, she appeared pale and cachectic. Physical findings consistent with tetrasomy-X included the following: epicanthal folds, hypertelorism, a flattened nasal bridge, and clinodactyly. Sexual development was Tanner stage of 1 (prepubertal status was also confirmed by hormonal testing). A malar rash was present. A chest radiograph showed small bilateral pleural effusions. Erythrocyte sedimentation rate was increased to 130 mm/h. There was normocytic anemia (hemoglobin ranged between 8.6 and 10.9 gr/dL with MCV of 77.0 fL) and leukopenia (WBC between 2600 and 3600 mm^3, with lymphopenia as low as 1200 mm^3). The platelet counts remained normal (185–301 $\times$ 10^9 per L). Serum albumin was 3.5 g/dL, urea 11.2 mg/dL, and creatinine 0.46 mg/dL; all within normal limits. Urine dipstick showed 4+ proteinuria and 3+ hemoglobin. Microscopy of urine sediment revealed mixed cellular casts and red blood cells.

During hospitalization, the patient complained of arthralgia and had persistent fever $>39^{\circ}C$. Urinary excretion of protein was measured as 5.4 g/24 h. Anti-nuclear antibodies (ANA) exam was strongly positive, indicated by immuno-fluorescence, and antibodies to DNA and Smith antigen were present. C3 was 25 mg/dL (normal reference range, 50–120 mg/dL) and C4 was 17 mg/dL (normal reference range, 20–50 mg/dL). Antiphospholipid antibodies were absent. Renal biopsy revealed mild diffuse mesangial proliferative glomerulonephritis consistent with Class II mesangial proliferative nephritis.

Treatment with oral prednisone (1 mg/kg/d), azathioprine (1 mg/kg/d), and enalapril (7.5 mg/d) was initiated, leading to rapid improvement with resolution of cytopenias and hypocomplementemia. Full clinical remission was achieved after 4 months, and prednisone was subsequently tapered to 5 mg once daily, without flaring of her disease. Anti-DNA antibodies remained present in low titer.

Literature review

The prevalence of tetrasomy-X is unknown, but it appears to be quite rare. There is only one other published description of lupus in a woman with this condition [2]. In addition, two women with a 47, XXX karyotype with lupus have been reported [3,4], although one of them had findings suggestive of probable mixed connective tissue disease. The clinical and laboratory characteristics of these four patients are summarized in Table 1. No consistent pattern of disease was observed in these patients.

The 47, XXX karyotype occurs in 1:1000 females. Because women with this karyotype are typically healthy or display only subtle abnormalities, only about 10% are diagnosed [5]. Recent preliminary data from a study that examined X-chromosome copy number found the frequency of the 47, XXX karyotype to be increased among women with SLE or Sjogren's syndrome as compared to controls [6]. A hypogonadotropic female patient with SLE and 45, X0/46, XX/47, XXX mosaicism has also been reported, but the details of her SLE disease were not fully provided [7]. There are scattered reports of autoimmune diseases, including autoimmune diabetes and immune thrombocytopenic purpura, in 47, XXX women [8–10]. In general, it seems clear that SLE occurs in only a small minority of females with X-polysomy. Thus, additional genetic, epigenetic, or environmental factors are necessary to confer the SLE phenotype.

Male X-chromosomal polyploidy is termed Klinefelter syndrome (KS) and occurs in approximately 1:1000 live births. There are several reports of SLE in men with KS, as well as a number of reports of men with KS and other forms of connective tissue disease (reviewed in [11]). Prospective studies have been performed to examine the prevalence of 47, XXY in men with SLE. In an initial report, sex genotyping was performed in 213 men with SLE, including 75 from multiplex families in which another individual was affected with SLE. Five KS men were identified, representing a 14-fold excess over the expected prevalence [12]. This result was subsequently confirmed in a larger group of 316 men with SLE [13].

Two male patients with lupus with a 46, XX karyotype have been reported. The first was a pre-adolescent boy, in whom an unbalanced Xp22.23; Yp11.2 translocation had occurred, resulting in partial duplication and over-expression of 13 genes in the pseudo-autosomal region of the X-chromosome (PAR1), as well as expression of the sex-determining Y region (SRY) on the

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