

Letter

Near Tetraploidy in a Patient with Systemic Lupus Erythematosus

To the Editor:

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that predominantly affects females¹. As for the higher susceptibility to SLE for women, different hypotheses were proposed to explain this phenomenon, including sex hormones² and the dose effect of X chromosome number³. Some congenital sex chromosome abnormalities, such as Klinefelter syndrome (47, XXY karyotype) and trisomy X (47, XXX karyotype), have received much attention, for the reason that people with X chromosome polysomy may be at an increased risk of developing some autoimmune diseases including SLE. However, SLE patients with polyploidy or near polyploidy, a condition in which a cell has more than 2 sets of chromosomes, were not reported previously. Here we present a patient whose chromosomal analysis showed near tetraploidy in a bone marrow (BM) specimen.

Ethics approval was obtained for this case report from the Ethics Committee of Ruijin Hospital (ethics committee approval no. 235). Because all the medical data were acquired from the previous diagnosis and treatment procedures of the patient, and no personal identity information was revealed in this case report, the ethics board granted a waiver of written informed consent.

A 36-year-old Chinese woman who had arthralgia for more than 10 years was admitted to our rheumatology department for gradually distended abdomen and puffiness of face and both lower limbs. There was no family history of autoimmune disorders. On physical examination, weakened pulmonary alveolar respiratory sounds and shifting dullness were noted.

Complete blood count showed normocytic anemia (hemoglobin 72 g/L) and thrombocytopenia (platelet count $91 \times 10^9/L$), whereas leukocytes were normal. Her renal function was impaired (serum creatinine 249 $\mu\text{mol/L}$). During hospitalization, C3 was 18 mg/dl (reference range 79–152 mg/dl) and C4 was 2 mg/dl (reference range 16–38 mg/dl). Antinuclear antibody (ANA) test was strongly positive with ANA titer 1:640 (homogeneous pattern), and antibodies to dsDNA, Smith, as well as β_2 -glycoprotein antigen were also present. Coombs test was negative. Urinary excretion of protein was 3.99 g/24 h. Computed tomography scan showed pleural effusion as well as seroperitoneum and pelvic effusion.

To rule out neoplastic disease, BM aspiration was conducted, which revealed active proliferation with decreased myeloid erythroid ratio (1.43:1) and maturation disorder of megakaryocytes. Flow cytometric analysis and gene rearrangement test were unremarkable. The BM biopsy specimen showed erythrocytosis and granulocytosis with maturation disorder of megakaryocytes. The RHG (R-bands by heating using Giemsa) banding chromosomal analysis of the BM cells revealed 85~92, XXXX (cp4)/46, XX (4 near tetraploid karyotypes vs 14 normal karyotypes; Figure 1).

The diagnosis of SLE was clearly made according to 2019 American College of Rheumatology/European League Against Rheumatism classification criteria⁴. Treatments with methylprednisolone 80 mg/day and mycophenolate mofetil (MMF) 750 mg/day were given. Although intensive treatments were administered, the patient's cytopenia progressed. When discharged, the patient's leukocyte count was $1.6 \times 10^9/L$, hemoglobin was 56 g/L, and the platelet count was $53 \times 10^9/L$. A half-year follow-up showed a slight improvement in blood count (leukocytes $1.47 \times 10^9/L$, hemoglobin 79 g/L, platelets $71 \times 10^9/L$). The patient continued the combined therapy of prednisolone with MMF. One year later, the patient's leukocytes ($4.79 \times 10^9/L$) and hemoglobin (112 g/L) showed significant improvement while

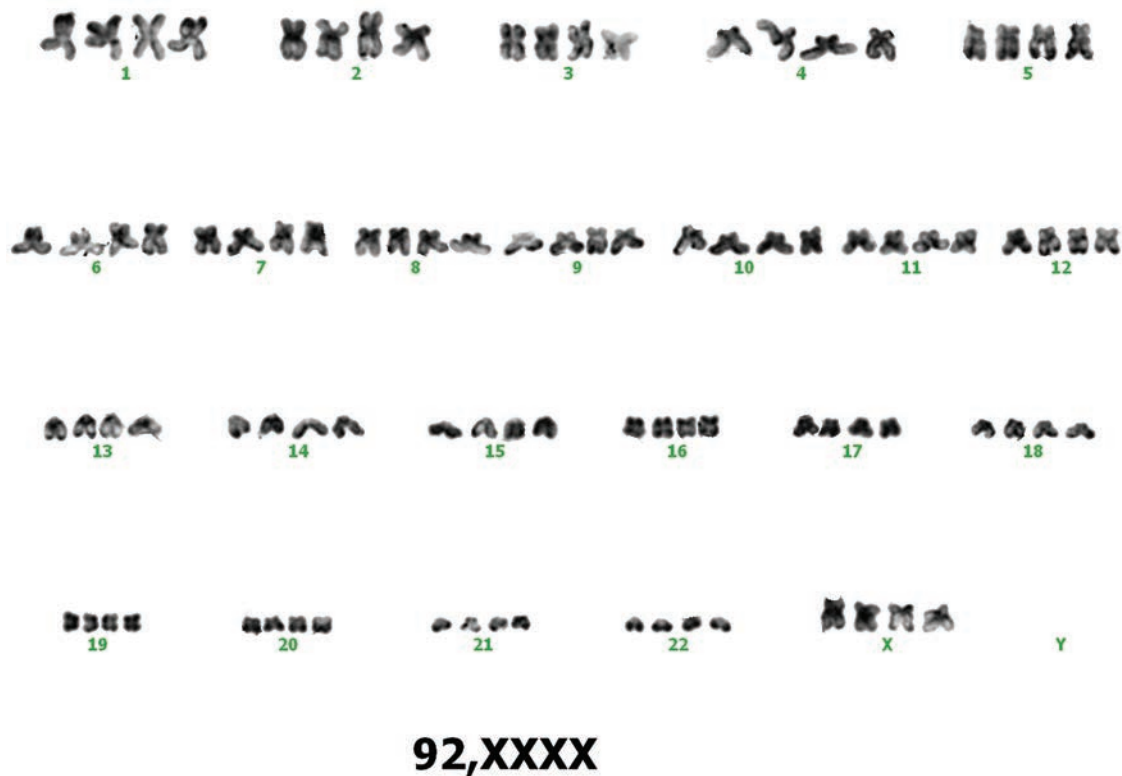


Figure 1. Karyotype determined by RHG banding in a representative metaphase cell. RHG: R-bands by heating using Giemsa.

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her platelets ($55 \times 10^9/L$) remained low. Her renal function deteriorated with serum creatinine at $426 \mu\text{mol/L}$. However, the patient refused to be hospitalized for further investigation.

Previous reports of chromosomal abnormalities in patients with SLE mainly focused on the abnormal number of X chromosomes. The most accepted hypothesis for the chromosome aberrations in the pathogenesis of SLE is the dose effect of X chromosome number, or more accurately, gene dose effect of X chromosome^{3,5,6}. Altered X chromosome inactivation and overexpression of some genes related to SLE, such as *CD40L*, *TLR7*, *IRAK1*, and *MECP2*, could cause predisposition to SLE through dysregulation of cytokine signaling, abnormal activation of T cells and B cells, or increased immunoglobulin secretion^{3,5,7}. Thus, we speculated that the presence of 4 X chromosomes in tetraploid BM cells of our patient might contribute to the pathogenesis of SLE. However, patients with tetraploidy, which means 4 sets of chromosomes in a single cell, were rarely observed in rheumatic diseases. Polyploidy, including tetraploidy, has been reported in hematological diseases, especially in hematologic malignancies such as leukemia^{8,9}. The specific association between tetraploidy and hematologic malignancies is unclear. It is reported that, however, tetraploidy-associated chromosomal instability (CIN), which means imbalance of loss and gain of chromosomes, could lead to production of aneuploid cells and accumulation of oncogenetic potentials¹⁰. Thus, CIN may link tetraploidy to hematologic malignancies.

In our case, the patient had resistant hematological abnormalities under positive treatments and presented presumably acquired near-tetraploid karyotype, which gave us some hint that the continuous abnormal hematologic findings in our patient might be related to tetraploidy. We propose BM aspiration and chromosomal analysis for suspected SLE patients with hematological involvement or confirmed patients whose persistent hematological abnormalities do not respond well to treatment. Moreover, a close follow-up should be considered for these tetraploid patients in case of hematologic malignancies. In addition, BM aspiration and chromosomal analysis should be repeated to identify whether their tetraploid karyotype continues to exist after treatment and to help us evaluate the correlation among tetraploidy, SLE, and hematological involvement.

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