Case Report

A CASE OF ANKYLOSING SPONDYLITIS AND ICHTHYOSIS VULGARIS IN A TURNER SYNDROME PATIENT WITH A RARE KARYOTYPE

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ABSTRACT

Objective: Turner syndrome (TS) is a chromosomal disorder in which patients have either a missing X chromosome (45,X), a structural aberration of sex chromosome, or mosaicism including mos 45,X/46,XY. We present a case of TS with unusual ankylosing spondylitis (AS) and ichthyosis vulgaris (IV) carrying a rare karyotype of 45,X[100]/46,X,idic(Yp)[12](pter-q11::q11-pter).

Methods: A review of the literature was conducted to identify previous case reports pertaining to TS accompanied with AS and compare them with the current case.

Results: The patient presented with positive human leukocyte antigen (HLA) B27, lowered estrogen, and elevated follicle-stimulating hormone and luteinizing hormone levels. Ultrasound examination showed no uterus or ovaries. The patient carried a mosaic karyotype of 45,X[100]/46,X,idic(Yp)[25].ish(DXYS129+,DXYS153++,SRY++,DYZ3++,Yq12-) for metaphase peripheral blood lymphocytes and 45,X[100].ish(DYZ3-) for interphase buccal cells. Molecular genetic analysis revealed that the sex-determining region Y (*SRY*) gene was present in the patient's peripheral blood but negative in buccal cells.

Conclusion: TS patients can develop autoimmune diseases such as AS. Fluorescence in situ hybridization (FISH) can provide more detailed karyotypical information than common cytogenetic methods. **(AACE Clinical Case Rep. 2015;2:e105-e110)**

Abbreviations:
AS = ankylosing spondylitis; **FISH** = fluorescence in situ hybridization; **IV** = ichthyosis vulgaris; **SRY** = sex-determining region Y; **TS** = Turner syndrome

INTRODUCTION

Turner syndrome (TS), also known as congenital ovarian hypoplasia, is one of the most common sex chromosomal disorders caused by sex chromosome monosomy (45,X), which is present in 50 to 60% of subjects. The remaining cases present as mosaicism, with a 45,X cell line accompanied by 1 or more other cell lines with a completely or structurally abnormal X or Y chromosome. The clinical manifestations of TS include but are not limited to phenotypic female, short stature, premature ovarian failure, renal malformation, and skeletal deformity (1). TS patients present various autoantibodies and are susceptible to diverse autoimmune diseases such as inflammatory intestinal diseases, autoimmune thyroiditis, and even different types of rheumatoid arthritis (2). To date, only 2 cases of TS accompanied with ankylosing spondylitis (AS) have been reported, and both were determined to have 45,X karyotypes (3,4). Here we present an unusual TS case with AS and ichthyosis vulgaris (IV), whose karyotype was 45,X[100]/46,X,idic(Yp)[12](pter-q11::q11-pter).

CASE REPORT

A 22-year-old phenotypic female presented to our genetics clinics complaining of hip pain for 2 years and bilateral knee pain for 3 years. The patient was born after an uncomplicated pregnancy from a nonconsanguineous

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marriage. There was no family history of TS. Two older sisters had normal intelligence, got married, and gave birth to healthy children. The patient visited the local hospital at the age of 17 for no menarche and short stature and was diagnosed with a "congenital absence of the uterus" based on ultrasound imaging. The patient did not receive any medical treatment after the diagnosis.

The patient's height, weight, and body mass index were 140 cm, 39 kg, and 19.9 kg/m^2, respectively. The patient presented with claudication, systemic skin dryness, and off-white rhombus- or polygon-shaped scaling and desquamation on the trunk and limb extensor surfaces (Fig. 1 *A*). The patient had a short and thick neck with a low posterior hairline, undeveloped mammary glands with widely spaced hypoplastic nipples, elbow valgus deformity, and mildly swollen knees. The pelvic compression and Patrick/Fabere tests were bilaterally positive. Her modified Schöber test was 4 cm, chest expansion was 4 cm, finger-to-ground distance was 5 cm, and occiput-to-wall distance was 0 cm.

Laboratory studies showed an erythrocyte sedimentation rate of 85 mm/hour (normal: 0-20 mm/hour), C-reactive protein >10.70 mg/dL (normal 0-0.80), and positive human leukocyte antigen type B 27 (HLA-B27). Serum sex hormone assays showed lowered estrogen and elevated follicle-stimulating hormone and luteinizing hormone levels. Routine serum chemistry tests and assays for rheumatoid factor, electrolytes, and growth hormone were within normal ranges.

Echocardiography examination indicated normal cardiac structure. Pelvic ultrasound did not detect ovaries or a uterus. Computed tomography (CT) scans showed horseshoe kidneys and mild dilation of the kidney pelvis but no uterus. CT scanning revealed increases in bone mineral density and illegibility of the articular face of the sacroiliac joints, asymmetry of bilateral joint spaces, and bone destruction with a moth-eaten appearance and decrements in bone density of the sacrum and ilium, which indicated bilateral grade 3 sacroiliitis and osteoporosis (Fig. 1 *B*). Magnetic resonance imaging of the knees showed bilateral synovitis and osteochondroma in the upper shaft of the left tibia.

Peripheral blood lymphocyte culturing, and karyotype analysis established the patient's karyotype as 45,X[100]/46,X,del(Y)[12] (Fig. 2 *A* and *B*). The C-banding pattern did not show a densely stained heterochromatic region of the Y chromosome (data not shown). Fluorescence in situ hybridization (FISH) examination showed that the karyotype was 45,X[100]/46,X,idic(Yp)[25].ish(DXYS129+,DXYS153++,SRY++,DYZ3++,Yq12-) for metaphase peripheral blood lymphocytes (Fig. 3 *C-E*), and 45,X[100].ish(DYZ3-) for buccal cells. The patient's father's karyotype was normal for metaphase peripheral blood lymphocytes, and FISH examination showed that his karyotype was 46,XY.ish (SRY+,DYZ3+,Yq12+) (data not shown).

The sex-determining region Y (*SRY*) gene was further amplified using DNA extracted from the patient's peripheral blood and buccal cells and her father's peripheral blood. The electrophoresis results of polymerase chain reaction (PCR) products showed that the *SRY* gene was negative in the patient's buccal cells but positive in both her and her father's peripheral blood cells (Fig. 3 *A*). The PCR products were then sequenced and compared with the NCBI database, which showed that the sequences were consis-

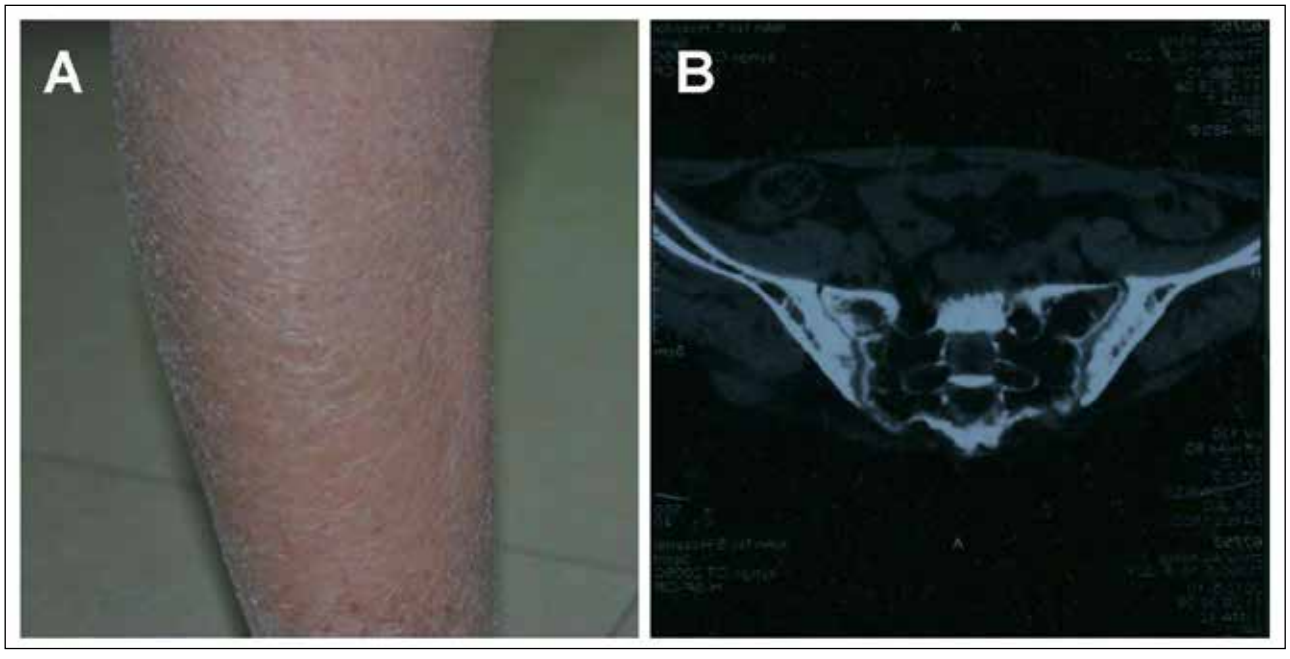

Fig. 1. Physical features of the patient. (*A*) Skin manifestation. Off-white scaling is clearly visible on the lower limbs. (*B*) Computed tomography scan of the bilateral sacroiliac joints.

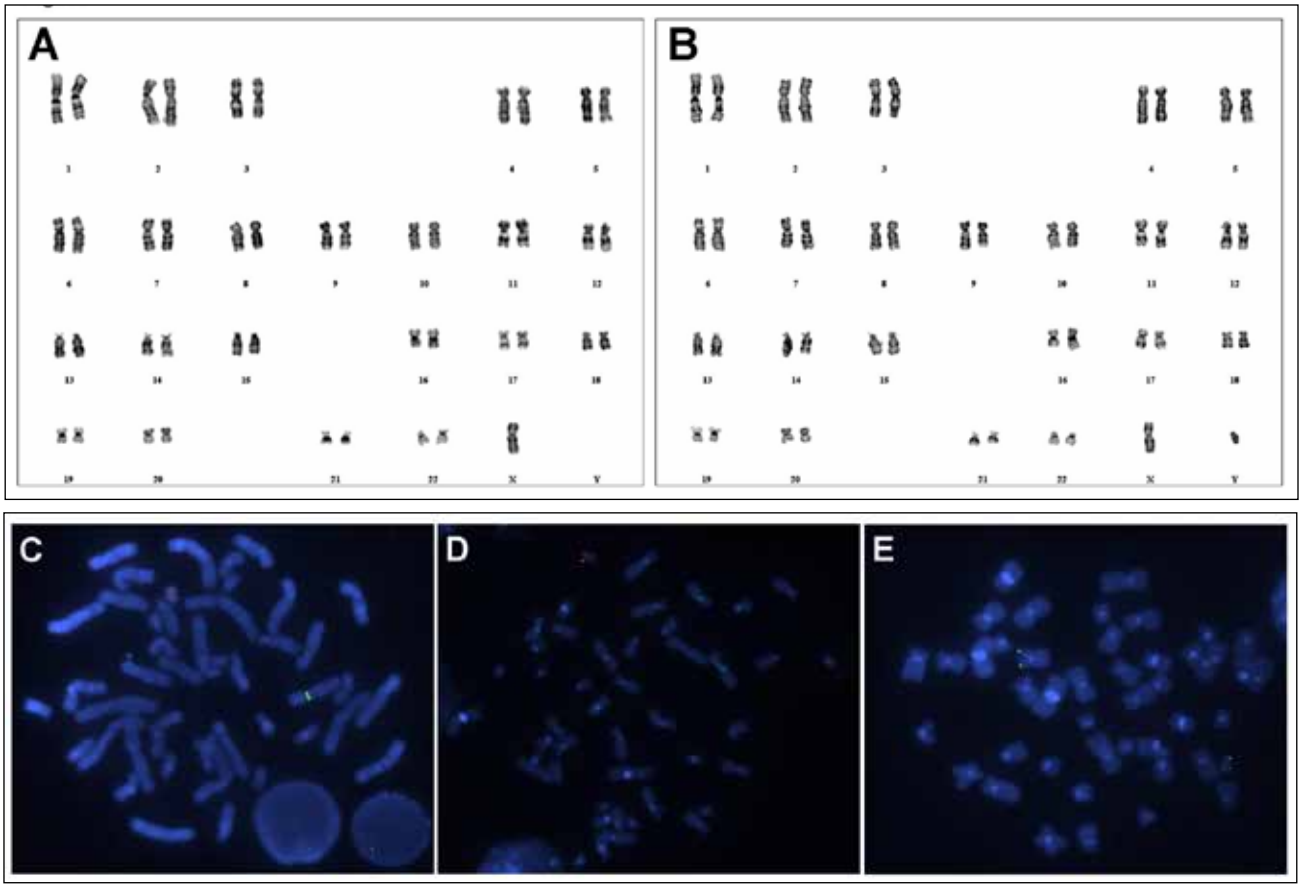

Fig. 2. Cytogenetic study and fluorescence in situ hybridization analysis of the patient's peripheral blood lymphocyte. (*A* and *B*) Cytogenetic study of the patient's peripheral blood lymphocytes showing a karyotype of 45,X[100]/46,X,del(Y)[12]. (*C*) A metaphase spread of the peripheral blood lymphocyte culture was analyzed with CEPYα-satellite and CEPXα-satellite probes. One green signal of the X chromosome and 2 red dots of the dic (Yq) were observed. (*D*) The metaphase spread was analyzed with Vysis *SRY* spectrum Orange/CEP X spectrum Green probes and the Vysis CEP Y(DYZ1) spectrum Aqua probe. One green signal of the X chromosome and 2 red dots of the *SRY* gene could be demonstrated, and no aqua signal was found. (*E*) The metaphase spread was analyzed with Vysis TelVysion XpYp spectrum Green probes. One green signal of the X chromosome short-arm terminal (DXYS129+) and 2 green dots of the Y chromosome short arm terminal (DXYS153++) were observed.

tent with that of normal males. To identify the break sites, 15 sites on the Y chromosomes in the patient's peripheral blood and buccal cells and her father's peripheral blood cells were further examined. In the patient's peripheral blood cells, only 4 sites (SRY, SY82, SY84, and SY124) were positive, whereas the buccal cells were negative on all 15 sites. Contrarily, her father's peripheral blood cells were positive on all 15 sites (Fig. 3 *B*). The patient's karyotype was ultimately defined as 45,X[100]/46,X,idic(Yp)[12](pter-q11::q11-pter), and she was diagnosed with TS, AS, IV, osteoporosis, and horseshoe kidney. Considering the Y chromosome material present in the patient's karyotype, we suggested that she undergo an exploratory laparotomy, which was refused by the patient.

DISCUSSION

TS is one of the most common chromosome abnormalities, and there is a guideline for its diagnosis and management. Rare case reports will help clinicians further understand TS and promote systematic clinical monitoring and care for TS patients. Here, we report an unusual case of a patient with TS associated with AS and IV who was determined to have a karyotype of 45,X/46,X,idic(Yp)(pter-q11::q11-pter). We determined the structure of the abnormal Y chromosome and found that its distribution varied among cells that differentiated from different embryonic germ layers. We also reviewed other reported cases of AS in TS patients with a 45,X karyotype (Table 1).

Approximately 50 to 60% of TS patients have an 45,X karyotype. About 6% of TS patients carry a second cell line with a structurally abnormal Y chromosome (5). The phenotypes of patients with the 45,X/46,XY karyotype vary from normal female, female with bilateral streak gonads, to infertile male (6). It is hypothesized that the *SRY* gene on the short arm of Y chromosome initiates genital ridge differentiation at the early stage of embryo development. Other researchers report that the copy number

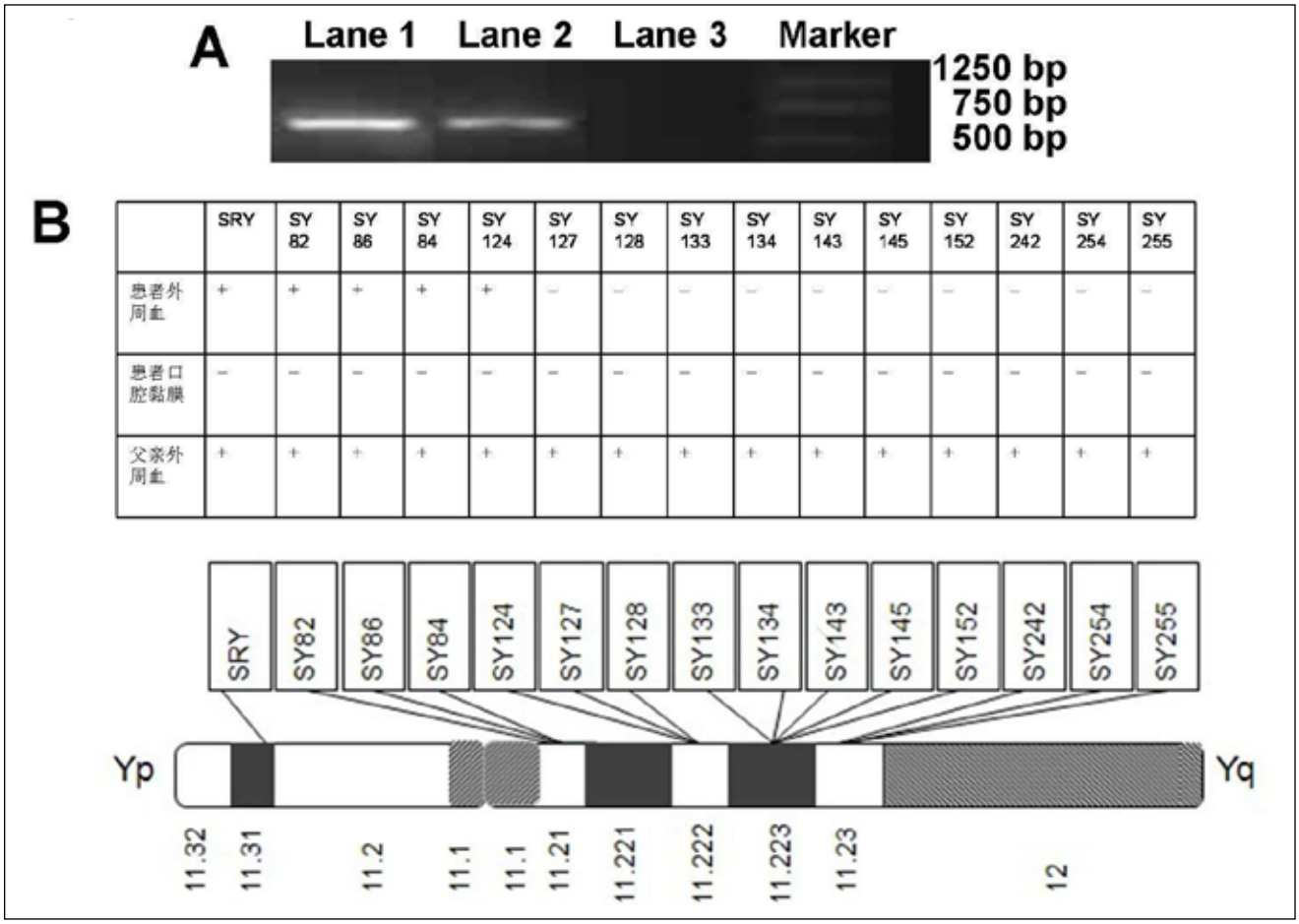

Fig. 3. Molecular genetic analysis of the patient's peripheral blood and buccal cells and her father's peripheral blood according to the loci order at http://www.genome.ucsc.edu.

of the *SRY* gene in gonads is more important for gonad development. Although the patient reported here carried a nonmutated *SRY* gene, the G-banding analysis and FISH results showed that the metaphase karyotype of her peripheral blood lymphocytes was 45,x[100]/46,x,dic(y)[12] and 45,x[100]/46,xy(DYZ3++)[25], respectively, and the karyotype of her buccal cells was 45,X(DYZ3-)[100]. Because lymphocytes differentiate from mesoderm and buccal cells from the ectoderm, our findings indicate that the patient possessed a tissue- and embryonic germ layer-specific mosaic karyotype. Structural abnormalities caused Y chromosome instability, and it was randomly lost at an early stage of embryo development (7). We speculate that the gonad of our patient most likely has a 45,X cell line and no Y chromosome material because both buccal and gonad cells differentiated from the ectoderm, and the former showed a karyotype of 45,X(DYZ3-). Additionally, the gonad might have produced androgenized external genitalia if there had been a Y chromosome component. Theoretically, a gonad without a Y chromosome cannot secrete anti-Müllerian hormone. The absence of this hormone allows Müllerian structures such as the uterus to persist through embryogenesis. However, no uterus was found during imaging examination of our patient. One possibility is that the gonads and uterus were present but diminutive in size, which could be confirmed by exploratory laparotomy. On the other hand, 2 cases of TS patients without uteruses who had karyotypes of 45,X and 46,X,i(Xq) have also been reported(8, 9). One of the patients underwent laparoscopy surgery, and no uterus was found.

The presence of Y chromosome material predicts whether virilism or gonadoblastoma will affect patients with undifferentiated gonads. Specifically, the risk of gonadoblastoma is 15 to 30% for this patient subgroup, and it increases with age (10). For a patient with Y chromosome material, some researchers suggest regular transrectal or transvaginal color Doppler sonography to monitor gonadal tumor occurrence (11), while others suggest routine gonad resection (12). Our patient refused to undergo exploratory laparotomy, so we advised that she undergo hormone replacement therapy and transrectal color Doppler sonography to monitor gonad development.

Although TS is frequently associated with autoimmune disease and this association has been extensively investi-

Table 1
Papers Reporting TS Patients With Ankylosing Spondylitis

	Güler-Uysal et al (2001)	Armagan et al (2007)	Current case
Karyotype	45,X	45,X	45,X/46,X,idic(Y)
Clinical manifestation	Typical TS features	Typical TS features	Typical features of TS and horseshoe kidney
Sacroiliac joint changes	Radiological examination showed sacroiliitis (bilateral grade 3)	Radiological examination and MRI showed bilateral sacroiliitis	Radiological examination and MRI showed sacroiliitis (bilateral grade 3)
Peripheral joints	Swelling and pain in knee and ankle joints, limitation of right knee function	Undescribed	Swelling and pain in knee joints
BMD	Lumbar spine (L1-L4) T = –5.58 SD	Lumbar spine (L1-L4) T = –2.25 SD	Lumbar spine (L1-L4) T = –5.20 SD
Laboratory findings	Lowered estrogen, elevated FSH and LH, HLA-B27 negative, C-reactive protein negative, ANA negative, rheumatoid factor negative, ESR 34 mm/h	Lowered estrogen, elevated FSH and LH, HLA-B27 positive, C-reactive protein increase, ANA negative, rheumatoid factor negative, TGAB 151 IU/mL, TMAB 1,000 IU/mL	Lowered estrogen; elevated FSH and LH; HLA-B27 positive; C-reactive protein increase; ANA negative; rheumatoid factor negative; normal T3, T4, TSH, TGAB, and TMAB
Complication	Undescribed	Autoimmune thyroiditis	Ichthyosis vulgaris
Family history	Undescribed	Undescribed	Her father showed HLA-B27 positive and ankylosing spondylitis
Different karyotypes existing in tissues from different embryonic germ layers	Undescribed	Undescribed	Yes
Ultrasonic examination	Hypoplastic uterus and fibrotic gonads	Hypoplastic uterus and fibrotic gonads	Pelvic ultrasound did not detect a uterus or ovaries

Abbreviations: ANA = antinuclear antibody; BMD = bone mineral density; FSH = follicle-stimulating hormone; HLA = human leukocyte antigen; LH = luteinizing hormone; T3 = triiodothyronine; T4 = thyroxine; TGAB = anti-thyroglobulin antibody; TMAB = anti-thyroid microsomal antibody; TS = Turner syndrome.

gated (6), its mechanism has not been clarified (13). TS is characterized by partial or entire sex chromosome loss. Studies regarding the association of autoimmune diseases with TS have proposed targeted haploinsufficiency of the X chromosome, mutation of genes on the X chromosome, loss of major histocompatibility complex on the X chromosome long arm, blastoderm-specific mosaicism in different tissues, the parental source of X chromosome, abnormalities of Y chromosome (e.g., deletion, repetition, and ring chromosome), and hormone level (14-17). The hemizygosity of X-linked genes means that pathogenic genes on the haploid X chromosome are not compensated for by corresponding normal genes. In addition, non-TS females with a number of autoimmune diseases have larger population of lymphocytes with monosomy X karyotypes, raising the possibility that some of the X chromosome-related mechanisms contributing to autoimmunity in females with TS may also contribute to autoimmune disease in other females (18,19).

Unlike many other autoimmune diseases, AS is more prevalent in males than in females (20). If AS is more common in patients with TS than in other females, it raises the possibility that a second X chromosome might be protective, but the Y chromosome is unable to serve a protective function (or that the Y chromosome itself increases susceptibility). In this regard, the present patient may be at increased risk given that she possesses cell lines with monosomy X and a (structurally abnormal) Y chromosome. Additionally, the current patient also presented with IV, which is usually caused by mutation of genes on chromosome 1p21. Because IV was also observed in her father and sisters, whether it was a monogenic disease associated with gene mutations needs to be studied further.

CONCLUSION

Cytogenetic examination of metaphase peripheral blood lymphocytes has been considered the gold standard

for TS diagnosis. Our results further demonstrate that FISH technique can provide more detailed karyotypical information than common cytogenetic methods, especially for mosaic detection. The TS case we reported here presented with a rare karyotype and phenotype, and autoimmune diseases such as AS should be considered when monitoring TS patients.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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