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Case Report

Tocilizumab in the Treatment of A Girl with Juvenile Ankylosing Spondylitis and Turner Syndrome: Case Report

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Abstract

Juvenile ankylosing spondylitis (JAS) refers to ankylosing spondylitis that develops before age 16; it is characterized by a chronic painful inflammatory reaction primarily in the spine. We describe a 12-year-old girl who has JAS and Turner Syndrome (TS). TS is a chromosomal disorder where phenotypic females have either a missing chromosome (45, X) or a structural aberration of one of the chromosomes. Our patient was found to be a mosaic for 45, X/46, XX. At the same time, she was thought to have a latent tuberculosis (TB) infection. To date, there is only one case of JAS and two cases of AS in association with TS reported in the literature. But none of these three patients were treated with Tocilizumab. This is the first report of Tocilizumab in treatment of the disease. Herein, we describe the clinical features of the patient and her individualized treatment with tocilizumab. With tocilizumab, her arthritis was relieved. We suggest that sacroiliitis should be kept in mind in TS patients, and tocilizumab can be used to treat this disease.

Keywords: Ankylosing spondylitis; Turner Syndrome; Tocilizumab; Case report

1. Introduction

Juvenile ankylosing spondylitis (JAS) refers to ankylosing spondylitis that develops before age 16. JAS is a chronic inflammatory autoimmune disease involving the attachment of the axial and tendon ligaments [1]; this type of enthesitis-related arthritis (ERA) accounts for around 10-20% of cases of juvenile idiopathic arthritis (JIA) [2]. JAS can cause considerable morbidity when left untreated [3]. Turner Syndrome (TS) was first described by Turner in 1938 and is characterized by short stature, undeveloped genitalia, and secondary sexual characteristics [4]. TS is a

chromosomal disorder where phenotypic females have either a missing chromosome (45, X) or a structural aberration of one of the chromosomes [5].

Several reports have shown an association between JIA and TS [6-12]. To date, there is only one case of JAS [13] and two cases of AS in association with TS [14, 15]. The main affected joints in these patients are the hip joints. Magnetic resonance imaging showed the presence of sacroiliitis. Herein, we report, the second case of comorbid JAS and TS reported in the literature. Further, the patient in this case study had a latent tuberculosis (TB) infection. We will present the clinical features of this patient and describe her individualized treatment with tocilizumab.

2. Case Report

The girl was 12 years old. She presented with difficulty walking, a stiff, forward-flexed spine, and mild sacroiliac joint pain for four years. In the past year, the child suffered from iridocyclitis. She attended our pediatric rheumatology clinic complaining of bilateral hip pain. There was no history of fever, rash, or pain and swelling of any other joints. The pain was more significant in the early evening, especially after school, and was improved after a night's sleep. Her past medical history indicated a diagnosis of TS with a 45, X/46, XX karyotype (Figure 1). In the meantime, the only clinical manifestation was short stature. She did not have a short-webbed neck or a low hairline. There were no abnormalities in bilateral renal size or morphological structure, and no expansion of the renal pelvis. She was born of nonconsanguineous parents. Both parents are healthy.

After admission, she underwent a physical examination. She had a short stature with a height of 142 cm (less than 3rd centile). Her Schober test was 7 cm, finger to ground distance was 5 cm, and occiput to wall distance was 0 cm. Patrick–Fabere tests were negative. However, she exhibited severe back pain when she underwent these examinations. Secondary sexual characteristics were not well developed. She attained menarche this year (12 years old) and her axillary hair was absent.

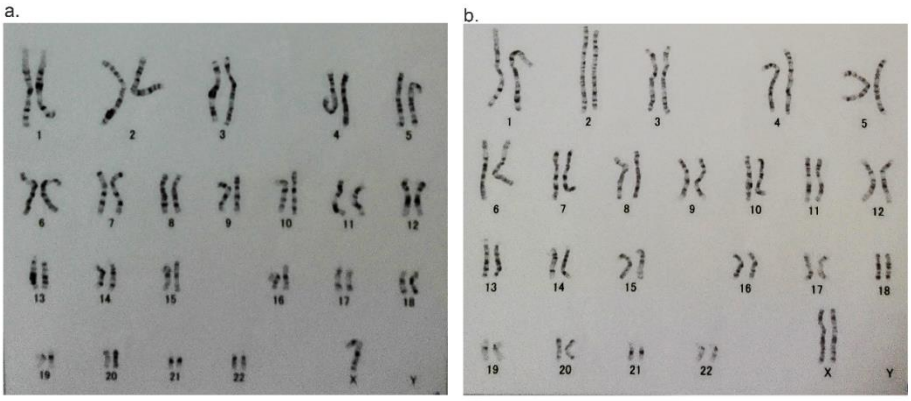

Figure 1: Karyotype of the patient. a. Karyotype showing 45, X; b. Karyotype showing 46, X.

Laboratory analysis of fecal and urine was normal. Erythrocyte sedimentation rate was 31 mm/h (0-20 mm/h) and C-reactive protein was 6 mg/L (normal 0.0–8.0 mg/L). Her blood cell examination showed an increased platelet count (608 × 109/L). Liver and renal function tests were normal. Assays for antinuclear antibody (ANA), anti-dsDNA, rheumatoid factor, anti-extractable nuclear antigen antibody, and rheumatoid arthritis-related autoantibody profiles, including anti-cyclic citrullinated peptide antibody (CCP), anti perinuclear factor (APF), anti-keratin antibody (AKA), and glucose-6-phosphate isomerase (GPI), were negative. Her test for HLA-B27 was positive. Serum estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) were normal. Her thyroid function tests were normal. She had normal levels of free T3, T4, thyroid stimulating hormone (TSH), anti-thyroglobuline antibody, and thyroid binding globulin (TBG). Insulin-like growth factor 1 (IGF1) and glycated hemoglobin were also normal. Magnetic resonance imaging of the sacroiliac joints confirmed the presence of sacroiliitis (Figure 2).

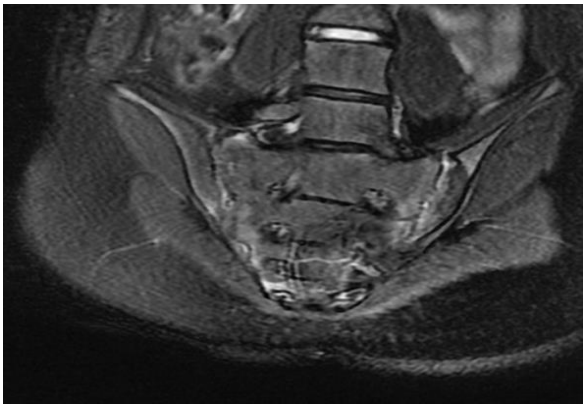

Figure 2: MRI of the bilateral sacroiliac joints.

The bilateral sacroiliac joint surface is less smooth and no obvious narrowing of joint space is found. According to her clinical manifestations and examinations, she was diagnosed as having TS. She also fulfilled the modified New York classification criteria for AS [16].

Initially her treatment included NSAIDs, sulphasalazine, and methotrexate. However, this therapy was suspended because of liver function abnormalities. Given that her PPD test was positive, we attempted to treat her JAS with tocilizumab (8 mg/kg, once per month). After two months, her pain was relieved and ESR had returned to normal (7 mm/h). At the same time, anti-tuberculosis drugs (isoniazid and rifampin) were administered for three months. The patient came to the hospital for treatment once a month. After nine months, it was evident that she was in good condition without any adverse reactions.

3. Discussion

Chromosomal abnormalities have been shown to predispose individuals to autoimmune diseases such as thyroid disease, inflammatory bowel disease, and diabetes [17]. TS is a chromosomal disease characterized by monosomy X or a structural aberration of one of the chromosomes [4, 5]. JAS refers to ankylosing spondylitis that develops before age 16; it is characterized by a chronic inflammatory reaction of the spine. JAS is a type of ERA accounting for around 10-20% of JIA [1-3]. Wihlborg et al. [11] described the association between TS and JIA. Of about 65 patients at their center with TS, three had JIA, supporting their association. The overall incidence of TS and JIA in the population is estimated to be 5 per 10,000 and approximately 10 per 100,000, respectively. Zulian et al. [10] reported 18 cases of TS in a population of approximately 15,000 JIA patients. Thus, they proposed that JIA is another autoimmune condition linked to TS. The association between JIA and TS was also reported in other case studies [6-9, 12]. To the best of our knowledge, there is only one reported case of JAS and two reported cases of AS together with TS [13, 14, 15]. We present a case of a 12-year-old girl with JAS who also had TS and a latent TB infection. The clinical features and treatment of this patient are described in Table 1.

Similar to AS, short stature, neck webbing, increased carrying angle, and horseshoe kidneys are characteristic dysmorphic features of classical TS [17]. However, our patient's only clinical manifestation was short stature. A diagnosis of TS was made because she had a 45, X/46, XX karyotype. The chimera karyotype is a common karyotype of TS. The chimera karyotype is complex, and the corresponding clinical symptoms and severity are different because of the different types of karyotypes and proportions of the chimeric karyotype. The clinical manifestations and severity of TS are related to the percentage of abnormal karyotype. The larger the percentage the more severe the manifestations are [18]. We speculate that our patient has a low percentage of abnormal karyotype so she exhibits less manifestations After the TS diagnosis, somatotropic hormone therapy (8 U/day) was commenced.

The treatment for JAS in our case was a little complicated. Administration of NSAIDs, sulphasalazine, and methotrexate was suspended because of liver function abnormalities. Given that she appeared to have a latent TB infection, we attempted treatment of JAS with tocilizumab. Tocilzumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody. Systemic-onset JIA (SoJIA) presents a favourable response. But there is controversy as to whether TCZ treatment for AS is effective. In contrast to our report, a 12-week randomized trial found that TCZ had no benefit on clinical outcomes in 99 AS patients compared with placebo [20]. However, TCZ has been reported to be beneficial in AS patients in small case studies [21]. After treatment with TCZ in our case, the sacroiliac joint pain symptoms disappeared and the ESR dropped to normal. However, long-term efficacy requires further observation.

clinical information	**Patient1 [15]**	**Patient 2 [14]**	**Patient 3 [13]**	**Patient 4**
Report time	2001	2007	2013	2018(now)
Race	Turk	Turk	Asian Indian	China
Age	30 years old	24 years old	20 years old	12 years old
Onset time	Since childhood	24 years old	6 years old	8 years old
Arthritis	AS	AS	JAS	JAS
Complaints	Buttock and low back pain	Low back pain Morning stiffness	Back pain, progressive stiffness of the back and both hip joints	Walking with a stiff, forward-flexed spine mild sacroiliac joint pain
Physical examination	Limited neck rotation	Limitation of lumbar spine movement and lumbar lordosis Schober test was 4 cm Chest expansion was 3 cm Finger to ground distance was 5 cm Occiput to wall distance was 0 cm Patrick–Fabere and sacroiliac compression tests were bilateral positive	Bilateral hip flexion contractures of 30°	Schober test was 7 cm Finger to ground distance was 5 cm Occiput to wall distance was 0 cm Patrick–Fabere tests were negative
Laboratory studies	Limited trunk flexion with forward bending mainly performed via hip flexion	ESR was 44 mm/h CRP was 7.88 mg/dl HLA-B27 was positive	HLA-B27 was positive	ESR was 31 mm/h CRP was 6 mg/L HLA-B27 was positive
Videography	Sacroiliac provocation tests were painless but limitation of bilateral hiprotation	Bilateral sacroiliitis	A bamboo spine Sacroiliitis	Sacroiliitis
TS	Shortened ham string muscles and pain in the right knee on performing			

	passive range of motion			
Clinical manifestations and Physical examination	ESR was 34 mm/h	Amenorrhea Short stature Short-webbed neck with a low hairline Juvenile female external genitalia	Short stature Webbing of the neck	Short stature
Laboratory studies	CRP was normal	45, X Low serum estradiol Elevated FSH and LH levels Normal Free T3, T4 and TSH Anti-thyroglobuline antibody and anti-microsome antibody were high	45,X/46X, psu idic (X)(p11) idic(X)(qter!p11::p11→qter) Serum follicle-stimulating hormone was elevated to menopausal range normal TSH and anti-thyroid antibodies	45, X/46, XX Normal levels of free T3, T4, TSH, TBG, IGF1and glycated hemoglobin
Videography	HLA-B27 was negative	Hypoplastic uterus and fibrotic gonads DEXA technique revealed osteoporosis	DEXA technique revealed osteoporosis Abdominal and pelvic ultrasound revealed a hypoplastic uterus, absent ovaries and horseshoe kidneys.	Magnetic resonance imaging of the sacroiliac joints confirmed the presence of sacroiliitis
Others	Bilateral grade III sacroiliitis and signs of inflammation in both hip joints	Autoimmune thyroiditis	-	Potential TB infection
Treatment		Sulfasalazine Vitamin D Calcium A home exercise program	NSAIDs Sulphasalazine Methotrexate	Tocilizumab instead of NSAIDs, sulphasalazine and methotrexate

Table 1: Comparison of clinical manifestations of 3 patients with Juvenile ankylosing spondylitis and Turner Syndrome.

4. Conclusion

The three cases in the literature together with the case reported here suggest an association between TS and AS. In these cases, the diagnosis of JAS was delayed. It is possible that the symptoms of joint pain were assumed to be related to the TS. The rarity of both the conditions in the general population makes it highly likely to be an association, rather than a coincidence. However, the pathogenesis require further study. The possibility of sacroiliitis should be kept in mind in TS patients. Tocilizumab can be used to treat this disease.

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Ethics Statement

Written informed consent was obtained from the patient. The Institutional Review Board (IRB) of Peking Union Medical College Hospital gave official approval.

Disclosure

The author reports no conflicts of interest in this work.

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