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Diagnosis of Turner syndrome after presenting with ischemic cardiomyopathy: A case report

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Abstract

Untreated Turner syndrome increases the risk of ischemic cardiomyopathy. We report a 44-year-old Chinese woman who was diagnosed with Turner syndrome owing to symptoms of ischemic cardiomyopathy and heart failure confirmed through cardiac magnetic resonance imaging, coronary angiography, and abnormal brain natriuretic peptide levels. The patient had a short stature, underdeveloped uterus with primary amenorrhea, and congenital left upper pulmonary vein reflux to the right atrium; she was diagnosed with Turner syndrome through karyotype analysis. Because she refused coronary artery bypass grafting, she received aspirin, torasemide, atorvastatin, bisoprolol, sacubitril/valsartan, empagliflozin, spironolactone, and complex packing estradiol tablets/estradiol and dydrogesterone tablets (1–10 mg). After 3 months of treatment, her heart failure symptoms disappeared. Ischemic heart disease is a high-risk complication in patients with Turner syndrome. Prompt diagnosis and comprehensive management through a multidisciplinary approach can improve patient outcomes. Further evidence is needed to establish a secondary prevention strategy for Turner syndrome with ischemic cardiomyopathy.

Keywords

Turner syndrome, ischemic cardiomyopathy, heart failure

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Introduction

Turner syndrome (TS) is a chromosomal disorder that affects phenotypic females who have one intact X chromosome and complete or partial absence of the second sex chromosome in association with one or more clinical manifestations.[1] It affects approximately 1 in every 2000–2500 live female births. TS is associated with a 1.66-fold increased risk of ischemic cardiomyopathy and a 3.15-fold increased risk of heart failure.[2] Although ischemic cardiomyopathy is not known to be related to X chromosome defects, it is closely associated with estrogen deficiency as well as the increased incidence of hypertension and metabolic diseases, including hyperglycemia and obesity, in TS. We report a case of TS diagnosed after the patient presented with symptoms of heart failure induced by ischemic cardiomyopathy.

Case

A 44-year-old Chinese woman had persistent lower limb edema for 3 months, accompanied by shortness of breath, cyanosis, and fatigue, and had been experiencing intermittent chest pain and sweating when exerting force for the past 6 years. She was previously diagnosed with acute glomerulonephritis at 12 years of age and was successfully treated. Her medical history included surgical treatment for left ear glioma at 26 years old, radiofrequency ablation because of supraventricular tachycardia at 28 years old, hypertension for the last 6 years, and primary amenorrhea. She denied

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consuming alcohol or smoking. Her father died of diabetes associated with cerebral infarction; however, her mother, brother, and sister were in good health.

On physical examination, her heart rate was 79 bpm and her blood pressure was 115/70 mmHg; her stature was short (weight = 45.2 kg; height = 145 cm; BMI = 21.5 kg/m^2). She had scattered black moles on her neck, chest, back, limbs, and epicanthic folds; a flattened nose bridge; a small jaw; protruding earlobes; a webbed and thick neck; low hairline; wide breast distance; Tanner scale of IV; and cubitus valgus and genu valgum. The jugular vein was distended. Respiratory, abdominal, and central nervous system examination findings were unremarkable. She had a hypoplastic uterus (2.7 × 2.0 × 1.1 cm); abdominal pelvic ultrasound failed to detect endometrium or bilateral ovaries (Figure 1(a)).

The patient's lumbar spine bone density *T*-value was −3.0. A 24-h Holter monitor revealed an average corrected QT interval of 603 ms. Her *N*-terminal B-type natriuretic peptide precursor level was 5381 pg/mL. Cardiac magnetic resonance imaging revealed an enlarged left ventricle (62 mm) and reduced ejection fraction (19%), indicating an old myocardial infarction; her aortic size index was 2.34 cm/m^2 (Figure 1(b)). Coronary angiography showed 80%–90% stenosis at the end of the left main artery, anterior descending artery, circumflex artery, and right coronary artery with complete occlusion after the second inflection point in the distal segment, and no congenital coronary anomalies (Figure 1(c) and (d)); her SYNTAX score was 47.[3] Large vessel computed tomography revealed reflux from the left upper pulmonary vein into the right atrium (Figure 1(e)).

The patient had elevated low-density lipoprotein (LDL) (3.57 mmol/L). An oral glucose tolerance test revealed impaired glucose tolerance (IGT) with 6.4% for her glycated hemoglobin. She was initially diagnosed with Hashimoto's thyroiditis combined with subclinical hypothyroidism (thyrotropin-releasing hormone, 13.07 μIU/mL; thyroid peroxidase antibody, >600.0 IU/mL). Based on the patient's unique physical signs and medical history, we believed her symptoms were attributable to a single congenital defect. With the patient's consent, a peripheral blood chromosome karyotype test was conducted (Tianjin Jinyu Medical Laboratory, China). The G-banding technique, used on human peripheral blood metaphase cell culture, involves using a chromosome scanning analyzer to count the chromosomes of 30 metaphase cells. A detailed analysis of 400 chromosomal bands was conducted on five cells. The final report showed a 45,X karyotype according to ISCN2020 (Figure 2). We also assessed the patient's sex hormones; the levels of estrogen and progesterone were low. The growth hormone, insulin growth factor-1, cortisol, adrenocorticotropic hormone, aldosterone, and renin levels were normal.

The patient was finally diagnosed with TS, ischemic cardiomyopathy, heart failure (NYHA Class IV), abnormal pulmonary venous drainage, old myocardial infarction, hypertension, IGT, Hashimoto's thyroiditis combined with subclinical hypothyroidism, and osteoporosis. She refused coronary artery bypass grafting (CABG) due to concerns about its high risks. Her ischemic cardiomyopathy, heart failure, coronary heart disease, hypertension, and hyperlipidemia were treated according to national guidelines, including aspirin (100 mg q.d.), torasemide (20 mg q.d.), atorvastatin (20 mg q.d.), bisoprolol (2.5 mg q.d.), sacubitril/valsartan (25 mg b.i.d.), empagliflozin (10 mg q.d.), and spironolactone (20 mg q.d.), combined with lifestyle interventions. Hormone replacement therapy was initiated with complex packing estradiol tablets/estradiol and dydrogesterone tablets (1–10 mg) until the average age of menopause (50–55 years). At her 3-month follow-up, the heart failure symptoms had resolved, the inner diameters of the left ventricle, right ventricle, and right atrium had decreased, the ejection fraction had increased (19%–39%), her NYHA Class improved to I, and her blood lipid and glucose levels were controlled to normal.

Discussion

TS combined with acquired heart disease, including coronary heart disease and ischemic cardiomyopathy, can cause heart failure. Our patient was only diagnosed with TS when heart failure occurred. This report provides insights on the systemic effects of long-term estrogen deficiency and treatment strategies for TS combined with ischemic heart disease.

Ischemic cardiomyopathy in patients with TS is closely related to the associated increased incidence of hypertension, hyperglycemia, and hyperlipidemia. Our patient had a history of hypertension for 6 years and had achieved standard blood pressure control. Approximately 50% of patients with TS in their 50s receive antihypertensive treatment, attributable to the associated obesity and estrogen deficiency.[4] In addition, our patient was first diagnosed with IGT. X-chromosome short arm deletions may be closely related to β-cell dysfunction[5,6], and the prevalence of diabetes in patients with TS may be as high as 83%.[7] Hypercholesterolemia is a common and characteristic lipid profile in individuals with TS.[8] Compared with women with premature ovarian failure, patients with TS have higher LDL-c levels and are more likely to experience atherosclerosis.[9]

In the present case, the simultaneous occurrence of these risk factors for ischemic cardiomyopathy was likely caused by both the X chromosome deletion and the lack of estrogen treatment. Based on our ultrasound results and sex hormone levels, this patient has been diagnosed with uterine dysplasia. The diagnosis of uterine absence is inaccurate when initially presenting with primary amenorrhea in her teens. In the presence of severe estrogen deficiency, the uterus can be invisible to imaging modalities including ultrasound, especially during adolescence. There may be a place for repeat imaging after a 6-month course of estrogen. The degree of

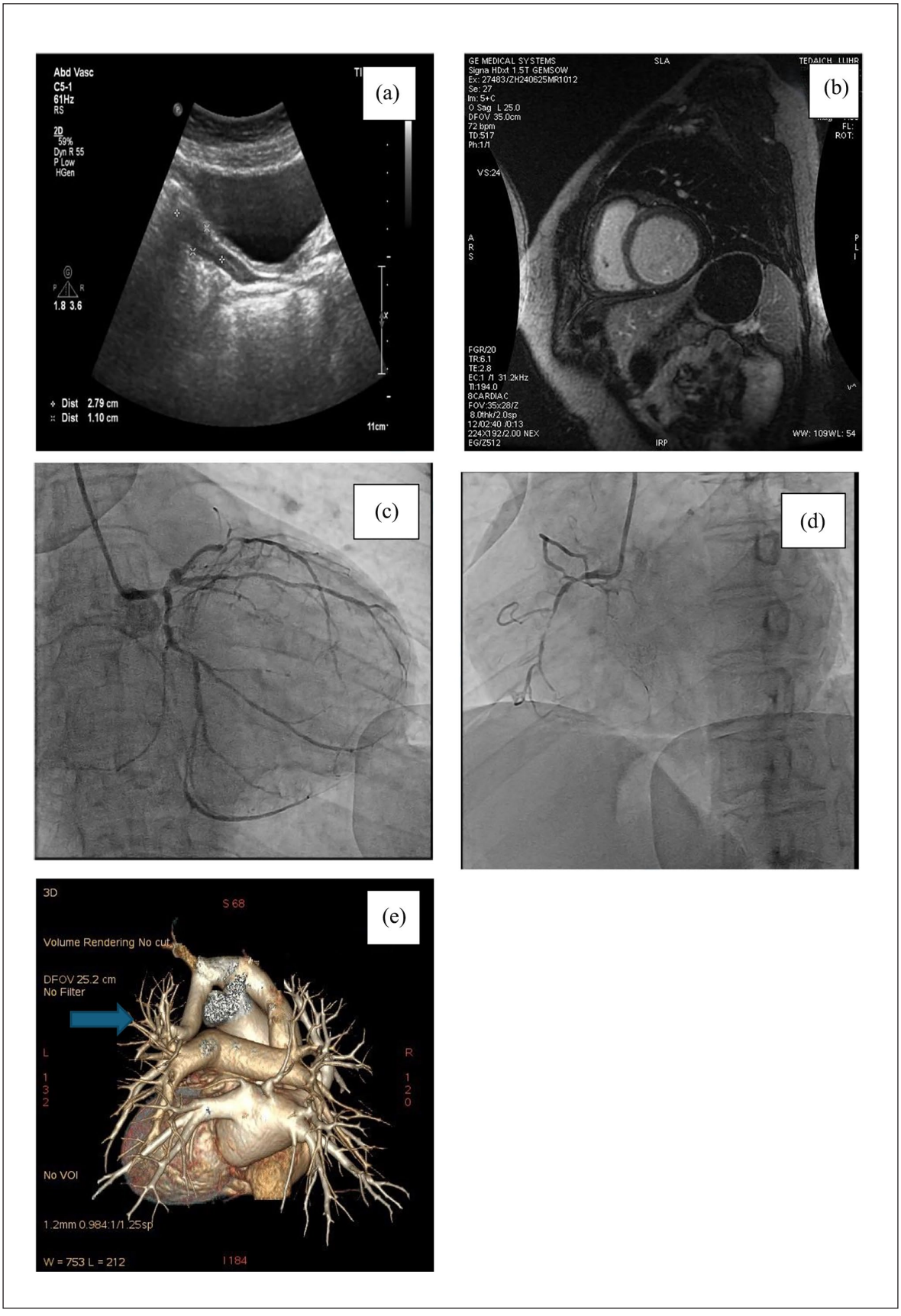

Figure 1. (a) Transabdominal pelvic ultrasound. (b) Cardiac magnetic resonance imaging. (c and d) Coronary angiography images. (e) Large vessel computed tomography scan results.

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染色体核型分析报告单
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医院名称	泰达国际心血管病医院			医院标识	
患者姓名		社会性别	女	年　龄	44岁
科　室	心衰科病区	住院/门诊号		室房/床号	631
申请医生		临床诊断			
联系电话		项目名称	外周血染色体核型分析		
标本条码	0347110181	实验号	Y24013551	接收时间	2024-06-27 14:38:16
采样时间	2024-06-27 09:10:00	标本类型	全血(肝素钠抗凝)	标本状态	无肉眼可见异常
接种时间	2024-06-28 14:28:57	计数细胞数	30	分析细胞数	5
拍摄细胞数	35	制片人	王新阳	条带水平	400

初步报告内容（口头或电话）

原始图像：

核型分析图像：

核型分析结果 核型：45,X

结果解释 本报告核型结果按照《ISCN2020》书写。此核型符合特纳综合征核型。

建议其他检测 建议遗传咨询。

1. 核型分析属于形态学检测，仅能检出该条带水平下的染色体结构或数目异常，超出该条带水平可见的微小异常和低密度嵌合体可能无法检出。
2. 若染色体核型分析检测阴性建议进一步做染色体微阵列(CMA)检测，适应症例如：不明原因智力低下，发育迟缓，先天畸形，孤独症等，习惯性流产和原发不孕不育等。

参考文献：Miller DT, Adam MP, Aradhya S,et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010 May 14; 86(5):749-64.

本检测仅对来样负责，如果对结果有疑义，请在报告发出后7天内与我们联系，多谢合作！
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Figure 2. Chromosome karyotype report of peripheral blood metaphase cells.

uterine maturity was positively associated with years of estrogen use regardless of karyotype. Unfortunately, the patient refused hormone replacement therapy. Compared to patients with TS receiving estrogen therapy, untreated patients have a significantly higher mortality rate; estrogen therapy can reduce the risk of metabolic abnormalities.[10] The protective effect of estrogen in cardiovascular disease is associated with reduced fibrosis, stimulation of angiogenesis and vasodilation, improved mitochondrial function, and reduced oxidative stress.[11] After communication with the patient, we administered treatment using complex packing estradiol tablets/estradiol and dydrogesterone tablets, to be continued until she reaches the age of 50–55 years. However, limited evidence supports estrogen replacement therapy as a secondary preventive measure in ischemic cardiomyopathy.

Regarding the treatment of coronary heart disease, our patient's SYNTAX score was 47. When the SYNTAX score is greater than 33, CABG is recommended, even if high-risk.[12] Our patient agreed to receive medication but refused surgery. More evidence is needed to establish an optimum treatment strategy for patients with TS combined with ischemic cardiomyopathy and heart failure.

Our patient's aortic size index was 2.35 with concomitant hypertension, posing a high risk of aortic dissection. Heart and magnetic examinations every 6 months to 1 year are recommended. The incidence rate of TS complicated with abnormal pulmonary venous return is 2.9%–25%.[13,14] The clinical significance and treatment of this defect depends on the degree of left to right shunting.[15] As the abnormal pulmonary venous return in our patient did not cause any right heart dysfunction (right heart ejection fraction, 40%), no intervention was performed.

Conclusion

This case emphasizes the importance of identifying the cause of early-onset ischemic cardiomyopathy and of early and active treatment of TS. Early estrogen replacement therapy is crucial for the prevention of long-term cardiovascular disease as well as to achieve normal height and secondary sexual development. TS significantly increases the incidence of premature ischemic heart disease in women. For patients with TS who have already developed severe cardiovascular disease and are approaching menopause, secondary prevention requires multidisciplinary management and follow-up; further clinical research is required to establish an optimum treatment strategy.

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Author contributions

H.Z., L.G., and Y.W. collected case data and wrote the article; Y.Z. followed up with the patient; and YG reviewed the radiation examination reports.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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