CASE REPORT

Hypertrophic Cardiomyopathy in a Patient of Klinefelter Syndrome – a Rare Association

Shahid Ahmed, Shahid Hafeez, Nadir Ali* and Taimoor Ahmed

ABSTRACT

A 36-year-old man presented with exertional dyspnoea and chest pain. He also had sexual dysfunction with poorly developed secondary sex characteristics. Echocardiography and thorough cardiac evaluation revealed obstructive hypertrophic cardiomyopathy. Hormonal profile suggested primary hypogonadism and cytogenetics report suggested a karyotype, 47, XXY, in all counted cells, consistent with the diagnosis of Klinefelter syndrome. He is being managed with beta-blocker and androgen replacement therapy.

Key words: *Exertional dyspnoea. Sexual dysfunction. Obstructive hypertrophic cardiomyopathy. Klinefelter syndrome. Beta-blocker. Androgen replacement.*

INTRODUCTION

Klinefelter syndrome is the most common chromosomal disorder, in which there is one extra X chromosome resulting in the karyotype of 47,XXY. As more individuals suspected of having Klinefelter syndrome had chromosome studies done, other karyotypes were sometimes observed, such as 48,XXYY, 48,XXXY and 49,XXXXY.[1] The diagnosis is commonly made during adolescence or adulthood in males, who have small testes with hypogonadism and gynaecomastia. Virtually all men with Klinefelter syndrome are infertile.[2,3] The most overt phenotypic features of Klinefelter syndrome are caused by testosterone deficiency and, directly or indirectly, by unsuppressed follicle-stimulating and luteinizing hormones. Affected men typically have (in decreasing order of frequency) infertility, small testes, decreased facial hair, gynaecomastia, decreased pubic hair, and a small penis.[3] Persistent androgen deficiency in adulthood may result in loss of libido, decreased muscle bulk and tone, decreased bone mineral density, a propensity for thromboembolism, and an increased risk of mortality from diabetic and cardiovascular complications.[4] Neurobehavioural disorders, speech difficulties[5,6] and congenital heart malformations have also been found to be associated with Klinefelter syndrome.[7] Congenital heart malformations are rare in Klinefelter syndrome. A few cases of mitral valve prolapse, ventricular septal defect, tetralogy of Fellot, patent ductus arteriosus and atrial septal defect have been reported. There is a single case report of an elderly man with Klinefelter syndrome associated with hypertrophic cardiomyopathy, sick sinus syndrome and coronary arteriovenous fistula, published in 1998 in a Japanese journal.[8]

We are reporting a case of obstructive hypertrophic cardiomyopathy in a patient of Klinefelter syndrome, which is a very rare association.

CASE REPORT

A 36-year-old man presented with one-and-a-half year history of breathlessness on exertion and retrosternal and left anterior chest pain. The pain was dull in nature, sometimes radiating to left arm and aggravated by exertion. The pain was not associated with sweating and he never had any dizziness or syncope. He was never investigated for these symptoms previously. There was no history of any other significant illness in the past. He was married for 7 years but his wife could never conceive. Some practitioner advised him to get his semen analysis done, which revealed azoospermia. He had been having erectile dysfunction and decreased libido since early adult life, using herbal medicines and androgen replacements off and on, prescribed by local quacks and practitioners. He was non-diabetic, normotensive and non-smoker. He was a cook by profession and was having some difficulty in carrying out his job due to his symptoms. On examination, he was a tall young man weighing 88 kg, having long legs, narrow shoulders, broader pelvis and had more fat at lower abdomen, hips and buttocks. His height was 180 cm. He had decreased facial, axillary and pubic hair, mild bilateral gynaecomastia, small penis and testes (4 ml by Prader's orchidometer). Examination of cardiovascular system revealed double spiky pulse with a regular rate

Department of Medicine/Pathology, Combined Military Hospital, Malir Cantt, Karachi.*

Correspondence: *Lt. Col. Dr. Shahid Ahmed, Classified Medical Specialist and Endocrinologist, Combined Military Hospital, Lahore Cantt.*
E-mail: shahidahmed833@hotmail.com

Received October 2, 2007; accepted May 9, 2009.

of 80 beats per minute, 120/80 mmHg blood pressure and a heaving apex beat in the fifth intercostal space in the left midclavicular line. Auscultation of heart revealed normal heart sounds and an ejection systolic murmur along left sternal edge. Electrocardiography (ECG) suggested left ventricular hypertrophy by voltage criteria and T-wave inversion in leads III and aVF. Chest radiograph was normal. Hormonal profile showed LH 14.4 (reference range: 1-5 mIU/ml), FSH 51.0 (reference range: 0.5-5 mIU/ml), testosterone 2.76 (reference range: 9.9-52.3 nmol/l), prolactin 4.90 (2.2-18.5 ng/ml) and normal thyroxine, TSH and cortisol levels. Echocardiography revealed dilated left atrium, normal left ventricular size with diastolic dysfunction, asymmetrical hypertrophy, with interventricular septal thickness of 17.7 mm with a relatively normal posterior wall thickness of 9.1 mm (Figure 1). Continuous wave Doppler image recorded through left ventricular outflow tract suggested relatively late peaking of systolic gradient resulting in a dagger shaped contour, with a peak pressure gradient of 56.91 mmHg (Figure 2). Pulsed wave Doppler imaging suggested a dynamic Left Ventricular Outflow Tract (LVOT) obstruction (Figure 3). As the sample volume was moved from the apex towards aortic valve along the septum, the outflow tract velocity exceeded the Nyquist limit and aliasing occurred. 2D and M-mode echocardiogram showed systolic anterior motion of anterior mitral leaflet (Figure 4) with grade-1 mitral regurgitation. Holter monitoring demonstrated 0.4% ventricular premature contractions. Coronary angiogram showed normal coronary arteries with hypertrophic heart and pressure gradient 64 mm across left ventricular cavity.

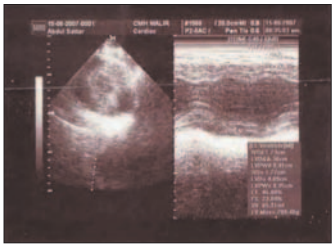

Figure 1: 2D and M-mode echocardiography showing marked thickening of interventricular septum.

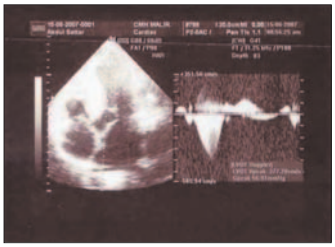

Figure 2: Continuous wave Doppler image recorded through left ventricular outflow tract.

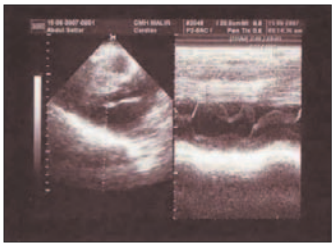

Figure 3: Pulsed wave Doppler imaging recorded in LVOT with dynamic outflow tract obstruction.

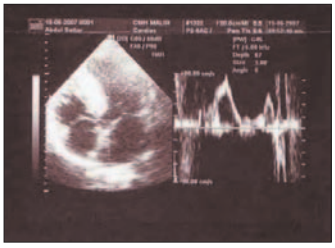

Figure 4: 2D and M-mode echocardiography showing systolic anterior motion of anterior mitral leaflet.

Cytogenetics report suggested 47,XXY karyotype in all the counted cells (Figure 5). He was placed on medical management consisting of Metoprolol 50 mg 12 hourly, aspirin 75 mg daily and injection testosterone enanthate 250 mg, intramuscularly, every 3 weeks. He was doing well on Metoprolol (beta-blocker), with significant improvement in exercise tolerance. He has also felt improvement in erectile function, muscle strength and general well-being, with androgen replacement.

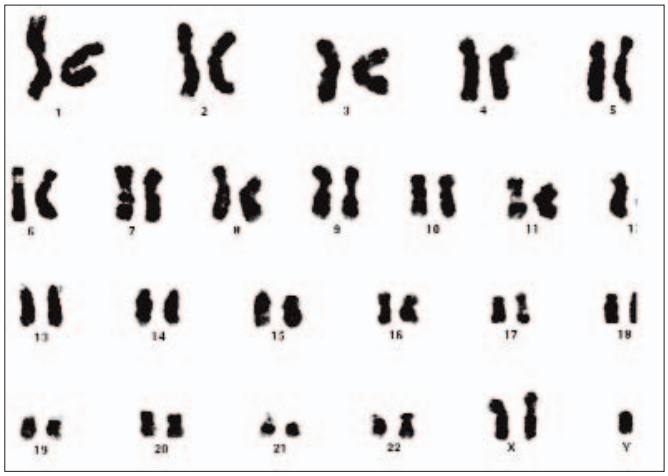

Figure 5: Cytogenetics report showing 47, XXY. Klinefelter Syndrome.

DISCUSSION

Recently, Anders Bojesen, *et al.* created a cohort of more than 800 Klinefelter Syndrome Subjects from the Danish Cytogenetic Central Register.[9] They subsequently used discharge diagnoses from the National Register of Patients to describe the morbidity in all the males diagnosed with KS in Denmark compared to an age-matched control group drawn randomly from the Danish Civil Register. They found a 69% increased risk in KS patients, of being admitted to hospital with any diagnosis. Only a minority (25%) of men suffering from KS were diagnosed, and most of them were diagnosed in adulthood.[10] They found an increased risk of malformations of the heart and the urinary tract. No previous studies reported an increased risk of congenital malformations apart from retention of the testes, which previously has been described in as many as 27% of KS subjects, referred to an infertility clinic.[4] Mitral leaflet prolapse has been the most frequently reported congenital malformation.[7] Hypertrophic cardiomyopathy has rarely been reported in association with Klinefelter syndrome.[8] Increased incidence of morbidity due to anaemia, cancers (breast cancer and mediastinal tumours mainly), type 1 and type 2 diabetes, obesity, metabolic syndrome, ischaemic heart disease and cerebrovascular disorders has frequently been reported in KS patients.[1,4,6]

In a cohort study of mortality in patients with Klinefelter syndrome in Britain, out of 461 deaths, 60 occurred due to ischaemic heart disease, 3 due to aortic valve disease, 5 due to congenital cardiac anomalies and 16 due to some other cardiac causes.[11]

Hypertrophic cardiomyopathy is a genetic disorder, which is inherited as an autosomal dominant disorder.[12] The hallmark of the disorder is myocardial hypertrophy, which is often asymmetric, and occurs in the absence of an obvious inciting hypertrophy stimulus. This hypertrophy can occur in any region of the left ventricle but frequently involves the interventricular septum, which results in an obstruction of flow through the Left Ventricular Outflow Tract (LVOT).[13] Overall incidence of HCM in general population is 0.05 to 0.2 percent.[12] Only one case report was found from Japan of an elderly man with Klinefelter syndrome associated with hypertrophic cardiomyopathy, sick sinus syndrome, and coronary arteriovenous fistula.[8] Symptoms can include sudden cardiac death, dyspnoea, syncope and presyncope, angina, palpitations, orthopnea, paroxysmal nocturnal dyspnoea, congestive heart failure and dizziness.[12] Sudden death in hypertrophic cardiomyopathy generally results from ventricular tachycardia or fibrillation.[14] The cornerstone of treatment for control of symptoms is beta-blockade therapy.

REFERENCES

1. Visootsak J, Graham JM Jr. Klinefelter syndrome and other sex chromosomal aneuploidies. *Orphanet J Rare Dis* 2006; **1**:42
2. Simpson JL, de la Cruz F, Swerdloff RS, Samango-Sprouse C, Skakkebaek NE, Graham JM Jr, *et al.* Klinefelter syndrome: expanding the phenotype and identifying new research directions. *Genet Med* 2003; **5**:460-8.
3. Simpson JL, Graham JM Jr, Samango-Sprouse C, Swerdloff R. Klinefelter syndrome. In: Cassidy SB, Allanson JE (eds). Management of genetic syndromes. 2nd ed. New York: *Wiley & Sons;* 2005.p.323-33.
4. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 2004; **364**:273-83.
5. Shen D, Liu D, Liu H, Clasen L, Giedd J, Davatzikos C. Automated morphometric study of brain variation in XXY males. *Neuroimage* 2004; **23**:648-53.
6. DeLisi LE, Maurizio AM, Svetina C, Ardekani B, Szulc K, Nierenberg J, *et al.* Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. *Am J Med Genet B Neuropsychiatr Genet* 2005; **135**:15-23.
7. Fricke GR, Mattern HJ, Schweikert HU. Mitral valve prolapse in Klinefelter syndrome. *Lancet* 1981; **2**:1414.
8. Yoshida K, Ryu T, Ogata T, Tsuji S, Tokushima T, Utsunomiya T, *et al.* An elderly man with Klinefelter syndrome associated with hypertrophic cardiomyopathy, sick sinus syndrome, and coronary arteriovenous fistula. *Jpn Circ J Mar* 1998; **62**:222-4.
9. Bojesen A, Juul S, Birkebaek NH, Gravholt CH. Morbidity in Klinefelter syndrome: A danish register study based on hospital discharge diagnoses. *J Clin Endocrinol Metab* 2006; **91**:1254-60.
10. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a National Registry Study. *J Clin Endocrinol Metab* 2003; **88**:622-6.
11. Swerdlow AJ, Higgins CD, Schoemaker MJ, Wright AF, Jackobs PA. United Kingdom Clinical Cytogenetics Group. Mortality in patients with Klinefelter syndrome in Britain: a cohort study. *J Clin Endocrinol Metab* 2005; **90**:6516-22.
12. Nishimura RA, Holmes DR Jr. Hypertrophic obstructive cardiomyopathy. *N Engl J Med* 2004; **350**:1320-7.
13. Lombardi R, Betocchi S. Aetiology and pathogenesis of hypertrophic cardiomyopathy. *Acta Paediatr Suppl* 2002; **91**:10-4.
14. Maron BJ, Olivotto I, Spirito P, Carey SA, Bellone P, Gohman TE, *et al.* Epidemiology of hypertrophic cardiomyopathy related death: revisited in a large non-referral-based patient population. *Circulation* 2000; **102**:858-64.