Leopard Syndrome

K L Tong, Z P Ding, T Chua

ABSTRACT

The Leopard syndrome is a complex of multi-systemic congenital abnormalities characterised by lentiginosis, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth and deafness (sensorineural). Hypertrophic cardiomyopathy, though not included in the mnemonic, is often associated. Although the Leopard syndrome is rare, it is important to recognise it since it can be associated with serious cardiac disease. It is advisable to follow up patients with Leopard syndrome for new onset of cardiac abnormalities and to monitor the progression of existing cardiac disease. We present a case report and review of the literature of this syndrome.

Keywords: Leopard syndrome, lentiginosis, hypertrophic cardiomyopathy

Singapore Med J 2001 Vol 42(7):328-331

INTRODUCTION

The acronym LEOPARD serves as a mnemonic for the classical features of this disorder, which consists of L, lentigines; E, electrocardiographic conduction abnormalities; O, ocular hypertelorism; P, pulmonary stenosis; A, abnormalities of genitalia; R, retardation of growth; D, deafness (sensorineural). Other reported abnormalities include mental retardation and more importantly, hypertrophic cardiomyopathy. Synonyms of Leopard syndrome include multiple lentigines syndrome, progressive cardiomyopathic lentiginosis and cardiocutaneous syndrome. Precise definition of this syndrome is difficult because of the absence of any pathognomonic morphologic or biochemical markers and its protean manifestations. We report a case of Leopard syndrome with typical cardiac involvement and review the literature.

CASE REPORT

The patient, a 39-year-old Chinese, was admitted with a complaint of palpitations. He had been noted to be dysmorphic, deaf and mute since infancy but was able to communicate using sign language. Since the age of 2 years, he developed numerous brownish spots over his body. At the age of 29 years, he was diagnosed to have hypertrophic cardiomyopathy following the discovery of a cardiac murmur. He was maintained on beta-blocker since then. He worked as a book binder with The Society for the Aid of the Paralysed.

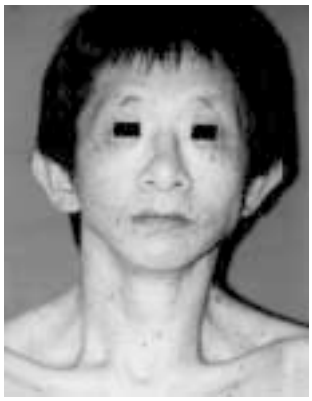

Fig. 1 Photograph of the patient showing multiple lentigines, hypertelorism, low-set ears and webbing of the neck.

On physical examination, he had numerous symmetrically distributed dark brown macules, involving the palms, soles, lips, scalp and buccal mucosa. His height was 1.52 m and his weight was 40 kg, giving a body mass index of 17.3 kg/m^2. He was mute and hearing tests confirmed the presence of profound sensorineural deafness.

His face was triangular in shape, with ocular hypertelorism and bilateral ptosis (Fig. 1). Ophthalmic examination revealed left retinal pigmentation and severe myopia in both eyes. There was webbing of the neck with low-set ears and winging of the scapulae.

Cardiac examination showed that he was in atrial fibrillation with a ventricular rate of 80 bpm. The blood pressure was 97/55 mmHg. The carotid pulse was not jerky. The apex beat was at the fourth intercostal space in the mid-clavicular line. There was a left parasternal heave. The first and second heart sounds were well heard. A pansystolic murmur, grade 3/6, was heard loudest over the left lower sternal edge, radiating to the apex.

The genitalia were normal. Both testes were descended. There was no hypospadius.

Department of Cardiology
National Heart Centre
Mistri Wing
17 Third Hospital Avenue
Singapore 168752

K L Tong, MBBS, MRCP (UK)
Registrar

Z P Ding, MBBS, MMed (Int Med), FAMS
Senior Consultant

T Chua, MMed (Int Med), FRCP (Lond), FAMS
Senior Consultant

Correspondence to:
Dr Terence Chua
Tel: (65) 436 7543
Fax: (65) 227 3562
Email: t.chua@pacific.net.sg

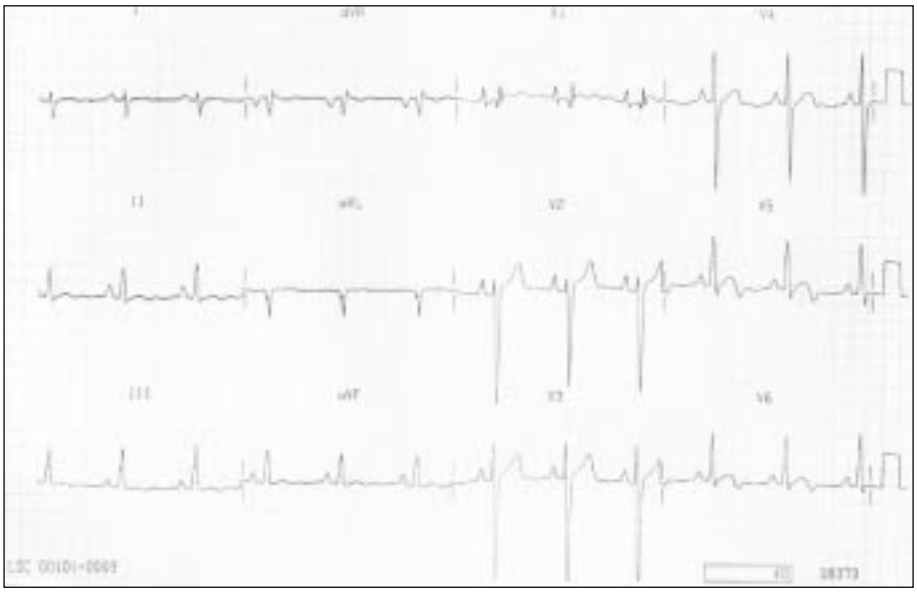

Fig. 2 Initial ECG in 1990 showing sinus rhythm with right axis deviation, p-pulmonale and right ventricular hypertrophy.

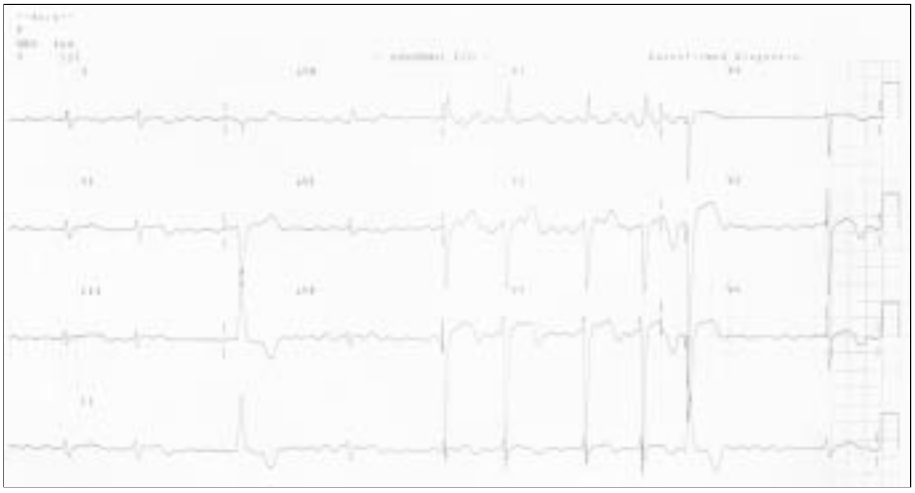

Fig. 3 ECG in December 1999 showing atrial fibrillation, ventricular ectopics, superior axis and partial RBBB.

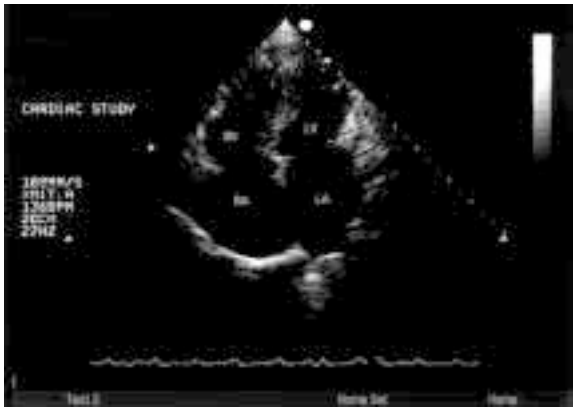

Fig. 4 2D echo showing biventricular hypertophy with biatrial dilatation.

A review of his previous electrocardiographs (ECG) showed that when first seen in November 1990, the 12 lead ECG showed normal sinus rhythm, right atrial enlargement, right axis deviation of 110 degrees and right ventricular hypertrophy (tall R in V1, S in I and V6) (Fig. 2). During follow up, subsequent ECGs showed left atrial enlargement and first degree heart block, and later, frequent ventricular ectopics. For the present admission in December 1999, the ECG showed new onset of atrial flutter-fibrillation. There was also a new partial right bundle branch block, with a superior axis of -140 degree (Fig. 3).

A previous transthoracic echocardiogram done in March 1992 showed non-obstructive hypertrophic cardiomyopathy with normal left ventricular systolic function. The left ventricle was thickened at the mid and apical segments. The right ventricle was moderately thickened. There was mild valvular pulmonary stenosis with moderately severe pulmonary regurgitation and mild post-stenotic dilatation of the main pulmonary artery. The tricuspid regurgitation was mild and pulmonary hypertension was not detected at that time.

When the transthoracic echocardiogram was repeated in December 1999, there was still marked biventricular

hypertrophy. Compared to the previous echocardiogram, both atria were more dilated (Fig. 4). The tricuspid regurgitation had worsened with an elevated right ventricular systolic pressure of 56 mmHg. Systolic blood pressure was 94 mmHg then. The pulmonary stenosis remained mild. The mitral inflow pattern was suggestive of restrictive left ventricular diastolic function.

Following his admission for atrial fibrillation, pharmacological cardioversion was attempted with intravenous amiodarone 300 mg 8 hourly. This was successful after 48 hours. He was anticoagulated initially with IV heparin for atrial fibrillation before cardioversion and was subsequently converted to oral warfarin. His INR was 2.04 before discharge.

On follow up one week later, he had remained asymptomatic and in sinus rhythm. Oral amiodarone 200 mg was maintained. Warfarin was then stopped.

A skin biopsy of one of the macules showed hyperpigmented elongated rete ridges, consistent with lentigines.

His parents were deceased and were reportedly unaffected. His mother died of carcinoma of the breast at the age of 68 years while his father died of pneumonia at the age of 88 years. He had two sisters aged 36 years and 41 years respectively. There was a history of several young deaths involving the father's siblings. However, no further detailed history was obtainable as there was no other contactable living relative.

In view of the possibility of a familial inheritance, a full physical examination, ECG and transthoracic echocardiogram were performed for the two sisters. Neither of his sisters had evidence of lentigines or any other abnormality attributable to Leopard syndrome. Both had normal ECGs and echocardiograms.

DISCUSSION

Gorlin[1] introduced the name 'Leopard' syndrome as a mnemonic in 1969 to describe the spotted appearance from lentiginosis in these patients. Our patient had lentiginosis, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis and sensorineural deafness but did not have abnormalities of genitalia. In addition, he had hypertrophic cardiomyopathy, which was not part of the original mnemonic but has been reported in numerous series[8,10].

The inheritance of this rare disorder is believed to be autosomal dominant with variable penetrance and expressivity. Our patient did have a vague history of early deaths on the paternal side. It is unfortunate that no further details can be obtained from the sisters. The physical examinations, ECGs and echocardiograms of both sisters were all normal. There have been sporadic cases of Leopard syndrome reported[2,8]. In a series of cases of obstructive hypertrophic cardiomyopathy and lentiginosis seen at the Mayo Clinic, detailed family studies showed no evidence of inheritance[9].

Theories regarding the pathogenesis of the Leopard syndrome are entirely speculative. Some investigators have suggested the possibility of a mutation in the embryonic neural crest. However, organs of mesodermal origin are also involved in this syndrome. Others have suggested that gene products from a mutant neuroectodermal cell population interact with cells of mesodermal origin to produce the multisystemic anomalies[7].

Lentigines are brown to black macules, usually 2 to 8 mm in diameter, but sometimes larger. They are distinguishable from freckles which appear later than lentigines and are induced by exposure to sunlight. They are often present on the face, scalp, limbs, palms, soles and genitalia; the mucosal membranes are usually spared. It can also be wrongly identified as café-au-lait spots which are found in neurofibromatosis and Albright's syndrome[10]. Biopsy of lentigines shows characteristic histological features of increased number of melanocytes per unit area of skin, accumulation of pigment in the dermis as well as the deeper layers of epidermis and prominent rete ridges. Gorlin et al had diagnosed Leopard syndrome without lentiginosis. However, Voron et al[6] felt that lentiginosis should be an essential feature of the Leopard syndrome to distinguish it from Noonan's syndrome. Our patient had innumerous dark brown to black macules which were confirmed histologically to be lentigines.

The presence of lentigines on his buccal mucosa and lips was unusual for Leopard syndrome. It is found in Name syndrome (Naevi, Atrial myxoma, Myxoid neurofibromata and Endocrine neoplasia), but the presence of dysmorphic features and the absence of subcutaneous myxomas help to differentiate our patient from this syndrome[10].

ECG abnormalites were frequently present in Leopard syndrome, in as much as 50% of the patients. The more common abnormalities are left axis deviation and right bundle branch block. Others include S123, S V1-5, RVH and/or LVH, right axis deviation, paroxysmal atrial tachycardia, premature ventricular ectopics and complete heart block[3-10]. Our patient demonstrated several classical ECG features of Leopard syndrome. The initial ECG changes of right ventricular hypertrophy and right atrial enlargement followed by the gradual development of conduction disturbances of right bundle branch block and first degree heart block illustrate very well the progressive nature of the underlying cardiomyopathy. ECG abnormalities are often asymptomatic and well tolerated, as in our patient. He only became symptomatic with the onset of atrial fibrillation. This emphasizes the importance of regular follow-up in patients with Leopard syndrome.

Ocular hypertelorism, bilateral ptosis and retinal pigmentation, which have been previously described in Leopard syndrome were also present in our patient. He had severe myopia, which was not previously reported in the literature.

Pulmonary stenosis, if present, is usually mild in Leopard syndrome[1-3]. Valvular pulmonary stenosis is the commonest anomaly, occurring in 40% of reported cases. It occurs either as typical pulmonary stenosis, or more commonly, as dysplastic pulmonary valves (three distinct cusps with no commissural fusion)[13]. Our patient had mild valvular pulmonary stenosis.

Hypertrophic cardiomyopathy, though uncommon, is a major concern in patients with Leopard syndrome since it is associated with arrhythmia and sudden death. It causes the greatest morbidity and has been responsible for the few deaths reported. Hence, it should be excluded in any patients with lentiginosis, systolic murmur and ECG abnormalities, regardless of symptoms[1-4,9,10]. It may progress and may appear later in life than the other features of the syndrome. Thus, any patient with lentiginosis should have cardiological assessment at regular intervals.

Hypertrophic cardiomyopathy usually involves the left ventricle, especially the interventricular septum. However, right ventricular hypertrophy with right ventricular outflow tract obstruction has been described in Leopard syndrome[7]. It had been suggested that right ventricular outflow tract obstruction from septal hypertrophy might have been mistaken for pulmonary stenosis in the initial reports of this syndrome and prior to the availability of echocardiography. Our patient's initial ECG was suggestive of right heart involvement.

Our patient was first documented to have hypertrophic cardiomyopathy in 1990 and has been on regular follow-up. His current admission was for atrial fibrillation which is a typical feature of progression of disease in hypertrophic cardiomyopathy. The onset of atrial fibrillation corresponds to the echocardiographic finding of an increase in the size of the atria and is associated with a worse prognosis.

Abnormalities of genitalia and retardation of growth were absent in our patient. Genital hypoplasia in males including a small penis and small, often undescended, testicles, are the commonest association. Our patient's body mass index was 17.3 kg/m^2, which indicated that he was underweight.

Sensorineural deafness is the rarest of the mnemonic features, occurring in 15-25% of reported cases. Our patient had bilateral profound sensorineural deafness which was first diagnosed in infancy.

The overall prognosis of patients with Leopard syndrome is determined by the presence of cardiac anomalies. In our patient who had hypertrophic cardiomyopathy with atrial fibrillation, the long term prognosis is guarded. The likelihood of recurrence of atrial fibrillation is high. The management of this patient is essentially the management of hypertrophic cardiomyopathy. In obstructive hypertrophic cardiomyopathy, calcium channel blockers and beta-blocker may reduce the left ventricular outflow tract gradient and the incidence of sudden death. Atrial fibrillation, if recurrent and persistent, will require anticoagulation for prophylaxis against cardioembolism.

He was also referred to the ENT surgeon for hearing tests with a possibility of equipping him with hearing aids.

CONCLUSION

Leopard syndrome is an unusual condition with protean manifestations. Although rare, the findings of lentiginosis should always alert one to the possibility of this syndrome and the need for thorough cardiac assessment. Cardiac disease can be progressive, and is associated with a worse prognosis. Thus, patients should be evaluated regularly. This case illustrates many of the classical findings in this syndrome and highlights the need to be alert to the possibility of cardiac abnormalities.

REFERENCES

1. Robert J. Gorlin, Ray C. Anderson, Michael Blaw. Multiple Lentigenes Syndrome. Amer J Dis Child. 1969; 117:652-62.
2. Robert J. Gorlin, Ray C. Anderson, James H. Moller. The Leopard Syndrome Revisited. Birth defects: Original Article Series. 1971; VII(4):110-5.
3. Douglas Pickering, Bernard Laski, D. C. Macmillan, Vera Rose. 'Little Leopard' Syndrome. Arch Dis in Childhood. 1971; 46:85-90.
4. Raphael F. Smith, Louis U. Pulicicchio, Alden V. Holmes. The Amer J Cardio. 1970; 501-6.
5. Annemarie Sommer, Stella B. Contras, Jo M. Craenen, Don M. Hosier. A Family Study of the Leopard Syndrome. Amer J Dis Child. 1971; 121:520-3.
6. David A. Voron, Hayes H. Hatfield, Ronald K. Kalkhoff. Multiple Lentigines Syndrome Case Report and Review of the literature. The American Journal of Med. 1976; 60:447-56.
7. Jane Somerville and R E. Bonham-Carter. The heart in lentiginosis. British Heart Journal. 1972; 34:58-66.
8. Seuanez H, Mane-Garzon F, Kolski R. Cardio-cutaneous syndrome (the 'Leopard' syndrome). Review of the literature and a new family. Clinical Genetics 1976; 9:266-76.
9. St. John Sutton, Abdul J. Tajik, Milio R. Giuliani, Gordon, Daniel Su. Hypertrophic cardiomyopathy and Lentiginosis: A Little Known Neural Ectodermal Syndrome. Am J Car 1981; 47:214-7.
10. Coppin BD, Temple IK. Multiple Lentigines Syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis) J Med Genet 1997; 34:582-6.
11. H L Chan. Cutaneous Manifestations of Cardiac Diseases. SMJ 1990; 31:480-5.
12. Sadollah Shamsadini, Hosein Abazardi, Farajollah Shamsadini. Leopard Syndrome. Lancet 1999; 354:1530.
13. Emil D. Koretzky, B.S. James H. Moller, Michael E. Korns, Colin J. Schwartz, Jesse E. Edwards. Congenital Pulmonary Stenosis Resulting from Dysplasia of Valve. Circulation 1969; Vol. XL:43-53.
14. Luis E. Alday, Eduardo Moreyra. Secondary hypertrophic cardiomyopathy in infancy and childhood. Am Heart J 1984; 108:996-1000.