Familial LEOPARD Syndrome With Hypertrophic Cardiomyopathy

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Multiple lentigines syndrome is an autosomal dominant inherited condition with variable expressivity that is also known as LEOPARD syndrome. LEOPARD stands for lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary valve stenosis, abnormalities of genitalia, retardation of growth, and deafness. LEOPARD syndrome most frequently develops secondary to a missense mutation of protein-tyrosine phosphatase nonreceptor type 11 gene, which encodes tyrosine phosphatase. The missense mutation p.Tyr279Cys can either occur as a de novo mutation or affect multiple family members. Although hypertrophic cardiomyopathy is not part of the LEOPARD acronym, it is the most frequent cardiac anomaly observed in this syndrome. The recognition of increased left or right ventricular wall thickness in patients with LEOPARD syndrome may have significant impact on their clinical course similar to classic hypertrophic cardiomyopathy, which may require septal reduction procedures for relief of left or right ventricular outflow tract obstruction or implantable cardioverter-defibrillator placement for sudden cardiac death prevention. We describe a case series of a family with diffuse lentigines and hypertrophic cardiomyopathy in which the son carries the protein-tyrosine phosphatase nonreceptor type 11 (p.Tyr279Cys) gene mutation and both the son and daughter underwent left ventricular myectomy at an early age. In conclusion, our case series of a family with LEOPARD syndrome illustrates the importance of recognizing hypertrophic cardiomyopathy as part of this syndrome. **(Am J Cardiol 2020;135:168−173)**

Multiple lentigines syndrome, also known as LEOPARD syndrome, is an autosomal dominant cardiocutaneous syndrome that has high penetrance with variable expressivity.[1] In 1968, Moynahan and Polani initially described a neuroectodermal association between hypertrophic cardiomyopathy phenotype and lentiginosis.[2] Subsequently, Gorlin et al in 1969 coined the term "LEOPARD" as an acronym for lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary valve stenosis, abnormalities of genitalia, retardation of growth, and deafness.[3] Although it is not included in the acronym, hypertrophic cardiomyopathy is the most frequent cardiac anomaly observed in LEOPARD syndrome, and this cardiac pathology should be promptly recognized in these patients.[1] We present a case series of a family with diffuse lentigines and hypertrophic cardiomyopathy to highlight issues in the clinical course and management of LEOPARD syndrome with increased myocardial wall thickness.

Case Series

Patient 1 (proband) is a 31-year-old man with a history of biventricular hypertrophy status postbiventricular myectomy at age 4 with numerous lentigines and some café au lait spots covering most of his face, trunk, arms, and upper body (Figure 1). His echocardiogram revealed atypical pattern of severe left ventricular hypertrophy of the mid lateral and apical left ventricular wall segments with a maximal thickness of 30 mm (Figure 1). Cardiac magnetic resonance imaging demonstrated a similar atypical pattern of left ventricular hypertrophy (Figure 1) with patchy delayed enhancement in the thickest segments (Figure 1). Genetic screening for the sarcomeric form of hypertrophic cardiomyopathy was negative; however, the patient tested positive for a heterozygous pathogenic variant of gene protein-tyrosine phosphatase nonreceptor type 11 (*PTPN11)* (p. Tyr279Cys). The proband patient's sister, Patient 2, also underwent left ventricular myectomy at 4 months of age for relief of severe subaortic stenosis and had numerous lentigines covering most of her body (Figure 2). Her echocardiogram demonstrated severe septal and apical hypertrophy with a maximum left ventricular septal wall thickness of 20 mm and apical hypertrophy of 17 mm (Figure 2). Cardiac magnetic resonance imaging redemonstrated hypertrophy of the basal anteroseptum and of the apical lateral and anterior walls with dense delayed enhancement of the apex (Figure 2). Patient 3, the mother of Patients 1 and 2, also had numerous

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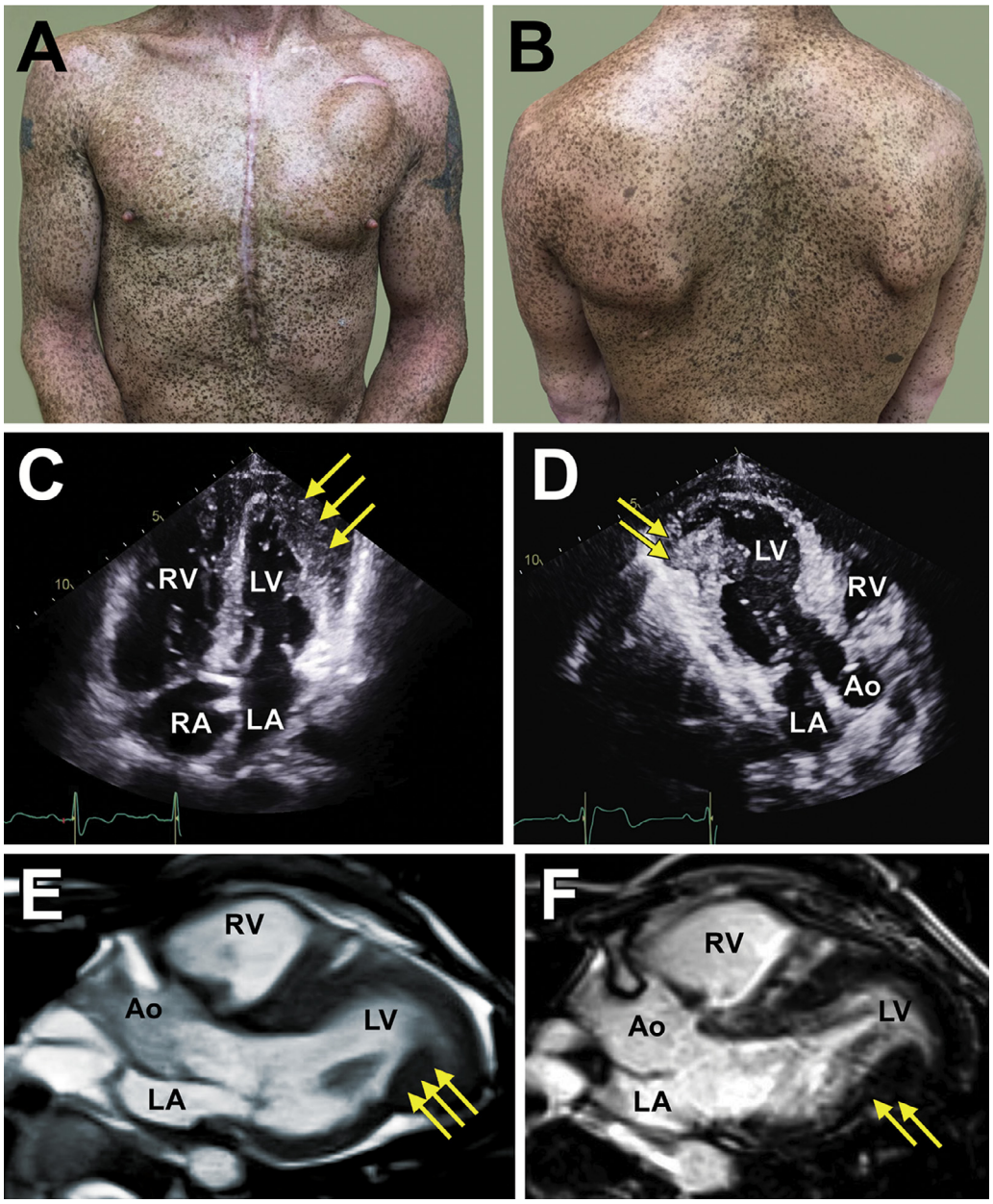

Figure 1. Patient 1 (Proband) *(A, B)* Numerous lentigines and a few scattered café au lait spots cover Patient 1's face (not shown), trunk, arms, and upper body. Echocardiography in the *(C)* apical 4-chamber and *(D)* apical 3-chamber views shows left ventricular hypertrophy of the mid lateral and apical left ventricular wall segments (arrows) with a maximal thickness of 30 mm. *(E)* The SSFP cine 3-chamber view redemonstrates an uncommon pattern of hypertrophic segments in the mid lateral and apical left ventricular walls (arrows) and *(F)* very subtle patchy late gadolinium enhancement of the hypertrophied segments (arrows). Photographs published with patient's permission. Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

lentigines scattered over her face, trunk, arms, and legs. Her echocardiogram showed basal septum and apical hypertrophy (Figure 3). Patient 3 underwent cardiac computed tomography angiography, which demonstrated a left ventricular apical "mass," likely representing an atypical form of severe left ventricular hypertrophy (Figure 3). Table 1 summarizes physical examination and imaging findings of the 3 patients with familial LEOPARD syndrome and hypertrophic cardiomyopathy. Electrocardiograms of the son (proband) and daughter are presented in Figures 4 and 5; findings are presented in Table 1.

Discussion

Diagnostic criteria for LEOPARD syndrome were proposed by Voron et al in 1976 and include lentigines and 2 other recognized features of LEOPARD syndrome or a first-degree relative with lentigines and 3 other features in the patient.[4] Typically, multiple lentigines appear during childhood and expand in number until puberty.[5]

The most common cardiac pathology that appears in LEOPARD syndrome is increased ventricular wall thickness.[6] This hypertrophic cardiomyopathy phenotype was

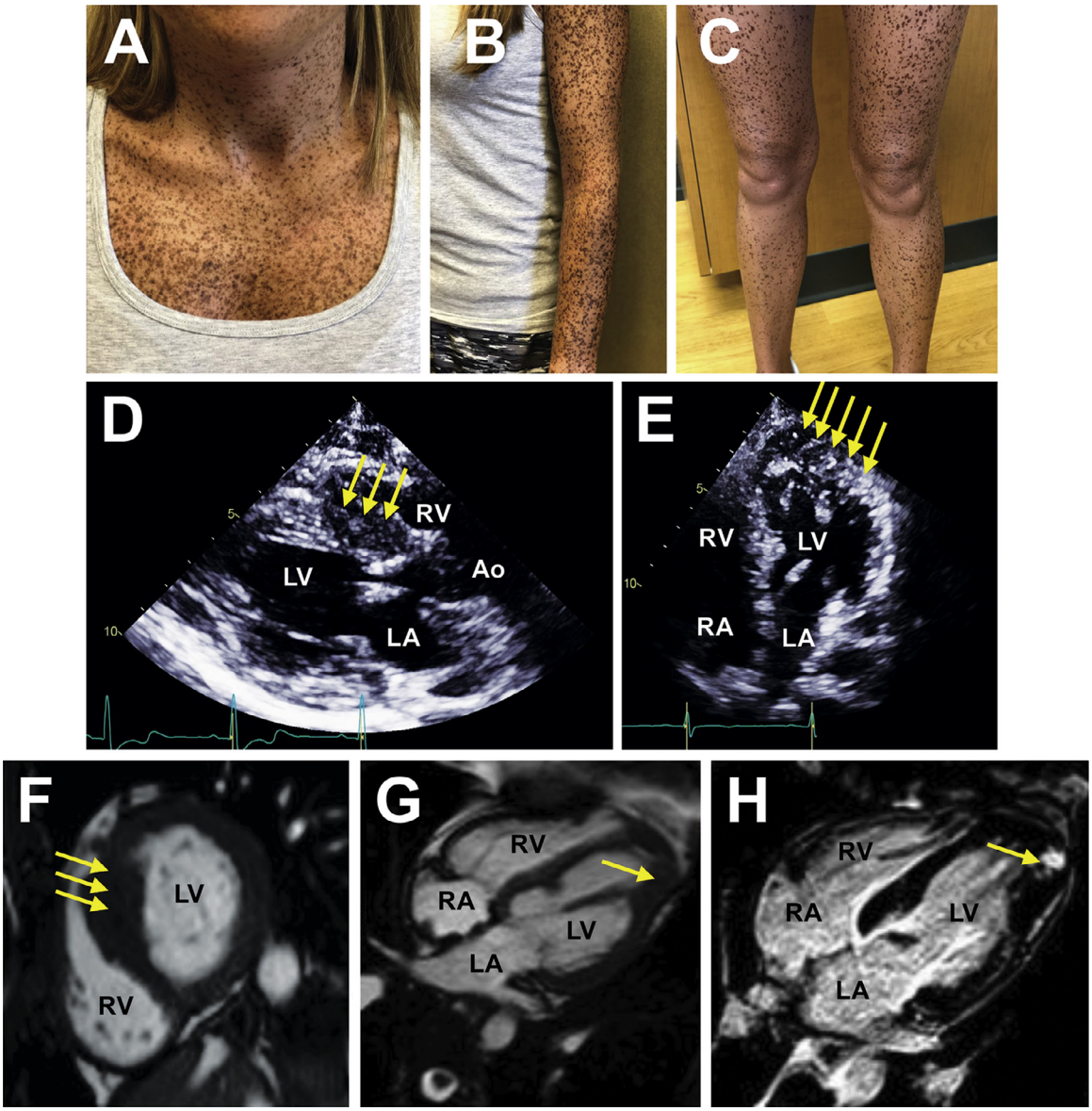

Figure 2. Patient 2 Numerous lentigines cover most of Patient 2's body, including *(A)* her trunk, *(B)* arms, *(C)* legs, and face (not shown). Echocardiography in the *(D)* parasternal long-axis view shows septal hypertrophy with maximal left ventricular septal wall thickness of 20 mm (arrows) and in the *(E)* apical 4-chamber view shows apical hypertrophy with maximal wall thickness of 17 mm (arrows). *(F)* A cardiac magnetic resonance SAX SSFP image shows hypertrophy of the basal anteroseptum (arrows) measuring 20 mm, and *(G)* an apical 4-chamber SSFP image shows apical lateral hypertrophy (arrow) measuring 17 mm with *(H)* dense late gadolinium enhancement involving apical segments (arrow). Photographs published with patient's permission. Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

described in 1972 by Somerville and Bonham-Carter on necropsy as severe obstructive hypertrophic cardiomyopathy,[7] and it has been reported to occur in ~70% of LEOPARD syndrome cases.[8] The pattern of increased wall thickness in LEOPARD syndrome may be typical, as demonstrated in our 2 patients who had the classic phenotype of obstructive hypertrophic cardiomyopathy and who underwent myectomies at an early age. It can also become atypical and present as apical hypertrophic pattern, which is evident now for all 3 of the family members. LEOPARD syndrome patients require detailed cardiac imaging with echocardiography or cardiac magnetic resonance to discern different patterns of hypertrophic cardiomyopathy. In addition to left ventricular hypertrophy, approximately 30% of patients can also develop right outflow tract hypertrophy with subsequent obstruction.[9] In an analysis of 48 multiple lentigines patients, the most common features were multiple lentigines, noted in 46 of 48 (92%) patients, followed by facial abnormalities and cardiovascular anomalies.[10] The dysmorphic features of LEOPARD syndrome patients include ocular hypertelorism; a broad, flat nose; low-set, posteriorly rotated ears; ptosis; and below-average height.[5] Additionally, patients can have urogenital abnormalities such as genital or ovary hypoplasia.[5] Deafness is the rarest, occurring only ~15% to 25% of the time.[11] The presence of lentigines and deafness are the 2 distinguishing features

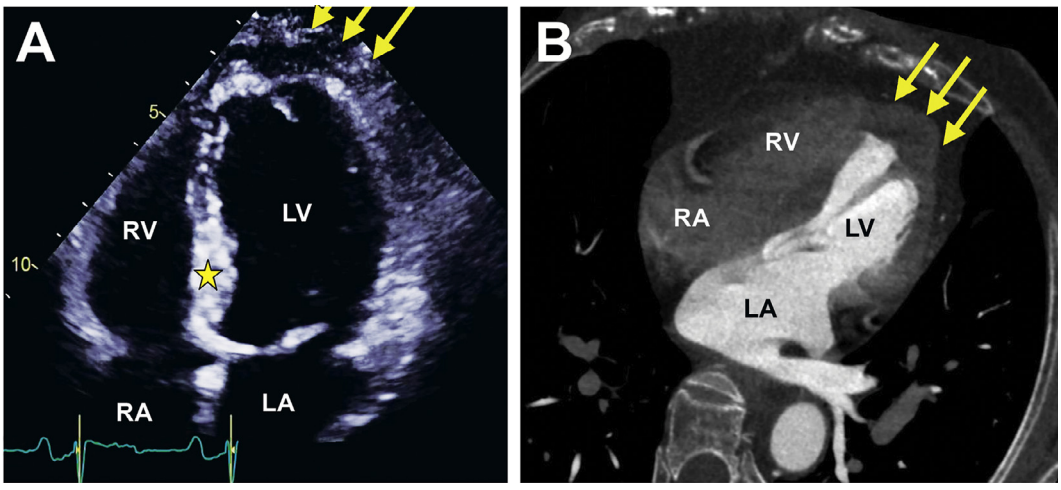

Figure 3. Patient 3 *(A)* An echocardiogram shows a prominent basal septum with a thickness of 14 mm (star) and apical hypertrophy (arrows). *(B)* Cardiac computed tomography angiography redemonstrates an atypical form of left ventricular hypertrophy (arrows). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Table 1
Clinical and imaging characteristics of 3 patients with familial LEOPARD syndrome

Variable	Patient 1 (proband, son)	Patient 2 (daughter)	Patient 3 (mother)
Lentigines	+	+	+
Age (years)	31	35	63
Sex	Male	Female	Female
Body weight (kg)	50.3	41.3	63.0
Height (cm)	157	152	163
BMI (kg/m^2)	20	17.7	23.8
Hypertelorism	+	+	–
Webbed Neck	–	–	–
Low set ears	+	–	–
Blood pressure (mm Hg)	118/54	122/56	118/78
Heart rate	84	82	75
LVEF	76	75	72
LV thickest segments location and measurements (mm)	Mid lateral wall and apex/30 and 30	Basal septal wall and apex/20 and 17	Apex/14
Muscle ridge in RVOT	+	+	–
History of septal myectomy	+ (LVOT)	+ (LVOT and RVOT)	–
LVOT obstruction at rest (mm Hg)	20	–	–
LVOT obstruction with Valsalva (mm Hg)	50	42	–
RVOT peak gradient (mm Hg)	25	–	–
History of pulmonary valve stenosis	+	–	–
Elongated anterior leaflet/SAM	+	+	–
Mitral regurgitation	Mild	Mild	Mild
Delayed gadolinium enhancement on CMR (%)	10	13	Not available
NSVT on Holter monitor	–	–	–
ICD for primary prevention	+	–	–
ECG*	SR, RBBB, LAD, LVH	SB, LVH, Lateral TWI	SR, LAD, IRBBB, Nonspecific ST T wave changes
PTPN11 gene	+	Not available	Not available
NT-proBNP	2222	1902	293
Troponin	–	–	–

* Corresponding ECG images are Figures 4 to 6.

BMI = body mass index; CMR = cardiac magnetic resonance imaging; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NSVT = nonsustained ventricular tachycardia; NT-proBNP = N-terminal pro brain natriuretic peptide; RVOT = right ventricular outflow tract; SAM = septal anterior motion.

in LEOPARD syndrome that separate it from Noonan syndrome, which is part of the differential diagnosis in these patients.[5]

It is thought that the pathogenesis of the syndrome stems from abnormality of the neural crest cells, which give rise to melanocytes and also form spinal, autonomic ganglion

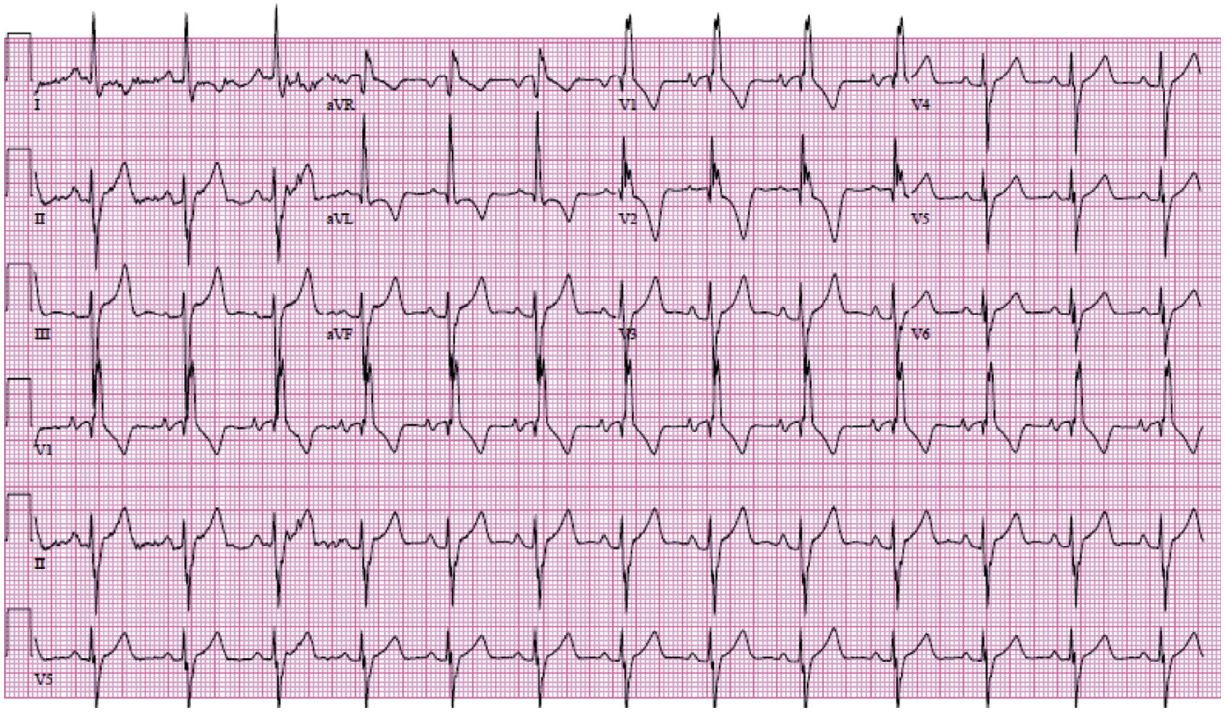

Figure 4. Patient 1 electrocardiogram Sinus rhythm, left-axis deviation, right bundle branch block, and left ventricular hypertrophy with repolarization abnormalities are seen.

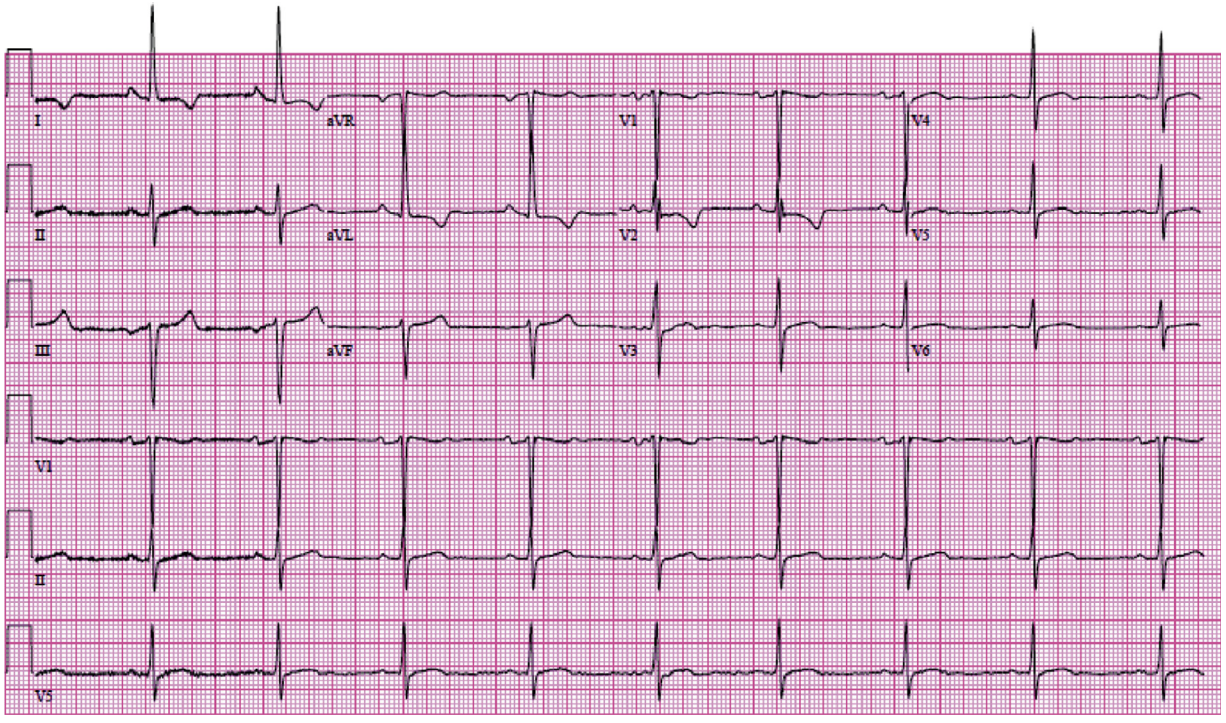

Figure 5. Patient 2 electrocardiogram Sinus bradycardia and left ventricular hypertrophy with repolarization abnormalities are seen.

cells, Schwann cells of peripheral nerves, and the sympathetic termination in the ventricles.[9]

The RAS/MAPK pathway proteins with germline mutations in their respective genes are connected with disorders such as Noonan, LEOPARD, neurofibromatosis type 1, Costello, and cardio-facio-cutaneous syndromes.[1] *PTPN11, RAF1,* and *BRAF* are the specific genes recognized to be associated with LEOPARD syndrome, with molecular genetic testing identifying the 3 gene mutations in about 95% of affected individuals.[1]

LEOPARD syndrome most frequently develops secondary to a mutation of *PTPN11* gene, which encodes tyrosine phosphatase (SHP-2), a cytoplasmic protein that regulates intracellular signaling and controls developmental processes.[12] In an estimated 85% of cases, a heterozygous missense mutation is detected in exon 7, 12, or 13.[13] From the identified missense mutations, there are specifically 2 (p. Tyr279Cys and p. Thr468Met) that account for 65% of the LEOPARD cases in the world.[10,13] The effects of *PTPN11* mutations on SHP-2 phosphatase activity are opposite in Noonan and LEOPARD syndromes, with gain of function noted in Noonan syndrome and loss of function in LEOPARD syndrome. The definition of Noonan syndrome is being expanded to include patients with lentiginosis, and increasingly LEOPARD syndrome is one of the RASopathies that is being classified as Noonan-like syndrome.[14]

In this family, the son carries the most common (p. Tyr279Cys variant) missense mutation. The missense mutation p.Tyr279Cys can either occur as a de novo mutation or affect multiple family members. In general, multiple lentigines, café au lait macules, ocular hypertelorism, palpebral ptosis, dysmorphic ears, and hypertrophic cardiomyopathy are hallmarks of the p.Tyr279Cys *PTPN11* mutation-related phenotype.[11]

Limongelli et al performed genotype-phenotype analysis and natural history of left ventricular hypertrophy in 24 patients with LEOPARD syndrome and found that 25% of patients had adverse cardiac events, including sudden death, resuscitated cardiac arrest, septal myectomy, and heart failure, during follow-up.[13] Therefore, it is important to identify increased ventricular wall thickness in LEOPARD syndrome as the hypertrophic cardiomyopathy phenotype may represent a risk factor for adverse cardiac events.

Similar to hypertrophic cardiomyopathy patients, LEOPARD syndrome patients should undergo sudden cardiac death risk stratification with echocardiography, cardiac magnetic resonance imaging, and ambulatory Holter monitoring. Also, comparable to hypertrophic cardiomyopathy, left or right ventricular outflow tract obstruction may occur in LEOPARD syndrome patients, potentially leading to left- or right-sided heart failure symptoms. In the same way as hypertrophic cardiomyopathy patients, LEOPARD syndrome patients may benefit from similar medical therapies or invasive septal reduction strategies such as myectomy or alcohol septal ablation for relief of symptoms. Prenatal diagnosis of hypertrophic cardiomyopathy phenotype in a fetus at risk for LEOPARD syndrome can be made as early as in utero.

Hypertrophic cardiomyopathy phenotype is the most common cardiac pathology in patients with multiple lentigines syndrome and, as in hypertrophic cardiomyopathy, may result in left or right ventricular outflow tract obstruction and even adverse cardiac events. Our case series of a family with LEOPARD syndrome illustrates the importance of recognizing it as part of this syndrome and implementing proper management.

Disclosures

The authors have no conflicts of interest to disclose.

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1. Martinez-Quintana E, Rodriguez-Gonzalez F. LEOPARD syndrome: clinical features and gene mutations. *Mol Syndromol* 2012;3:145–157.
2. Moynahan EJ, Polani P. Progressive profuse lentiginosis, progressive cardiomyopathy, short stature with delayed puberty, mental retardation or psychic infantilism, and other developmental abnormalities, a new familial syndrome. In: Jadassohn W, Schirren CG, eds. XIII Congressus Internationalis Dermatologiae., 2 Berlin: Springer-Verlag; 1968:1543–1544.
3. Gorlin RJ, Anderson RC, Blaw M. Multiple lentigenes syndrome. *Am J Dis Child* 1969;117:652–662.
4. Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigines syndrome. case report and review of the literature. *Am J Med* 1976;60:447–456.
5. Coppin BD, Temple IK. Multiple lentigines syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis). *J Med Genet* 1997;34:582–586.
6. Carcavilla A, Santomé JL, Pinto I, Sánchez-Pozo J, Guillén-Navarro E, Martín-Frías M, Lapunzina P, Ezquieta B. LEOPARD syndrome: a variant of Noonan syndrome strongly associated with hypertrophic cardiomyopathy. *Rev Esp Cardiol (Engl Ed)* 2013;66:350–356.
7. Somerville J, Bonham-Carter R. The heart in lentiginosis. *Br Heart J* 1972;34:58–66.
8. Gangiara N, Prabhu A, Kumar RS. LEOPARD synrome in an infant with severe hypertrophic cardiomyopathy and PTPN11 mutation. *Ann Pediatr Cardiol* 2011;4:74–76.
9. St John Sutton MG, Tajik AJ, Giuliani ER, Gordon H, Su WP. Hypertrophic obstructive cardiomyopathy and lentiginosis: a little known neural ectodermal syndrome. *Am J Cardiol* 1981;47:214–217.
10. Nemes E, Farkas K, Kocsis-Deak B, Drubi A, Sulak A, Tripolszki K, Dosa P, Ferenc L, Nagy N, Szell M. Phenotypical diversity of patients with LEOPARD syndrome carrying the worldwide recurrent p. Tyr279Cys PTPN11 mutation. *Arch Dermatol Res* 2015;307:891–895.
11. Sarkozy A, Conti E, Digilio MC, Marino B, Morini E, Pacileo G, Wilson M, Calabro R, Pizzuti A, Dallapiccola B. Clinical and molecular analysis of 30 patients with multiple lentigines LEOPARD syndrome. *J Med Genet* 2004;41:e68.
12. Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Patton MA, Kucherlapati RS, Gelb BD. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001;29:465–468.
13. Limongelli G, Sarkozy A, Pacileo G, Calabro P, Digilio MC, Maddaloni V, Gagliardi G, Di Salvo G, Iacomino M, Marino B, Dallapiccola B, Calabro R. Genotype-phenotype analysis and natural history of left ventricular hypertrophy in LEOPARD syndrome. *Am J Med Genet A* 2008;146A:620–628.
14. Kontaridis MI, Swanson KD, David FS, Barford D, Neel BG. PTPN11 (Shp2) mutations in LEOPARD syndrome have dominant negative, not activating, effects. *J Biol Chem* 2006;281:6785–6792.