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CASE REPORT

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Hypertrophic cardiomyopathy in an adult patient with Noonan syndrome with multiple lentigines

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Key Clinical Message

Noonan syndrome with multiple lentigines (NSML) is a rare RASopathy caused by pathogenic variants (PV) predominantly in *PTPN11* gene. We report a 54-year-old male with apical hypertrophic cardiomyopathy, who was diagnosed with NSML due to his short stature, multiple lentigines, winged neck, pectus excavatum, and a heterozygous PV in *PTPN11* c.836A > ¡G.

KEYWORDS

LEOPARD syndrome, Mexico, Noonan syndrome with multiple lentigines, PTPN11, RASopathy

1 | INTRODUCTION

Noonan syndrome with multiple lentigines (NSML, OMIM #151100), previously known as LEOPARD syndrome, is an autosomal dominant RASopathy caused by pathogenic variants (PV) in the *PTPN11* gene, which codes for a protein tyrosine phosphatase nonreceptor type 11.[1] However, some studies have reported NSML patients with PV in *RAF1*, *BRAF*, and *MAP2K1*.[2] Prevalence is currently unknown, and only about 200 cases have been reported worldwide. Other than NSML, the RASopathy group includes Noonan Syndrome, Neurofibromatosis type 1, and Neurofibromatosis type 1-like syndrome. The common pathophysiology is a Ras/mitogen-activated protein kinase (MAPK) pathway dysregulation. They all result in an overlapping phenotype, which includes facial dysmorphism and cardiac and cutaneous manifestations.[3] NSML phenotype is remarkable for multiple lentigines, which present during infancy and increase in number by puberty, heart disease (in 85%), short stature (in <50%), sensorineural hearing deficit (in 20%), and mild intellectual disability (in 30%).[1] The most commonly reported heart disease in NSML is hypertrophic cardiomyopathy (HCM) in 70%–80% of the cases and pulmonary valve

stenosis in 25%.[4] Other less frequent manifestations include cryptorchidism, skeletal abnormalities, and café au lait macules.

We report the first Mexican patient with a heterozygous PV in *PTPN11* and NSML in a 54-year-old male, contributing to the genotype and phenotype of RASopathies in the Mexican population. In addition, we highlight the importance of suspecting a RASopathy in the context of HCM when accompanied by short stature and syndromic features, such as hypertelorism, downslanted palpebral fissures, and low-set ears.

2 | CASE REPORT

We present the case of a 54-year-old Mexican man, born to healthy nonconsanguineous parents from an uneventful pregnancy. Strabismus was noted and was surgically corrected at 2 years of age. During infancy, multiple flat brown macules became evident, located predominantly in the face and trunk. Psychomotor development was normal.

At 50 years of age, in perioperative studies for surgical correction of umbilical and bilateral inguinal hernias, an electrocardiogram (ECG) was found with T-wave inversion in the leads 1, V1-V6 and increased voltage in precordial leads; this was complemented with a transthoracic echocardiogram in which apical HCM was evidenced with ventricular cavity with the morphology of ace of spades and increased septal thickness at the apical level up to 21 mm. In addition, a 24-h Holter showed ventricular extrasystoles in 5.8% of the beats and 15 episodes of nonsustained ventricular tachycardia of up to 13 beats with a right bundle branch block morphology.

A cardiac magnetic resonance was performed (Figure 1), consistent with apical HCM, with a left ventricular ejection fraction of 55%, and late enhancement was found in 16.6 g equivalent to fibrosis in 19.6% of the mass. Based on the American Heart Association 5-year sudden death calculator (6.25% risk), he was considered a candidate for implantable cardioverter defibrillator placement, performed without complications at age 53.

Due to these findings, he was referred to the genetics consult for the diagnostic approach of HCM. Physical

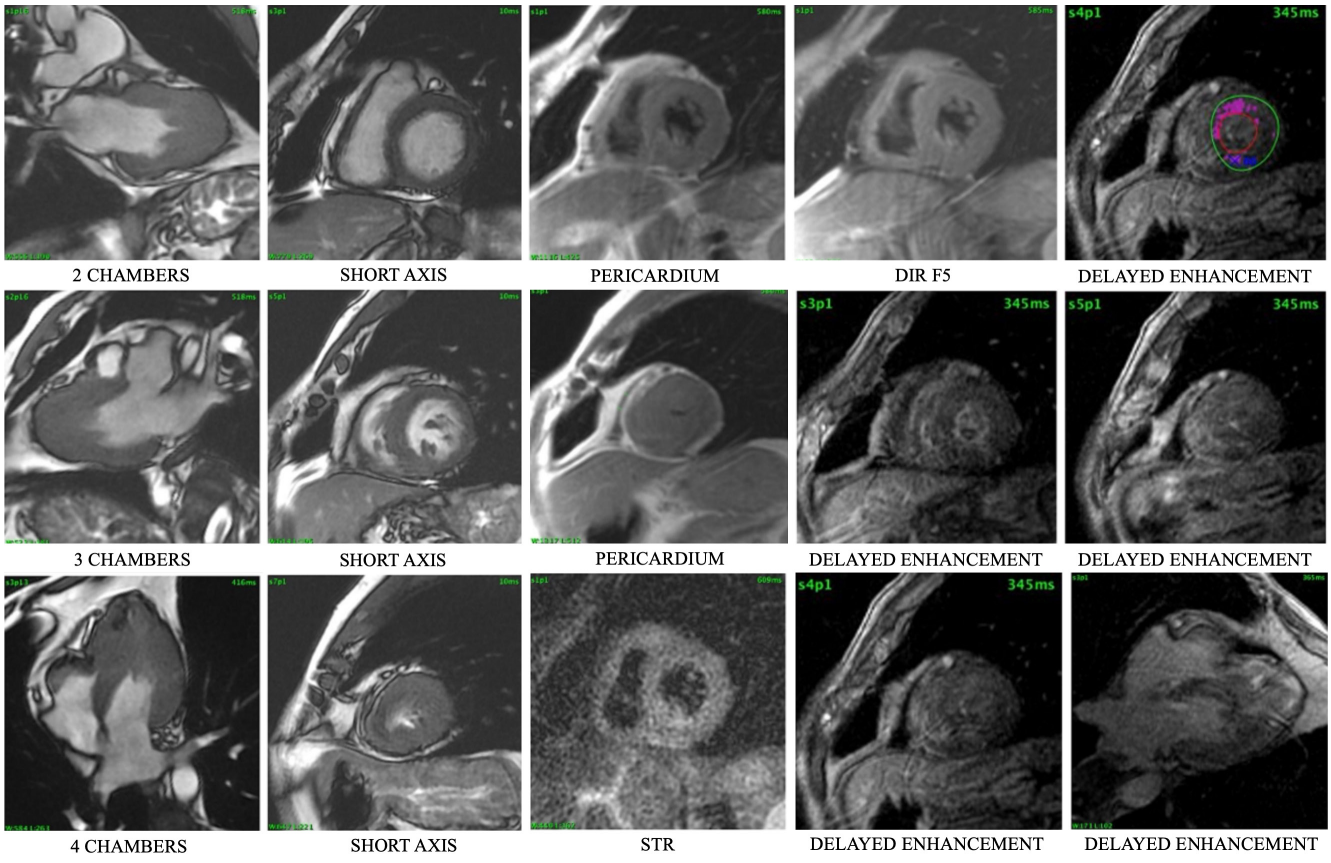

FIGURE 1 Cardiac MRI of a patient with Noonan syndrome with multiple lentigines. Apical hypertrophic heart disease. Abnormal myocardial viability study in relation to fibrosis in a zone of hypertrophy. Diffuse late mesocardium basal anteroseptal, anterior and middle anteroseptal, and apical and transmural strengthening of the apex. The late reinforcement adds 16.6 g, equivalent to 19.6% of the mass. Left ventricular ejection fraction conserved 55%. Right ventricular ejection fraction conserved 61%. Presence of an apex aneurysm.

examination was remarkable for short stature of 163 cm (height potential: 171.5 cm), high anterior hairline, downslanted palpebral fissures, hypertelorism, long depressed philtrum, prominent nasolabial folds, low-set ears, winged neck, pectus excavatum, wide-spaced nipples, and multiple lentigines (Figure 2). NSML was suspected; therefore, a panel of genes associated with RASopathies using next-generation sequencing was performed, finding a heterozygous pathogenic variant in *PTPN11* c.836A>G (p.Tyr279Cys), confirmed with Sanger sequencing. Extension studies were carried out on siblings and parents, which were all negative, establishing that the variant is de novo. The patient has no offspring. The evaluation of comorbidities included an audiometry which revealed no hearing impairment, and a spinal X-ray that showed accentuated lordosis.

3 | DISCUSSION

To our knowledge, this is the first case of NSML of Mexican origin with a confirmatory molecular test and a PV in *PTPN11*. Rodríguez Cruz et al.[5] reported a case of a 21-year-old patient with NSML phenotype and pulmonary stenosis. Revollo-Guerra et al.[6] described a case of overlap syndrome with NSML and neurofibromatosis.

The PV identified in the patient, *PTPN11* c.836A>G, is a missense mutation that produces a change in the protein from a tyrosine to a cysteine in the amino acid position 279. It is located at exon 7 and was first described by Tartaglia et al in 2001 in patients with Noonan syndrome (NS)[7] and was later associated with NSML syndrome by Digilio et al.[8] It is considered a recurrent PV highly specific to NSML.[9]

The pathogenesis of NSML is due to neural crest cell abnormalities since they give rise to melanocytes, spinal autonomic ganglion cells, and Schwann cells of peripheral nerves. Also, they participate in the formation of the structures derived from the arterial pole of the developing heart, the great arterial vessels, and their collateral branches, as well as in their innervation and conduction system.[1]

The molecular differences between NS and NSML have been previously described.[10,11] PTPN11 protein comprises three functional domains: N-SH2, C-SH2, and tyrosine phosphatase (PTP). The PVs associated with NS, which are mostly located between the N-SH2 and protein PTP domains, induce an elevated enzymatic activity and increased RAS/ERK activation. In contrast, the NSML PTPN11-PV are usually located at the PTP domain residue, leading to a decrease in catalytic activity, and thus,

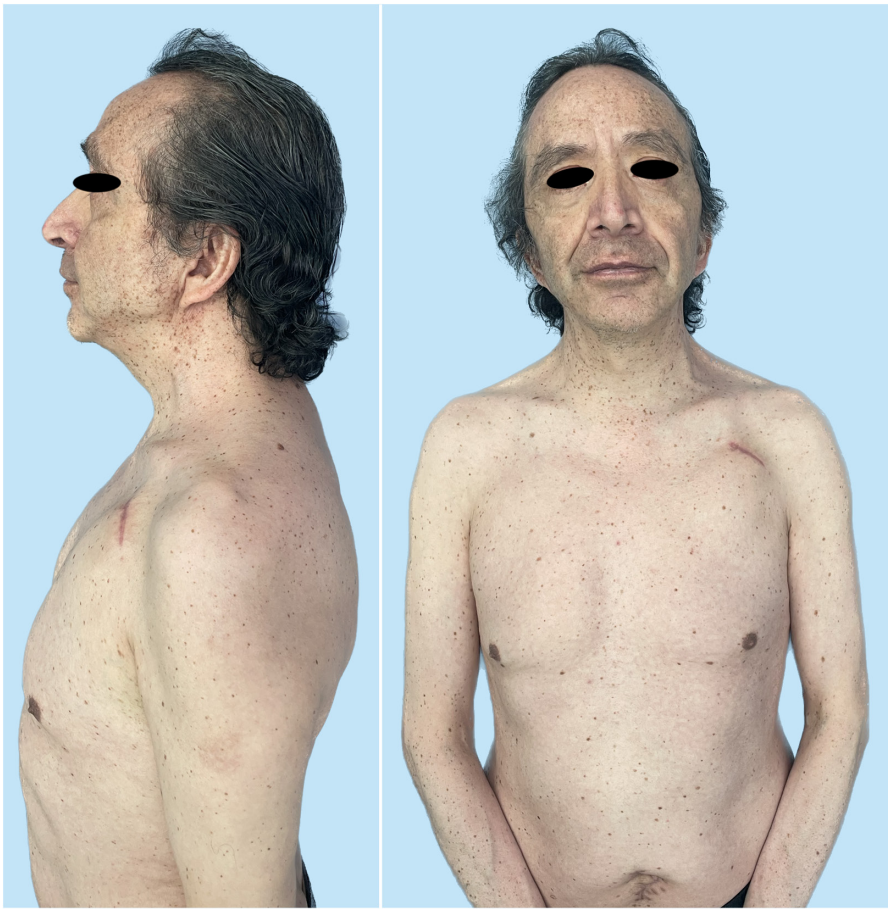

FIGURE 2 Mexican patient with Noonan syndrome with multiple lentigines.

a lower RAS/ERK activation.[12] Also, studies in mice with the *PTPN11* c.836A>G variant have found a dominant negative effect in other cell types.[10]

Our patient presented bilateral inguinal and umbilical hernias. Although not considered part of the NSML spectrum, we found four cases of Noonan syndrome associated with inguinal hernias.[13–16] Even though one out of four men will develop a symptomatic inguinal hernia, recently it was found that the PTPN11 protein is related to hernia development along with PIK3R1, TGFBR1, CDC42, and SOS1 proteins.[17]

Hypertrophic cardiomyopathy has a prevalence of one out of 500 adults in the general population.[18] However, it is strongly associated with NSML,[4] present in up to 80% of patients with this syndrome, the highest rate among the RASopathies.[19] ECG findings associated with HCM are T-wave inversion and large precordial voltage (as seen in our patient), ST depression, and pathologic Q waves, among others.[20] Early diagnosis is critical since sudden death associated with HCM is the main cause of mortality in NSML. Studies have shown that defibrillator implantation is successful in aborting life-threatening ventricular arrhythmia in HCM and is recommended as primary prevention in high-risk patients.[21] Another important comorbidity found in patients with PV in *PTPN11* is cancer, predominantly hematologic neoplasias (such as juvenile myelomonocytic leukemia and acute myeloid leukemia) and solid tumors, including neuroblastoma and rhabdomyosarcoma. Jongmans et al found a 23% cumulative risk for developing cancer of 23%, which is 3.5-fold higher than the general population.[22]

Our report reinforces the importance of suspecting NSML in cases presenting with HCM, short stature, and lentigines. The molecular test can aid in the diagnosis of specific RASopathies due to overlapping symptoms between them.

AUTHOR CONTRIBUTIONS

Pamela Rivero-García: Conceptualization; investigation; supervision; writing – original draft; writing – review and editing. **Jorge Humberto Hernandez-Felix:** Conceptualization; investigation; writing – review and editing. **Isabel Del Carmen Campuzano-Estrada:** Conceptualization; investigation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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REFERENCES

1. Santoro C, Pacileo G, Limongelli G, et al. LEOPARD syndrome: clinical dilemmas in differential diagnosis of RASopathies. *BMC Med Genet*. 2014;15:44. doi:10.1186/1471-2350-15-44
2. Koudova M, Seemanova E, Zenker M. Novel BRAF mutation in a patient with LEOPARD syndrome and normal intelligence. *Eur J Med Genet*. 2009;52(5):337-340. doi:10.1016/j.ejmg.2009.04.006
3. Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. *Curr Opin Genet Dev*. 2009;19(3):230-236. doi:10.1016/j.gde.2009.04.001
4. Carcavilla A, Santomé JL, Pinto I, et al. LEOPARD syndrome: a variant of Noonan syndrome strongly associated with hypertrophic cardiomyopathy. *Rev Esp Cardiol (Engl Ed)*. 2013;66(5):350-356. doi:10.1016/j.rec.2012.09.015
5. Rodríguez Cruz R, López Gómez L, Valle Molina L. Síndrome de Leopard asociado a estenosis pulmonar. *Rev. Medica del Hosp.* 2011;78(3):179-181.
6. Revollo-Guerra IM, Vázquez-Román R. Síndrome de superposición. LEOPARD con neurofibromatosis. Reporte de caso [Overlap syndrome. LEOPARD and neurofibromatosis. A case report]. *Rev Med Inst Mex Seguro Soc*. 2017;55(4):540-543.
7. Tartaglia M, Mehler EL, Goldberg R, et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet*. 2001;29(4):465-468. doi:10.1038/ng772
8. Digilio MC, Conti E, Sarkozy A, et al. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. *Am J Hum Genet*. 2002;71(2):389-394. doi:10.1086/341528
9. Zhang J, Shen J, Cheng R, et al. Identification of a PTPN11 hot spot mutation in a child with atypical LEOPARD syndrome. *Mol Med Rep*. 2016;14(3):2639-2643. doi:10.3892/mmr.2016.5547
10. Qiu W, Wang X, Romanov V, et al. Structural insights into Noonan/LEOPARD syndrome-related mutants of protein-tyrosine phosphatase SHP2 (PTPN11). *BMC Struct Biol*. 2014;14:10. doi:10.1186/1472-6807-14-10

11. Martínez-Quintana E, Rodríguez-González F. LEOPARD syndrome: clinical features and gene mutations. *Mol Syndromol*. 2012;3(4):145-157. doi:10.1159/000342251
12. Tartaglia M, Martinelli S, Stella L, et al. Diversity and functional consequences of germline and somatic PTPN11 mutations in human disease. *Am J Hum Genet*. 2006;78(2):279-290. doi:10.1086/499925
13. Shibata Y. An adult case of Noonan syndrome associated with persistent right primitive olfactory artery and Vertebrobasilar artery hypoplasia. *Int J Radiol*. 2018;5(1):177-178.
14. Kumar V, Goswami A, Anand S, et al. Noonan syndrome with plastic bronchitis in an adult. *HSOA J Pulm Med Respir Res*. 2021;7(1):58-61. doi:10.24966/pmrr-0177/100058
15. Moreno-Loaiza O, Flores-Lovon K, Montes-Madariaga ES. Síndrome de Noonan e insuficiencia aórtica severa en un paciente adulto. *Rev Cuba Med Gen Integr*. 2020;36(4):e1324.
16. Van den Berg H, Schreuder WH, Jongmans M, van Bommel-Slee D, Witsenburg B, de Lange J. Multiple giant cell lesions in a patient with Noonan syndrome with multiple lentigines. *Eur J Med Genet*. 2016;59(8):425-428. doi:10.1016/j.ejmg.2016.05.013
17. Mao Y, Chen L, Li J, Shangguan AJ, Kujawa S, Zhao H. A network analysis revealed the essential and common downstream proteins related to inguinal hernia. *PLoS One*. 2020;15(1):e0226885. doi:10.1371/journal.pone.0226885
18. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary artery risk development in (young) adults. *Circulation*. 1995;92(4):785-789. doi:10.1161/01.cir.92.4.785
19. Gelb BD, Roberts AE, Tartaglia M. Cardiomyopathies in Noonan syndrome and the other RASopathies. *Prog Pediatr Cardiol*. 2015;39(1):13-19. doi:10.1016/j.ppedcard.2015.01.002
20. Pelto H, Owens D, Drezner J. Electrocardiographic findings suggestive of cardiomyopathy: what to look for and what to do next. *Curr Sports Med Rep*. 2013;12(2):77-85. doi:10.1249/JSR.0b013e3182874abb
21. Francia P, Olivotto I, Lambiase PD, Autore C. Implantable cardioverter-defibrillators for hypertrophic cardiomyopathy: the times they are a-Changin. *Europace*. 2022;24(9):1384-1394. doi:10.1093/europace/euab309
22. Jongmans MC, van der Burgt I, Hoogerbrugge PM, et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. *Eur J Hum Genet*. 2011;19(8):870-874. doi:10.1038/ejhg.2011.37

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