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CASE REPORT

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Co-occurrence of hypertrophic cardiomyopathy and juvenile myelomonocytic leukemia in a neonate with Noonan syndrome, leading to premature death

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Key Clinical Message

We report a case of a neonate with Noonan syndrome presenting with concurrent hypertrophic cardiomyopathy and juvenile myelomonocytic leukemia, which resulted in premature death. Cases with Noonan syndrome diagnosed during the neonatal period might not necessarily show mild clinical course, and premature death is a possible outcome to be considered.

KEYWORDS

hypertrophic cardiomyopathy, juvenile myelomonocytic leukemia, Noonan syndrome, p.Thr42Ala, premature death

1 | BACKGROUND

Noonan syndrome (NS) is an autosomal-dominant disease characterized by distinctive facial dysmorphism, congenital heart disease (CHD), hypertrophic cardiomyopathy (HCM), short stature, webbed neck, cryptorchidism, skeletal abnormalities, and hematologic disorders[1,2] Recent evidence revealed that gain-of-function germline mutations affecting components of the RAS-mitogen-activated protein kinase (MAPK) signaling pathways are involved in NS. *PTPN11* mutations (40%-50%), *SOS1* mutations (10%-20%), *RAF1* (3%-17%), and *RIT1* (9%) are common, followed by *KRAS*, *NRAS*, *BRAF*, *SHOC2*, *MAP2K1*, *CBL, LZTR1, SOS2, RRAS, and CDC42*.[1-9]

The prognosis of NS is generally favorable, and cases with fatal outcomes are rarely reported. Pulmonary stenosis (PS) (57%) is the most common type of CHD in individuals with NS, followed by atrial septal defect (ASD; 32%), and HCM (16%).[10,11] *PTPN11* mutations are predominantly associated with PS and ASD, while HCM is less prevalent.[10-13] HCM is associated with mutations in exons 7 and 12 of *PTPN11*.[14,15] Myeloproliferative disease (MPD) and juvenile myelomonocytic leukemia (JMML) are other relatively common manifestations of patients with NS with germline *PTPN11* mutations.[16,17]

So far, only two neonates with NS presenting with concurrent HCM and MPD with p.Thr73Ile and p.Arg498Trp have been reported in the literature.[18,19] Furthermore, the co-occurrence of HCM and JMML in patients with NS leading to premature death has never been reported before. Here, we report a unique case of a neonate with NS with p.Thr42Ala mutation in *PTPN11* presenting with concurrent HCM and JMML, that resulted in premature death.

2 | METHODS

The study was approved by the Ethics Committee on Medical Research of Tohoku University, Sendai, Japan. Informed consent was obtained from the guardians with regard to conducting molecular diagnosis. All exons of *PTPN11* and *KRAS*; exons 7, 14, and 17 of *RAF1*; and exon 1 of *SHOC2* were analyzed by direct sequencing using peripheral blood and bone marrow cells.

3 | CLINICAL CASE REPORT

The patient was the first son of healthy and nonconsanguineous Japanese parents. The primigravida mother was 37 years old. Fetal ultrasonography showed right pleural effusion at 33 weeks of gestation. The patient was delivered vaginally at 39 weeks of gestation with a birth weight of 3190 g, body length of 46.0 cm, and head circumference of 33.8 cm. There was no family history of NS, any heart disease, or early death during early infancy. The one- and five-min Apgar scores were 8 and 9, respectively. Meconium staining of amniotic fluid was observed. After birth, the patient was admitted to the neonatal intensive care unit owning to respiratory failure. The patient's respiratory effort was stabilized within 2 days with oxygen supplementation. The patient was noted to have down-slanted palpebral fissures, hypertelorism, short nose with depressed root, unilateral cryptorchidism, micropenis, and hepatosplenomegaly, suggesting NS. Echocardiography showed HCM with an intraventricular septum of 6.0 mm (*Z* score: +2.4) and a left ventricular posterior wall dimension of 3.0 mm at end-systolic phase (*Z* score: +1.1), bicuspid aortic valve, and ASD (Figure 1A,B). Cardiac function was within the normal range with a percent fractional shortening of 36%, a left ventricular end-systolic dimension of 9.0 mm, and a left ventricular end-diastolic dimension of 14.0 mm. Peripheral blood analysis at birth showed increased white blood cell (WBC) counts of 18×10^9/L with 1.0% blasts, increased absolute monocyte counts of 1.6×10^9/L, and decreased platelet counts of 22×10^9/L. These hematological abnormalities persisted during the first 2 months of life in the range of WBC counts of 10-20 $\times 10^9$/L with 1%-3% blasts, absolute monocyte counts of 2-4 $\times 10^9$/L, and platelet counts of 20-80 $\times 10^9$/L. Fetal hemoglobin at day 29 was 68.4% of the red blood cells, which was appropriate for his age. Bone marrow aspiration analysis by Giemsa staining at day 30 showed absolute nucleated cell counts of 313×10^9/L with no obvious blasts, decreased erythroid cells of 4.4%, myeloid cells of 32.1% (myeloblasts: 1.5%,

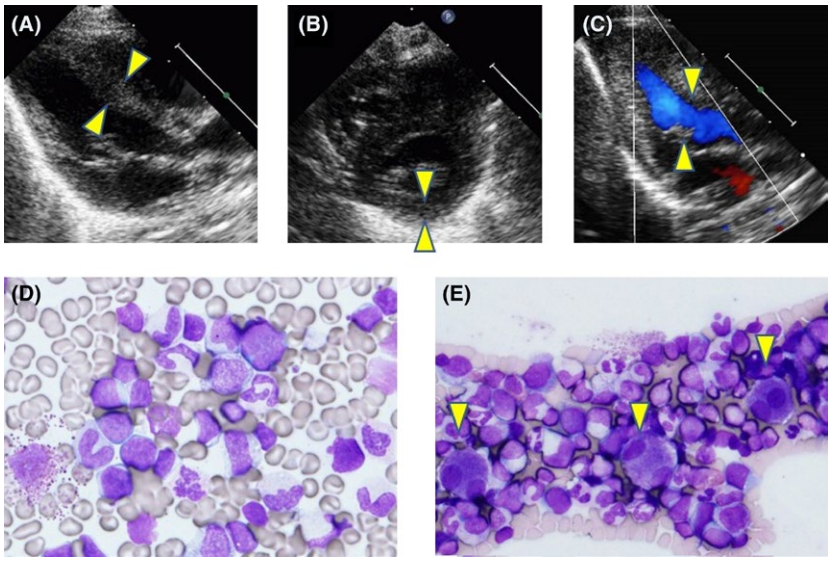

FIGURE 1 Echocardiography of the long (A) and short (B) axes at birth that shows HCM with an intraventricular septum (arrowheads) of 6.0 mm and a left ventricular posterior wall dimension (arrowheads) of 3.0 mm at end-systolic phase. (C) Color Doppler echocardiography of the left ventricle at day 28 shows a pressure gradient of 20 mm Hg in the mid-ventricle (arrowheads). Giemsa staining of the bone marrow aspirate at day 30 shows decreased erythroid cells (D) and binucleated micromegakaryocytes (arrowheads) (E)

promyelocytes: 1.4%, myelocytes: 5.6%, metamyelocytes: 5.0%, band: 9.8%, seg: 5.9%, and monocytes: 4.9%), and lymphocytes of 58.8% (Figure 1D). Binucleated micromegakaryocytes were noted although no obvious dysplasia was observed in other cell lineages (Figure 1D,E). The patient's peripheral blood mononuclear cells displayed spontaneous granulocyte-macrophage (GM) growth and hypersensitivity to GM colony stimulating factor. G-banding analysis showed a normal karyotype of 46, XY. Based on the absence of *BCR/ABL1*, $>1 \times 10^9$/L circulating monocytes, <20% blasts in the peripheral blood and bone marrow, and presence of splenomegaly, he was diagnosed with JMML. After obtaining informed consent from his parents, we performed Sanger-sequencing analysis of blood and bone marrow cells and identified a heterozygous missense mutation of c.124 A > G (p.Thr42Ala) in exon 2 of *PTPN11*. Accordingly, the diagnosis of NS was confirmed. Echocardiography at day 28 showed a pressure gradient of 20 mm Hg at the mid-portion of the left ventricle, which could be responsible for the pale appearance of the patient during crying (Figure 1C). He did not demonstrate arrhythmia during hospitalization. The patient was discharged at day 30 without medication. The patient was doing well, with a WBC count of 7.6×10^9/L with 1.0% blasts, absolute monocyte counts of 1.3×10^9/L, and platelet counts of 75×10^9/L at day 64. However, on day 69, the patient died suddenly at home just after feeding. Consent for an autopsy could not be obtained from the guardians. We assumed that the cause of death might be cardiogenic, such as fatal arrhythmia, because hematologic abnormalities and hepatosplenomegaly were not progressed after day 30.

4 | DISCUSSION

Here, we report a unique case of a neonate with NS with c.124 A > G (p.Thr42Ala) mutation in exon 2 of *PTPN11* presenting with concurrent JMML and HCM, leading to sudden death at 2 months of age.

JMML/MPD is observed in 5.6% of patients with NS associated with germline *PTPN11* mutations, which may regress spontaneously or follow an aggressive clinical course.[16,17] p.Thr73Ile is associated with JMML/MPD in individuals with NS.[20,21] The prognosis of patients with NS associated with JMML is much worse than those with MPD who do not fully meet the diagnostic criteria for JMML (a two-year overall survival rate, 40% vs 100%).[17] Therefore, differentiating those who follow a fatal clinical course from those who follow good clinical course in children with NS is important.

PTPN11 encodes SHP2, which is a ubiquitous cytoplasmic phosphatase and plays a key role in RAS/MAPK signaling downstream of a variety of growth factors, cytokines, and integrins.[22] In the absence of phosphotyrosyl peptides, N-SH2 domain is bound to PTP domain, blocking substrate access (inactive state).[23] Upon binding of phosphotyrosyl peptides, the self-locking conformation is disrupted, freeing the PTP domain for catalysis (active state).[23] Most *PTPN11* mutations in NS are clustered in exons 3, 4, 7, 8, 12, and 13, which mainly affect residues involved in the interface between N-SH2 and PTP domains, leading to gain-of-function.[5,12,24]

So far, characteristics of patients with NS with p.Thr42Ala in *PTPN11* have not been systematically reviewed. To the best of our knowledge, 22 patients with NS with p.Thr42Ala have been reported in literature (Table 1).[12,13,15,17,21,25-32] However, data were limited because of the lack of a detailed description of their clinical features (Table 1). Among these reported patients with NS with p.Thr42Ala mutation in *PTPN11*, ASD or atrioventricular canal defect (AVCD) were reported in six patients (Table 1). However, HCM and MPD were described only in two patients each; furthermore, the co-occurrence of HCM and JMML/MPD has not been reported (Table 1).[15,17,25] Two patients with NS with p.Thr42Ala mutation presenting with MPD during the neonatal period were alive for 3.9 and 4 years without treatment, respectively (Table 1).[17] However, HCM was not described in these patients. To the best of our knowledge, this is the first case of a neonate with NS with p.Thr42Ala mutation that leads to a fatal outcome (Table 1).

In contrast to the vast majority of mutations affecting amino acid residues residing at or close the interface between the N-SH2 and PTP, Thr42 is spatially apart from the N-SH2/PTP interaction surfaces.[33] p.Thr42Ala might gain function to promote dissociation of N-SH2/PTP binding through increased phosphopeptide-binding affinity.[34,35] RAS-MAPK hyperactivation is implicated in JMML/MPD in NS.[3] In contrast, HCM in LEOPARD syndrome (LS) is associated with loss-of-function mutations in *PTPN11*, which result in enhanced PI3K-AKT and reduced RAS-MAPK pathway activities.[36] Our patient demonstrated the rare manifestation of concurrent JMML and HCM. Recent research demonstrated that catalytically impaired LS-associated SHP2 mutants could display gain-of-function properties because of their ability to localize to the vicinity of substrates for longer periods of time, thereby affording the opportunity for prolonged substrate turnover and sustained RAS/ERK1/2 activation.[37,38] These observations may account for this apparent contradiction of having both HCM and JMML due to p.Thr42Ala mutation in *PTPN11*. To the best of our knowledge, two neonates with NS presenting with co-occurrence of HCM and MPD with p.Thr73Ile and p.Arg498Trp mutations have been reported in the literature.[18,19] However, the co-occurrence of HCM and JMML in neonates with NS with p.Thr42Ala has not been reported before.

The prognosis of patients with NS is generally considered to be favorable, and cases with fatal outcomes are rarely

TABLE 1 Clinical characteristics of patients with Noonan syndrome with p.Thr42Ala mutation in *PTPN11*

HCM or CHD	MPD/JMML	Concurrent HCM and MPD/JMML	Others	No of patients	Status at last follow-up (age)	References
N/D	N/D	N/D	N/D	2	N/D	12
N/D	N/D	N/D	N/D	1	N/D	13
HCM (1), AVCD (1)	N/D	N/D	N/D	2	N/D	15
N/D	MPD (2)	N/D	N/D	2	Alive (3.9 and 4.0 y)	17
N/D	N/D	N/D	N/D	3	N/D	21
AVCD and sub AS (1), cleft MV, ASD and HCM (1)	N/D	N/D	N/D	2	N/D	25
N/D	N/D	N/D	N/D	1	N/D	26
LVH and MV insufficiency (1)	N/D	N/D	Developmental delay, sensorineural hearing loss, and microcephaly (1)	1	Alive (22 mo)	27
ASD, bilateral SVC, double IVC, large aorta, and hypoplastic pulmonary artery annulus (1)	No	N/D	Developmental delay, cryptorchidism, renal anomaly, chest deformity, enlarged mesenteric lymph nodes, and spleno-megaly (1)	1	Alive (5 y)	28
PS (1)	N/D	N/D	Developmental delay, chest deformity, and cryptochidism (1)	1	Alive (12 y)	29
ASD (2)	N/D	N/D	Abnormal lymphatic architecture (1), sensorineural hearing loss (1)	2	N/D	30
N/D	N/D	N/D	Sensorineural hearing loss (2)	3	N/D	31
N/D	N/D	N/D	N/D	1	N/D	32
HCM, ASD and bicuspid AV (1)	JMML (1)	Yes (1)	Cryptorchidism and splenomegaly (1)	1	Dead (2 mo)	Our patient

Number in parenthesis indicates the number of patients with each manifestation.
ASD, atrial septum defect; AV, aortic valve; AVCD, atrioventricular canal defect; HCM, hypertrophic cardiomyopathy; IVC, inferior vena cava; LVH, left ventricular hypertrophy; MV, mitral valve; N/D, not described; No, number; PS, pulmonary valve stenosis; sub-AS, subvaluvar aortic valve stenosis; SVC, superior vena cava.

reported. However, Wilkinson et al[39] reported very poor outcomes for children with NS presenting with HCM who were diagnosed within 6 months of life, with a one-year survival rate of 31%. Strull et al[17] also reported higher rates of mortality than expected, particularly in neonates with NS with JMML. Therefore, outcomes of cases with NS with HCM or JMML diagnosed during the neonatal period might not necessarily be favorable.

In conclusion, we first identified a case of a neonate with NS with p.Thr42Ala mutation in *PTPN11* presenting with concurrent HCM and JMML that resulted in premature death. This case teaches clinicians that death is a possible outcome to be considered when following patients with NS diagnosed during the neonatal period.

CONFLICT OF INTEREST

The authors have no conflicts of interests to declare.

AUTHORSHIP

AT: reviewed the medical records, interpreted data, and drafted the manuscript. KM: provided medical care, interpreted data, and drafted the manuscript. SU, EK, TT, NN,

TY, AS, TI, and DH: provided medical care, and interpreted data. IU, TN, and YA: performed genetic analysis, interpreted data, and provided critical discussion. YN and KK: performed colony formation assay analysis, provided critical discussion, and drafted the manuscript. YK: provided medical care and supervised the study.

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REFERENCES

1. Tartaglia M, Zampino G, Gelb BD. Noonan syndrome: clinical aspects and molecular pathogenesis. *Mol Syndromol*. 2010;1:2-26.
2. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet*. 2013;381:333-342.
3. Aoki Y, Matsubara Y. Ras/MAPK syndromes and childhood hemato-oncological diseases. *Int J Hematol*. 2013;97:30-36.
4. Aoki Y, Niihori T, Banjo T, et al. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. *Am J Hum Genet*. 2013;93:173-180.
5. Niihori T, Aoki Y, Ohashi H, et al. Functional analysis of PTPN11/SHP-2 mutants identified in Noonan syndrome and childhood leukemia. *J Hum Genet*. 2005;50:192-202.
6. Yamamoto GL, Aguena M, Gos M, et al. Rare variants in SOS2 and LZTR1 are associated with Noonan syndrome. *J Med Genet*. 2015;52:413-421.
7. Cordeddu V, Yin JC, Gunnarsson C, et al. Activating mutations affecting the Dbl homology domain of SOS2 cause Noonan syndrome. *Hum Mutat*. 2015;36:1080-1087.
8. Flex E, Jaiswal M, Pantaleoni F, et al. Activating mutations in RRAS underlie a phenotype within the RASopathy spectrum and contribute to leukaemogenesis. *Hum Mol Genet*. 2014;23:4315-4327.
9. Martinelli S, Krumbach OHF, Pantaleoni F, et al. Functional dysregulation of CDC42 causes diverse developmental phenotypes. *Am J Hum Genet*. 2018;102:309-320.
10. Jhang WK, Choi JH, Lee BH, Kim GH, Yoo HW. Cardiac manifestations and associations with gene mutations in patients diagnosed with RASopathies. *Pediatr Cardiol*. 2016;37:1539-1547.
11. Prendiville TW, Gauvreau K, Tworog-Dube E, et al. Cardiovascular disease in Noonan syndrome. *Arch Dis Child*. 2014;99:629-634.
12. Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet*. 2002;70:1555-1563.
13. Yoshida R, Hasegawa T, Hasegawa Y, et al. Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. *J Clin Endocrinol Metab*. 2004;89:3359-3364.
14. 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;71:389-394.
15. Sarkozy A, Conti E, Seripa D, et al. Correlation between PTPN11 gene mutations and congenital heart defects in Noonan and LEOPARD syndromes. *J Med Genet*. 2003;40:704-708.
16. Bader-Meunier B, Tchernia G, Miélot F, et al. Occurrence of myeloproliferative disorder in patients with Noonan syndrome. *J Pediatr*. 1997;130:885-889.
17. Strullu M, Caye A, Lachenaud J, et al. Juvenile myelomonocytic leukaemia and Noonan syndrome. *J Med Genet*. 2014;51:689-697.
18. Kratz CP, Nathrath M, Freisinger P, et al. Lethal proliferation of erythroid precursors in a neonate with a germline PTPN11 mutation. *Eur J Pediatr*. 2006;165:182-185.
19. Yagasaki H, Nakane T, Hasebe Y, et al. Co-occurrence of hypertrophic cardiomyopathy and myeloproliferative disorder in a neonate with Noonan syndrome carrying Thr73Ile mutation in PTPN11. *Am J Med Genet A*. 2015;167A:3144-3147.
20. Tartaglia M, Niemeyer CM, Fragale A, et al. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. *Nat Genet*. 2003;34:148-150.
21. 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;78:279-290.
22. Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem Sci*. 2003;28:284-293.
23. Barford D, Neel BG. Revealing mechanisms for SH2 domain mediated regulation of the protein tyrosine phosphatase SHP-2. *Structure*. 1998;6:249-254.
24. Aoki Y, Niihori T, Narumi Y, Kure S, Matsubara Y. The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. *Hum Mutat*. 2008;29:992-1006.
25. Digilio MC, Romana Lepri F, Dentici ML, et al. Atrioventricular canal defect in patients with RASopathies. *Eur J Hum Genet*. 2013;21:200-204.
26. Digilio MC, Lepri F, Baban A, et al. RASopathies: clinical diagnosis in the first year of life. *Mol Syndromol*. 2011;1:282-289.
27. Kleefstra T, Wortmann SB, Rodenburg RJ, et al. Mitochondrial dysfunction and organic aciduria in five patients carrying mutations in the Ras-MAPK pathway. *Eur J Hum Genet*. 2011;19:138-144.
28. Lee ST, Ki CS, Lee HJ. Mutation analysis of the genes involved in the Ras-mitogen-activated protein kinase (MAPK) pathway in Korean patients with Noonan syndrome. *Clin Genet*. 2007;72:150-155.
29. Papadopoulou A, Issakidis M, Gole E, et al. Phenotypic spectrum of 80 Greek patients referred as Noonan syndrome and PTPN11 mutation analysis: the value of initial clinical assessment. *Eur J Pediatr*. 2012;171:51-58.
30. Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. *Arch Dis Child*. 2007;92:128-132.
31. van Trier DC, van Nierop J, Draaisma JM, et al. External ear anomalies and hearing impairment in Noonan Syndrome. *Int J Pediatr Otorhinolaryngol*. 2015;79:874-878.
32. Zhen L, Zhang Y, Li DZ. Prenatal DNA diagnosis of Noonan syndrome in a fetus with increased nuchal translucency using next-generation sequencing. *Eur J Obstet Gynecol Reprod Biol*. 2016;201:229-230.
33. Hof P, Pluskey S, Dhe-Paganon S, Eck MJ, Shoelson SE. Crystal structure of the tyrosine phosphatase SHP-2. *Cell*. 1998;92:441-450.
34. Martinelli S, Torreri P, Tinti M, et al. Diverse driving forces underlie the invariant occurrence of the T42A, E139D, I282V and

T468M SHP2 amino acid substitutions causing Noonan and LEOPARD syndromes. *Hum Mol Genet*. 2008;17:2018-2029.
35. Müller PJ, Rigbolt KT, Paterok D, et al. Protein tyrosine phosphatase SHP2/PTPN11 mistargeting as a consequence of SH2-domain point mutations associated with Noonan Syndrome and leukemia. *J Proteomics*. 2013;84:132-147.
36. Marin TM, Keith K, Davies B, et al. Rapamycin reverses hypertrophic cardiomyopathy in a mouse model of LEOPARD syndrome-associated PTPN11 mutation. *J Clin Invest*. 2011;121:1026-1043.
37. Yu ZH, Zhang RY, Walls CD, et al. Molecular basis of gain-of-function LEOPARD syndrome-associated SHP2 mutations. *Biochemistry*. 2014;53:4136-4151.
38. Yu ZH, Xu J, Walls CD, et al. Structural and mechanistic insights into LEOPARD syndrome-associated SHP2 mutations. *J Biol Chem*. 2013;288:10472-10482.
39. Wilkinson JD, Lowe AM, Salbert BA, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. *Am Heart J*. 2012;164:442-448.

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