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 disorders1,2 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 × 10⁹/L with 1.0% blasts, increased absolute monocyte counts of 1.6 × 10⁹/L, and decreased platelet counts of 22 × 10⁹/L. These hematological abnormalities persisted during the first 2 months of life in the range of WBC counts of 10-20 × 10⁹/L with 1%-3% blasts, absolute monocyte counts of 2-4 × 10⁹/L, and platelet counts of 20-80 × 10⁹/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 × 10⁹/L with no obvious blasts, decreased erythroid cells of 4.4%, myeloid cells of 32.1% (myeloblasts: 1.5%,
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 × 10⁹/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 × 10⁹/L with 1.0% blasts, absolute monocyte counts of 1.3 × 10⁹/L, and platelet counts of 75 × 10⁹/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. p.Thr73Ile is associated with JMML/MPD in individuals with NS. 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%). 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. In the absence of phosphotyrosyl peptides, N-SH2 domain is bound to PTP domain, blocking substrate access (inactive state). Upon binding of phosphotyrosyl peptides, the self-locking conformation is disrupted, freeing the PTP domain for catalysis (active state). 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.

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). 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). 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). 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. p.Thr42Ala might gain function to promote dissociation of N-SH2/PTP binding through increased phosphopeptide-binding affinity. RAS-MAPK hyperactivation is implicated in JMML/MPD in NS. 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. 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. 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. 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
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,
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**How to cite this article:** Tamura A, Uemura S, Matsubara K, et al. Co-occurrence of hypertrophic cardiomyopathy and juvenile myelomonocytic leukemia in a neonate with Noonan syndrome, leading to premature death. *Clin Case Rep*. 2018;6:1202-1207. [https://doi.org/10.1111/ccr3.1568](https://doi.org/10.1111/ccr3.1568)