At 38 weeks gestation, a 3,210-g male infant was born via normal spontaneous vaginal delivery to a healthy 23-year-old white mother, G4P3, with no prenatal or delivery complications. Two days after delivery, the baby was transferred to the neonatal intensive care unit (NICU) for respiratory distress, leukocytosis, severe thrombocytopenia, and elevated hematocrit. The baby was afebrile and found on physical examination to have slight dysmorphic features, including low-set ears and hypertelorism; he also had splenomegaly.

Further workup was significant for renal ultrasound with left pelviectasis; for X-ray of the limbs showing features of trident hand; and for brain ultrasound showing questionable hypoplasia of the corpus collosum. Echocardiogram study revealed a fenestrated atrial septal defect, bicuspid aortic valve, and septal hypertrophy. Chest X-ray was normal.

Laboratory workup revealed a high white blood count of 35.8 (normal range, 9 K/uL to 30 K/uL); hemoglobin 20 (10 g/dL to 18 g/dL); hematocrit 60 (31% to 55%); and low platelet level of 24 (150 K/uL to 500 K/uL).

On the fifth day of life, erythematous vesicopustules were noted on the baby’s cheeks.

Over the course of a week, the baby developed more erythematous vesicles on bilateral dorsal hands, feet, extremities, and few within scalp, with sparing of palms and soles (Figures 1, 2, and 3, see pages 186, 187).

Dermatology was consulted on the 14th day of life for consultation of the skin lesions. Cultures sent from pustules for viral, fungal, and bacterial cultures were all negative. Titers for cytomegalovirus (CMV) and toxoplasmosis were negative. A smear was performed from a vesicle on the right dorsal foot and prepared with Wright’s stain. The smear results (Figure 4, see page 187) showed numerous atypical myeloblasts and mixed infiltrate of neutrophils and few eosinophils. Supportive skin care regimen was recommended, including mupirocin ointment to any eroded lesions. The baby was transferred to another medical center for further evaluation.

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For diagnosis, see page 187

Editor’s note: Each month, Case Challenge features an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. Your comments are welcome via email at pediatrics@healio.com. To submit a case, visit: www.Healio/PedAnnals.com/Submit.
Diagnosis:
Noonan’s Syndrome/Juvenile Myelomonocytic Leukemia

The patient subsequently had a skin biopsy consistent with leukemia cutis myeloid type. A bone marrow biopsy revealed normocellular marrow with myeloid hyperplasia; mildly increased myeloblasts (<5%); erythroid hypoplasia; and decreased megakaryocytes. Flow cytometry analysis of the bone marrow aspirate detected the presence of 3% myeloblasts with the following phenotype: CD34+, CD117+, CD33+, CD13+, and HLA-DR+.

Genetic testing was performed for chromosomal analysis and fluorescent in situ hybridization (FISH) for deletion of 11q25, 22q11.2, 22q13.3, and FISH myelodysplastic syndrome (MDS) panel.

The final results for genetic testing from peripheral blood and bone marrow showed 46XY, with no mosaicism for trisomy 21, and no deletions detected by FISH analysis using MDS panel of probes showing no evidence of clonal abnormality.

Genetic analysis to confirm the diagnosis of juvenile myelomonocytic leukemia (JMML) revealed the presence of a 218 C>T mutation in the PTPN11 gene, typically reported in patients with Noonan’s syndrome (NS) and JMML-like myeloproliferative disorder; PTPN11 mutation analysis from the buccal smear confirmed the germline nature of this mutation, thus establishing the diagnosis of NS.1 The baby was treated with supportive care and monitored over the course of 4 months with continued stability and improvement of the Noonan’s syndrome/myeloproliferative disorder (NS/MPD).

DISCUSSION

NS is a developmental disorder characterized by dysmorphic facial features, short stature, hematologic abnormalities, and congenital heart defects, all of which occur on a clinical spectrum.2,3 NS may occur in an autosomal dominant or sporadic manner in nearly 50% of cases, occurring between 1/1,000 to 1/2,500 individuals.1,4 Mild cases may be even more common and underdiagnosed.3

Patients with NS have an increased likelihood of developing a NS/MPD; however, the accurate epidemiology is unavailable and the MPD will often remit without treatment or rarely develop into an aggressive process such as JMML.2,4,5 PTPN11 mutations on chromosome 12q24.1 have been found to occur in NS and in nonsyndromic JMML, at the rate of 45% to 50% and 35%, respectively.2,6 NS/MPD has a less aggressive course and often resolves spontaneously with supportive care.2

Figure 3. Dorsal foot with numerous vesicles on an erythematous base; some crusting of vesicles noted.

Figure 4. Wright’s stain of smear from a pustule, revealing numerous neutrophils, few eosinophils, and multiple myeloblasts with large atypical nuclei and basophilic cytoplasm.
Nearly 50% of patients with NS have the PTPN11 mutation. The PTPN11 gene located on chromosome 12q24.1 encodes the protein tyrosine phosphatase (PTP) SHP-2, which regulates proliferation, differentiation, and migration, also playing a signal transduction role in the RAS/RAF/ERK pathway. In the absence of the PTPN11 mutation, other genes involved in the RAS/RAF/ERK pathway, such as SOS1, KRAS, and RAF1 have been shown to occur in NS in 15% to 20%, 5%, and 3% to 17% of patients, respectively.2,3

In this case, the patient had a somatic PTPN11 mutation with a Thr73Ile substitution, which was reported in eight of 19 cases of NS/MPD by Kratz et al in 2005.1 Thr73Ile mutation is the most common mutation in patients with NS/MPD; it is uncommon in NS patients without MPD; and has not been observed to occur in JMML.1 It has been proposed that there is a disease spectrum of MPD in patients with NS, with 40% of cases having mild MPD that spontaneously remits, and 15% of cases that progress to aggressive leukemias.1,4,5,8,9

During the neonatal period, it is not unusual to have vesicopustular eruptions in the healthy neonate. The more common diagnoses include erythema toxicum neonatorum; pustular miliaria; neonatal cephalic pustulosis; transient neonatal pustular melanosis; acropustulosis of infancy; Langerhans cell histiocytosis; neonatal eosinophilic pustulosis; and also viral, fungal, and bacterial infections.10,11

The differential diagnosis for our patient initially included transient myeloproliferative disorder (TMD), which is rare and usually occurs in children with Down syndrome. TMD has been well documented to present with the finding of a vesicopustular eruption; for this reason, it is important that we keep this entity in the differential of vesicopustular eruptions in the newborn.

**CONCLUSION**

The time line of the skin eruption, distribution, and morphology of skin lesions with comprehensive birth history, prenatal history, and any available laboratory data can be useful when making the appropriate diagnosis. Practitioners should have high suspicion, and a low threshold for performing smears and or skin biopsies on vesicles and pustules. The pustular eruption of a myeloproliferative process may be the only presenting abnormality in affected neonates.

To our knowledge, this is the first report of NS/MPD occurring in a newborn with a vesicopustular presentation. When the diagnosis of a MPD is confirmed, genetic analysis of inherited disorders associated with a myeloproliferative disease should be considered. PTPN11 mutations are present in approximately 50% of cases of NS, and 35% of nonsyndromic JMML. New genes in the RAS/RAF/ERK pathway have recently been shown to be involved, such as SOS1, KRAS, and RAF1.2,3,7,9

We present a case of NS/MPD occurring with PTPN11 gene mutation and a Thr73Ile substitution. The Thr73Ile substitution is the most common reported mutation in NS/MPD, and it rarely occurs in NS patients without MPD.1

There has been an increase in the number of cases of MPD and JMML-like MPD occurring in NS. Our case is unique in that it includes cutaneous manifestations of a myeloproliferative process, whereas previous reports did not.1

**REFERENCES**


