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Case Report

Efficacy of Sirolimus in Treating Refractory Lymphatic Malformation in Noonan Syndrome: A Case Study

Yuka Nakajima,[1,*] Yoh Watanabe,[1,*] Kohei Iwata,[1] Yuki Yamada,[1] Shinji Higuchi,[1] and Jun Mori[1]

[1]Division of Pediatric Endocrinology, Metabolism and Nephrology, Children's Medical Center, Osaka City General Hospital, Osaka 534-0021, Japan

Correspondence: Jun Mori, MD, PhD, Division of Pediatric Endocrinology, Metabolism and Nephrology, Children's Medical Center, Osaka City General Hospital, 2-13-22 Miyakojimahondori, Miyakojima-ku, Osaka 534-0021, Japan. Email: jun1113@koto.kpu-m.ac.jp.
*These authors contributed equally to this work and share first authorship.

Abstract

A female patient with Noonan syndrome, attributed to a pathogenic *RIT1* variant, presented with white perineal discharge at 8 years and 5 months of age. She had a history of chylothorax and recurrent respiratory infections requiring hospitalization. Discharge analysis revealed 99.5% lymphocytes and elevated triglyceride levels (1939 mg/dL; 21.9 mmol/L). Magnetic resonance imaging and contrast-enhanced computed tomography identified lymphatic abnormalities extending from the thoracic to the pelvic region. We suspected that the chylous ascites was being discharged through the genitals. Administration of sirolimus, an mTOR inhibitor, was initiated, leading to a significant reduction in perineal chyle discharge and improved respiratory function with no adverse events. Sirolimus shows promise as a therapeutic intervention for lymphatic abnormalities in patients with Noonan syndrome; however, long-term follow-up is necessary to evaluate its efficacy and safety.

Key Words: Noonan syndrome, lymphatic abnormalities, chyle discharge, sirolimus

Abbreviations: MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MRI, magnetic resonance imaging; NS, Noonan syndrome.

Introduction

Noonan syndrome (NS) is a genetic disorder caused by germline pathogenic variants of genes associated with the Ras/mitogen-activated protein kinase (MAPK) signaling pathway [1]. This syndrome is characterized by distinct facial features, short stature, congenital heart disease, chest wall anomalies, delayed puberty, cryptorchidism in boys, developmental delays, and lymphatic abnormalities. Lymphatic dysfunction can lead to lymphedema, chylothorax, and ascites, with postnatal lymphedema often affecting the lower extremities and genital areas. Genital lymphangiomas, commonly presenting as localized lymphangioma circumscriptum, may be mistaken for genital warts; however, perineal chyle discharge has not been previously reported. Here, we describe an unusual case of an 8-year-old girl with NS who presented with persistent perineal chyle discharge, and we discuss the clinical course and treatment outcomes.

Case Presentation

A female patient was referred to our hospital at 8 years and 5 months of age with a complaint of perineal discharge. At approximately 7 years and 9 months of age, the patient developed persistent vulvar wetness with noticeable milky-white secretions. By 8 years and 5 months, the discharge required frequent underwear changes throughout the day.

The patient's family history of NS was unremarkable. She was delivered at 33 weeks of gestation via emergency cesarean section due to fetal pleural effusion. At birth, her weight was 2423 g, her height was 44 cm, and her Apgar scores were 7 at 1 minute and 8 at 5 minutes. She was intubated immediately after birth due to respiratory distress caused by chylothorax, which required drainage. Her clinical features included hypertelorism, downward-slanting palpebral fissures, auricular hypoplasia, micrognathia, and mild mitral regurgitation. Based on these findings, NS was suspected, and genetic testing identified a pathogenic variant of *RIT1* (c. 284G>C, p. G95A), confirming the diagnosis. The patient was diagnosed with asthmatic bronchitis each time she had an infection, and she was hospitalized several times during her infancy. Pulmonary function tests at 8 years and 5 months of age showed that her lung capacity was 76.9% of the predicted value, indicating restrictive lung disease before treatment.

Diagnostic Assessment

The secretions were milky-white, had low viscosity, and closely resembled chyle (Fig. 1). Cytological examination of the secretion revealed no malignant findings, with a predominance of lymphocytes (99.5%) and a triglyceride level of 1931 mg/dL (21.9 mmol/L); the normal reference range is not specified (Table 1). The catheterized urine was clear yellow with undetectable triglycerides.

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Figure 1. Appearance of the vulvar secretions. The secretion was white, low viscosity, milk-like, and involuntary.

Physical examination revealed atypical external genitalia, including swelling of the prepuce surrounding the clitoris and bilateral hole-like structures near the urethral meatus (Fig. 2). Chromosomal analysis confirmed a 46,XX karyotype.

Magnetic resonance imaging (MRI) and contrast-enhanced computed tomography revealed lymphatic abnormalities extending from the thoracic to the pelvic region. Notably, pelvic MRI showed a high-signal area on T2-weighted imaging (T2WI) along the vessels from the pelvis to the inguinal region, with high diffusion-weighted imaging (DWI) signals and high apparent diffusion coefficient (ADC) values, suggestive of a lymphatic malformation (Fig. 3A). The uterus was small, and no significant abnormalities were observed in the ovaries (Fig. 3B and 3C).

A trace amount of ascitic fluid was observed, and pelvic MRI confirmed that the bladder, uterus, and rectal walls were preserved; no findings suggested a fistula between the pelvic organs. Contrast-enhanced computed tomography of the chest showed prominent soft tissue shadows with increased density around the trachea, bilateral pulmonary hilum, and pelvis, suggesting lymphangioma and enlarged lymph nodes.

Based on these findings, we considered the possibility that chylous ascites was being discharged from a site within the perineum. A pediatric urologist examined the patient and determined that the hole-like structures on either side of the urethra were not fistulas but rather simple folds, as a probe could not pass through them during the examination. Increased leakage was observed after exercise; upon closer examination, the secretions were confirmed to leak from the vaginal opening after jumping.

Treatment

Lymphangiomas are treated using various approaches, including surgery and sclerotherapy (OK-432, bleomycin, doxycycline), depending on their size, location, and symptoms. In this patient, lymphangiomas were found throughout the body, making these treatments difficult to perform. Recently, sirolimus has been reported as an effective treatment for refractory lymphangiomas. In 2021, sirolimus received insurance coverage in Japan for the treatment of refractory lymphangiomas; therefore, we decided to administer it. Sirolimus treatment was initiated at 1 mg/day at 8 years and 10 months of age and was adjusted to maintain a trough blood concentration of 5 to 10 ng/mL. The patient, at the age of 9 years and 11 months, is currently taking sirolimus at a dose of 2 mg/day.

Table 1. General examination results of the vulvar secretions

Color	Milky
Appearance	Opacity
Specific gravity	1.035
RBC count	<10 000/μL
Cell count	3190/μL
Lymphocyte	99.5%
Neutrophil	0.0%
Eosinophil	0.0%
Histiocyte	0.5%
Atypical cell	0.0%
Mesothelial cell	—
Triglyceride	1931 mg/dL

Abbreviation: RBC, red blood cell.

Outcome and Follow-Up

Three weeks after starting sirolimus, the amount of chylous discharge decreased to one-tenth of the pretreatment level. After 1 month, chylous discharge was almost completely absent except during vigorous exercise, allowing the patient to lift exercise restrictions and improving her quality of life.

When the patient developed a fever, sirolimus was discontinued due to concerns about immunosuppression, leading to a return of chylous discharge to pretreatment levels. After restarting treatment, it took about 2 weeks for the therapeutic effect to return to pre-discontinuation levels.

Pulmonary function tests showed an improvement in lung capacity from 76.9% of the predicted value before treatment to 86.9% at 6 months after starting treatment. To date, no adverse effects of sirolimus have been reported for this patient.

Discussion

NS is caused by genetic abnormalities in molecules that constitute the RAS/MAPK signaling pathway, which plays a crucial role in cell proliferation and other biological processes. Currently, 9 main genes (*PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *SHOC2*, *CBL*, and *BRAF*) are known to be responsible for NS. However, mutations in these genes are confirmed in only 60% to 80% of patients with a clinical diagnosis of NS, leaving 20% to 40% of cases with an unknown genetic cause.

In this patient, NS was diagnosed based on clinical findings and a pathogenic *RIT1* variant [2]. There is a known genotype-phenotype correlation in NS, particularly in cardiac manifestations [3, 4]. *PTPN11* mutations have been associated with pulmonary valve stenosis and dysplasia, while *SOS1* mutations are linked to valve defects. Mutations in

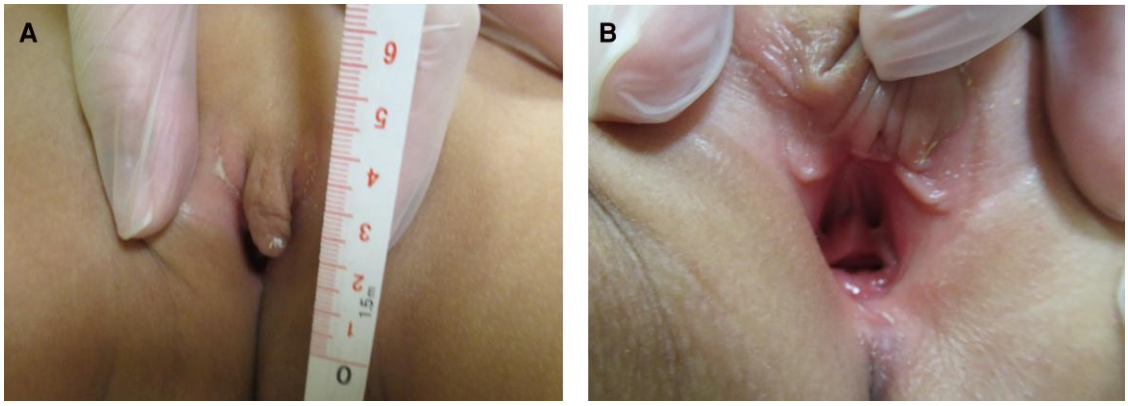

Figure 2. Ambiguous genitalia. (A) Clitoromegaly. (B) A hole-like structure was observed on either side of the urethral opening.

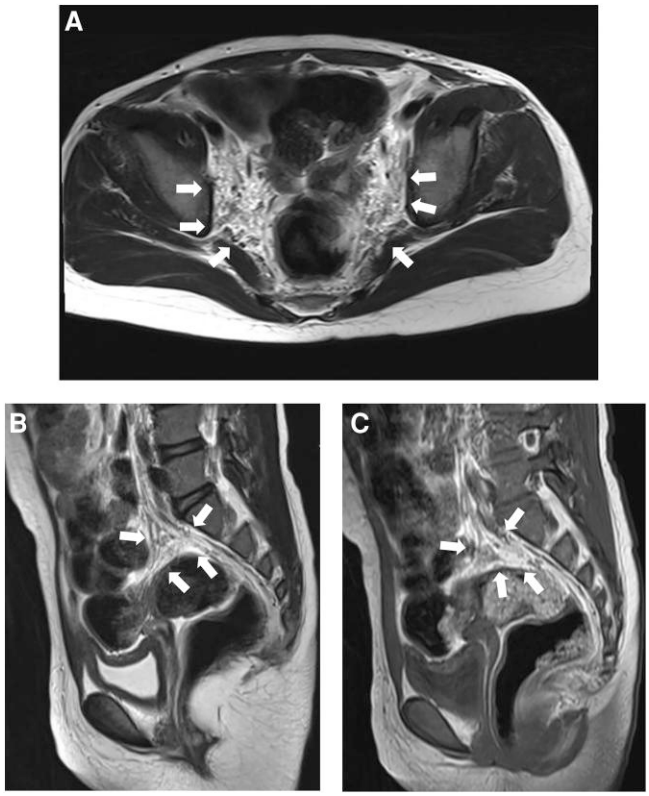

Figure 3. Pelvic magnetic resonance imaging of lymphatic abnormalities in the pelvic region. (A) Axial view; (B and C) Sagittal views. White arrows indicate the lymphatic abnormalities.

RAF1 and *HRAS* are associated with hypertrophic cardiomyopathy. The *RIT1* mutation identified in this patient has also been reported in association with hypertrophic cardiomyopathy; however, this was not observed in our patient.

Lymphatic abnormalities are a primary feature of NS, with a reported prevalence of approximately 20% [2, 5]. During the fetal period, these abnormalities may be detected via ultrasonography, which can reveal findings such as increased nuchal translucency, pleural effusion, and cystic hygroma [6, 7]. In the neonatal period, this patient also exhibited lymphatic abnormalities, including fetal pleural effusion and respiratory failure due to chylothorax.

The incidence of increased nuchal translucency is higher in patients with *RIT1* mutations (38%) compared to those with the most common *PTPN11* mutations (7%) [8]. Genital lymphedema is one of the most common types of postnatal lymphedema in patients with NS [8]. In this report, the patient exhibited external genital abnormalities, specifically swelling of the prepuce surrounding the clitoris. The onset of genital lymphedema has been reported between the ages of 3 and 63 years, with an average age of 8 years [8].

In this patient, an external genital abnormality—an uncommon feature of NS in females—was observed at birth. Reports indicate that all cases of external genital edema in NS are accompanied by lower limb edema. However, no obvious lower limb edema was observed in this patient, suggesting that her external genital abnormalities may not have been caused by lymphedema. We conducted a thorough evaluation for potential causes of clitoromegaly and external genital abnormalities, including congenital adrenal hyperplasia, androgen exposure, and chromosomal abnormalities, but no abnormalities were found.

NS is a genetic disorder caused by mutations that activate the RAS/MAPK pathway, which is also activated in lymphangioma. Therefore, inhibiting RAS/MAPK pathway activation with RAS/MAPK inhibitors is expected to provide a treatment option for both conditions. Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase Kinase (MEK) inhibitors have been shown to be effective against severe lymphatic abnormalities in patients with NS with *SOS1* mutations [9, 10]. Recently, the efficacy of sirolimus was reported in a phase 3 clinical trial for refractory lymphatic disorders [11]. Both MEK inhibitors and mTOR inhibitors are being considered for this condition. We decided to administer sirolimus to this patient, as it is covered by insurance for lymphangioma in Japan.

Sirolimus significantly reduced chyle leakage, eliminated the need for exercise restrictions, decreased the frequency of underwear changes, and improved the patient's quality of life. Additionally, the patient's restrictive lung disease improved.

A report indicated that in a patient with restrictive lung disease due to lymphatic abnormalities, sirolimus was initially effective but gradually became less so. Although switching to an MEK inhibitor did not improve the condition, adding sirolimus to MEK inhibitors led to clinical improvement [12]. Similarly, if the effect of sirolimus weakens in this patient, it may be necessary to consider using it in combination with MEK inhibitors.

A systematic review has shown that surgical interventions may improve lymphatic abnormalities in patients with NS;

however, postoperative complications have also been reported [13]. Given the invasiveness and potential postoperative complications of surgical interventions, RAS/MAPK inhibitors like sirolimus, along with MEK inhibitors, may be considered the first-line treatment for patients with extensive lymphangioma in NS.

To our knowledge, this is the first reported case of perineal chyle discharge in a patient with NS. The condition was successfully managed with sirolimus, highlighting its potential as a safe and effective treatment for refractory lymphatic disorders. Long-term follow-up is essential to monitor for recurrence and side effects.

This case report emphasizes the importance of recognizing unusual lymphatic complications in NS and the potential role of sirolimus in managing extensive lymphatic malformations. Additional research is needed to optimize treatment strategies and improve patient outcomes.

Learning Points

- Lymphatic abnormalities are a major complication of Noonan syndrome with a frequency of approximately 20%.
- Chyle leakage due to lymphatic abnormalities should be considered in patients with Noonan syndrome who present with white discharge.
- Sirolimus may be a promising treatment option for lymphatic abnormalities in patients with Noonan syndrome.

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Contributors

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this study because no datasets were generated or analyzed.

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