

Successful treatment of refractory chylothorax with MEK inhibitor trametinib in a child with Noonan syndrome: case report

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Background

Refractory chylous effusions due to lymphatic dysplasia related to Noonan syndrome cause significant morbidity and mortality due to protein and immunoglobulin losses. Very few cases have been published reporting successful treatment of patients with trametinib where all conventional treatments had failed.

Case summary

We present a girl with Noonan syndrome and hypertrophic cardiomyopathy who presented with life-threatening refractory chylothorax where all conventional treatment options failed. She was successfully treated with mitogen-activated extracellular signal-regulated kinase inhibitor trametinib.

Discussion

MEK inhibition with trametinib is emerging as a possible salvage treatment option for a subset of patients with Noonan syndrome and severe pulmonary lymphangiectasia. More experience is required to establish optimal treatment regimen and long-term outcomes.

Keywords

Noonan syndrome • Chylothorax • MEK inhibition • Trametinib • Case report

ESC Curriculum

6.5 Cardiomyopathy • 7.3 Critically ill cardiac patient

Learning points

- To understand the molecular genetic basis of MEK inhibition as a treatment option for lymphatic dysplasia in Noonan syndrome
- To recognise possible fatality of intractable chylothorax in Noonan syndrome and escalate management accordingly

Introduction

Noonan syndrome is an autosomal dominant multisystem disorder with an estimated prevalence of 1 in 1000–2500.¹ It can be accompanied by congenital heart disease, hypertrophic cardiomyopathy (HCM), and lymphatic malformations. Although the pathogenetic mechanisms are poorly understood, variable gene mutations result in activation of the Ras-mitogen activated protein kinase (RAS-MAPK) pathway.²

Trametinib is a reversible and highly selective allosteric inhibitor of the activation and kinase activity of the mitogen-activated extracellular signal-regulated kinases 1 (MEK1) and 2 (MEK2).³ MEK proteins are critical components of the extracellular signal-regulated kinase pathway, which is commonly hyperactivated in tumour cells. MEK are part of the protein cascade in the RAS-MAPK pathway that is up-regulated in Noonan syndrome.² MEK inhibition has been recognised as a therapeutic target to treat HCM in Noonan syndrome with severe neonatal presentation.⁴

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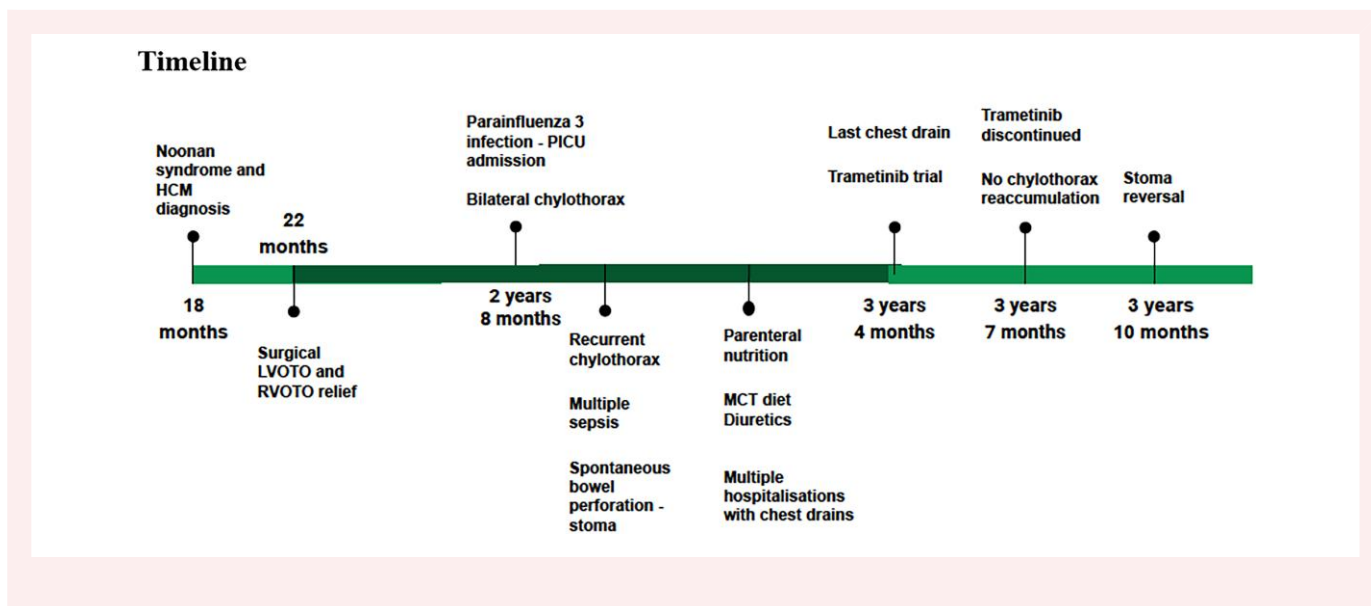
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Timeline



Refractory chylous effusions due to lymphatic dysplasia related to Noonan syndrome cause significant morbidity and mortality due to protein and immunoglobulin losses. Very few cases have been published reporting successful treatment of patients with trametinib where all conventional treatments had failed.^{5,6} We present a girl with Noonan's syndrome, HCM, and refractory chylothorax who developed life-threatening chyle loss related complications. Lymphatic remodelling with complete resolution of chylothorax was achieved by MEK inhibition with trametinib.

Case presentation

A 3-year-old Caucasian girl with Noonan syndrome (heterozygous RIT1 mutation) initially presented at the age of 18 months with a heart murmur and was diagnosed with HCM causing mid cavity left ventricular outflow tract (LVOT) obstruction, severe right ventricular outflow tract (RVOT) obstruction, and a dysplastic stenotic pulmonary valve (Figure 1A and B). She underwent surgical relief of LVOT obstruction with myectomy and relief of RVOT obstruction with muscular resection and a transannular patch at 22 months. An epicardial pacemaker was required for post-operative complete heart block. She recovered well following the procedure with no progression of HCM.

She was admitted to intensive care unit at 2 years and 8 months due to respiratory failure caused by parainfluenza 3 infection, 10 months following her cardiac surgery. She developed significant bilateral pleural effusions requiring drainage. The fluid analysis confirmed chylothorax: fluid triglycerides 1.9 mmol/L (reference value >1.24 mmol/L diagnostic of chylothorax) and fluid protein 30 g/L (gram stain negative, mononuclear white blood cells). She was treated with a low fat and high medium chain triglycerides (MCT) diet, as well as an octreotide infusion. Despite this, she was losing a significant amount of chyle, which resulted in low immunoglobulin levels. She acutely deteriorated with spontaneous bowel perforation, requiring 10 cm of terminal ileum to be resected, and a stoma formed. Her acquired immunocompromised state led to bacterial and candida sepsis. She was treated with multiple courses of antibiotics and antifungals, as well as immunoglobulin replacements.

Parenteral nutrition was started in view of ongoing refractory pleural effusions and high stoma losses. She was gradually transitioned back to

MCT and was discharged home after 3 months of hospital stay. However, she repeatedly represented with reaccumulation of pleural effusions despite MCT diet and underwent multiple chest drains for respiratory compromise (Figure 2A and B).

Pulmonary lymphangiectasia secondary to the underlying syndrome or to residual cardiac anomalies were considered as differential diagnoses. Surgical damage to the thoracic duct was felt to be unlikely due to a long-time period (ten months) between the surgical repair and first presentation with chylothorax. Transoesophageal echocardiogram confirmed no residual left or right ventricular outflow tract obstruction (Figure 3A and B); there was a small atrial septal defect with a bidirectional shunt and consistent with restrictive right ventricular (RV) physiology. Invasive haemodynamic measurements showed elevated bi-atrial pressures at 14 mmHg (reference value 3–6 for right atrium and 6–9 for left atrium in children)⁷, mean pulmonary artery pressure of 20 mmHg (reference value 15 mmHg)⁷, mildly increased pulmonary vascular resistance at 2.1 indexed Wood units (reference value <2 indexed Wood units)⁷, and calculated cardiac index of 3.8 L/min/m². Innominate vein (IV) wedge angiogram did not demonstrate the thoracic duct entry point, and the IV was unobstructed (see Supplementary material online, Video S1). We concluded that the main underlying pathology was likely lymphatic dysplasia driven by her primary syndrome with some contribution from her elevated right-sided filling pressures.

In view of restrictive RV physiology, we initially tried to manage her with parenteral nutrition and intense diuresis, with no improvement. We exhausted all conventional treatment options and considered the condition incompatible with long-term survival, especially as she had already suffered from life-threatening complications. The family was offered a trial of trametinib treatment as the last resort with the potential for lymphatic remodelling. Side effects were discussed in detail and written information given to the family. Hospital Trust board approval was obtained and managed access for unlicensed use was arranged with Novartis (Novartis International AG, Basel, Switzerland). She was started on trametinib 0.032 mg/kg/dose once a day following a prescribing guideline for trametinib use for oncological indications. Monitoring plans were put in place with clear instructions for side-effect management. Baseline bloods were monitored weekly (full blood count, urea and electrolytes, creatine kinase, liver function tests, and

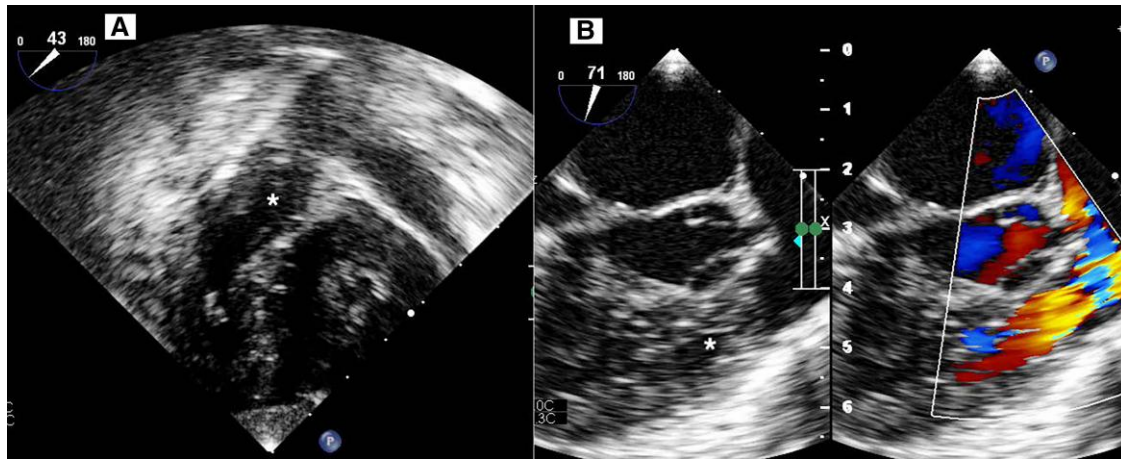


Figure 1 (A and B) Transoesophageal echocardiogram before surgery. (A) Short axis view showing right ventricular outflow with subpulmonary muscular hypertrophy (asterisk) and concentrically hypertrophied left ventricle. (B) Severe right ventricular outflow tract obstruction (asterisk).

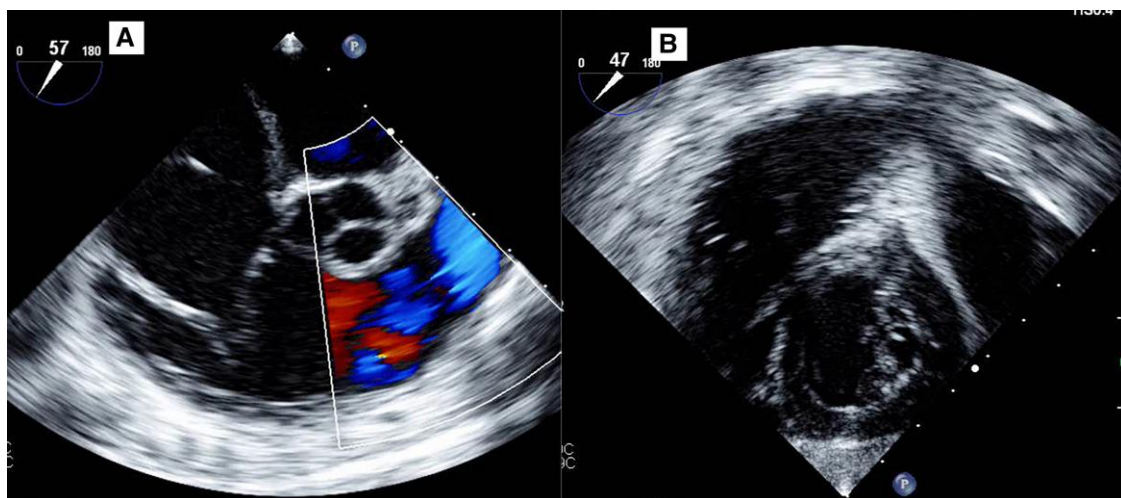


Figure 2 (A and B) Transoesophageal echocardiogram before starting trametinib treatment. (A) No residual right ventricular outflow tract obstruction. (B) Short axis view showing no significant left ventricular hypertrophy and widely open right ventricular outflow tract.

HbA1c), and ophthalmology review was performed monthly. Weekly echocardiograms were performed to monitor ventricular function and pleural spaces. Both pleural spaces were drained prior to commencing treatment.

She developed severe eczema affecting the arms, legs, and trunk, which responded to emollients and topical steroids. Her stoma output increased, but was manageable with parenteral nutrition (small amounts of fat-free oral feeds were allowed) and stayed below an agreed cut-off for discontinuation of treatment (30 mL/kg/day). No other significant side effects were seen. Reduction in left ventricular mass was noticed on serial echocardiograms.

We set a goal of completing a 3-month course of trametinib at the outset. Following completion, she was gradually transitioned to enteral feeds (initially with MCT diet, followed by a diet with normal fat content) and discharged home. She has since been followed in the

outpatient clinic and remains free of chylothorax recurrence (monitored by chest X-ray, [Figure 3C](#), and ultrasound) for the last eight months since completing her treatment and eleven months since commencing treatment and her last pleural drainage.

Discussion

Pulmonary lymphangiectasia in Noonan syndrome is a debilitating condition and can be fatal.⁸ An aggressive approach to treatment in these patients is necessary but even then, complications from excessive chylous loss are frequent and difficult to manage.

The time lag between surgery and first occurrence of chylothorax suggested that lymphatic leak due to surgical damage to the thoracic duct was unlikely. Even though most cases of lymphatic dysplasia in

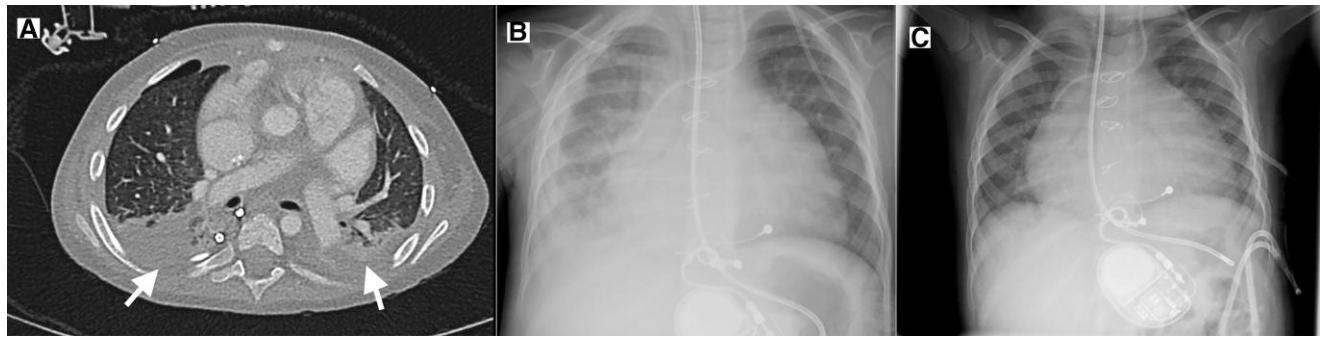


Figure 3 (A–C) Chest imaging for chylothorax before and after trametinib treatment. (A) Computed tomography chest showing right-sided pleural effusion with a smaller left-sided effusion (arrows). (B) Right-sided pleural effusion (chylothorax) on chest X-ray just before starting trametinib. (C) Chest X-ray at the end of a 3-month course of trametinib therapy.

Noonan syndrome present at or early after birth, onset in later childhood or adulthood is described.⁹ We were not able to demonstrate the thoracic duct angiographically by innominate vein wedge angiogram, at its usual entrance point. Intranodal lymphangiography and dynamic contrast-enhanced magnetic resonance lymphangiography are becoming the gold standard for diagnosing lymphatic pathologies,^{10,11} but are not available in most institutions.

MEK inhibition with trametinib as a possible treatment has been described in few case reports of patients with Noonan syndrome and either hypertrophic cardiomyopathy or refractory life-threatening chylothorax.^{4,5,6,12,13} The literature is sparse however and lacks guidelines regarding best treatment course. Doses between 0.01 to 0.027 mg/kg^{4,5,12} have been reported, and all cases seem to continue on trametinib for a prolonged time and without a predetermined duration (Nakano *et al.*¹² report successful treatment in two cases that remained on therapy for 12 and 24 months). We followed paediatric oncology dosing guidelines which state a fixed dose of 0.025 mg/kg/day (patients ≥ 6 years) or 0.032 mg/kg/day (patients < 6 years)¹⁴. The higher dose for small children has not been used in previously reported cases. The dose is administered once daily. The most frequent trametinib side effects are skin rashes and require meticulous skin care regimens.¹² Other toxicities include paronychia, diarrhoea, fatigue, stomatitis/mucositis, chorioretinopathy and retinal vein occlusion, oedema, reduction in left ventricular ejection fraction, hyponatraemia, hypernatraemia, and/or abnormalities of liver enzymes.

We elected to stop medication after a set period of 3 months, which is the shortest duration of treatment reported so far. The decision was made before starting the treatment and followed the rationale that complete resolution of symptoms has been described to occur in 3 months in a previously reported case.⁵ The patient was not free of a chest drain for more than 6 weeks over the preceding 6 months, and we felt that we would be confident of a treatment effect over a 3-month time period if no further reaccumulation occurred (twice the previous period). Prolonging the duration of trametinib administration was felt to lack benefit for the patient and expose her to significant risk in view of side effects and dependency on parenteral nutrition for the length of treatment due to her high-stoma output. Her stoma has subsequently been reversed.

Conclusion

MEK inhibition with trametinib is emerging as a possible salvage treatment option for a subset of patients with Noonan syndrome and severe pulmonary lymphangiectasia. We are hoping for more centres to

report their experience to establish the best treatment approach, long-term outcomes and patient safety.

Lead Author biography



Paediatric Cardiologist with subspecialty interest in Congenital Interventional Cardiology. Trained in Leeds, UK (Yorkshire Heart Centre).

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: Informed consent by the patient's family has been obtained for this case in accordance with COPE guidelines.

Conflict of interest: None declared.

Funding: None declared.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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