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Case Report

Use of Sirolimus in Managing Protein-Losing Enteropathy: A Case Study of Noonan Syndrome in a Chinese Adolescent

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Abstract Noonan syndrome is an autosomal dominant genetic disorder which causes malformation of the lymphatic system, leading to lymphangiectasia of the intestines and protein-losing enteropathy. We report a case of a 15-year-old Chinese girl with PTPN11-mutation Noonan syndrome with recurrent lower limb oedema and hypoalbuminaemia. Multiple targeted investigations confirmed the diagnosis of lymphangiectasia leading to protein-losing enteropathy, including a Tc99m human serum albumin, an oesophageoduodenoscopy with biopsy, and magnetic resonance lymphangiogram showing features of central conducting lymphatic anomaly with abnormal lymphatic flow. Being refractory to conventional treatment strategies, initiation of Sirolimus, an m-TOR inhibitor, yielded satisfactory clinical improvement in this patient. This case demonstrated the diagnostic complexity and management challenge in patients with protein-losing enteropathy caused by lymphangiectasia, which is one of the rare complications in Noonan syndrome. Early commencement of Sirolimus with close monitoring of side effects is helpful in disease control and symptom resolution.

Key words *Noonan syndrome; Protein-losing enteropathy; Sirolimus*

Introduction

Noonan syndrome is an autosomal dominant genetic disorder carrying a wide spectrum of phenotypic attributes as distinguished by distinctive facial dysmorphism, congenital cardiac malformations, chest deformities, short stature, and anomalies spanning the genitourinary, haematological, neurological and lymphatic systems. The pathogenic underpinning involves a complex interplay of genetic factors, with over 19 genes predominantly influencing the RAS-MAPK (mitogen-activated protein kinase) signal transduction pathway.[1] Amidst the myriad anomalies associated with Noonan syndrome, instances of protein-losing enteropathy (PLE) resulting from intestinal lymphangiectasia have been sporadically documented, potentially leading to substantial morbidity. Persistent hypoalbuminaemia resulting from PLE renders patients prone to recurrent infections, malnutrition, and failure to thrive. No standardised guidelines have been published regarding the treatment for PLE. Hereby, we report a case of a 15-year-old girl with Noonan syndrome diagnosed with PLE refractory to conventional treatment, who subsequently achieved satisfactory clinical response to oral Sirolimus. We aim to highlight the clinical features, diagnostic journey, and exploration of novel treatment options contribute to the evolving landscape of PLE management.

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Case Report

A Chinese infant, referred to as YT, was born full term with normal birth weight by her non-related parents. YT exhibited facial dysmorphism with down-slanting eyes and low-set ears at birth. She received surgical intervention for atrial septal defect and valvular pulmonary stenosis, and gastrostomy with fundoplication for severe gastroesophageal reflux disease at her first few months of life. She suffered from profound sensorineural hearing loss requiring bilateral hearing aids. She exhibited global developmental delay, requiring specialised school education. Her diagnosis of Noonan syndrome was substantiated at the age of three when the genetic analysis revealed the presence of a heterozygous NM_002834.5(PTPN11):c.854T>C (p.Phe285Ser) variant.

YT's health remained relatively stable until the age of 15, when she presented with bilateral lower limb swelling, shortness of breath upon exertion and a drastic weight gain. Physical examination revealed bilateral non-pitting oedema extending up to the knees.

Blood tests revealed hypoalbuminaemia at 17 g/L (normal range: 33-48 g/L). Liver and renal function tests, clotting profile, D-dimer level and spot urine protein to creatinine ratio yielded normal values, which collectively discounted possibilities including nephrotic syndrome and deep vein thrombosis. Given the clinical presentation and biochemical evidence, PLE attributable to underlying Noonan syndrome was identified as a leading diagnostic consideration. YT received conservative management with dietary intervention emphasizing a high protein intake and the application of lower limb pressure garments. Her serum albumin level exhibited an improvement to 21 g/L upon discharge.

A technetium-99 human serum albumin (Tc99m HSA) scan confirmed the diagnosis of PLE by demonstrating increased tracer uptake at right lower quadrant of the abdomen and lower pelvic region at four-hour images and with more pronounced 24-hour delay images.

YT was re-admitted three months later for progressive lower limb oedema, accompanied by a decline in serum albumin concentration to a level of 9 g/L. Hypocalcaemia with vitamin D deficiency was also noted likely secondary to impaired gastrointestinal absorption. She was given 20% albumin infusion, diuretics and vitamin D supplement. A medium-chain triglycerides (MCT)-rich diet was implemented. The above interventions were, however, futile in symptom relief, and YT's serum albumin levels persisted at a suboptimal level below 20 g/L.

To further identify the cause, an intranodal and intrahepatic dynamic magnetic resonance lymphangiogram (DCMRL) was performed, revealing features suggestive of central conducting lymphatic anomaly with absence of thoracic duct and abnormally dilated retroperitoneal and iliac lymphatics. Abnormal retrograde mesenteric lymphatic flow and chylous leakage into the small bowels were also noted (Figure 1). An oesophageal-duodenoscopy (OGD) revealed snowflake appearances at duodenal region (Figure 2). Biopsy of the duodenum and terminal ileum showed congested and ectatic lymphovascular spaces in keeping with the diagnosis of lymphangiectasia. The diagnosis of PLE caused by lymphangiectasia due to underlying Noonan syndrome was thereafter substantiated.

Considering her ongoing protein leak refractory to albumin infusion, YT was commenced on an mTOR inhibitor - Sirolimus at 1 mg twice daily orally. Clinical response was evident few weeks after initiation of Sirolimus, with serum albumin level stabilised at levels above 20 g/L, with less frequent albumin infusion from fortnightly initially to four weekly. Her lower limb oedema improved, and serum calcium levels were also normalised such that vitamin D supplements can be stopped. Sirolimus trough levels measured were maintained at normal ranges.

Discussion

PLE is a condition characterised by impaired protein absorption and excessive protein loss through the gastrointestinal tract. Underlying pathophysiology can be classified into three main categories, namely mucosal erosions, increased lymphatic pressure e.g. lymphangiectasia and increased intestinal permeability.[2] In patients with intestinal lymphangiectasia, breakdown of intestinal mucosal lymphatics causes retrograde drainage of systemic lymph into the intestinal lumen leading to intestinal mucosal oedema, hence protein loss and fat-soluble vitamin deficiency due to reduced reabsorption of chylomicrons.

Individuals with Noonan syndrome harbour genetic aberrations that result in the hyperactivity of the RAS-MAPK cascade pathway and extracellular signal-regulated kinase. These molecular pathways play a pivotal role in the intricate orchestration of lymphatic system development. However, in the context of Noonan syndrome, this dysregulation leads to aberrant lymphangiogenesis and compromised lymphatic drainage throughout the body.

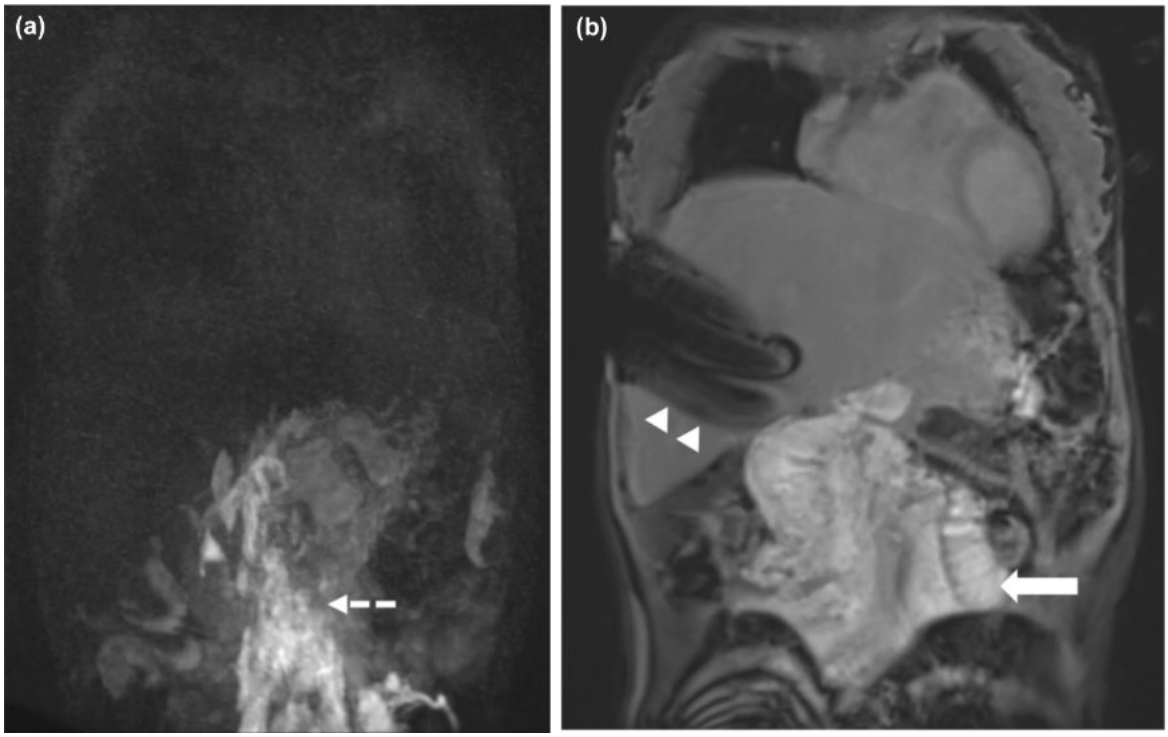

Figure 1 (a) Coronal maximum intensity projection time-resolved MR lymphangiography image acquired at 15 minutes post-contrast injection demonstrates abnormal retrograde mesenteric flow (dashed arrow) and absence of thoracic duct. (b) Coronal T1-weighed post contrast image acquired at 20 minutes shows contrast leakage into the small bowel (arrow), confirming chyle leak. Linear susceptibility artifacts from the intrahepatic needle was indicated by arrowheads.

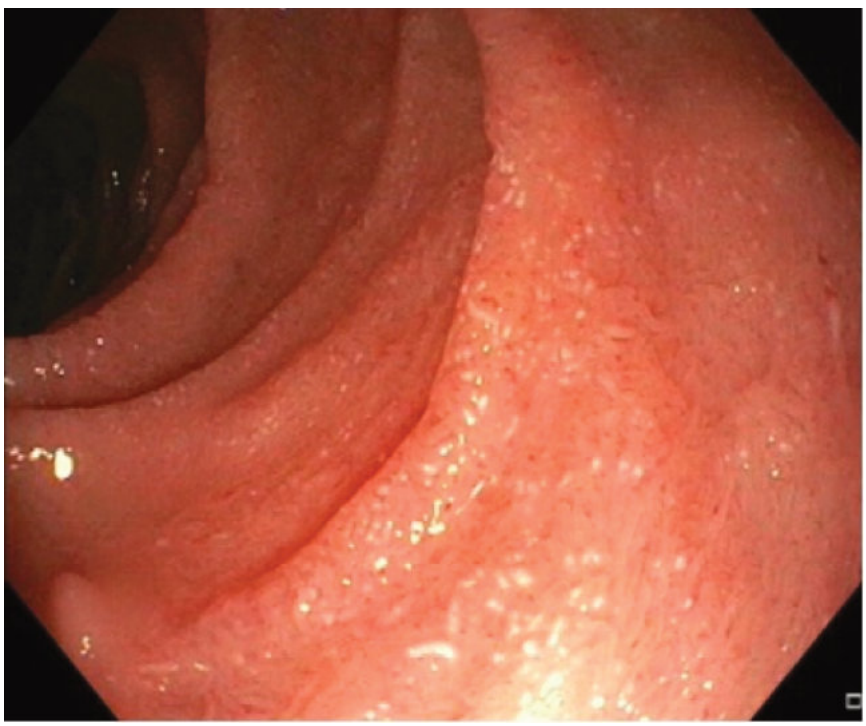

Figure 2 Oesophageoduodenoscopy (OGD) demonstrating classic snowflake appearance in the duodenum (D2) region.

Consequently, a spectrum of clinical manifestations ensue, encompassing pulmonary or intestinal lymphangiectasia, chylothorax, ascites and lymphoedema.[3] The occurrence of intestinal lymphangiectasia precipitates a cascade of events culminating in PLE.

A combination of biochemical, radiological and endoscopic evaluation is essential for diagnosing PLE. Blood tests would demonstrate hypoalbuminaemia. Faecal alpha-1 antitrypsin level is considered a reliable indicator for protein loss from the gut. DCMRL has recently emerged as the radiological imaging modality of choice for evaluation of central conducting lymphatic disorders including PLE. Compared to Tc99m HAS, DCMRL is radiation-free with higher spatial and temporal resolution compared to lymphoscintigraphy for demonstrating anatomical and flow abnormalities in the central conducting system.[3] OGD plays an important role by demonstrating classic snowflake appearance in the duodenal mucosa which is diagnostic of intestinal lymphangiectasia. It is caused by abnormal dilatation and ectasia of the mucosal and submucosal lymphatic vessels at the tip of intestinal villi.[4]

Conventional treatment options include dietary modification and medical therapy. Introduction of low fat, MCT-rich and protein-rich diet helps reduce lymphatic pressure thus limit protein leakage from the gut.[5] Gastrointestinal disturbances, however, could lead to non-compliance. Regular intravenous albumin infusion provides symptomatic relief of oedema, though it fails to revert the on-going protein loss through the gut. Diuretic therapy can be used in conjunction to relieve oedema. Octreotide, a somatostatin analogue, helps reduce lymphatic flow through the gut by reducing splanchnic blood flow, intestinal motility and triglyceride absorption. Propranolol is another alternative that reduces the expression of vascular endothelial growth factor (VEGF) levels and induce apoptosis in lymphatic capillary endothelial cells.[2] Surgical lympho-venous anastomosis can be performed in selected cases. However, for extensive intestinal lymphangiectasia as seen in patients with Noonan syndrome, the above treatment modalities are often ineffective for disease control.

Mammalian target of rapamycin (mTOR) inhibitors have recently been suggested for the treatment of PLE caused by extensive intestinal lymphangiectasia. mTOR is a serine/threonine kinase regulated by phosphoinositide-3-kinase (PI3K) that controls cellular metabolism, angiogenesis and cell growth. Patients with RASopathies were found to have hyperactivated mTOR signalling due to the recently-discovered interconnection between the RAS/MAPK/MEK and PI3K/AKT/mTOR signalling pathways, as well as the role of *PTPN11* gene mutation causing hyperactivation of cytoplasmic tyrosine phosphatase with 2 Src-homology 2 domains (SHP2) which upregulates the PI3K/AKT/mTOR pathway.[6] Hyperactive mTOR signalling increases VEGF expression resulting in abnormal angiogenesis and lymphangiogenesis.[7] Tissues affected by lymphangiectasia were found to have enhanced mTOR expression unsurprisingly. mTOR inhibitors can therefore potentially act on these lymphatic endothelial cell to inhibit mTOR signalling and suppress abnormal lymphatic proliferation. With the same mechanism, mTOR inhibitors are also used to treat tumours[8] and hypertrophic cardiomyopathy[6] associated with RASopathies.

Both Sirolimus and Everolimus are commonly used mTOR inhibitors. Sirolimus has a longer half-life than Everolimus (62 hours versus 28 hours) , while Everolimus has higher bioavailability than Sirolimus.[7] Common side effects include hyperlipidaemia, cytopenia, tachycardia, hepatotoxicity, hyperglycaemia, and electrolyte imbalance, which should be regularly monitored. Recommended dosage for sirolimus ranges from 1 to 1.6 mg/m^2/day in patients less than 40 kg, and 2 mg per day in patients more than 40 kg.[2] Sirolimus trough level should be regularly monitored with 5-15 ng/ml being the optimal therapeutic trough dosage. Clinical effectiveness is usually observed around four weeks after initiation of m-TOR inhibitors.

Only two cases were reported so far regarding the use of mTOR inhibitors in treat paediatric patients with PLE due to intestinal lymphangiectasia. In 2016, Ozeki et al[7] reported a 12-year old Japanese boy with PLE caused by primary intestinal lymphangiectasia, treated with Everolimus at 1.6 mg/m^2/day, who attained clinical response within four weeks and radiological resolution of protein-losing in six months. In 2019, Strauss et al[9] reported another 12-year-old boy with PLE caused by intestinal lymphangiectasia treated with sirolimus, showing stable serum albumin levels without regular albumin infusion.

Conclusion

PLE attributed to intestinal lymphangiectasia represents an uncommon medical condition. A

comprehensive review of the PubMed literature spanning from 1972 to 2022 revealed a mere 11 documented cases wherein individuals with Noonan syndrome experienced PLE.[10-13] Of the few cases, majority were treated with dietary modification or albumin infusion with diuretics. This is the first reported case of using Sirolimus in the treatment of PLE caused by intestinal lymphangiectasia due to Noonan syndrome. With this, we aim to highlight the potential benefits of early initiation of mTOR inhibitors in these groups of patients. Longer duration of follow up for monitoring of clinical response and side effects, however, will be needed to predict its long-term outcome.

Declaration of Interest

The authors have indicated they have no conflicts of interest relevant to this article to disclosure.

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