

A Case of a Central Conducting Lymphatic Anomaly Responsive to Sirolimus

Andrew McCormick, MD,^a Stacy Rosenberg, MD,^b Katherine Tier, MD,^b Arcangela Balest, MD^b

The study of vascular anomalies is a rapidly progressing field in medicine. The development of new knowledge in the pathology and management of these disease processes are exemplified in the treatment of hemangiomas with propranolol and generalized lymphatic malformations with sirolimus. Central conducting lymphatic anomalies have traditionally been refractory to medical and surgical interventions. We report a case of a central conducting lymphatic anomaly that was responsive to sirolimus. A 14-year-old boy presented with chylothorax and chyluria with a lymphangiogram demonstrating abnormal lymphatic flow and reflux along the entire course of the central channels. Traditionally, medical management has been limited to somatostatin and low-fat diet with poor response and surgical interventions that are palliative. Sirolimus allows a new medical option that could improve management of this unresponsive population.

A recent *Pediatrics* article reviewed the newest classification of vascular anomalies and demonstrated the expanding nature of this field of medicine. Within the grouping of vascular malformations is a family of slow-flowing lesions that affect the lymphatic system.¹ Although recent research has demonstrated the responsiveness of sirolimus in the treatment of potentially devastating generalized lymphatic malformations,² there has been a paucity of treatment of the central channel lymphatic anomaly. This closely related disease of generalized lymphatic anomalies reflects a dysplastic formation of the major lymphatic channels in the body (ie, thoracic duct).³ The difficulty is that these lesions can be difficult to delineate and they have demonstrated a refractory response to both medical and surgical treatment.⁴

CLINICAL RECORD

A 14-year-old boy with a large, hyperpigmented patch of the left flank presented with a 2-month history of “white urine” (Fig 1) and progressive dyspnea on exertion. A chest radiograph (Fig 2A) was obtained and demonstrated a large left pleural effusion. Initial evaluation included a thoracentesis, which demonstrated “milky white” pleural fluid (Fig 1). The appearance of the pleural fluid raised concern for chylothorax and chyluria and was confirmed with pleural triglyceride level of 1614 mg/dL and urine triglyceride level of 498 mg/dL. There was a high level of concern for a complex vascular anomaly syndrome with associated generalized lymphatic malformation. Therefore, a biopsy of the hyperpigmented lesion was obtained. The biopsy suggested capillary malformation. MRI including arterial and venous phases of chest,

abstract

^aDepartment of Pediatrics, Vascular Anomalies Center, and
^bDepartment of Pediatrics, Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania

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Address correspondence to Andrew McCormick, MD, Department of Pediatrics, Vascular Anomalies Center at Children’s Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Faculty Pavilion 3rd Floor, Pittsburgh, PA 15224. E-mail: mccormickaa@upmc.edu

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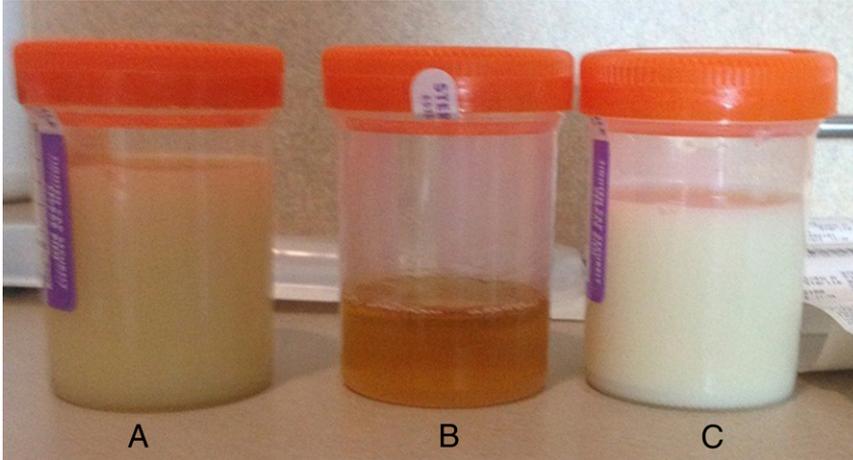


FIGURE 1
A, Urine at presentation. B, Urine after chest tube placement. C, Pleural fluid at presentation.

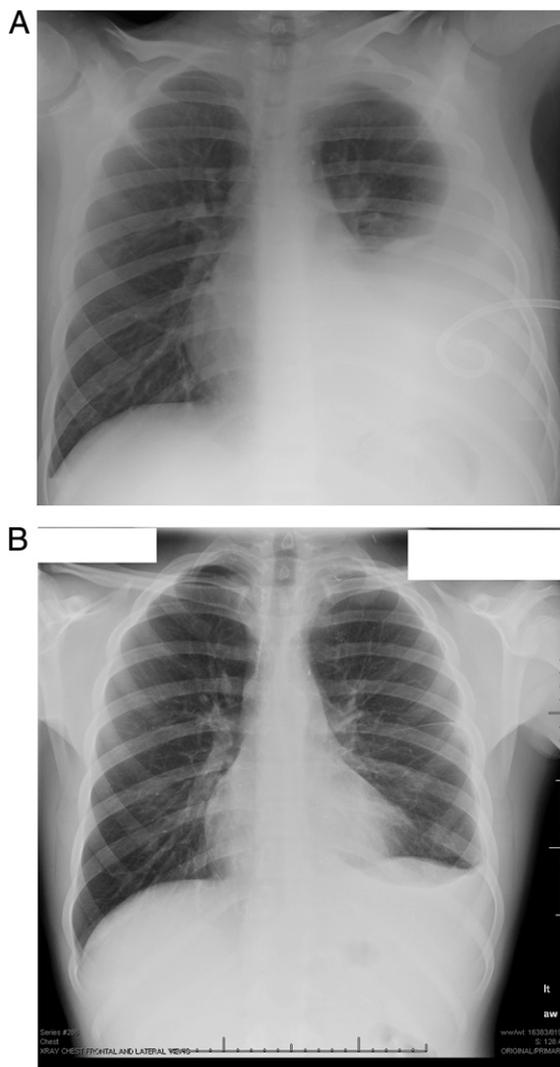


FIGURE 2
A, Chest radiograph demonstrates large left pleural effusion before initiation of sirolimus. B, Chest radiograph demonstrates tiny left pleural effusion while patient is therapeutic on sirolimus in outpatient follow-up.

abdomen, and pelvis demonstrated no generalized lymphatic malformation. A lymphangiogram (Fig 3) was performed to better delineate the etiology of the chylous formation. The lymphangiogram demonstrated abnormal flow and reflux along the entire course of the central channels with significant collateral flow suggestive of a central conducting lymphatic anomaly. Due to significant dyspnea and hypoxia, a chest tube was placed and revealed chylous chest tube output of 2 to 3 L per day over the following week. He was started on a low-fat diet and Octreotide with no significant improvement in his output. After 3 weeks with no clinical improvement, he was started on sirolimus and achieved therapeutic levels (rapamycin 10–15 ng/mL). At this point he had resolution of his chylous output over the course of a week with removal of his chest tube. He was able to liberalize his diet with no reaccumulation of his pleural effusion. He returned for follow-up 6 weeks after discharge and had continued therapeutic sirolimus levels, a chest radiograph (Fig 2B) that demonstrated a small pleural effusion, and no functional impairment (able to climb 6 flights of stairs with no dyspnea). Unfortunately, the patient became noncompliant with his sirolimus (measured rapamycin levels of 0) and at follow-up 2 months later he had return of dyspnea on exertion and chest radiograph/ultrasound demonstrated a large pleural effusion. He subsequently underwent thoracic duct reimplantation surgery with sustained clinical response after 6 months.

DISCUSSION

Chylothorax is the most common cause of pleural effusions in neonates, but in older pediatric patients it is a relatively rare finding. It can arise from a wide variety of conditions, either as the result of trauma or atraumatic illness.⁵ Large multicenter trials in adults have demonstrated

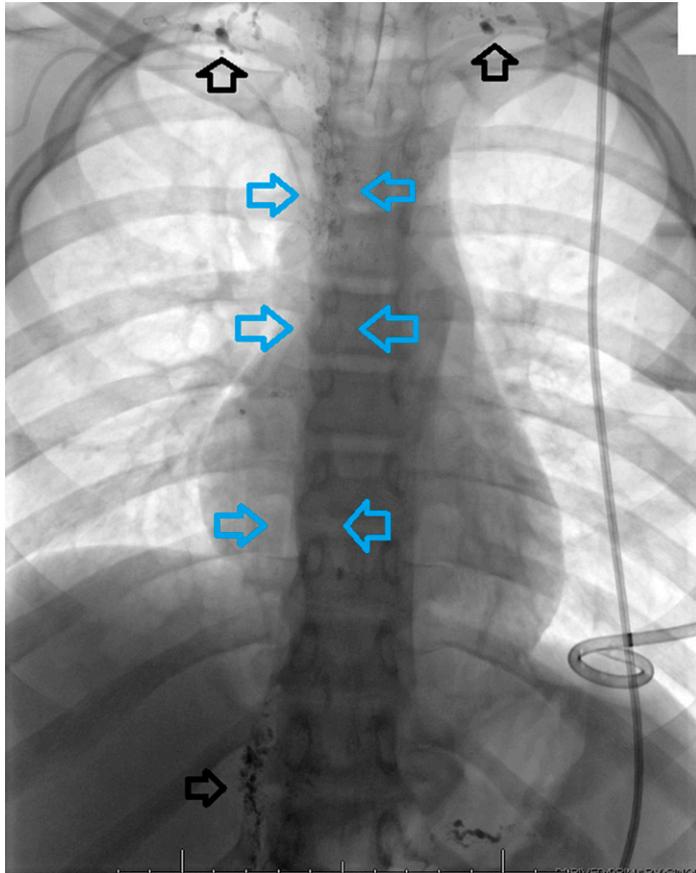


FIGURE 3

Lymphangiogram demonstrates paucity of flow through thoracic duct (outlined by blue arrows) but areas of uptake (black arrows) demonstrate collateral flow.

a relatively even distribution: approximately 50% of cases are found to be traumatic and 44% atraumatic.⁶ Fewer pediatric trials are available, but one study suggests that up to 90% of chylothoraces in pediatric patients are related to surgery, and 65% are directly caused by trauma to the thoracic duct.⁵ Although most cases of trauma-related chylothorax in pediatrics are related to congenital heart surgery, there are a wide variety of atraumatic causes. The most common is malignancy, and in some cases, chylothorax has been the presenting feature of lymphoma. Less commonly, congenital malformations including the thoracic duct anomalies found in central conducting lymphatic anomalies can result in chylothorax.⁷

The thoracic duct is a major lymphatic drainage pathway. It is the

largest lymphatic duct in the body, and lymph may pass through it at up to 190 mL/h.⁸ Congenital anomalies of the thoracic duct are rare and their origin is not well understood. The paradigm is that a lymphatic malformation arises through a dysfunction in embryogenesis of the lymphatic system and a variety of mutations related to vascular endothelial growth factor (VEGF) have been implicated in many types of lymphatic malformations.⁹ The thoracic duct anomalies found in central conducting lymphatic anomalies are poorly characterized and therefore understanding their development and ultimately their management has been a challenge. Central conducting lymphatic anomaly pathology may be evident on imaging, such as MRI or lymphoscintigraphy.¹⁰ Often, however, imaging cannot identify

the source of the apparent chyle leak and often the malformations are complicated with no simple anatomic solution. As a result of the difficulty in delineating lesions and the complex nature of these lesions, the central conducting lymphatic anomalies can be refractory to both medical and surgical management.⁴ In fact, most interventions are considered palliative rather than curative.

Sirolimus, a mechanistic target of rapamycin (mTOR) inhibitor, was derived from the actinomycete, *Streptomyces hygroscopicus*, and initially evaluated as an antifungal agent in the 1970s.¹¹ When its immunosuppressive effects were discovered, along with its structural similarity to tacrolimus, further evaluation for possible use in organ transplantation was evaluated¹² and has since expanded to a variety of other diseases.

mTOR is a serine-threonine kinase that regulates cell growth, cell cycle progression, cell motility, angiogenesis, and cell growth.¹³ mTOR is a member of the phosphatidylinositol 3-kinase superfamily and is downstream from several tyrosine kinases, including VEGF. VEGF is a known key regulator in lymphangiogenesis and angiogenesis. Also supporting a role for sirolimus to treat vascular and lymphatic abnormalities, the human diseases tuberous sclerosis and lymphangioleiomyomatosis both involve mutations upstream from mTOR, and sirolimus treatment has led to significant reduction of lesion size.¹⁴ In a recent case series by Hammill et al,² 4 children with diffuse microcystic lymphatic malformations involving bone and significant chyloous effusions had substantially decreased pleural effusion output soon after initiation of treatment with chest tube removal.

Other case reports also discuss clinical improvement and reduction of lymphatic malformation size with sirolimus treatment.¹⁵ To gain further understanding of

treatment with sirolimus for these complicated vascular disorders, a prospective clinical trial is being conducted (clinicaltrials.gov NCT00975819). Although sirolimus has demonstrated clinical success in management of many lymphatic malformations, there is a paucity of literature to demonstrate its utility in management of central conducting lymphatic anomalies.

CONCLUSIONS

The importance of this clinical case is to demonstrate sirolimus responsiveness in treatment of a central conduction lymphatic anomaly that has classically been refractory to medical and surgical interventions. The expansion of the treatment armament for this poorly responsive disease would assist in reducing the morbidity and mortality of our patients.

ABBREVIATIONS

mTOR: mechanistic target of rapamycin
VEGF: vascular endothelial growth factor

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