Case report: hepatobronchial lymphatic communications in single ventricle patients as a pathophysiological mechanism of plastic bronchitis: diagnosis and treatment

Deborah Rabinowitz [1,2]*, **Wolfgang Radtke** [2,3], **Majeed Bhat**[3], and **Maxim Itkin** [4,5]

[1]Division of Interventional Radiology, Department of Medical Imaging, Nemours/Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803, USA;
[2]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA; [3]Nemours Cardiac Center, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA; [4]Center for Lymphatic Imaging, Penn Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; and [5]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Background	Plastic bronchitis is a rare but devastating complication in single ventricle patients after Fontan completion. Recent advances in dynamic contrast-enhanced magnetic resonance lymphangiogram demonstrate the typical pathophysiological mechanism of the thoracic duct leaking lymphatic fluid towards the bronchi resulting in intraluminal casts. This has been termed abnormal pulmonary lymphatic perfusion and has been successfully treated in 94% of patients with thoracic duct occlusion. However, in some cases, this aberrant flow is not identified and therefore no intervention is available. This case report identifies a newly discovered origin of abnormal lymphatic flow from the liver to the bronchi and the treatment of these patients.
Case summary	We report two cases of plastic bronchitis in single ventricle patients with no identified abnormal lymphatic pulmonary perfusion from the thoracic duct. Both patients underwent liver lymphangiogram and demonstrated aberrant flow from the hepatic lymphatic ducts to the bronchi. These were successfully occluded, and plastic bronchitis symptoms resolved in both cases.
Discussion	The recent discovery of the abnormal pulmonary lymphatic perfusion from the thoracic duct to the bronchi has allowed successful treatment of 94% of single ventricle patients with plastic bronchitis. The discovery of hepatobronchial lymphatic perfusion reveals an occult aetiology of plastic bronchitis and a second target for embolization and successful treatment.
Keywords	Fontan • Lymphatics • Plastic bronchitis • Embolization • Case report

---

Learning points

- Plastic bronchitis in single ventricle patients is caused by lymphatic leakage into the bronchi with inspissation of these secretions.
- Dynamic contrast-enhanced magnetic resonance lymphangiogram can accurately diagnose lymphatic abnormalities, and thoracic duct embolization can successfully cure plastic bronchitis in 94% of patients.
- The source of lymphatic leakage may also originate in the liver lymphatics, and selective lymphatic embolization can successfully treat these patients.

Introduction

Plastic bronchitis is a rare but devastating complication in single ventricle patients with an estimated incidence of 4% and reported mortality rate of up to 50%.[1] A lymphatic aetiology of this disease has been reported in the past.[2] Recently described dynamic contrast-enhanced magnetic resonance lymphangiogram (DCMRL) led to discovery of the pathophysiological mechanism of plastic bronchitis, demonstrating abnormal lymphatic flow from the thoracic duct into lung parenchymal lymphatic ducts reaching the bronchial submucosa and lymphatic 'weeping' into bronchial lumen.[3] This phenomenon was termed abnormal pulmonary lymphatic flow. Cessation of this flow by percutaneous thoracic duct embolization resulted in resolution of symptoms in 94% of patients.[3]

Here we describe two patients with Fontan physiology with plastic bronchitis with no abnormal lymphatic flow from the thoracic duct into pulmonary parenchyma on either DCMRL or thoracic duct injection. Liver lymphangiography, however, showed communication of the liver lymphatics directly with patients' airways. Percutaneous embolization of the liver lymphatic ducts resulted in resolution of plastic bronchitis. These cases demonstrate a new pathophysiological mechanism of plastic bronchitis in Fontan patients.

Timeline

Case presentation

Patient 1

The first patient was a 14-year-old boy with hypoplastic left heart syndrome, acquired left pulmonary artery obliteration despite multiple attempts at salvage, extra-cardiac conduit total cavopulmonary anastomosis to right lung, and mild systolic and diastolic ventricular dysfunction. He had recently developed plastic bronchitis with intermittent cast expectoration necessitating multiple hospitalizations. Symptomatic management of plastic bronchitis included inhaled tissue plasminogen activator (tPA) and hypertonic saline and levalbuterol nebulizations. Magnetic resonance lymphangiogram (MRL), conventional lymphangiogram with catheterization of the thoracic duct, and liver lymphangiogram at an outside hospital demonstrated a normal thoracic duct without abnormal pulmonary lymphatic flow. However, on heavily T2-weighted images during the MRL, a small tortuous tubular hyperintensity was noted, which appeared to arise from the level of the right diaphragm, extending into the mediastinum (*Figure 1*).

The patient was then transferred to our institution for further lymphatic imaging and interventions. Cardiac catheterization revealed central venous pressure/pulmonary artery pressure (CVP/PAP) of 17 mmHg and a transpulmonary gradient of 3–4 mmHg with

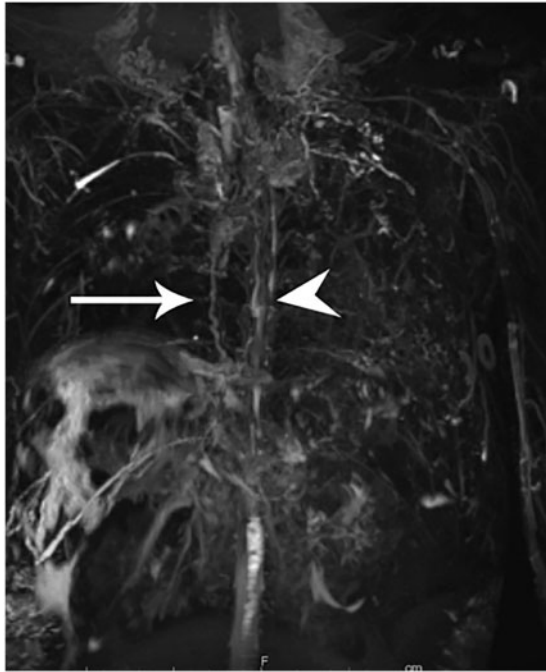| Patient 1	
Fontan completion	October 2012
Fenestration closure	January 2014
Onset persistent cough	October 2017
First cast identified	22 November 2017
First magnetic resonance (MR) lymphangiogram (OSH)	7 March 2018
First Conventional thoracic and liver lymphangiogram (OSH)	15 August 2018
Second MR/interventional radiology (IR)/liver lymphangiogram (no source identified)	19 December 2018
Third liver lymphangiogram with hepatobronchial duct identified and partial embolization	7 February 2019
Fourth liver lymphangiogram (unsuccessful embolization)	13 February 2019
Fifth liver lymphangiogram and successful hepatobronchial duct embolization	21 February 2019
Patient 2	
Fontan completion	July 2009
Emergency department (ED) admission (OSH) for respiratory failure	12 January 2020
MR/IR/liver lymphangiogram with hepatobronchial duct embolization	30 January 2020
Tissue plasminogen activator nebulization discontinued	12 February 2020
Pulmozyme nebs discontinued	6 March 2020
Discharge to home	10 March 2020

Figure 1 Patient 1: Heavy T2W imaging of the chest. Demonstrated tortuous vascular structure (arrow) to the right of the thoracic duct (arrowhead).
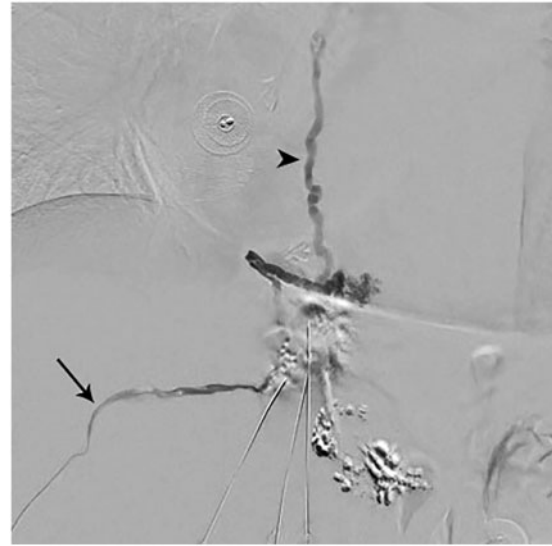

Figure 2 Patient 1: Digital subtraction image of the injection of the microcatheter with iodinated contrast positioned in the liver lymphatic ducts (arrow). The injection demonstrated opacification of the lymphatic structure, originating in the area of the falciform ligament and extending into the upper mediastinum.

Figure 3 Patient 1: Bronchoscopy image demonstrating the opacification of the submucosal lymphatic vessels with methylene blue injected through microcatheter positioned in the liver lymphatics.

pulmonary artery wedge pressures of 13–14 mmHg. During cardiac catheterization, a veno-venous collateral from the right innominate vein to right pulmonary veins was occluded using two Amplatzer Vascular Plugs (Abbott, Santa Clara, CA, USA).

Repeat MRL and intranodal lymphangiography confirmed the findings from the outside institution demonstrating no abnormal flow from the thoracic duct towards the mediastinum or airway. Liver lymphangiogram was performed as previously described.[4] In short, using ultrasound guidance, a 25-gauge spinal needle (BD, Franklin Lakes, NJ, USA) was positioned close to the wall of one of the branches of the portal vein, and a small amount of water-soluble contrast was injected. Once intra-lymphatic position was confirmed, contrast was injected under digital subtraction angiography. The liver lymphangiography demonstrated dilated liver lymphatic ducts; however, there was normal communication with the thoracic duct. Because of exacerbation of the symptoms, the patient then underwent repeat liver lymphangiogram 2 months later, which demonstrated a liver lymphatic duct arising from the superior surface of the liver extending into the mediastinum (Figure 2). An endovascular 0.014″ wire (Transcend, Boston Scientific, Marlborough, MA, USA) and then microcatheter (Renegade, Boston Scientific, Marlborough, MA, USA) were percutaneously advanced into the intrahepatic portion of this duct. Methylene blue was injected into the catheter during concurrent bronchoscopy. It demonstrated immediate brisk lymphatic submucosal bronchial perfusion of the carina, tracking into the right mainstem bronchus, right bronchus intermedius, and right lower lobe bronchus (Figure 3). N-BCA glue (TRUFILL, Codman Neuro, Raynam, MA, USA) diluted 3:1 with Lipiodol (Guerbet LLC,

Princeton, NJ) was injected via the microcatheter after priming the catheter with 5% dextrose solution. Embolization of lymphatics looks similar to contrast injection as the N-BCA glue is injected in the same distribution as the contrast and has similar radio-opacity.

However, the patient's symptoms persisted and another two attempts of liver lymphangiogram were performed, demonstrating persistent opacification of the aberrant hepatic duct. At the last liver lymphangiogram, two more intrahepatic lymphatic ducts connecting
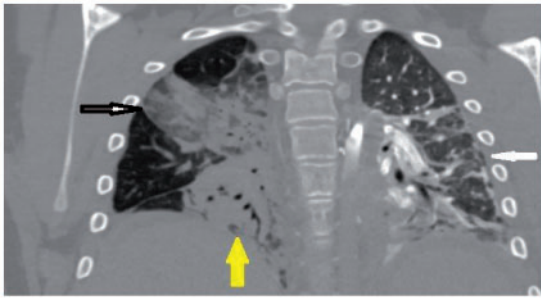
Figure 4 Patient 2: Coronal post-contrast arterial phase computed tomography image of the chest demonstrating ground-glass appearance (black arrow), segmental parenchymal collapse (yellow arrow), and interstitial thickening (white arrow).

Figure 5 Patient 2: Fluoroscopic image of the liver lymphangiography through the needle (arrow) positioned in the liver lymphatic ducts resulting in opacification of the hepatobronchial lymphatic duct (arrowhead).

to the aberrant leaking duct were visualized. Both of these ducts were embolized, and completion liver lymphangiogram demonstrated no further opacification of the duct.

The patient had an uneventful post-procedural course and was discharged home. All medications for plastic bronchitis were successfully weaned, and he has been asymptomatic for 13 months since the procedure.

Patient 2

The second patient was a 13-year-old boy with double-outlet right ventricle (S, D, D) with malalignment ventricular septal defect with inlet extension and straddling of the tricuspid valve, right aortic arch with mirror image branching, severe valvar and subvalvar pulmonic stenosis, and left superior vena cava without bridging vein, after staged palliation culminating in a fenestrated lateral tunnel Fontan with covered stent recanalization of the central pulmonary artery between the hemi-Fontan and bidirectional Glenn anastomosis. He is a former 30-week twin premature infant with history of long ventilator dependence, persistent impaired gas exchange, and elevated pulmonary vascular resistance (Rp). He presented to an outside emergency department with a 4-month history of cough and expectoration of 'worm-like material', shortness of breath, decreased appetite, and fatigue. He had oxygenation in the low 80 s and was placed on 15 L of oxygen delivered through a Vapotherm respiratory system (Vapotherm, Inc., Exeter, NH) at 80% FiO_2 and transferred to our cardiac intensive care unit. He remained afebrile without leucocytosis or other signs of infection. Chest computed tomography demonstrated multifocal lobar and segmental atelectasis with interstitial thickening and scattered ground-glass opacification (*Figure 4*). He underwent a cardiac catheterization 2 weeks into admission that demonstrated elevated CVP/PAP of 19 mmHg with elevated transpulmonary gradient of 11–12 mmHg and elevated Rp of 5.2 units m²insignificant response to oxygen. His hospital course was significant for waxing and waning respiratory distress with oxygen requirement as high as 8 L on 100% O_2. Bronchoscopy demonstrated multifocal casts consistent with plastic bronchitis. He underwent DCMRL, which demonstrated bilateral thoracic ducts extending to the bilateral subclavian veins, respectively, without definitive leak of
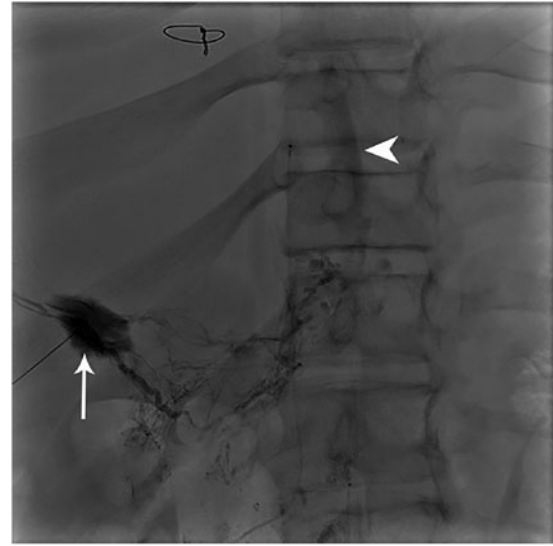
the abnormal pulmonary lymphatic flow. He then underwent intranodal lymphangiography and cannulation of both thoracic ducts. These were both normal in course and calibre without identified abnormal flow into pulmonary parenchyma. He therefore underwent liver lymphangiogram, which demonstrated a markedly ectatic hepatic duct extending to the mediastinum and terminating in smaller abnormal ducts entering the carina as well as the bilateral upper lobe bronchi (*Figure 5*). This duct was then cannulated with a 3 Fr microcatheter (Renegade, Boston Scientific, Marlborough, MA, USA), and methylene blue was injected while performing the bronchoscopy (*Figure 6*). It demonstrated abnormal bronchial submucosal lymphatic perfusion of the bilateral mainstem and lower lobe bronchi (*Figure 7*). This lymphatic duct was then embolized with endovascular coils and N-BCA glue (Codman Neuro) diluted with Lipiodol in a 2:1 ratio to the access point in the liver. He immediately stopped producing casts and was weaned from tPA and Pulmozyme (Genentech, San Francisco, CA, USA) nebulizations. The patient did experience an increase in his pre-existing ascites after the procedure; however, this improved significantly with diuretics within a week and he returned to his preadmission weight. He was discharged home with oxygen saturation greater than 90% on 2 L 100% nasal cannula with normal chest radiograph results. He has remained symptom free without further cast expectoration in the 2 months since embolization.

Discussion

In this case series, we described a new pathophysiological mechanism of plastic bronchitis—hepatobronchial lymphatic ducts conducting liver lymph into the bronchial tree.
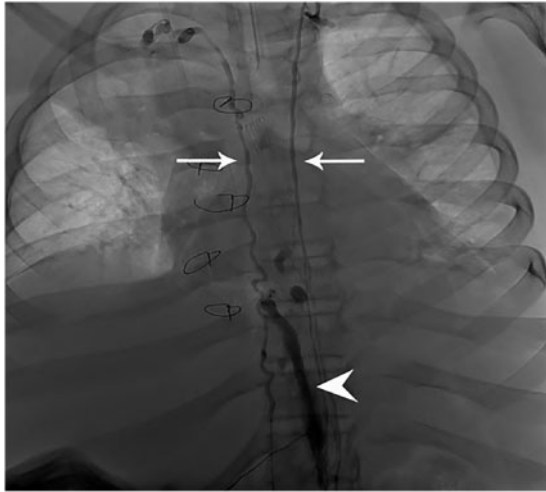
Figure 6 Patient 2: Fluoroscopic image of the simultaneous injection of both thoracic duct (arrows) and hepatobronchial lymphatic duct (arrowhead) through the endovascular catheters.
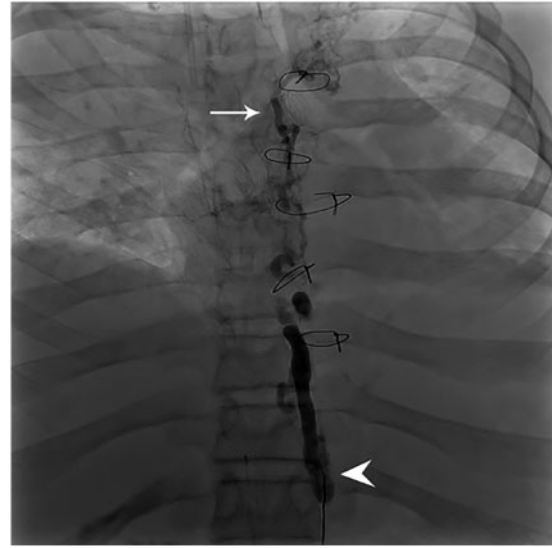

Figure 7 Patient 2: Fluoroscopic image of injection of the hepatobronchial lymphatic duct through the catheter (arrowhead). The duct extends to the level of bronchial carina (arrow).

The diagnosis of plastic bronchitis in single ventricle patients with Fontan physiology has undergone tremendous advancement with the advent of DCMRL and percutaneous thoracic duct embolization.[5] It has been shown that in patients with plastic bronchitis, there is abnormal pulmonary lymphatic flow from the thoracic duct into lung parenchyma resulting in lymph seeping into the airways. This pathophysiological mechanism is likely a combination of congenital, aberrant lymphatic anatomy and increase of the lymphatic fluid production in the setting of elevated central venous pressure. However, in some patients, no abnormal lymphatic flow from the thoracic duct into lung parenchyma was demonstrated.[3]

The liver is probably the most important lymphatic organ in the body, normally contributing ~40% of the flow in the thoracic duct.[6] In conditions of liver congestion, such as Fontan physiology and congestive heart failure (CHF), the flow in the liver lymphatics increases 10-fold.[5]

Liver lymphatic anatomy is very complex, poorly understood, and primarily based on the studies of Henri Rouvière from 1938.[1] Generally, it has been divided into two subsystems: superficial and deep.[7] The superficial lymphatics drain the surface of the liver and extend into the mediastinum through the falciform and coronary ligaments, joining mediastinal lymph nodes and thoracic duct. Deep lymphatics drain the majority of the liver and follow the portal vein, joining the thoracic duct below the diaphragm and following the hepatic veins. It is said that the majority of the liver lymph (80%) drains through the deep lymphatics.

Liver lymphangiography and embolization are relatively new techniques that were used to diagnose and treat post-surgical liver lymphorrhoea and protein-losing enteropathy in patients with congenital heart disease.[4,8] In the latter study, the abnormal hepatoduodenal lymphatics were described as a cause of the leakage of the liver lymph into the duodenum. It was suggested that these lymphatics represent an anatomical lymphatic variant, which presents clinically because of increased lymphatic flow in patients with elevated central venous pressure.

In our first patient, the presence of an abnormal lymphatic duct between the diaphragm and mediastinum on T2 magnetic resonance imaging that was not opacified from groyne lymph node injection prompted us to perform liver lymphangiography. Because of the complexity of the liver lymphatic anatomy, it took several attempts in this patient to discover the abnormal pathway and embolize it. The foreknowledge of the liver as a source of plastic bronchitis guided us to perform a liver lymphangiogram immediately in the second patient. The small number of patients described is a weakness of our report. As more patients with plastic bronchitis are evaluated and treated, the true incidence of hepatobronchial lymphatic connections will be illuminated, as will the efficacy of lymphatic embolization.

We postulate the pathophysiology of hepatobronchial lymphatic leak is also likely secondary to overproduction of lymphatic fluid within the liver and underlying variant lymphatic vessels that directly connect the liver lymphatics to the airways.

The discovery of the existence of the communications between hepatic lymphatic system and chest structures is groundbreaking. Its significance can go beyond the specific case of patients with plastic bronchitis. It is possible that some unexplained pulmonary symptoms in patients with liver congestion syndromes (CHF and liver cirrhosis) can be explained by the presence of these communications.

Further dissemination of lymphatic imaging methods will allow for discovery of more pathophysiological mechanisms and improve the diagnostic and treatment approaches.

Lead author biography

Deborah Rabinowitz graduated from Perelman School of Medicine at the University of Pennsylvania in 2004. After completing a paediatrics intern year at Cohen Children's Hospital, she completed a radiology residency at George Washington University Hospital and 2 years of fellowship in Pediatric Interventional Radiology and Pediatric Radiology at the Children's Hospital of Philadelphia. She began working as the Division Chief of Interventional Radiology at Nemours/Alfred I. duPont Hospital for Children in 2011. She co-founded the Lymphatics Center at Nemours/Alfred I. duPont Hospital for Children, which is a multidisciplinary programme treating children with lymphatic flow disorders.

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.

References

1. Rouvière H, Tobias MJ. *Anatomy of the Human Lymphatic System.*Ann Arbor, MI: Edwards Brothers, Inc; 1938.
2. Languepin J, Scheinmann P, Mahut B, Le Bourgeois M, Jaubert F, Brunelle F *et al.* Bronchial casts in children with cardiopathies: the role of pulmonary lymphatic abnormalities. *Pediatr Pulmonol* 1999;**28**:329–336.
3. Dori Y, Keller MS, Rome JJ, Gillespie MJ, Glatz AC, Dodds K *et al.* Percutaneous lymphatic embolization of abnormal pulmonary lymphatic flow as treatment of plastic bronchitis in patients with congenital heart disease. *Circulation* 2016;**133**: 1160–1170.
4. Itkin M, Piccoli DA, Nadolski G, Rychik J, DeWitt A, Pinto E *et al.* Protein-losing enteropathy in patients with congenital heart disease. *J Am Coll Cardiol* 2017;**69**: 2929–2937.
5. Wegria R, Zekert H, Walter KE, Entrup RW, de Schryver C, Kennedy W *et al.* Effect of systemic venous pressure on drainage of lymph from thoracic duct. *Am J Physiol* 1963;**204**:284–288.
6. Ohtani O, Ohtani Y. Lymph circulation in the liver. *Anat Rec* 2008;**291**:643–652.
7. Trutmann M, Sasse D. The lymphatics of the liver. *Anat Embryol* 1994;**190**: 201–209.
8. Guez D, Nadolski GJ, Pukenas BA, Itkin M. Transhepatic lymphatic embolization of intractable hepatic lymphorrhea. *J Vasc Interv Radiol* 2014;**25**: 149–150.