Successful Treatment of Plastic Bronchitis by Selective Lymphatic Embolization in a Fontan Patient

abstract

Plastic bronchitis is a rare and often fatal complication of single-ventricle surgical palliation after total cavopulmonary connection. Although lymphatic abnormalities have been postulated to play a role in the disease process, the etiology and pathophysiology of this complication remain incompletely understood. Here we report on the etiology of plastic bronchitis in a child with total cavopulmonary connection as demonstrated by magnetic resonance (MR) lymphangiography. We also report on a new treatment of this disease. The patient underwent non-contrast T2-weighted MR lymphatic mapping and dynamic contrast MR lymphangiography with bi-inguinal intranodal contrast injection to determine the anatomy and flow pattern of lymph in his central lymphatic system. The MRI scan demonstrated the presence of a dilated right-sided peribronchial lymphatic network supplied by retrograde lymphatic flow through a large collateral lymphatic vessel originating from the thoracic duct. After careful analysis of the MRI scans we performed selective lymphatic embolization of the pathologic lymphatic network and supplying vessel. This provided resolution of plastic bronchitis for this patient. Five months after the procedure, the patient remains asymptomatic off respiratory medications. Pediatrics 2014;134:e590–e595

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KEY WORDS
lymphatics, single ventricle, Fontan, plastic bronchitis

ABBREVIATIONS
CVP—central venous pressure
MR—magnetic resonance
PB—plastic bronchitis
TCPC—total cavopulmonary connection
TD—thoracic duct

Dr Dori conceptualized and designed the study, performed the MRI studies and lymphatic interventional procedure, and drafted the manuscript; Drs Keller and Rychik were an integral part of the case and reviewed and revised the manuscript; Dr Itkin conceptualized and designed the study, performed the MRI studies and lymphatic interventional procedure, and edited the manuscript; and all authors approved the final manuscript as submitted.

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Plastic bronchitis (PB) is rare and often fatal complication of single-ventricle surgical palliation after total cavopulmonary connection (TCPC).1–3 The disease is caused by exudation and desiccation of proteinaceous material in the airways, leading to formation of casts composed mainly of fibrin.4 Once formed, the casts are expectorated by coughing or, if not, can lead to asphyxiation and death. Lymphatic abnormalities have been thought to play a role in the disease process, but the etiology and pathophysiology of this disease remain incompletely understood.2

CASE REPORT

A 6-year-old boy with hypoplastic left heart syndrome presented to our institution 6 months after being diagnosed with PB. At age 3 he underwent extracardiac fenestrated TCPC, complicated by chyloous effusions. At age 5 and a half he was admitted to a local hospital with respiratory distress. There he was diagnosed with pneumonia and treated with antibiotics. Two months later he started to expectorate bronchial casts and was diagnosed with PB. After the diagnosis he underwent cardiac catheterization that showed a TCPC pressure of 14 mm Hg and a patent fenestration. Oxygen saturation in the descending aorta was measured at 70%, with a mixed venous saturation of 59%. There was a low pulmonary to systemic flow ratio of 0.5:1 because of a large veno-veno collateral vessel that was embolized. He also underwent bronchoscopy that demonstrated right-sided excess secretions and a cast in the right upper lobe. Sildenafil, saline nebulizations, acetylcysteine, dornase alfa, albuterol, and steroid treatments were initiated, and he was discharged from the hospital. Despite this aggressive conservative therapy, he continued to have frequent casts. The boy was referred to our institution for evaluation and possible treatment of PB. He underwent noncontrast T2-weighted MR lymphatic mapping and dynamic contrast MR lymphangiography. Noncontrast T2-weighted mapping was performed as previously described.5 It demonstrated significant dilation of the right peribronchial lymphatic ducts and dilated, proliferative supraclavicular and lumbar lymphatic networks (Fig 1).

Contrast-enhanced dynamic MR lymphangiography was performed with bilateral intranodal contrast injection using the technique described by Nadolski and Itkin.6 It involved bilateral ultrasound-guided needle punctures of inguinal lymph nodes outside the MRI scanner; followed by positioning of the patient in the scanner and simultaneous slow-hand injections of 2 mL gadolinium contrast (Magnevist; Bayer Healthcare Pharmaceuticals Inc, Wayne, NJ) and 2 mL saline into each lymph node during time-resolved central k-space dynamic T1-weighted MRI over 10 minutes. The imaging was started 1 minute after the beginning of contrast injection. The sequence parameters were adjusted with a time delay (3 seconds imaging, 27 seconds pause) such that a complete imaging volume partition was acquired approximately every 30 seconds. Dynamic contrast MR lymphangiography demonstrated progression of the contrast through dilated lumbar lymphatics, through the cisterna chyli, to the thoracic duct (TD) outlet (Fig 2). At the level of the lower mediastinum, a separate dilated lymphatic duct originating from the TD was seen (Fig 2 B and C). Contrast progressed retrograde through this branch toward the carina and right lung hilum. Multiple lymphatic vessels at the right hilum surrounding the airway were then observed (Fig 2C).

The imaging results were reviewed with the parents, and the notion of a selective lymphatic embolization procedure was discussed. At this point, a decision was made to attempt more aggressive conservative therapy with higher sildenafil dosage and inhaled tissue-type plasminogen activator to consider an embolization procedure only if medical treatment failed. Over the next 3 weeks the patient had only slight improvement in symptoms, so he returned to our institution for a planned interventional treatment of his PB.

After careful analysis of the MRI scans we hypothesized that the cause of PB in this child was abnormal retrograde lymphatic flow from the TD toward the right lung hilum that resulted in peribronchial lymphatic congestion. This congestion eventually results in leak of proteinaceous fluid into the airway when the barrier for protein leak is broken down. A schematic of the lymphatic anatomy derived from the MRI scans is shown in Fig 2D. Furthermore, we hypothesized that selective embolization of the abnormal duct and network would be feasible. After obtaining informed consent, we proceeded to intervention.

The procedure, which was performed under general anesthesia, consisted of 2 parts: initial cardiac catheterization followed by TD catheterization with selective lymphatic branch embolization. The goal of cardiac catheterization was to occlude right-to-left shunts to reduce the risks of systemic embolization from the Lipiodol (Guerbert, Villepinte, France) used for the lymphangiogram. The patient was found to have low TCPC pressures of 10 mm Hg, and a large veno-veno collateral vessel was embolized. In addition, temporary balloon occlusion of the TCPC fenestration was performed with a German catheter. Next, intranodal lymphangiogram was performed as described by Nadolski and Itkin with injection of ~2 mL Lipiodol into right and left inguinal lymph nodes.6,7 Under fluoroscopic guidance, using a 22-gauge Chiba needle (Cook
Medical Inc, Bloomington, IN), the cisterna chyli was fluoroscopically accessed via anterior transabdominal approach. A guidewire (V18 Control, Boston Scientific, Natick, MA) was advanced into the TD and manipulated cephalad. Over the wire, a 60-cm 2.3F Rapid Transit microcatheter (Cordis Corp, Warren, NJ) was advanced further into the TD. Injection of water-soluble contrast into the TD opacified a large lymphatic collateral branching off the main TD, progressing toward the right hilum, confirming the MRI findings (Fig 3A and B). The microcatheter was then advanced over the wire and selectively positioned inside this lymphatic collateral. Embolization of the collateral was then performed by using 4 mL Lipiodol to occlude distal small lymphatics, followed by injection of 1 to 2 mL n-Butyl cyanoacrylate (Trufill; Cordis Corporation, Warren, NJ) diluted 1:2 with Lipiodol in the proximal part of the collateral (Fig 3C and D).

The patient recovered from the procedure without complications. The next day his oxygen saturation increased from 80% before the procedure to 90%. The patient was discharged from the hospital after 3 days of observation. On day 2 after the procedure he experienced several episodes of transient chest pain that resolved after 48 hours with conservative treatment. The tissue-type plasminogen activator inhalation and respiratory therapies were discontinued after 2 weeks. For the past 5 months he has been asymptomatic, free of coughing spells and casts.

**DISCUSSION**

Plastic bronchitis is a rare and often fatal complication of single-ventricle palliation surgery.1–3 The etiology and pathophysiology of this complication are incompletely understood, although lymphatic abnormalities have been shown to be present in patients with PB and are believed to play a role in the disease process.2,8–10 In this case we demonstrate by MRI the presence of a collateral lymphatic vessels originating from the TD, carrying retrograde lymphatic flow to a dilated peribronchial lymphatic network in the right lung hilum. The imaging results are consistent with previously reported microscopic examination of the lung tissue in patients with PB, which demonstrated lymphangiectasia.10 They are also consistent with a previous lymphoscintigraphy report that demonstrated unilateral enhancement of the peribronchial lung field in a patient with PB.8–10

Significantly elevated inferior vena cava pressure in patients after single-ventricle palliation surgeries results in venous congestion that in turn increases lymph production, primarily by the liver and to a lesser extent in the soft tissues.11 In addition, elevated central venous pressure (CVP) in the innominate vein, at the site of the TD outflow, impedes lymphatic drainage.12 Both pathophysiological mechanisms cause significant lymphatic congestion that leads to structural lymphatic changes, such as lymphatic dilation and collateralization, as seen in this case. It is assumed that cast formation in PB is a result of protein leak into the airway, caused by lymphatic congestion and increased permeability of bronchial mucosa. The cause of increased permeability of the bronchial mucosa is not completely understood, but inflammation, which has been seen in lung biopsies of patients with PB, might initiate this process and is the reason that steroids have been shown to improve PB in some patients.13

Treatment of PB by creation or dilation of a fenestration, optimization of the Fontan pathway, and medical therapies...
such as sildenafil can potentially reduce lymphatic production and increase drainage by lowering CVP without necessarily affecting the abnormal lymphatic ducts. This is also probably the main mechanism by which heart transplants result in cessation or cure of PB. However, other mechanisms, such as change in mucosal inflammation with resumption of pulsatile pulmonary blood flow, could also be important and should be considered. Occlusion of veno-veno collateral vessels is not normally performed with the diagnosis of PB unless the patient is significantly hypoxic because this might increase CVP and have deleterious effects. In this case veno-veno collateral embolization was performed to minimize the risk of stroke from the oil-based contrast agent.

The findings of this study can explain the success of TD ligation, which has been reported to be curative in some cases of PB. An alternative to TD ligation, percutaneous TD embolization, has been described as a successful alternative to surgical TD ligation. Selective lymphatic collateral embolization, described here, offers several important advantages over TD ligation. First, this procedure maintains the patency of the TD, which we believe is especially important in patients with significant lymphatic congestion. Second, the precise visualization of the TD and targeted treatment of only the pathologic lymphatic vessels can potentially improve the outcome of such procedures. Third, in blood vessels we know that revascularization can occur quickly after an acute occlusive event. It is possible that lymphatic revascularization can also occur and could result in recurrence of the symptoms. However, recurrence is not seen in patients with

FIGURE 2
Maximal intensity projection images of the dynamic lymphangiogram at 4 different time points. A, Maximal intensity projection of the volume acquired 275 seconds after the scan started, demonstrating contrast in a network of dilated lumbar lymphatic channels (arrows). B, At 342 seconds, contrast has passed the cisterna chyli (arrowhead) and is seen inside a dilated lymphatic collateral originating from the inferior portion of the TD, coursing leftward, then superior, then to the right (arrows). C, At 541 seconds, contrast has progressed through the dilated lymphatic collateral into the dilated peribronchial lymphatic network (box) surrounding the right bronchus. The entire TD and a network of lymphatic collaterals in the left supraclavicular region (arrowheads) are also seen. D, Schematic of the lymphatic anatomy derived from the MRI data and confirmed by conventional lymphangiography. Black arrows indicate the direction of lymph flow.
chyloous leaks who have undergone TD embolization with resolution of the leak. Consequently, it is possible that in patients with PB, occlusion of pathologic lymphatic vessels can result in long-term cure. Finally, the minimally invasive nature of percutaneous embolization can reduce postprocedure mortality and morbidity.

Selective embolization of the pathologic lymphatic vessel resolved PB for this patient. However, it is important to note that this treatment does not address the underlying cause of this disease, which is significant lymphatic congestion due to the TCPC physiology of elevated CVP. We are convinced that a comprehensive therapeutic approach to reduce systemic venous hypertension and reduce lymphatic congestion is needed to reduce ongoing lymphatic complications in these patients.

In planning for such a procedure it is important to consider the skills needed and possible associated risks. Intranasal lymphangiography and lymphatic embolization procedures use minimally invasive lymphatic interventional techniques that have been described by Dr Itkin and are now used by other centers. As stated earlier, the use of an oil-based contrast agent in children with right-to-left shunting poses a risk for stroke. In addition, the oil-based contrast agent can lead to fatty pulmonary emboli, and so minimizing the amount

FIGURE 3
A. Contrast lymphangiogram 7 seconds after contrast injection inferior to cisterna chyli (arrowhead), confirming the MRI finding of retrograde lymphatic flow into a dilated lymphatic collateral that originated from the inferior TD, coursing first to the patient’s left then cephalad. White arrows show the direction of lymphatic flow. Also seen is contrast in the TD. B. Contrast lymphangiogram 15 seconds after the start of the injection. Contrast in the dilated collateral has now turned toward the right and is filling the lymphatic network surrounding the right bronchus (box). C. System during embolization with Lipiodol through a catheter now positioned inside the collateral vessel (arrowhead). Again, filling of the right-sided peribronchial network is seen (box). ETT, endotracheal tube. D. Lymphangiogram of the system after completion of the embolization procedure. Lipiodol is seen filling many of the dilated peribronchial lymphatic network branches (box), with glue filling the proximal collateral (arrow).
of contrast agent is of utmost importance. The long-term complications associated with TD embolization procedures have been reported by Laslett et al.16 Most common was an ~10% rate of transient abdominal swelling and diarrhea. Even though in this case the risks for these complications are probably much lower because the TD was left intact, they still must be considered. Two potential additional complications that can occur with transabdominal needle access are bleeding and perforation of the visceral organs leading to infection. These complications have not been reported in the literature, and we have not yet encountered them in our practice.

CONCLUSIONS

We demonstrated that the cause of the PB in a patient with Fontan physiology was retrograde flow from the TD into a lymphatic collateral supplying a dilated peribronchial lymphatic network surrounding the right hilum. MR T2 mapping and dynamic MR contrast lymphangiography were key for delineating the lymphatic anatomy and lymphatic flow pattern and for planning an interventional approach to treat this patient. Selective lymphatic embolization is a potential new treatment of patients with this disease.

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