Treatment of Plastic Bronchitis in a Fontan Patient With Tissue Plasminogen Activator: A Case Report and Review of the Literature

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ABSTRACT. Plastic bronchitis is a condition in which large, bronchial casts with rubber-like consistency develop in the tracheobronchial tree and cause airway obstruction. We describe a 4-year-old girl who had Fontan physiology and who developed plastic bronchitis and report for the first time the use of aerosolized tissue plasminogen activator for treatment of this condition. The literature is reviewed with emphasis placed on the occurrence of this disorder in patients with single ventricle physiology. Pediatrics 2002;109(4). URL: http://www.pediatrics.org/cgi/content/full/109/4/e67; plastic bronchitis, bronchial cast, Fontan, congenital heart disease, tissue plasminogen activator.

Plastic bronchitis is a condition in which large, pale tan, bronchial casts with rubber-like consistency develop in the tracheobronchial tree and cause airway obstruction.¹ It is an unusual disorder that occurs in various disease states, and fewer than a dozen cases have been reported regarding patients with palliated congenital heart disease. We describe a 4-year-old girl who had Fontan physiology and who developed plastic bronchitis and report for the first time the use of aerosolized tissue plasminogen activator (t-PA) for treatment of this condition. The literature is reviewed with emphasis placed on the occurrence of this disorder in patients with single ventricle physiology.

CASE REPORT

Our patient’s double-inlet left ventricle and L-transposition of the great arteries were diagnosed at birth. Her cardiac palliation performed at an outside institution consisted of a pulmonary artery band at 1 month of age; a bidirectional Glenn operation at 12 months; and a fenestrated, lateral tunnel Fontan operation at 26 months. Fenestration closure using a subcutaneous snare was performed 6 months later. Cardiac catheterization at 48 months of age revealed excellent hemodynamics without Fontan pathway obstruction. The mean pressure in the lateral tunnel was 10 mmHg, and there was no gradient to the left or right pulmonary arteries. The left ventricular end diastolic pressure was 4 mmHg, and there was no gradient to the left or right pulmonary arteries. The left ventricular end diastolic pressure was 4 mmHg, and there was no gradient to the left or right pulmonary arteries.

At 53 months of age, she presented to our institution with respiratory failure requiring mechanical ventilation. She improved with nebulized bronchodilator therapy and chest physiotherapy. This episode of respiratory decompensation was attributed to a mucus plug. During the next 4 months, she had 4 additional hospital admissions for perceived asthma exacerbations and pneumonia. Chest radiographs on each of these admissions revealed shifting infiltrates and atelectasis. A bronchoscopy performed during the third admission was unremarkable. The diagnosis of plastic bronchitis was made when the patient’s parent brought an expectorated bronchial cast to the pediatrician after the fourth admission and bronchoscopy during a subsequent admission revealed a large bronchial cast. She was then treated on an outpatient basis with chest physiotherapy, inhaled steroids, albuterol, and acetylcysteine.

At 58 months of age, she again presented to our emergency department with a 24-hour history of wheezing, cough, and progressive respiratory distress requiring admission to the intensive care unit. Rigid bronchoscopy was performed, and large bronchial casts were removed (Fig 1). Microscopic examination of these casts revealed fibrinous exudate admixed with mucin, exfoliated epithelial cells, foamy macrophages, and inflammatory cells. A culture obtained during this bronchoscopy grew Candida albicans and normal bacterial flora. Despite aggressive medical therapy with steroids, albuterol, dornase alfa, and antibiotics, she continued to have progressive and severe oxygen desaturations requiring repeat rigid bronchoscopy and removal of large casts on hospital days 2 and 3. On hospital day 4, she was endotracheally intubated and pulmonary lavage was attempted using acetylcysteine administered via a flexible bronchoscope with limited success. A fourth rigid bronchoscopy was performed, and large casts were again removed. A trial of high-frequency oscillatory ventilation resulted in hemodynamic deterioration and was abandoned. Extracorporeal membrane oxygenation was considered, but the family refused given their beliefs as Jehovah’s witnesses and the unproved value of extracorporeal membrane oxygenation in this setting.

On hospital day 5, the clinical picture was consistent with the recurrence of large bronchial casts. Systemic oxygen saturation ranged from 50% to 70% despite a fraction of inspired oxygen of 1.0. Asymmetric breath sounds and atelectasis on chest radiograph were present, similar to the findings after the first 3 rigid bronchoscopies when recurrent bronchial casts were subsequently found. A trial of aerosolized t-PA was administered on hospital days 5 and 6 on the basis of the experience of Quasney et al.² Aerosolized dosing for t-PA was empirically derived from adult studies of myocardial infarction. In this 14-kg patient, aerosolized t-PA was administered on the following schedule: 12 mg starting dose, 10 mg 1 hour later, and 5 mg 2 hours later. She then received 5 mg of aerosolized t-PA every 2 hours. Within 24 hours of starting t-PA, the patient developed a significant improvement in oxygenation with a systemic saturation of 75% to 85% on a fraction of inspired oxygen of 0.9. Flexible bronchoscopy on hospital day 6 was markedly improved, revealing widely patent bronchi to the lower lobes. Medical therapy with steroids, albuterol, dornase alfa, and antibiotics was continued. The patient was extubated, and she was discharged home on hospital day 6 after a 10-day hospitalization. An infectious disease consult was obtained, and the patient was treated with nebulized bronchodilators, inhaled steroids, and antibiotics. A trial of aerosolized t-PA was then initiated to prevent recurrence of large bronchial casts. At the time of the report, the patient had been discharged home on hospital day 10 after a 20-day hospitalization with no recurrence of large bronchial casts.

ABBREVIATION. t-PA, tissue plasminogen activator.
Plastic bronchitis is characterized by the acute and often recurrent development of bronchial casts, which cause obstruction of the tracheobronchial tree and respiratory distress.\(^1\) The casts are of variable sizes and take the shape of the bronchi in which they formed. Seear et al\(^3\) proposed that bronchial casts may be divided into 2 distinct clinicopathologic groups. Inflammatory casts are composed primarily of fibrin with little mucin and have an eosinophilic infiltrate. Inflammatory casts are typically seen in patients who develop plastic bronchitis with underlying bronchial diseases such as asthma and cystic fibrosis. Acellular casts are composed mainly of mucin with little fibrin and no inflammatory infiltrate except for occasional mononuclear cells. Patients with palliated congenital heart disease and plastic bronchitis primarily have acellular casts. Our patient’s casts had pathologic features from both groups.

Plastic bronchitis occurs in a wide variety of noncardiac conditions, including asthma,\(^3\)–\(^6\) pneumonia,\(^7\)–\(^9\) lymphangiomatosis,\(^10\) allergic bronchopulmonary aspergillosis,\(^10\) cystic fibrosis,\(^11\) bronchiectasis,\(^6,12\) acute chest syndrome associated with sickle cell disease,\(^13\) smoke inhalation,\(^14\) and idiopathic states.\(^1,3,9,15,16\)

In pediatric patients with congenital heart disease, 15 cases of plastic bronchitis have been described previously in the literature (Table 1). Including our patient, 12 children with palliated single-ventricle physiology have been reported. Langeupin et al\(^17\) suggested that the pathophysiology in these patients involves the development of endobronchial lymph leakage. Pulmonary lymphatic abnormalities may be congenital or acquired as a result of lymphatic trauma during surgery, adhesions, and elevated central venous pressure. Endobronchial chyle leakage has also been reported to cause plastic bronchitis in a postoperative Fontan patient after pleurodesis for persistent chylothoraces.\(^21\) Although our patient did not have elevated systemic venous pressures or evidence of Fontan pathway obstruction at recent cardiac catheterization, the majority of Fontan patients who are doing poorly as a result of pump failure or refractory atrial arrhythmias have significant hemodynamic derangements.\(^23\) Of these 12 palliated sin-

**TABLE 1.** Summary of Recently Reported Cases of Congenital Heart Disease Associated With Plastic Bronchitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (Year)</th>
<th>Diagnosis</th>
<th>Physiology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5</td>
<td>Tricuspid atresia</td>
<td>Fontan</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>CCCHD*</td>
<td>BDG</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>CCCHD*</td>
<td>Fontan</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>CCCHD*</td>
<td>BTS</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>CCCHD*</td>
<td>BTS</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Tricuspid atresia</td>
<td>Fontan</td>
<td>Await TX</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>Tricuspid atresia</td>
<td>Fontan</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>Tricuspid atresia</td>
<td>Fontan</td>
<td>Alive</td>
</tr>
<tr>
<td>18</td>
<td>7</td>
<td>DORV, PA</td>
<td>Fontan</td>
<td>Alive</td>
</tr>
<tr>
<td>19</td>
<td>3</td>
<td>Tricuspid atresia</td>
<td>Fontan</td>
<td>Dead</td>
</tr>
<tr>
<td>20</td>
<td>17</td>
<td>Tetralogy of Fallot</td>
<td>Repaired</td>
<td>Alive</td>
</tr>
<tr>
<td>17</td>
<td>5</td>
<td>ASD, PAPVR</td>
<td>Repaired</td>
<td>Alive</td>
</tr>
<tr>
<td>17</td>
<td>7</td>
<td>TOF, absent PV</td>
<td>Repaired</td>
<td>Dead</td>
</tr>
<tr>
<td>21</td>
<td>4</td>
<td>PA, IVS, D-TGA, MA, hypoplastic LV</td>
<td>Fontan</td>
<td>Dead</td>
</tr>
<tr>
<td>22</td>
<td>12</td>
<td>Mitral regurgitation, constrictive pericarditis</td>
<td>Repaired</td>
<td>Alive</td>
</tr>
</tbody>
</table>

ASD indicates atrial septal defect; BDG, bidirectional Glenn; CCCHD, complex cyanotic congenital heart disease; DORV, double-outlet right ventricle; D-TGA, d-transposition of the great vessels; IVS, intact ventricular septum; LV, left ventricle; MA, mitral atresia; PAPVR, partial anomalous pulmonary venous return; PA, pulmonary atresia; PV, pulmonary valve; TOF, tetralogy of Fallot, TX, transplant. * Details not provided.
gle-ventricle patients, 6 had died and a seventh was awaiting heart transplantation at the time that these cases were reported. The primary cause of death in these 6 patients was asphyxiation caused by airway obstruction. We speculate that this high mortality may reflect the severity of plastic bronchitis in such patients combined with the lack of proven medical therapy. As was seen in our patient, severe hemodynamic instability can occur when high mean airway pressure is used in an attempt to oxygenate and ventilate patients with passive pulmonary blood flow.

Other pediatric heart conditions associated with plastic bronchitis include single case reports of tetralogy of Fallot,17,20 atrial septal defect with partial anomalous pulmonary venous return,17 and constrictive pericarditis22 (Table 1).

A high index of suspicion is necessary to make a diagnosis of plastic bronchitis if a cast has not yet been expectorated. In patients who are at risk and develop unexplained wheezing and desaturation, high-resolution computed tomography may be useful as a noninvasive diagnostic test, although we have no personal experience to support this speculation. A low threshold for diagnostic bronchoscopy is also warranted. Supportive care, therapeutic bronchoscopy, and treatment of underlying disease states form the basis for treatment of plastic bronchitis.1,3,4 Because plastic bronchitis is a rare disorder associated with variable disease states, specific therapeutic options are based primarily on anecdotal experience. Thoracic duct ligation has been curative in 2 cases,7,17 and pericardectomy may be beneficial.22 Specific medical therapy directed at the bronchial casts includes nebulized acetylcysteine,1,3,16 which breaks disulfide bonds in mucoproteins, thus lowering their viscosity. A single case report by Quasney et al2 described the use of aerosolized urokinase in a 5-year-old patient with Fontan physiology and life-threatening plastic bronchitis. A temporal relationship was noted between the initiation of urokinase nebulizations and marked clinical improvement in this patient. These authors also demonstrated that bronchial casts removed from their patient were unchanged with in vitro saline incubation but became soft and friable when incubated with urokinase and dissolved completely when incubated in t-PA solution. t-PA causes fibrin-enhanced conversion of plasminogen to plasmin, which initiates local fibrinolysis. We speculate that patients with inflammatory casts with high fibrin concentration may benefit more from nebulized t-PA than those with acellular casts. Given the unknown safety of nebulized t-PA and our limited experience in a single patient, we recommend reserving the use of this drug for patients with plastic bronchitis refractory to conventional therapies.

CONCLUSION

Plastic bronchitis is a rare but important cause of hypoxemia in Fontan patients. We report for the first time the use of nebulized t-PA in this condition, which, although ultimately unsuccessful in our patient, may benefit patients with bronchial casts that do not respond to standard interventions.

REFERENCES

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