Management of Plastic Bronchitis With Topical Tissue-type Plasminogen Activator

abstract

Plastic bronchitis or cast bronchitis is a rare disease of unclear etiology characterized by formation of airway casts that can lead to life-threatening airway obstruction. There is currently limited data regarding optimal treatment of plastic bronchitis. Several therapies have been suggested, but recurrences are common and mortality remains high. We report the case of a 6-year-old boy with refractory eosinophilic bronchial casts, unresponsive to low-dose systemic corticosteroids, inhaled corticosteroids, azithromycin, and dornase alfa, who was treated successfully and safely with direct instillation of tissue-type plasminogen activator (tPA) to the obstructing casts during flexible bronchoscopy and inhaled tPA. Our case illustrates that the current therapy for plastic bronchitis remains inadequate. To our knowledge, this case is the first to show that direct instillation of tPA can be used safely for treatment of this disease. The use of tPA via direct administration into the airways during bronchoscopy and via a nebulizer appeared to be a safe and effective therapy for plastic bronchitis and should be considered early in the course of the disease to prevent complications of severe airway obstruction. Pediatrics 2012;130:e446–e450

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KEY WORDS

cast bronchitis, plastic bronchitis, tissue plasminogen activator, bronchoscopy

ABBREVIATIONS

DNase—dornase alfa (recombinant deoxyribonuclease)
FB—flexible bronchoscopy
FVC—forced vital capacity
tPA—tissue-type plasminogen activator

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Plastic bronchitis is a rare disease characterized by formation of airway casts that can lead to life-threatening airway obstruction. Previously, casts were classified histologically as “inflammatory” type I casts, which are cellular with abundant fibrin, eosinophils, and Charcot-Leyden crystals, or “noninflammatory” type II casts, which are acellular with mucin and little fibrin.1–3 Because inflammation is thought to play a role in the formation of all casts, however, Madsen et al3 more recently have reclassified bronchitis associated disease based on associated disease first and on cast histology second. The etiology remains unknown, but cast bronchitis is associated with a variety of cardiac and inflammatory conditions, including cyanotic congenital heart disease,2,4–7 respiratory infections,8–10 asthma,2 cystic fibrosis,11 malignancy,10 and sickle cell disease.12 The true prevalence of the disease is unknown, and it is likely underdiagnosed.3 Mortality secondary to cast bronchitis depends on the underlying disease. In general, patients with cyanotic heart disease have a poor prognosis, with mortality rates of 28% to 60%, whereas those with inflammatory disease have lower mortality (6%–50%).3,13 Several therapies have been used for patients with cast bronchitis, including optimizing cardiac function, thoracic duct ligation,14 bronchoscopic removal,7,15–17 antiinflammatory medication,18 and both mucolytics12 and fibrinolytics,4,19–21 but recurrences are common and mortality remains high.

We report the case of a 6-year-old boy with a history of asthma and recurrent left lung atelectasis who was found to have eosinophilic bronchial casts and was treated successfully with direct instillation of tissue-type plasminogen activator (tPA) to the obstructing casts and inhaled tPA.

CASE REPORT

A 6-year-old boy with a history of asthma was admitted to the hospital with respiratory distress and cough. The chest examination findings revealed decreased breath sounds on the left. The initial chest radiograph demonstrated opacification of the left hemithorax (Fig 1A). A chest computed tomographic scan showed a possible filling defect in the left mainstem bronchus (Fig 1B). He was treated for asthma and pneumonia with bronchodilators, hypertonic saline, dornase alfa (recombinant deoxyribonuclease or DNase), systemic corticosteroids, ceftriaxone, and azithromycin. The next day, the patient expectorated a mucous plug. His breath sounds markedly improved, and there was near normalization of his chest radiograph, although a small area of subsegmental atelectasis remained at the left base. He was discharged from the hospital with albuterol to use as needed.

Four months later, the patient presented with respiratory distress, fever, cough, and chest pain. He was admitted to our hospital, where his chest radiograph (Fig 4A) improved dramatically, and his forced vital capacity (FVC) improved from 39% to 88%; 2.5 mg total) were instilled topically at 30-minute intervals (Fig 2D), his breath sounds and vocal fremitus improved, and his lung fields normalized on chest radiograph (Fig 4A). Based on a previous case report,18 azithromycin was added to the treatment regimen.

When the patient did not improve after 2 weeks of treatment, use of tPA was considered based on several successful case reports.4,19–21 After consent was obtained, we directly evaluated the efficacy of DNase versus tPA for our patient. Repeat FB revealed persistent cast fragments (Fig 3A–C), which were too distal to be reached with the rigid bronchoscope. By using the flexible bronchoscope, DNase (2.5 mg) and tPA (diluted to 0.5 mg/mL, 0.5 mg aliquots; 2.5 mg total) were instilled topically on separate cast fragments. The cast treated with DNase remained unchanged after 15 minutes, but the cast treated with tPA started to dissolve immediately, allowing the fragments to be removed via the flexible bronchoscope (Fig 3D–F). The patient tolerated the procedure well and had no bleeding. Immediately after tPA instillation, he began to cough up large cast fragments (Fig 2D), his breath sounds and chest radiograph (Fig 4A) improved dramatically, and his forced vital capacity (FVC) improved from 39% to 88% of predicted. The patient was discharged.

FIGURE 1
A, Initial chest radiograph demonstrates complete opacification of the left hemithorax. B, Computed tomographic scan of the chest reveals left lung collapse with narrowing of the left mainstem bronchus and a possible endobronchial mass.
from the hospital to continue oral prednisone (0.25 mg/kg) every other day, in addition to azithromycin, inhaled beclomethasone, and levalbuterol.

The patient was managed closely in the pulmonary clinic, with serial examinations, spirometry, and chest radiographs. Medication adherence was assessed and thought to be good. He had slightly decreased breath sounds at the left base, and mild atelectasis was noted on his chest radiograph, which persisted. Four months after discharge, the FVC had dropped to 72% of predicted. The patient was admitted for an airway examination that revealed an increase in cast burden. A dosage of 3.5 mg of tPA (given in 0.5-mg aliquots) was instilled on the casts. The patient was then started on treatment with aerosolized tPA (1 mg/mL, 5 mg every 8 hours) with vest therapy. One week later, the FVC had increased to 81%, and repeat FB revealed a marked improvement in cast burden. During this FB, a total of 2 mg of tPA was instilled directly on the only visible remaining cast fragment. The chest radiograph revealed improved aeration of the left base (Fig 4B). Nebulized home tPA was not feasible because of the patient’s unstable housing. The patient was discharged from the hospital while taking his chronic medications, with his prednisone dose increased to 0.5 mg/kg every other day. Currently, he is 2.5 months past his last tPA treatment, and his FVC is 93% of predicted. He is participating in sports without any shortness of breath, but he does occasionally cough up cast material. He has good aeration as found during chest examination, including the left base.

DISCUSSION

Patients with plastic bronchitis typically present with cough, shortness of breath, chest pain, and fever. Chest examination findings reveal decreased breath sounds or wheezing. The classic examination finding of the “bruit de drapeau” is

FIGURE 2
A, A low-power view of the foreign material. The purple and pink stripes represent alternating eosinophil and inflammatory cells with mucus and fibrin, typical of “allergic mucin.” B, In the regions with necrotic cells, there are numerous elongated, pine needle–shaped crystals. These are Charcot-Leyden crystals, which commonly form from degranulated eosinophils. C, In regions with better vascularity (areas of granulation tissue), numerous viable eosinophils are noted. D, A large cast fragment coughed up by the patient after treatment with topical tPA.

FIGURE 3
FB revealed cast fragments wedged in segments of the left upper and lower lobes (A–C). Direct application of DNase to the casts was ineffective in dissolving the cast fragments (not shown). In contrast, the casts treated with direct application of tPA started to dissolve immediately, and after 15 minutes, the smaller fragments could be removed via the flexible bronchoscope, allowing clearing of the affected segments (D–F).

FIGURE 4
A, The chest radiograph findings improved markedly after serial bronchoscopy and direct instillation of tPA but did reveal a small persistent area of atelectasis at the base of the left lung. Breath sounds in the left lower lung fields also improved dramatically. B, The chest radiograph showed improved aeration of the left base after addition of nebulized tPA to the treatment regimen.
thought to be due to the mucous plug hitting the airway wall, but it is rarely heard.\textsuperscript{3,13} Chest radiographs show areas of atelectasis associated with areas of compensatory hyperinflation.\textsuperscript{5,13} A computed tomographic scan allows visualization of obstructing airway casts. Diagnosis is confirmed by expectoration of casts or by bronchoscopy.\textsuperscript{12} A high index of suspicion must be maintained, because expectorated casts are often mistaken for food such as chicken or noodles,\textsuperscript{3,17} and casts may be missed on routine histology if the pathologist is not experienced with cast bronchitis.

Supportive care is a critical component of plastic bronchitis management. Serial bronchoscopy with cast removal can be life-saving; however, the casts are often too friable to be grasped with forceps and too thick to be removed by suction.\textsuperscript{9,13,15–17} Lobectomy and extracloropore membrane oxygenation are last resorts when other therapies have failed.\textsuperscript{2,15,16}

In patients with heart disease, treatment includes optimization of cardiac output and consideration of a low-fat diet or thoracic duct ligation.\textsuperscript{14} In patients with inflammatory disease, systemic and inhaled corticosteroids have been the mainstays of therapy.\textsuperscript{13} Our patient had a normal cardiac echocardiography evaluation, but he did have a history of asthma and atopy with an elevated immunoglobulin E level and positive radioallergosorbent tests to several grasses, but not to \textit{Aspergillus}.

Schultz and Dermann\textsuperscript{18} reported the case of a teenager with recurrent episodes of plastic bronchitis despite treatment with inhaled corticosteroids and bronchodilators. After the addition of treatment with azithromycin, the episodes resolved. The macrolide antibiotics are thought to have an antinflammatory effect by modulating inflammatory cytokines and inhibiting human neutrophil elastase, reactive oxygen species, and adhesion molecules. They also have mucoregulatory effects.\textsuperscript{22} Our patient's health did not improve with administration of systemic corticosteroids and azithromycin.

Mucolytic therapies have been used to treat airway casts. Acetylcysteine thins mucous by breaking disulfide bonds. DNase decreases viscoelasticity of secretions by hydrolysis of extracellular DNA and may improve mucociliary clearance.\textsuperscript{13} Intrabronchial DNase was used successfully in a child with sickle cell disease,\textsuperscript{12} but it was not a successful treatment in several case reports of children with cardiac disease.\textsuperscript{4,19,21} Acetylcysteine was used successfully in treating a child with cystic fibrosis\textsuperscript{11} but not in cases of cardiac disease.\textsuperscript{4,19,21} Our patient did not improve with inhaled or directly instilled DNase.

Antifibrin therapies with heparin,\textsuperscript{23} urokinase, and tPA also have been used with variable success. A child with a Fontan improved after treatment with aerosolized urokinase.\textsuperscript{19} In vitro, a cast from the same patient incubated with urokinase became soft and friable, and a cast incubated with tPA fully dissolved.\textsuperscript{19} tPA is a serine protease that leads to local fibrinolysis by fibrin-enhanced conversion of plasminogen to plasmin. There are limited data on the nebulized or intratracheal use of tPA in humans. Mice receiving >1 mg/kg/day of intratracheal tPA had increased risk of acute fatal pulmonary hemorrhage.\textsuperscript{24} Nebulized tPA has been used successfully without adverse effects in several case reports of children with congenital heart disease complicated by cast bronchitis.\textsuperscript{4,20,21} One child was treated successfully and safely with a home regimen of azithromycin and nebulized tPA.\textsuperscript{21}

Currently, data are limited regarding optimal treatment of plastic bronchitis, so the clinician must rely on individual case reports to guide therapy. In this case report, we describe the first case of a patient with refractory inflammatory casts treated successfully using direct instillation of tPA onto the obstructing casts during FB. The patient continued to show marked improvement in cast burden and chest radiographic results with subsequent use of nebulized tPA. Neither direct instillation of tPA into the airways via bronchoscopy nor nebulized tPA was associated with bleeding or other complications. Treatment with systemic corticosteroids, inhaled corticosteroids, and azithromycin was insufficient to treat this disease. The use of tPA via direct administration into the airways during bronchoscopy and via a nebulizer appears to be a safe and effective therapy for plastic bronchitis and should be considered early in the course of the disease to prevent complications of severe airway obstruction.

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