Plastic bronchitis is an uncommon condition characterized by formation of branching casts in the tracheobronchial tree. Primarily a pediatric condition, most cases have either undergone a Fontan-type cardiac procedure to correct congenital cardiac defects, or have some form of pulmonary venous obstruction, but there is another less defined group of patients without evidence of pulmonary venous hypertension that develop thick proteinaceous cellular casts that result in acute and sometimes critical tracheobronchial obstruction. The latter group of patients usually have underlying pulmonary inflammatory diseases including cystic fibrosis, bronchial asthma, bronchitis or allergic bronchopulmonary aspergillosis. Symptoms include violent coughing, wheezing, and abrupt onset of episodes of severe dyspnea. This case report and mini-review will illustrate the less common presentation, tabulating the history, pulmonary function tests, diagnostic imaging and clinical lab reports as they evolved over a five-year follow-up. The discussion compares and contrasts the two fundamental types of plastic bronchitis patients, with implications for differential diagnosis, prognosis and treatment options.

CASE DESCRIPTION
A seven-year-old girl with history of recurrent severe asthmatic exacerbations since 14-months of age, was followed regularly by the pediatric respiratory medicine service. Over the approximately five-year follow-up, there were 19 admissions to a pediatric intensive care unit for recurrent episodes of acute respiratory distress occurring three-to-seven months apart. Hypoxemia developed rapidly and was resistant to high fractional concentration of inspired oxygen (FiO₂), beta-agonist bronchodilators (i.e., salbutamol by inhalation and intravenously), and high-dose glucocorticosteroids (i.e., dexamethasone). Typically, the arterial oxyhemoglobin saturation (SpO₂) would be around 70% on 100% rebreathing oxygen supplementation, but there would be little change in the arterial CO₂ or bicarbonate. As anticipated, use of glucocorticoids necessitated insulin therapy, and the use of beta-agonists provoked transient hypokalemia and tachycardia. Tracheal intubation was required during three hospital admissions, and in one instance extracorporeal membrane oxygenation (ECMO) was considered but not implemented. Following a delay of usually four days, she would recover rapidly and be discharged home within a week of admission. Initially, it was thought to be exacerbations of asthma triggered by bouts of bronchopulmonary pneumonia, however, she was usually afebrile, easily ventilated, and neither intensive asthma therapy nor antimicrobial prophylaxis seemed to prevent these episodes. She was mostly asymptomatic between each of the acute episodes, except that premonitory nocturnal cough, wheezing and tachypnea variably occurred without other explanation 48-hours prior to rapid deterioration.

PHYSICAL EXAM
Height: 90th percentile; weight: 75th percentile, afebrile, hemodynamically stable.

INVESTIGATIONS
Sweat chloride negative x 3. Skin testing for common allergens: negative. 24-hour pH probe and prone barium esophagram excluded gastroesophageal reflux and aspiration as triggers. Ciliary dyskinesia was excluded based on her history. PA & lateral chest x-rays during exacerbations usually showed multi-lobe atelectasis and consolidation, hyperinflation, and small pleural effusions. High-resolution spiral CT contrast ruled out pulmonary arteriovenous malformation. The combination of atelectasis with ground glass appearance and bronchial wall thickening was consistent with chronic inflammatory asthmatic changes and mucus plugging. A single attempt at bronchoscopy was aborted as it provoked generalized bronchospasm. A modest sample of bronchial secretions contained lipid-laden macrophages. Pulmonary function tests performed during the asymptomatic intervals showed progression of a moderately obstructive pattern, technically impaired respiratory muscle strength, mild gas-trapping, and a minimal bronchodilator-reversible component.

An extensive workup for immunodeficiency was undertaken on the premise that susceptibility to recurrent bronchopulmonary pneumonia might underlie the pathogenesis, especially after noting suboptimal titers to vaccine antigens despite up-to-date childhood immunizations plus varicella, influenza and Pneumovac-23. IgG subclasses were low x 3, but not absent, so with an otherwise normal immunologic profile, primary immunodeficiency was ruled out. Echocardiograms and cardiac catheterization revealed no evidence of structural cardiopulmonary abnormality or pulmonary venous obstruction.

PRINCIPAL COMPONENTS OF MANAGEMENT IN THIS CASE
- Corticosteroids (inhaled corticosteroids and systemic pulsed therapy)
- Bronchodilator therapy (iv. and neb. beta agonists, although

Continued on page 10
**Table 1:**

**Plastic Bronchitis, two main categories:**

<table>
<thead>
<tr>
<th>Cardiopulmonary hemodynamic variants</th>
<th>Airway inflammatory disease variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyanotic heart disease and after corrective surgeries e.g., Fontan-type; Sickle cell disease primarily transudative</td>
<td>asthma, cystic fibrosis, bronchitis primarily exudative</td>
</tr>
<tr>
<td>cast histopathology: hypo-cellular comprised primarily of eosinophilic fibrinous material with scant mucin. most cells are intact lymphocytes and entrapped alveolar macrophages, although some granulocytes may be present</td>
<td>cast histopathology: cellular composed of sheets of eosinophils, extracellular DNA, Charcot-Leyden crystals surrounded by mucin</td>
</tr>
<tr>
<td>Rational therapeutic choice to prevent cast formation and induce cast lysis: a fibrinolytic agent: rtPA</td>
<td>Rational therapeutic choice to prevent cast formation and induce cast lysis: deoxyribonuclease-1 [Dornase alpha]</td>
</tr>
<tr>
<td>Diseases of lymphatics seem to share hybrid characteristics.</td>
<td>Post-Fontan patients who are also asthmatic have had intermediate cast histopathology.</td>
</tr>
</tbody>
</table>

**Table 2:**

**Cast-directed options:**

<table>
<thead>
<tr>
<th>N-acetylcysteine [Mucomyst]</th>
<th>Recombinant deoxyribonuclease-1 [Dornase alpha]</th>
<th>direct endobronchial instillation of fibrinolytics (rtPA, streptokinase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The viscosity of mucous is conferred in large part by the disulfide linkages between sialic acid residues that comprise mucoproteins — mucin. The free sulfhydryl group of N-acetylcysteine interacts to relax the disulfide linkages between sialic acid residues of mucin, which results in less viscous mucous. That facilitates removal of obstructive airway secretions through coughing, mechanical mechanisms, or postural drainage. hypertonic saline neb: less evidence of benefit, similar potential to evoke bronchospasm</td>
<td>Hydrolyzes extracellular DNA into smaller more soluble fragments. Less viscoelastic sputum is easier to expel (no effect on intracellular DNA). Niche indication in CF patients to reduce the frequency of infections requiring parenteral antibacterial therapy, and to dissolve bronchiolar casts and reduce recurrence of acute plastic bronchitis, if casts are of predominantly cellular decomposition. CF patients with chronic bacterial lung infections and inflammation result in influx of neutrophils. The neutrophils, leucocytes and sloughed epithelium degenerate to release tightly polymerized extracellular DNA, which increases the viscosity and decreases the patient's ability to clear the sputum. By cleaving extracellular DNA, dornase alfa decreases the viscosity of the sputum and improves mucociliary clearance of sputum, and that reduces the incidence of recurrent bacterial infections.</td>
<td>Serine protease specifically activates bound plasminogen several hundredfold more than free plasminogen, causing lysis of fibrinous peptides. Resistant to t-PA Inhibitor-1 Inhaled aerosolized t-PA has lower efficacy, requires higher doses (optimal dose strategy unresolved), with higher rates of pulmonary hemorrhage and at far greater expense</td>
</tr>
<tr>
<td>Potential to trigger intense inflammatory airway reaction, bronchorrhea and bronchospasm</td>
<td>Costs &gt; $2,250.00/month</td>
<td>Potential to provoke bronchospasm, which is usually responsive to drugs.</td>
</tr>
</tbody>
</table>
sildenafil and epoprostenol have been used successfully in post-Fontan cases.9
• Azithromycin: in addition to antimicrobial action, low-dose azithromycin reduces Pro-Gly-Pro neutrophil chemoattractant product of extracellular matrix collagen degradation by suppressing myeloperoxidase-8 & 9 activity, and also enhances broncho-alveolar macrophage phagocytic function. Defective efferocytosis (phagocytic clearance of apoptotic cells) in the airway perpetuates inflammation via secondary necrosis in obstructive pulmonary disease.9,10
• High FiO2
• Rigid bronchoscopy: only for children without generalized bronchospasm11
• Recombinant deoxyribonuclease-1 [Dornase alpha]
• Aggressive respiratory physical therapy

This patient responded dramatically to dornase alpha on more than one occasion, and it did not provoke the intense bronchospastic or bronchorheic response that is often associated with N-acetylcysteine, hypertonic saline and tissue plasminogen activators. She was maintained on chronic azithromycin and three-day pulsed methylprednisolone cycles every 2-months. Nebulized dornase alfa 2.5 mg/day was initiated at home whenever nocturnal coughing or other signs and symptoms might herald an impending exacerbation. She has since not required urgent admissions despite a number of intervening upper respiratory infections and febrile illnesses. She has been followed regularly by pediatric endocrinology and ophthalmology to minimize the consequences of recurrent systemic glucocorticosteroid exposures. As she was already osteopenic, she was initially treated with pamidronate, then with denosumab.

DISCUSSION
The literature suggesting that plastic bronchitis in asthmatic patients represents an extreme asthma variant seems tenuous, as most do not benefit from intensification of asthma therapy between exacerbations, and the asthmatic girl in this case had relatively asymptomatic periods lasting months between sudden severe exacerbations.

Plastic bronchitis is uncommon, but should raise an index of suspicion in young patients with history of congenital cardiopulmonary defects with or without Fontan-type corrective surgery, sickle cell, asthma, or cystic fibrosis, who present with prodomal cough/wheeze prior to swift onset respiratory distress, low SaO2 despite 100% O2, not hard to ventilate, auscultatory flag-snapping bruit de drapeau results from a partial-obstructing cast moving in a bronchus. It can mimic foreign body aspiration.12 If radiographs demonstrate atelectasis with infiltrates, then a contrast-enhanced chest CT might diagnose and locate casts for bronchoscopy extraction.

Table 1 outlines how the category of plastic bronchitis guides choice of therapy: cardiopulmonary hemodynamic etiologies are likely to produce acellular fibrous casts, so it is reasonable to try rt-PA,11,12,13 whereas inflammatory airway disease casts are more likely comprised of extracellular DNA, so it is more rational to try dornase-alpha.16 In patients with a prominent reactive airway component, N-acetylcysteine and 3% saline are likely to provoke bronchospasm and bronchorrhea [Table 2]. Due to its complex non-antibacterial anti-inflammatory benefits, consideration should be given to chronic azithromycin therapy.9

REFERENCES

Indu Pathak, MD, Assistant Professor, Pediatrics, Director Hospitalist Division, Pediatric Hospital Medicine, El Paso Children's Hospital, Texas Tech University HSC, El Paso, Texas.

Dale Quest, PhD, Associate Professor, Clinical & Basic Medical Education, Texas Tech University HSC - Paul L. Foster School of Medicine, El Paso, Texas.