Bronchiolitis Obliterans Organizing Pneumonia Due to Gastroesophageal Reflux

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Abstract

The most common causes of bronchiolitis obliterans organizing pneumonia (BOOP) are connective tissue diseases, organ transplantation, drug reaction, and infections. Although rare, BOOP due to gastroesophageal reflux (GER) has been reported in adults but not to date in pediatric patients. This study describes 2 pediatric patients who developed GER and BOOP. One patient had superior mesenteric artery syndrome and Helicobacter pylori infection, and the other had a gastroduodenal ulcer with reflux esophagitis. Respiratory symptoms occurred concurrently or after gastrointestinal symptoms. Monitoring of esophageal pH for 24 hours revealed pathologic acid reflux. Lung biopsy findings confirmed BOOP. No other causes of BOOP were observed in these 2 patients. Both patients were cured with antireflux therapy and corticosteroids. To our knowledge, this is the first case report to implicate GER as a reversible cause of BOOP in children.

Case Presentation

Patient 1

A previously healthy 11-year-old boy was admitted to Beijing Children’s Hospital with a 6-week history of dry cough, tachypnea, and intermittent vomiting. The patient experienced severe vomiting 2 days before the onset of respiratory symptoms. As vomiting improved, he developed a nonproductive cough and a sore throat followed by tachypnea. These respiratory symptoms were particularly obvious late at night and before meals. Despite treatment with antibiotics and supportive therapy, his respiratory symptoms and chest radiography continued to deteriorate, and he lost about 5 kg in body weight during the previous 6 weeks.

Physical examination revealed a body weight of 27.5 kg and shortness of breath. Auscultation of the chest showed diminished breath sounds without obvious rales in the lungs. Chest CT scan disclosed prominent...
peripheral patchy consolidation and linear opacities (Fig 1A). Laboratory data showed a white blood cell count of 9400 cells/mL with 62.1% neutrophils, hemoglobin 13.8 g/dL, and C-reactive protein 7 mg/L. He was positive for anti–Helicobacter pylori immunoglobulin G in serum and on a carbon-13 urea breath test. Digestive tract ultrasound on the sixth day revealed superior mesenteric artery syndrome (SMAS), GER, and duodenogastric reflux. Monitoring of esophageal pH for 24 hours on the seventh day after admission revealed severe acid reflux associated with nocturnal cough (Boix–Ochoa score 55.6, normal value 11.99; total time pH <4, 13.1%; longest reflux episode, 26 minutes). Esophageal motility was not measured. On the eighth day after admission, a thoracoscopic biopsy of the lung was performed. A pathologic finding 6 days later was compatible with BOOP (Fig 1E).

After a lung biopsy, he was started on treatment with antireflux agents (omeprazole, 0.7 mg/kg per day by mouth [po]; domperidone, 0.3 mg/kg, thrice daily po) and anti–H. pylori agents (amoxicillin, 20 mg/kg, twice daily po; clarithromycin, 10 mg/kg, twice daily po). To control SMAS, he was placed in the left lateral position for one-half hour after every meal. His vomiting and cough disappeared, and his tachypnea and radiologic findings improved after 1 week. Because lung histology showed filling of his alveolar ducts and alveoli by fibroblastic plugs, we added intravenous methylprednisolone (2 mg/kg per day for 1 week, tapered to 1 mg/kg per day for 1 month and gradually to 0). His tachypnea disappeared completely with normal pulmonary function, and CT scan showed consolidation resolution except for linear opacities (Fig 1C) after 2 months of combination therapy with antireflux agents and corticosteroid. He continued taking corticosteroids for another 4 months, and the patient’s CT scan was normal.

Patient 2
A previously healthy boy, aged 8 years 7 months, presented with a 1-month history of tachypnea, paroxysmal cough with frothy white sputum, and extreme retrosternal pain. His previous history revealed a poor diet and thinness but no nausea or vomiting. Physical examination showed a body weight of 23 kg, shortness of breath, and no obvious rales in the lungs. High-resolution CT scans showed diffuse ground-glass opacity (Fig 1B). He was negative for anti–H. pylori immunoglobulin G in serum and on a carbon-13 urea breath test. Holter monitoring electrocardiography for 24 hours, electromyography, digestive tract ultrasound, and upper gastrointestinal study were normal.

Based on paroxysmal cough and retrosternal pain, we suspected that the patient had acid reflux. On the fourth day after admission, the patient was started on treatment with antireflux agents (omeprazole, 0.7 mg/kg per day po; domperidone, 0.3 mg/kg, thrice daily po). His cough...
and retrosternal pain improved after 4 days of treatment. He continued taking antireflux therapy.

To investigate the cause of lung lesion, transbronchoscopic lung biopsy and gastroscopy were performed on the sixth day and the tenth day of admission, respectively. Monitoring of esophageal pH for 24 hours on the ninth day after admission confirmed pathologic acid reflux associated with cough (Boix-Ochoa score 43, normal value 11.99; total time pH < 4, 9.6%; longest reflux episode, 33.9 minutes). Gastroscopy revealed coarse granulation in the esophageal mucosa, erosion, and superficial ulcer of the descending duodenum and gastric fundus. Histologic findings in the lung confirmed BOOP 4 days later after lung biopsy (Fig 1F), and then the patient was started on methylprednisolone (2 mg/kg per day for 2 weeks, tapered to 1 mg/kg per day for 2 weeks, and gradually to 0). After 1 month of treatment with steroid, his symptoms disappeared, his pulmonary function was normal, and the lung CT showed remarkable improvement (Fig 1D). He was maintained on antireflux for 2 months and steroid therapy for 3 months. The chest CT scan was normal after 3 months.

Both patients were negative for bacterial, fungal, and mycobacterial cultures in sputum and bronchoalveolar lavage liquid, and both were negative for antinuclear, anti–double stranded DNA, anti-Sm, anti-ribonucleoprotein, and antineutrophil cytoplasmic antibodies. Patients 1 and 2 showed normal weight and activity and no recurrence after follow-up for 25 and 14 months, respectively.

DISCUSSION

This report describes 2 pediatric patients with BOOP attributed to GER; to our knowledge, these are the first such pediatric patients reported. The diagnosis of BOOP in both patients was confirmed by clinical, radiologic, and pathologic findings. A clinical diagnosis of aspiration was considered based on digestive disease history, acid reflux testing, and the efficacy of antireflux agents. BOOP has been observed in patients with infectious diseases, adverse drug reactions, connective tissue diseases, organ transplantation, drug reactions, and immunologic disorders. GER or aspiration has been reported as an uncommon cause of BOOP in adults. In the present 2 cases, we speculated that BOOP was caused by pathologic acid reflux because biopsies revealed no evidence of infectious pathogens or drug reactions, and clinical and laboratory examinations showed no indications of connective tissue diseases, infections, or other diseases. In addition, 24-hour esophageal pH monitoring in both patients revealed severe pathologic acid reflux. Patient 1 had SMAS and H. pylori infection, and Patient 2 had antral gastritis and gastroduodenal ulcer with reflux esophagitis. Both patients had typical reflux symptoms, such as nocturnal dry cough and paroxysmal retrosternal pain, before or at the time of appearance of respiratory symptoms. Moreover, antireflux therapy significantly improved their respiratory symptoms and chest radiographic findings. Duodenogastric reflux was observed in Patient 1, and bile reflux may also have been present. However, the severe acid reflux in this patient and his response to antireflux therapy indicated that acid reflux contributed greatly to BOOP.

Digestive diseases in these 2 patients may explain the occurrence of GER. In Patient 1, SMAS resulted in delayed gastric emptying caused by obstruction of the duodenum, leading to GER. In Patient 2, gastritis and ulceration associated with elevated acid production may have resulted in GER and contributed to esophagitis. Surgery was not performed in either patient. SMAS often occurs in thin children, and digestive tract ultrasound revealed that SMAS disappeared in Patient 1 after he gained weight for 3 months.

GER has been associated with several interstitial lung diseases, including idiopathic pulmonary fibrosis and organizing pneumonia. Although several studies have assessed the relationship between aspiration and BOOP in adults, none have done so in children. The pathogenesis of lung diseases due to GER is complicated. Gastric juice and its constituents (acid, bile, and pepsin) may induce hypoxemia by a variety of mechanisms, including destruction and dilution of surfactant and pulmonary edema from extravasation of intravascular fluids and protein. Other early histologic findings include airway epithelial degeneration and reparative processes, including regeneration of bronchial epithelium, proliferation of fibroblasts, interstitial thickening, and granuloma formation.

The mechanisms by which GER and acid aspiration contribute to BOOP are not clear. There are no clear guidelines for the treatment of BOOP in pediatric patients. Both of our patients had rapid response to antireflux therapy and were treated with proton pump inhibitors for 2 months, at the gastroenterologist’s suggestion. Because of the presence of granulation plugs in the alveoli, both patients were also given with corticosteroids.

CONCLUSIONS

We have described 2 pediatric patients with BOOP probably caused by GER. To our knowledge, this is the first report of GER-associated BOOP in pediatric patients, suggesting that GER should be considered a potentially reversible cause of BOOP.
REFERENCES


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