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bronchoscopy

Plastic Bronchitis and the Role of Bronchoscopy in the Acute Chest Syndrome of Sickle Cell Disease*

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Study objectives: To review the prevalence, clinical features, and role of bronchoscopy in patients with plastic bronchitis during the acute chest syndrome (ACS) of sickle cell disease (SCD).

Design: Eight-year review of clinical experience.

Setting: Tertiary referral children's hospital.

Patients: Twenty-six pediatric inpatients with 29 ACS episodes requiring diagnostic bronchoscopy.

Results: Of the pediatric inpatients with ACS who underwent bronchoscopy, plastic bronchitis was diagnosed in 21 of 29 episodes (72%). There was no difference in clinical features between the patients with and without plastic bronchitis. Bronchoscopy was an essential diagnostic tool, but its therapeutic benefits were doubtful.

Conclusions: This is the first report of the prevalence of plastic bronchitis in patients with ACS of SCD. In our patient population, this condition was found to be common. The role of diagnostic bronchoscopy is essential. A large series, multicenter study is required to determine whether bronchoscopy and BAL are therapeutically beneficial when added to currently practiced supportive care. (CHEST 2001; 120:608-613)

Key words: acute chest syndrome; bronchial cast; bronchoscopy; plastic bronchitis; pneumonia; sickle cell

Abbreviations: ACS = acute chest syndrome; SCD = sickle cell disease

The acute chest syndrome (ACS) of sickle cell disease (SCD) is characterized by sudden-onset fever, cough, chest pain, and pulmonary opacity on radiographic examination. This broad definition does not specify the etiology of the pulmonary lesion manifested as pneumonia, atelectasis, or infarction.¹⁻⁴ Plastic bronchitis, a condition of branching bronchial cast formation, evidenced on bronchoscopic examination, has been reported in only three pediatric patients with ACS.⁵ This is the first review that attempts to (1) estimate the prevalence of plastic bronchitis in pediatric patients with ACS in a large

SCD center, (2) compare clinical features of the group with plastic bronchitis and the group without plastic bronchitis, and (3) explore the role of bronchoscopy and BAL as diagnostic and/or therapeutic modalities.

MATERIALS AND METHODS

We reviewed our personal experience (C.M., E.N.) and medical records of pediatric inpatients with ACS who underwent bronchoscopy at Miller Children's at Long Beach Memorial Medical Center in Long Beach, CA, over the past 8 years. Long Beach Memorial Medical Center has an active SCD treatment center currently caring for approximately 240 patients. Hospital admission note, bronchoscopy report, imaging studies, and laboratory results were reviewed. The authors (C.M., E.N.) were involved in the care of each patient and performed fiberoptic bronchoscopy and BAL as previously described.⁶ Descriptive statistical analysis was used, and data are presented as median, mean, SE, range, percentage, and risk ratio. All mean values are reported with 95% confidence levels. Comparisons between the group with plastic bronchitis and group without plastic bronchitis were calculated using unpaired Student's *t* test.

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RESULTS

There were a total of 29 ACS occurrences identified over the past 8 years. Three of these instances represented a second ACS episode in a single patient. Of the 26 patients, 15 were female. The patients' ages ranged from 3 to 20 years (median age, 8 years). Twenty-four patients had homozygous SCD, 1 patient had sickle-hemoglobin C disease, and 1 patient had sickle cell trait.

All patients presented with fever, cough, and chest pain. Vaso-occlusive crisis, characterized by acute intravascular hemolysis accompanied by pain, was diagnosed clinically in 27 of 29 episodes (93%). Clinical characteristics are shown in Table 1. All patients had pulmonary consolidation shown on chest radiography.

Initial therapy in all patients included IV antibiotics, oxygen, airway clearance measures, systemic steroids, and analgesia. Pulmonary consultation was obtained in the advanced stage of ACS based on the hematologist's discretion. The indication for bronchoscopy was worsening lung consolidation with hypoxemia in a relatively immunocompromised host.

Bronchoscopic Findings

All patients underwent diagnostic flexible fiberoptic bronchoscopy.⁶ In 21 episodes (72%), the operative finding was plastic bronchitis, which was described as white, gray, yellow, or green rubbery casts branching into the bronchial tree (Fig 1). These bronchial casts were surrounded by thin, bright yellow fluid identical to bilirubin in gross appearance. The locations of the casts corresponded to the radiographic findings. After being fragmented or disintegrated by repeated flushing using 0.9% NaCl, the casts were removed via the suction channel. Removal of larger bronchial casts or mucoid impaction required continuous suctioning in order to keep the cast adhered to the tip of the bronchoscope, and then the bronchoscope together with the cast were withdrawn from the patient's airway. With this tech-

FIGURE 1. A bronchoscopic view of a plastic bronchitis cast totally occluding the left mainstem bronchus of a 4-year-old boy with ACS.

nique, the large casts could be removed piece by piece. Removal of the casts was achieved in all but one incident (97%). The only unsuccessful case was a 4-year-old child with a cast starting in the left mainstem bronchus, who was referred for rigid bronchoscopy with only partial success. Bronchoscopic findings other than plastic bronchitis included airway inflammation characterized by marked edema and erythema of the bronchial mucosa (seven incidents) and pulmonary hemorrhage (one incident). There were no complications during or after bronchoscopy.

Pathology

Pathologic examination of the casts revealed bronchial epithelial cells and fibrinous material. The yellow bronchial fluid cytology showed pigmented histiocytes. Ten of 27 BAL specimens (37%) were stained positive for lipid-laden alveolar macrophages, and 2 of 27 BAL specimens (7%) were stained positive for iron-laden alveolar macrophages. In all

Table 1—Clinical Features of Children With ACS of SCD With and Without Plastic Bronchitis*

Patients	Episodes, No.	Median Age (range), yr	Female/Male Gender, No.	Mean ($\pm$ SD) WBC Count on Hospital Admission, $10^3/\mu\text{L}$	Episodes With Abnormal Chest Radiograph Finding on Hospital Admission, No.	Areas of Lung Involved: Upper/Lower/Bilateral/Effusion, No.	Median Interval (Range) From Hospital Admission to FFB, d	Documented Infectious Etiology: Bacteria/Virus/Mycoplasma, No.
With plastic bronchitis	21	8 (3–18)	11/10	17.3 $\pm$ 1.6	12	6/19/12†/6†	3 (1–8)	3/1/1
Without plastic bronchitis	8	8 (5–20)	7/1	22.6 $\pm$ 2.8	4	3/7/4/1/1	2 (1–17)	1/2/1
Total	29	8 (3–20)	18/11	18.7 $\pm$ 1.4	16	†9/26/16/7	3 (1–17)	4/3/2

*FFB = flexible fiberoptic bronchoscopy.

†Statistically significant.

‡Six patients had both upper and lower lobe involvement.

Table 2—Microbiological Studies in Children With ACS*

Studies	With Plastic Bronchitis, No.	Without Plastic Bronchitis, No.
Blood culture		
<i>Streptococcus pneumoniae</i>	1	
BAL		
Rhinovirus (culture)	1	
Influenza A (DFA)		2
<i>Staphylococcus aureus</i>	1	1
<i>Enterobacter aerogenes</i>	1	
Serology		
Mycoplasma	1	1
Legionella	1	

*DFA = direct fluorescent antibody.

cases, BAL was sent for microbiological studies including respiratory viral direct fluorescent antibody, and viral, bacterial, mycobacterial, and fungal cultures. Microbiological study results on the BAL were positive in 5 of 29 patients (17%; Table 1). Detailed results of microbiological studies are shown in Table 2.

Chest radiographic findings showed improvement either on the following day or a few days after the procedure (Fig 2). The duration of hospitalization ranged from 4 to 28 days (mean $\pm$ SE, 10.6 ± 1.3). There were no deaths. All patients had full recovery from ACS.

Comparison of Clinical Features Between the Groups With and Without Plastic Bronchitis

There was no significant difference in age, initial WBC count, or documented infectious etiology between the two groups (Table 1). The female-to-male ratio was higher in the group without plastic bronchitis. One individual with plastic bronchitis presented in respiratory failure and required bronchoscopy while intubated and receiving mechanical ventilation. The interval from hospital admission to bronchoscopy and the length of stay were comparable between the groups, as were levels of oxygen saturation before and after bronchoscopy. The risk ratio of abnormal chest radiographic findings on hospital admission was 1.72. Although the most affected areas (lower lobes) were similar, bilateral pulmonary infiltrates and pleural effusion (independently) were more common in the group with plastic bronchitis. Lipid-laden macrophages were found in seven patients (37%) in the group with plastic bronchitis and in two patients (25%) in the group without plastic bronchitis, with a risk ratio of 1.17.

DISCUSSION

ACS is the leading cause of death and the second most common reason for hospitalization in patients

FIGURE 2. Chest radiographs of an 11-year-old boy with SCD obtained during an episode of ACS. *Top:* Before bronchoscopy, left lower lobe consolidation was evidenced by loss of cardiac and diaphragmatic silhouettes (small arrows). *Bottom:* After bronchoscopy, marked improvement was shown by reappearance of the aortic and left diaphragmatic borders (large arrows).

with SCD.⁷⁻¹⁰ Its incidence among young patients with homozygous SCD is 25 occurrences per 100 patient-years.^{11,12} Repeated events have been associated with an increased risk of chronic lung disease and early death.^{7,11,13} Infections (*eg*, bacteremia, bacterial and viral pneumonia) are more commonly associated with ACS in children than in adults.¹⁴⁻¹⁶ Several pathophysiologic mechanisms are associated with ACS, such as microvascular occlusion due to sickled erythrocytes and increased adhesion of blood cells to vascular endothelium,¹⁷⁻¹⁹ disturbance of endothelial vasoactive mediators,^{20,21} release of inflammatory cytokines,²² activation of the coagulation system,^{23,24} fat embolism from bone marrow infarction,²⁵ and regional pulmonary vasoconstriction secondary to alveolar hypoxia.²⁶ How exactly these mechanisms interplay in the development of ACS is not yet known.

Plastic bronchitis, a condition of branching bronchial cast formation, complicating ACS was reported as an unusual finding in only a few pediatric patients with SCD.⁵ In contrast, we found a high prevalence of 72%. Even though our high prevalence may be, in part, due to population selection (patients with worsening consolidation), we speculate that this condition is generally undiagnosed because bronchoscopy is not routinely performed among SCD patients who have ACS,¹⁶ especially in the pediatric population.

Since plastic bronchitis in patients with SCD is not widely recognized, there is essentially no previous study of its pathogenesis. However, because plastic bronchitis also occurs in other illnesses, such as asthma, cystic fibrosis, bronchiectasis, pneumonia, tuberculosis, allergic bronchopulmonary aspergillosis, congenital cyanotic heart diseases, etc,²⁷ we speculate that these illnesses share some common pathways to developing bronchial casts.

Sear et al²⁸ proposed their classification of plastic bronchitis into two categories, "inflammatory" and "acellular," based on nine reported cases and a literature review. None of the nine patients had SCD. The inflammatory group represented patients with inflammatory airway disease who had casts containing inflammatory cells, mainly eosinophils and their degradation products. The acellular group represented patients with congenital cyanotic heart disease who had casts containing fibrin or mucin.

Multiple factors are likely to interplay in the pathogenesis of bronchial casts in patients with ACS of SCD. These include airway inflammation due to acute respiratory tract infections as documented in some of our cases. Several patients had asthma, a chronic inflammatory airway disease well-known to be associated with plastic bronchitis

as well as SCD.²⁷⁻³⁰ Both infection and asthma cause excessive production of thick bronchial secretions that could result in mucoid impaction and bronchial cast formation, especially when the mechanical clearance of secretion is impaired. SCD patients in pain crisis tend to splint their chest by avoiding cough or deep breaths. In addition, ischemia of the bronchial tree caused by vaso-occlusion may lead to ciliary motility dysfunction, which further worsens airway clearance mechanism.

It is suggested that lung blood volume during ACS is increased.³¹ This may also play a role in the pathogenesis of plastic bronchitis since plastic bronchitis is associated with increased pulmonary lymphatic load such as in cyanotic heart diseases after Fontan operation.^{31,32} Other reported cases of acellular casts include noncyanotic heart patients who had either mitral valve stenosis or constrictive pericarditis.³³⁻³⁵ Proposed explanations vary from pulmonary venous hypertension to surgical trauma to the lymphatic channels surrounding the bronchi, resulting in lymphatic leakage into the airway.³⁶ Besides elevated lung blood volume that increases lymphatic load, SCD patients with ACS may also have pulmonary vascular hypertension either from pulmonary microvascular occlusion, hypoxic vasoconstriction, or pulmonary fat embolism from bone marrow infarction. All of these conditions could participate in the leakage of lymph into the bronchi, and when paired with the defective airway clearance, may eventually result in formation of bronchial casts. Interestingly, several of our patients had lipid-laden alveolar macrophages in their BAL specimens that may represent fat from lymph.

Because of the complex, undefined disease process of ACS and its likely multiple etiologies, therapy has mainly been supportive.^{12,16} The benefits from treatments that improve alveolar oxygenation emphasize the important role of hypoxia-induced pulmonary vasoconstriction.²⁶ These treatments include prevention of atelectasis (incentive spirometry³⁷ and proper pain management to avoid chest wall splinting or narcosis), airway clearance (inhaled β_2 -agonist), and oxygen therapy. Because mechanical obstruction by bronchial casts and mucoid impaction results in hypoxemia from ventilation/perfusion mismatch, relieving such obstruction using bronchoscopy presents itself logically as a very attractive therapeutic option. We certainly observed radiographic improvement shortly after bronchoscopy though mean hospital stay of our population was not shorter than that of other centers where bronchoscopy was not routinely performed.^{12,16} The latter finding,

however, may be confounded by population selection and the lack of uniform discharge criteria.

In summary, bronchoscopy demonstrated high diagnostic value in distinguishing ACS patients with plastic bronchitis. A multicenter, prospective, controlled study may elucidate the role of diagnostic/therapeutic bronchoscopy in patients with ACS of SCD.

CONCLUSION

Plastic bronchitis is a common pulmonary complication of ACS in children and adolescents with SCD. Its existence could not be predicted using any particular clinical feature. Bronchoscopy is essential in the diagnosis of this condition. Although improvement was observed radiographically following removal of the bronchial casts, the contribution of bronchoscopy to currently practiced supportive therapy remains unclear.

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