

Analysis of the Risk Factors for Plastic Bronchitis in Children with Severe Adenovirus Pneumonia: A Retrospective Study

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Purpose: Plastic bronchitis (PB), a rare complication of respiratory infection characterized by the formation of casts in the tracheobronchial tree, can lead to airway obstruction and severe condition. Adenovirus is one of the common pathogens of PB caused by infection. This study aimed to evaluate the clinical features and risk factors for PB in children with severe adenovirus pneumonia.

Methods: A retrospective study of children with severe adenovirus pneumonia with bronchoscopy results at Guangzhou Women and Children's Hospital between January 2018 and January 2020 was performed. Based on bronchoscopy, we divided children with severe adenovirus pneumonia into two groups: PB and non-PB. Binary logistic regression analysis was used to identify independent risk factors for PB in patients with severe adenovirus pneumonia after univariate analysis.

Results: Our study examined 156 patients with severe adenovirus pneumonia with bronchoscopy results in hospital. Among them, 18 developed PB and 138 did not. On multivariate analysis, the independent risk factors of PB in children with severe adenovirus pneumonia were history of allergies (OR 10.147, 95% CI 1.727–59.612; $P=0.010$), diminished breath sounds (OR 12.856, 95% CI 3.259–50.713; $P=0.001$), and increased proportion of neutrophils ($>70\%$; OR 8.074, 95% CI 1.991–32.735; $P=0.003$).

Conclusion: Children with severe adenovirus pneumonia with a history of allergies, diminished breath sounds, and increased the proportion of neutrophils $>70\%$ may show higher risk of PB.

Keywords: plastic bronchitis, severe adenovirus pneumonia, risk factors, children

Introduction

Plastic bronchitis (PB), also termed fibrinous bronchitis or cast bronchitis, is an acute and serious disease featuring endogenous foreign bodies form branched mucinous bronchial casts, which partially or extensively block bronchi.¹ Due to the different degrees of obstruction, the clinical presentation ranges from mild respiratory symptoms to severe, potentially fatal respiratory failure, which induces the sudden onset of cough, wheezing, progressive dyspnea, and refractory hypoxemia.² Diagnosis of PB is made based on characteristic bronchial casts through bronchoscopy.

According to the pathology of the bronchial casts, there are two types of PB. Type I is associated with respiratory tract diseases consisting of inflammatory cells, fibrin, and eosinophils. Type II is mainly associated with congenital heart disease consisting of mucus and a few cellular infiltrates.³ Infection is a common cause of type I PB.⁴ Human adenovirus (HAdV), one of the main pathogens of severe pneumonia in children, can also lead to PB, especially HAdV7.^{2,5,6} Bronchoscopy combined with bronchoalveolar lavage (BAL) is not only a diagnostic method of PB but also plays an important role in the treatment of adenovirus pneumonia, especially with PB, because it can clamp the blocked mucus plug out of the small bronchi and

effectively ease the clinical symptoms of children with pulmonary consolidation and atelectasis.⁷ Our study aimed to evaluate the clinical features and risk factors for PB in children with severe adenovirus pneumonia.

Methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center, Guangzhou Medical University. All the patients or their guardians provided written informed consent to use clinical and laboratory data from the patients' medical reports.

Case Definition and Identification

This study enrolled 156 patients with severe adenovirus pneumonia who were admitted to Guangzhou Women and Children's Medical Center between January 2018 and January 2020.

The inclusion criteria were:

- 1) age >1 month and <18 years
- 2) evidence of HAdV infection based on HAdV positivity on multiplex polymerase chain reaction (PCR) performed using nasopharyngeal swab, sputum, and BAL fluid samples
- 3) diagnosis of severe community-acquired pneumonia according to the guidelines of the American Thoracic Society for the management of community-acquired pneumonia⁸
- 4) bronchoscopy performed during hospitalization

The guidelines of the American Thoracic Society for the management of community-acquired pneumonia are as follows.⁸ The criteria for severe pneumonia were having one or more major or two or more minor criteria.

- 1) Major criteria: invasive mechanical ventilation, fluid refractory shock, acute need for noninvasive positive pressure ventilation, and hypoxemia requiring fraction of inspired oxygen (FiO₂) greater than the inspired concentration or flow feasible in general care area
- 2) Minor criteria: respiratory rate greater than that recommended by the WHO classification for age, apnea, increased labored breathing (e.g., retractions, dyspnea, nasal flaring, and grunting), PaO₂:FiO₂ ratio <250, multilobar infiltrates, altered mental status, hypotension, presence of effusion, comorbid conditions, and unexplained metabolic acidosis

The exclusion criteria were:

- 1) incomplete medical records;
- 2) comorbidities, such as severe congenital heart disease, neuromuscular diseases, inherited metabolic diseases, severe immunodeficiency, and myelosuppression with hematologic malignancies.

Study Design and Data Collection

This retrospective observational study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. We collected and analyzed the bronchoscopy results of children with adenovirus pneumonia. All of the patients with PB were diagnosed with severe adenovirus pneumonia. Then, based on the bronchoscopy results, severe cases were divided into PB (n=18) and non-PB (n=138) groups (see Figure 1). Clinical data were collected from the patients' medical records, including demographic characteristics (e.g., age and sex), clinical symptoms and signs (e.g., fever duration, cough, wheezing, shortness of breath, hypoxia, digestive symptoms, neurological symptoms, diminished breath sounds, and moist crackles), laboratory findings (e.g., blood cell counts, inflammatory markers, and organ functions), coinfection pathogens (other viruses, bacteria, and *Mycoplasma*), chest

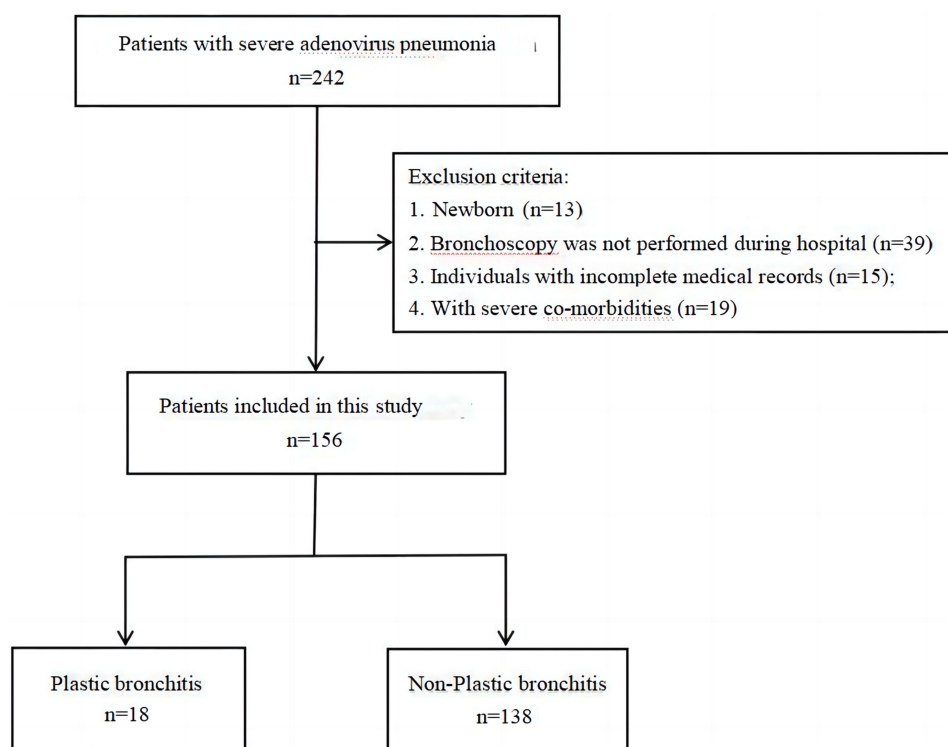


Figure 1 Study flowchart.

radiological manifestations (pulmonary consolidation and pleural effusion), treatments and complications. PCR testing, cultures of nasopharyngeal secretions, and BAL during hospital stay were used to identify infection with other pathogens in all patients. Those with a wide range of lesions found on chest radiography underwent high-resolution computed tomography (HRCT).

Statistical Analysis

Statistical analysis was performed using SPSS 22.0. Discrete data are expressed as numbers and percentages, and continuous data are presented as medians with interquartile ranges. Fisher's exact tests were used to evaluate the differences in categorical variables and the nonparametric Mann–Whitney test in continuous variables. Univariate analyses were performed to determine the risk factors significantly associated with PB in children with severe adenovirus pneumonia. To determine the independent contribution of each factor to the outcomes, multiple logistic regression analysis was performed. Statistical significance was set at $P < 0.05$.

Results

Baseline Characteristics

There were 156 children with severe adenovirus pneumonia who had received bronchoscopy in hospital in our study. Based on the bronchoscopy results, 18 patients had PB and 138 did not. The incidence of PB in children with severe adenovirus pneumonia was 11.54%. We analyzed the clinical features of PB caused by adenovirus by comparing the demographics, clinical symptoms and signs, laboratory indices and radiological findings between the PB and non-PB groups. There were 13 males in the PB group (72.22%) and 87 in the non-PB group (63.04%), a nonsignificant difference ($P > 0.05$). The median age in the PB and non-PB groups showed no statistically significant difference either ($P > 0.05$). About a third patients in the PB group had an allergy history (six of 18, 33.3%), while few patients in the non-PB did (nine of 138, 6.52%), a significant difference ($P < 0.05$; Table 1).

Table 1 Demographic characteristics and clinical features of PB and non-PB children with severe adenovirus pneumonia at admission

	Total, n=156	PB group, n=18	Non-PB group, n=138	P
Demographics				
Male, n (%)	100 (64.10)	13 (72.22)	87 (63.04)	0.6031
Female, n (%)	56 (35.90)	5 (27.78)	51 (36.96)	0.6031
Age, months, median (IQR)	24.0 (13.0–48.0)	24.0 (12.5–45.0)	24.0 (13.0–48.0)	0.7361
Age distribution				
≤1 year, n (%)	36 (23.07)	5 (27.78)	31 (22.45)	0.5660
1–3 years, n (%)	64 (41.03)	8 (44.44)	56 (40.80)	0.8020
≥3 years, n (%)	56 (35.90)	5 (27.78)	51 (36.95)	0.6031
Allergy history, n (%)	15 (9.62)	6 (33.33)	9 (6.52)	0.0027*
Clinical symptoms and signs				
Fever, n (%)	156 (100)	18 (100)	138 (100)	>0.9999
Fever duration, days, median (IQR)	13.0 (10.0–18.0)	12.5 (10.0–16.0)	13.0 (9.0–18.0)	0.6112
Cough, n (%)	156 (100)	18 (100)	138 (100)	>0.9999
Wheeze, n (%)	49 (31.41)	4 (22.22)	45 (32.61)	0.4320
Shortness of breath, n (%)	88 (56.41)	11 (61.11)	77 (55.80)	0.8022
Hypoxia, n (%)	52 (33.33)	10 (55.56)	41 (29.71)	0.0348*
Gastrointestinal symptoms, n (%)	40 (25.64)	7 (38.89)	33 (23.91)	0.2483
Neurological symptoms, n (%)	19 (12.18)	5 (27.78)	14 (10.14)	0.0476*
Diminished breath sounds, n (%)	47 (30.13)	14 (77.78)	33 (23.91)	<0.0001*
Moist rales, n (%)	91 (58.33)	10 (55.56)	81 (58.70)	0.8047
Hepatomegaly or splenomegaly, n (%)	25 (16.03)	4 (22.22)	21 (15.22)	0.4935

Note: * $P<0.05$.

As for clinical symptoms and signs, there were no significant differences in fever, cough, shortness of breath, wheeze, gastrointestinal symptoms (vomit and diarrhea), moist rales, hepatomegaly, or splenomegaly between the two groups ($P>0.05$). However, about half the children with PB (10 of 18, 55.56%) and about a third of those without PB (41 of 138, 29.71%) had hypoxia, a significant difference ($P<0.05$). About a quarter of the children in the PB group (five of 18, 27.78%) had neurological symptoms (e.g., hypnosia, dysphoria and convulsions), while just one in 10 in the non-PB group did (14 of 138, 10.14%), a significant difference ($P<0.05$). What is more, more than half the children with PB (14 of 18, 77.78%) showed diminished breath sounds, while about a quarter of those without PB did (33 of 138, 23.91%), also a significant difference ($P<0.05$; Table 1).

In terms of laboratory indices, levels of leukocytes, hemoglobin, HsCRP, LDH, liver enzymes, (ALT, AST) and coagulation functioning (PT, APTT, FIB) showed no statistically significant differences between children in the PB and non-PB groups ($P>0.05$). On the contrary, there were significant differences in thrombocytopenia (six of 18, 33.33%: 19 of 138, 13.76%) and high proportion of neutrophils (10 of 18, 55.56%: 36 of 138, 26.09%) between the two groups ($P<0.05$). As we all know, adenovirus pneumonia is prone to coinfection with other pathogens. In our study, children with severe adenovirus pneumonia, the most common coinfection was *Mycoplasma pneumoniae*, follow by bacteria and other viruses. There was no significant difference between the groups ($P>0.05$; Table 2).

With regard to radiological findings, about four in five of the patients shown lung consolidation in HRCT, with about one in five showing single-lobe consolidation and three in five multilobe consolidation, none of which was significantly different between the groups on HRCT (Figure 2). In addition, about half the children in both groups manifested pleural effusion ($P>0.05$; Table 3). As is well known, the gold standard for the diagnosis of PB is the detection of bronchial dendritic casts on bronchoscopy. Figure 3 shows an extracted bronchial cast by flexible bronchoscopy in a patient with PB caused by HAdV.

Most of the children had been treated with intravenous immunoglobulin and about half with systemic corticosteroids, whether in the PB or non-PB group. Even so, more children developed respiratory failure and more need of mechanical

Table 2 Laboratory indices of PB and non-PB children with severe adenovirus pneumonia

	Total, n=156	PB group, n=18	Non-PB group, n=138	P
Complete blood counts				
Leukocytosis (WBCs $>12 \times 10^9/L$), n (%)	20 (12.82)	3 (16.67)	17 (12.32)	0.7055
Leukocytopenia (WBCs $<5 \times 10^9/L$), n (%)	64 (41.03)	6 (33.33)	58 (42.03)	0.6128
Anemia (HGB <90 g/L), n (%)	57 (36.54)	7 (38.89)	50 (36.23)	0.8011
Thrombocytopenia (PLT $<100 \times 10^9/L$), n (%)	25 (16.03)	6 (33.33)	19 (13.76)	0.0445*
Increased proportion of neutrophils ($>70\%$), n (%)	46 (29.49)	10 (55.56)	36 (26.09)	0.0142*
Serum biochemical indices				
HsCRP >10 mg/L, n (%)	127 (81.41)	16 (88.88)	111 (80.43)	0.5292
ALT >100 U/L, n (%)	13 (8.33)	1 (5.56)	12 (8.69)	>0.9999
AST >100 U/L, n (%)	49 (31.41)	6 (33.33)	43 (31.16)	>0.9999
LDH >600 U/L, n (%)	92 (58.97)	10 (55.56)	82 (59.42)	0.802
ALB <35 g/L, n (%)	96 (61.54)	10 (55.56)	86 (62.32)	0.6127
Coagulation function tests				
PT >15 seconds, n (%)	23 (14.74)	3 (16.67)	20 (14.49)	0.7314
APTT >45 seconds, n (%)	61 (39.10)	5 (27.78)	56 (40.58)	0.4417
FIB >4 g/L, n (%)	45 (28.85)	7 (38.89)	38 (27.54)	0.4064
Coinfections				
Other viruses, n (%)	40 (25.64)	5 (27.78)	35 (25.36)	0.7807
Bacterium, n (%)	57 (36.54)	6 (33.33)	51 (36.96)	>0.9999
<i>Mycoplasma pneumoniae</i> , n (%)	73 (46.79)	5 (27.78)	68 (49.28)	0.1305

Note: * $P < 0.05$.

Abbreviations: WBCs, white blood cells; HGB, hemoglobin; PLT, platelet; HsCRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALB, albumin; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen.

ventilation in the PB group than the non-PB group, a significant difference ($P < 0.05$). Of the 18 patients with PB, 16 improved with treatment, while two patients died even after aggressive treatment, for a mortality rate of 11.11%. However, there were no significant differences in hospital stays or mortality between the two groups ($P > 0.05$; Table 4).

Risk Factors for PB in Children with Severe Adenovirus Pneumonia

On univariate analysis, sex, age, duration of fever, wheeze, shortness of breath, gastrointestinal symptoms, leucocyte level, anemia, HsCRP level, liver enzymes, LDH level, ALB level, coagulation function, coinfection, multilobe consolidation, and pleural effusion showed no relationship with the risk of PB in children with severe adenovirus pneumonia (all $P > 0.05$). Nevertheless, allergy history, hypoxia, neurological symptoms, diminished breath sounds, thrombocytopenia, and high proportion of neutrophils were associated with the risk of PB in children with severe adenovirus pneumonia (all $P < 0.05$). Furthermore, multivariate analysis revealed that a history of allergies (OR 10.147, 95% CI 1.727–59.612; $P = 0.010$), diminished breath sounds (OR 12.856, 95% CI 3.259–50.713; $P = 0.001$), and increased proportion of neutrophils ($>70\%$; OR 8.074, 95% CI 1.991–32.735; $P = 0.003$) were independent risk factors for PB in children with severe adenovirus pneumonia (Table 5).

Discussion

PB is a rare, highly variable, and potentially fatal complication.⁹ HAdV plays an important role in severe pneumonia.⁶ Owing to casts blocking the airway, PB may lead to serious clinical symptoms, acute respiratory failure, and even death.³ Therefore, our study aimed to evaluate the clinical features and risk factors for PB in children with severe adenovirus pneumonia.

In our 18 children with PB, similar to previous studies^{9,10} the most common symptoms were cough, hyperpyrexia, diminished breath sounds, shortness of breath, and hypoxemia. The proportion of patients with elevated white blood cells was not high, but elevated HsCRP, LDH, and neutrophils were high. Most of their chest imaging showed pulmonary

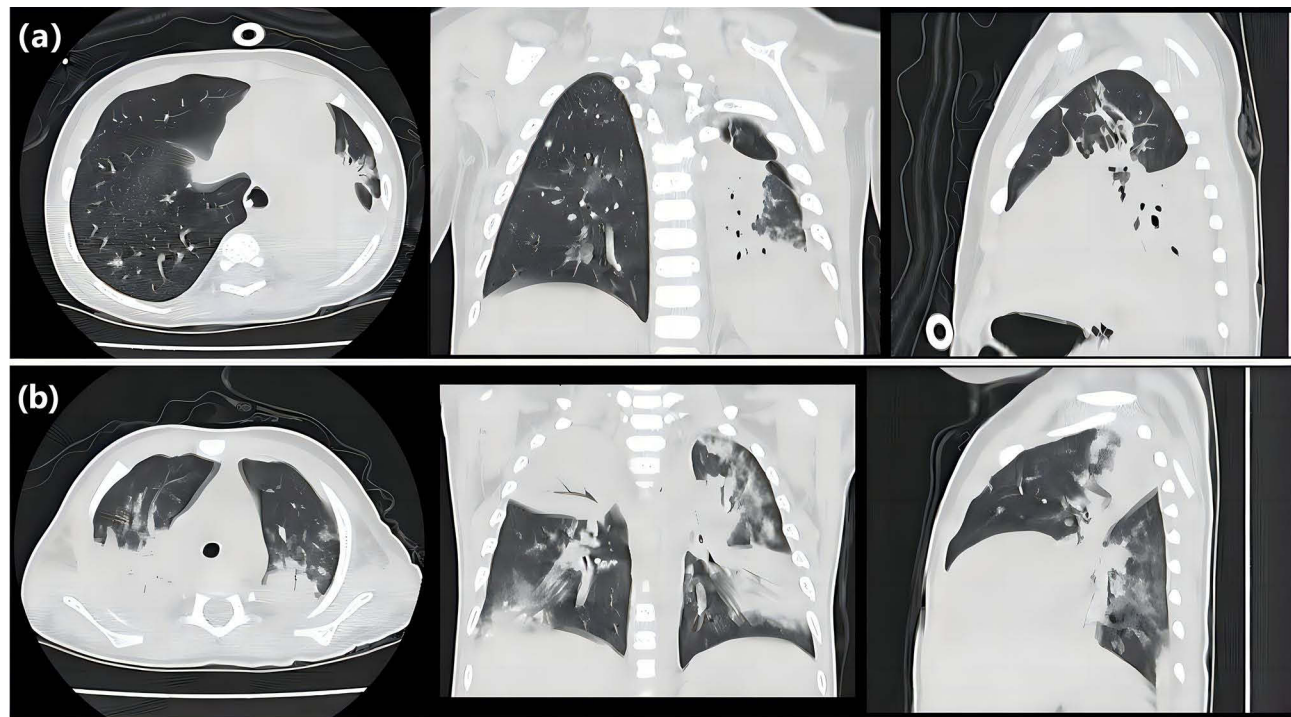


Figure 2 High-resolution CT scans of the chest. (a) Multiple consolidations in the left lung and compensatory emphysema of the right lung in a 1-year-old child with severe adenovirus pneumonia with PB. (b) Areas of airspace consolidations in the left lung and the superior lobe of the right lung in a 11-month-old child diagnosed with severe adenovirus pneumonia without PB.

consolidation or atelectasis, and about half had pleural effusion. Reported mortality rates for PB have ranged from 5% to 60%,^{11,12} and half the patients with PB in our study underwent respiratory failure and needed mechanical ventilation, while two died, for a mortality rate of 11.11%. Furthermore, we found that a history of allergies, diminished breath sounds, and increased proportion of neutrophils (>70%) were independent risk factors for PB in children with severe adenovirus pneumonia.

There are two types of PB based on cause and pathology. Type I is usually associated with respiratory diseases and type II with congenital heart disease.² All of our patients were considered to be type I PB, for all of them were undergoing respiratory infections and none had congenital heart disease, although without pathological results. Pathophysiology of type I PB is constant inflammation/irritation in the bronchial mucosa by allergens or infective agents, leading to induction of mucin hypersecretion by inflammatory cytokines (goblet cell hyperplasia), and finally thick mucinous material casts develop, consisting of fibrin, neutrophils, and eosinophils.¹³ PB may be associated with allergies, asthma, and allergic bronchopulmonary aspergillosis, among others.^{14,15} A previous study of 42 children with PB showed that 31% had a history of allergic illnesses.¹⁶ In our study, 33.33% children with PB had a history of allergies, including food allergy, drug allergy, and dust allergy. We drew the conclusion that allergy history is an independent risk factor for PB in children with severe adenovirus pneumonia. Allergy is an interrelated syndrome group that develops

Table 3 Radiological findings for PB and non-PB children with severe adenovirus pneumonia

	Total, n=156	PB group, n=18	Non-PB group, n=138	P
Lung consolidation, n (%)	124 (79.49)	15 (83.33)	109 (78.99)	>0.9999
Single-lobe consolidation, n (%)	31 (19.87)	4 (22.22)	27 (19.56)	0.7584
Multilobe consolidation, n (%)	93 (59.62)	11 (61.11)	82 (59.42)	>0.9999
Pleural effusion, n (%)	72 (46.15)	9 (50)	63 (45.65)	0.8041

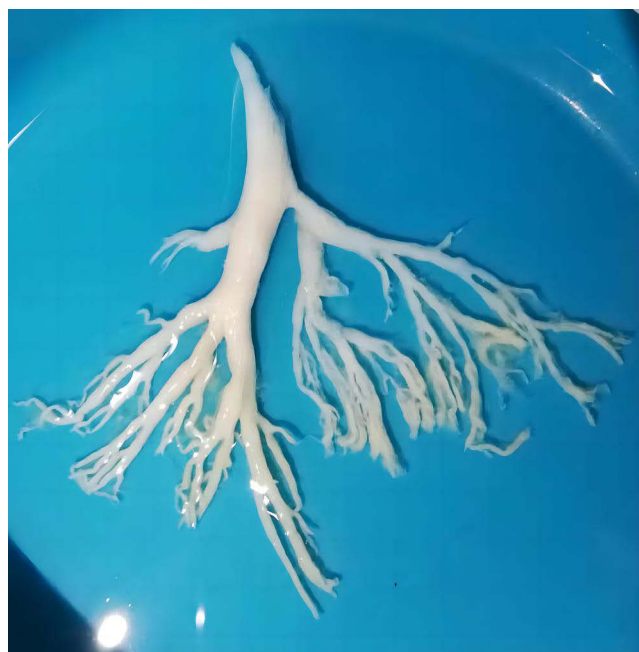


Figure 3 Extracted bronchial cast by flexible bronchoscopy in a patient with PB caused by HAdV.

through skin–digestive tract–respiratory tract sensitization.¹⁷ The relationship between airway allergy and respiratory virus infection is interactive. On the one hand, airway allergy may increase the risk and severity of respiratory viral infections.¹⁸ On the other hand, viral infection could initiate, maintain, and even overactivate the airway allergy.¹⁹ Both infection and allergy can lead to respiratory epithelial damage, inflammatory response, and excessive production of mucus, probably followed by the formation of bronchial casts, but the specific mechanism still needs to be explored.

HAdV can directly invade cells and indirectly induce immunoresponse to damage the respiratory epithelium, leading to cell lysis and eventual death.⁵ The epithelial cells on the surface of the airway are necrotic and denuded, and lamina propria of bronchi that are congested, edematous, and infiltrated with inflammatory cells, as well as airway mucus hypersecretions, results in occlusion of the bronchial lumen and even PB.^{6,20} Bronchial blockage can lead to pulmonary consolidation and atelectasis. The flow of air into the alveoli may be reduced or the flow rate slowed, and consequently

Table 4 Treatments and outcomes for PB and non-PB children with severe adenovirus pneumonia

	Total, n=156	PB group n=18	Non-PB group, n=138	P
Treatments				
Intravenous immunoglobulin, n (%)	135 (86.54)	16 (88.89)	119 (86.23)	>0.9999
Systemic corticosteroids, n (%)	87 (55.77)	10 (55.56)	77 (55.80)	>0.9999
Mechanical ventilation, n (%)	32 (20.51)	9 (50.00)	23 (16.67)	0.0028*
Continuous blood purification, n (%)	8 (5.13)	1 (5.56)	7 (5.07)	>0.9999
Extracorporeal membrane oxygenation, n (%)	12 (7.69)	2 (11.11)	10 (7.25)	0.6315
Complications				
Respiratory failure, n (%)	32 (20.51)	9 (50)	23 (16.67)	0.0028*
Pneumothorax/pneumomediastinum, n (%)	6 (3.85)	1 (5.56)	5 (3.62)	0.5269
Septic shock, n (%)	13 (8.33)	3 (16.67)	10 (7.25)	0.1756
Outcomes				
Hospital stays, days, median (IQR)	16.0 (12.0–21.0)	15.0 (10.0–19.0)	16.0 (12.0–21.0)	0.536
Death, n (%)	8 (5.12)	2 (11.11)	6 (4.35)	0.2316

Note: *P<0.05.

Table 5 Logistic regression analysis of risk factors for PB in children with severe adenovirus pneumonia

	β	P	OR	OR 95% CI	
				Lower	Upper
Allergy history	2.317	0.010*	10.147	1.727	59.612
Hypoxia	1.177	0.137	3.244	0.687	15.321
Neurological symptoms	0.551	0.607	1.735	0.212	14.185
Diminished breath sounds	2.554	0.001*	12.856	3.259	50.713
Thrombocytopenia	0.900	0.239	2.459	0.549	11.011
Increased proportion of neutrophils	2.089	0.003*	8.074	1.991	32.735

Note: * $P < 0.05$.

the auscultation of breath sounds may be diminished. As such, it is not difficult to understand that diminished breath sounds are risk factors for PB.

Routine blood testing is easily conducted in clinical practice, and contributes to early and rapid diagnosis of disease. Neutrophils, important blood cells, can endocytose and kill pathogens, playing an important role in maintaining human immunity. One study identified the neutrophil ratio as one of the significant predictive factors to construct nomograms for predicting PB.²¹ Similarly, we found that increased proportion of neutrophils $>70\%$ is one of the independent risk factors for PB in severe adenovirus pneumonia. Neutrophil infiltration occurs in the early stage of HAdV infection,²² and it is a double-edged sword. On the one hand, it plays an important role in pathogen clearance, and on the other hand, its excessive activation can lead to airway epithelium damage, adding to infiltration of inflammatory cells, and may lead to airway obstruction.²³ Our study only examined the level of neutrophils in blood and not in BAL. Future studies could evaluate the relationship between PB and neutrophils in BAL.

There are several limitations in this study. It was a single-center and retrospective study and included a small number of subjects. The other limitation is not examining the influence of the timing of BAL in the illness course. Finally, we did not explore the relationship between the specific serotyping of HAdV and PB in our study.

Conclusion

HAdV pneumonia can cause PB. When children with severe adenovirus pneumonia have a history of allergies, diminished breath sounds, and increased proportion of neutrophils ($>70\%$), HAdV PB should be strongly considered. The timely application of bronchoscopy plays an important role in disease recovery and prognosis.

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Disclosure

The authors report no conflicts of interest in this work.

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