Rare presentation of atypical pathogens pneumonia as fibrinous inflammation in 8 children in Anhui province, China from 2012 to 2019

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Abstract

Background *M. pneumoniae* and adenovirus are generally recognized as a self-limiting illness, but sometimes they will develop into macrolide-resistant *M. pneumoniae* or refractory adenovirus pneumonia associated with prolonged disease course with increased clinical severity, longer hospital stay and treatment failure.

Methods Children with a final diagnosis of atypical pathogens pneumonia presenting as mucus plugs to the Department of Pediatrics, the First Affiliated Hospital of Anhui Medical University were prospectively enrolled between June 2012 and June 2019. 7 patients were identified as *mycoplasma pneumoniae* positive IgM and 1 patient was diagnosed as adenovirus infection by enzyme-linked immunosorbent assay.

Results All the 8 cases reported in this study were diagnosed as lung infection, while 6 patients had pulmonary consolidation. Histological examination of mucus plugs in patient 3 and 8 revealed a fibrinous exudation. The average duration of macrolide antibiotics treatment was (12.86 ± 3.49) days, and the total course of treatment ranged from 7 to 17 days. Patient 5 with adenovirus infection was given ganciclovir for 10 days without using of antibiotics. Bronchoalveolar lavage, pulse methylprednisolone, atomization inhalation of salbutamol and budesonide suspension, and intravenous immunoglobulins were performed in these patients.

Conclusion We highly suspected that these mucus plugs might be the early presentation of plastic bronchitis. Use of anti-infection treatment (macrolide antibiotics), corticosteroid, gamma globulin, and other conventional treatments, lung lavage bronchofibroscope have good efficacy and can improve clinical outcomes.

Introduction

Globally, pneumonia is the leading cause of hospitalizations and death among children with nearly 120 million new cases and one million deaths each year [1]. In China, pneumonia among children ≥ 5 years old is associated with incidence ranging from 0.06–0.27 episodes per person-year, and mortality ranging from 184–1,223 deaths per 100,000 population [2]. Lobar pneumonia plays an important role in it [3].

Atypical pathogens infection played an important role in community-acquired pneumonia (CAP) in children. The most common aetiology is *mycoplasma pneumoniae* (*M. pneumoniae*) and adenovirus (ADV). In recent decades, increasing numbers of patients with *M. pneumoniae* or ADV infections showed persisting fever ($\geq 38.5^{\circ}\text{C}$) and radiological deterioration despite undergoing macrolide antibiotics or ganciclovir treatment. Here they required investigation using bronchoscopy. The presence of mucus plugs in severe *M. pneumoniae* and ADV infections have been extensively reported recently, especially in Asian countries [4–6]. However, formation and pathogenic mechanism of the mucus plugs are still remaining unclear. We encountered 8 cases of atypical pathogens pneumonia who had mucus plugs formation under bronchoscopy.

Methods

All the clinical data used in this study were obtained from the paper and electronic medical records (EMRs) of our hospital. The study protocol was approved by the Research Ethics Commission of the First Affiliated Hospital of Anhui Medical University.

2.1 Patients

Children with a final diagnosis of atypical pathogens pneumonia presenting as mucus plugs to the Department of Pediatrics, the First Affiliated Hospital of Anhui Medical University were prospectively enrolled between June 2012 and June 2019.

- Data collection

We collected the medical information on our patients, analyzed their demographics, clinical information, laboratory results, imaging performance and outcomes, and detected blood specimens, such as routine blood examination, liver function, myocardial enzymes, C-reactive protein (CRP), procalcitonin (PCT), specific antibody to atypical pathogens, and bronchoalveolar lavage fluid. A chest computed tomography (CT) scan was carried out during hospitalization, and ultrasound was used to diagnose pleural effusion. Flexible bronchoscopy (FOB) with bronchoalveolar lavage (BAL) was performed according to the Guide to pediatric bronchoscopy [7]. Abnormal blood indexes and CT were checked before hospital discharge. Patients who need oxygen therapy were assessed by the Guidelines [8]. All patients were followed up until the cough were absorbed.

2.3 Statistical analysis

Statistical analysis was carried out using SPSS software (version 25.0) (IBM Corp., Armonk, NY, USA). Data representing the normal distribution were expressed as (mean $\pm$ standard) deviation, while data showing a skewed distribution were exhibited as median values (interquartile range).

Results

3.1 Clinical features and the positive percentages of pathogens

The mean age of the patients was (4.09 ± 2.63) year old (min: 8 month-max: 8 year) and male-female ratio was 3:1. Initial symptoms, physical findings, and radiologic evaluations of patients were listed in Table 1. None of the patients had underlying cardiac disease, only one of them had a previous history of asthma and two of them had a previous history of eczema. The main symptoms of the 8 patients were fever and respiratory symptoms, with less or no infection-toxic manifestations. Lung

auscultation revealed short and labored inspiration without rhonchi and rales on both lung fields. 7 patients were identified as *M. pneumoniae* positive IgM and 1 patient was diagnosed as ADV infection by using enzyme-linked immunosorbent assay (ELISA). the median duration of *M. pneumoniae* pneumonia onset to appropriate antibiotic treatment was (8.43 ± 5.16) days. The mean duration of fever was (9.50 ± 5.86) days (min-max: 1–21 days), and (10.71 ± 5.12) days in *M. pneumoniae* pneumonia (Table 1).

3.2 Laboratory studies

Patient 1 with *M. pneumoniae* infection revealed: CRP, 373.10 mg/L; PCT, 3.52 ng/mL; White blood cell (WBC), $30.14 \times 10^9/L$; Neutrophil ratio (N%), 88.84%. Patient 2, 3, 7, 8 with *M. pneumoniae* revealed a slight increase in CRP and N%, but a normal PCT and WBC values. The other patients showed normal CRP, PCT, WBC and N% values (Table 2). Chest radiograph showed a right-sided lobar pneumonia of the right upper lung in patient 3 (Figure 1A). Chest CT scan showed lobar pneumonia in 6 patients (Figure 1B-C-D-E) (Table 3), and patient 7 showed a small amount of pleural effusion (Figure 1D) (Table 3). Suction of mucus plugs and BAL were performed in all patients with FOB. All of them showed obvious edema of trachea mouth; and mucus plugs, which is constantly overflowing from the opening of bronchia, was difficult to be sucked out (Figure 1F-G-H-I). Histological examination of mucus plugs in patient 3 and 8 revealed a fibrinous exudation containing large quantity of cellulose cells, and inflammatory cells such as eosinophils, neutrophils (Figure 2). Broncho alveolar lavage fluid (BALF) revealed that mean white blood cell count and percentage of multiple nucleated cells were (10036.00 ± 10164.40) and (84.52 ± 8.61), respectively (Table 3).

3.3 Treatment, outcome and follow-up

Macrolide antibiotics (erythromycin or azithromycin) were used for the patients with *M. pneumoniae*. The average duration of macrolide antibiotics treatment was (12.86 ± 3.49) days, and the total course of treatment ranged from 7 to 17 days. Patient 5 with ADV infection was given ganciclovir for 10 days without using of antibiotics. Moreover, for the treatment of lobar pneumonia, BAL and atomization inhalation of salbutamol and budesonide suspension with postural drainage were performed. The symptoms of fever disappeared, cough gradually alleviated, and repeated chest CT scan showed lobar pneumonia disappeared. Patient 1 was given intravenous immunoglobulins (IVIg) (400 mg/kg/d) for 1 day and cefoperazone sulbactam for a week. Patient 7 was given IVIg (400 mg/kg/d) for 3 days. Six patients started treatment with pulse methylprednisolone for 1–10 days (3–5 mg/kg/day). We monitored the heart rate, pulse oxygen saturation (SpO₂) and respiratory rate of the patients during the procedure. 8 patients in our report showed no signs and symptoms of hypoxia (cyanosis, low SpO₂ and/or high heart rate), therefore they were not given oxygen therapy. Nebulized budesonide suspension was administered at 2–3 months follow-up. The symptoms of cough disappeared. 6 months at follow-up revealed no respiratory problems.

Discussion

All the 8 cases reported in this study were diagnosed as lung infection with mucus plugs. Among them 1 patient had consolidation as well as pleural effusion, and 5 patients had consolidation. 7 cases were infected with *M. pneumoniae*, while 1 case was identified as ADV infection. Mucus plugs formation was actually a manifestation of severe cilia abnormalities. Severe cilia abnormalities disrupt the mucociliary clearance, causing mucus plugs which is responsible for the development of consolidation [4]. It was reported that, when systemic inflammatory reactions are similar, the degree of local airway mucosal damage caused by *M. pneumoniae* and ADV may be more severe than other pathogens, and *M. pneumoniae* pneumonia can occur mucus plugs when local airway secretions increase and the integrity of the tube wall is damaged [8–10].

In our report, mucus plugs difficult to be sucked out were identified in all patients, which is constantly overflowing from the opening of [bronchia](#). Histological examination of the 2 patients revealed fibrinous necrosis characterized by a large number of cellulose cells, and inflammatory exudate characterized by a variety of neutrophils and lymphocytes. Plastic bronchitis mainly occurring in childhood is a rare life-threatening disease characterized by progressive dyspnea and formation of bronchial casts, and the most common complication was respiratory failure with respiratory support [8–10], while 8 cases in our report even don't need oxygen therapy. Histological examination of the bronchial cast by using electronic fiber bronchoscopy from 5 patients in Guangzhou province, China, diagnosed as plastic bronchitis, revealed a fibrinous exudation and necrotic material containing large quantity of neutrophils [8–9]. Therefore, we highly suspected that these mucus plugs might be the early presentation of plastic bronchitis [5].

Although the clinical manifestations of 8 patients are similar, there are so many differences among their course of disease and laboratory values. Patient 1 showed a significant elevation of CRP, PCT, WBC and Neutrophil ratio, while white blood cell count and percentage of multiple nucleated cells in bronchoalveolar lavage fluid were $316 \times 10^6/L$, 75.3%. However, Patient 4 and patient 6 showed normal CRP, PCT, WBC and Neutrophil ratio, while white blood cell count and percentage of multiple nucleated cells in bronchoalveolar lavage fluid were more than $20000 \times 10^6/L$, 80%. It was Seear and Hui who first distinguished inflammatory casts (type 1) made up of infiltrates of inflammatory cells, fibrin, and eosinophils and acellular casts (type 2) made up of mucin and rare monocytic cells, in 1997 [11]. According to Seear and Hui's classification, considering that mucus plugs were difficult to be sucked out and fibrinous necrosis in our report, it might be type 2 cast in patient 1, It is a pity that our patient refused to accept pathologic examination. Type 1 cast could be identified in the others.

Conservative therapy, such as corticosteroids, antibiotics, mucolytic agents, bronchoscopy, chest physiotherapy, and inhalation treatment can be used in atypical pathogens pneumonia presenting as mucus plugs. We performed FOB plus BAL in all the patients and found that BAL could remove respiratory tract secretions and mucus plugs. Berlucchi et al reported that conservative therapy had been successfully used to treat a rare case of 5-year-old girl affected mucus plug infection and mucus plug

formation [12]. Recently Wang et al. showed that 25 children with necrotizing pneumonia caused by refractory *Mycoplasma pneumoniae* in China, who received FOB plus BAL, had got good outcomes [13].

Delayed macrolide antibiotics treatment, was defined as the duration of disease onset to appropriate antibiotic treatment was equal to or over the 6 days while the median duration of disease onset to appropriate antibiotic treatment was 5.6 days [14–15]. Yang et al. reported that delayed appropriate antimicrobial treatment, no matter macrolide resistance or not, was associated with more severe and/or prolonged disease, and extrapulmonary manifestations [14]. Most patients were prescribed with corticosteroids because a cell-mediated strong immune response plays an important role in the development of RMPP, and it was discovered that corticosteroids were of great benefit in improving conditions. In addition, Tamura et al. had reported several successful cases of treating RMPP using corticosteroids [13,16]. In our report, the mean duration of fever was (10.71 ± 5.12) days in *M. pneumoniae* pneumonia, the median duration of *M. pneumoniae* pneumonia onset to appropriate antibiotic treatment was (8.43 ± 5.16) days, and the mean total length of antibiotic therapy was (12.86 ± 3.49) days. However, the period of disease course and therapy were not as long as that of other reports [12–14]. What's more, we suggest performing inhalation therapy using salbutamol and budesonide suspension, and before endoscopic technique, which can resolve the disease avoiding to carry out more invasive managements.

Conclusions

In conclusion, early diagnosis of atypical pathogens pneumonia presenting as mucus plugs as well as the use of anti-infection treatment (macrolide antibiotics), corticosteroid, gamma globulin, and other conventional treatments, lung lavage bronchofibroscope have good efficacy and can improve clinical outcomes.

Abbreviations

CAP: Community-acquired pneumonia; *M. pneumoniae*: *Mycoplasma pneumoniae*;

ADV: Adenovirus; EMRs: Electronic medical records; CRP: C-reactive protein; PCT: Procalcitonin; CT: Computed tomography; FOB: Flexible bronchoscopy; BAL: Bronchoalveolar lavage; ELISA: Enzyme-linked immunosorbent assay; WBC: White blood cell; N%: Neutrophil ratio; BALF: Broncho alveolar lavage fluid; IVIg: Intravenous immunoglobulins; SpO₂: Pulse oxygen saturation

Declarations

Ethics approval and consent to participate

The study protocol was approval by the Research Ethics Commission of the First Affiliated Hospital of Anhui Medical University. The permission letter that allowed access to the medical records for this study

was obtained from the hospital management office. A Statement of consent to participate was obtained from the parents of the children included in this study.

Consent for publication

The patient's guardians have consented to submission of their case reports to the journal, and we have obtained written informed consents.

Availability of data and materials

The data supporting my findings can be found in medical-record department of the First Affiliated Hospital of Anhui Medical University. All data generated or analysed during this study are included in this published article.

Competing interests

The authors report no conflict of interest.

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Author's contributions

LW contributed to conception of the manuscript and drafted the manuscript. WW contributed to the obtaining and interpreting of the clinical information. SGD contributed the conception of the manuscript, and made substantial contribution to manuscript revision. All the authors have read and approved the manuscript for publication and agreed to be accountable for all aspects of the work.

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Tables

TABLE 1 The clinical features and Pneumoslides IgM test in 8 children with atypical pathogens pneumonia

Abbreviations: *M* Male, *F* Female, *Y* Year; *M* Month; *ERM* Erythromycin, *AZM* Azithromycin, *MP* Pulse methylprednisolone, *IVIg* Intravenous immunoglobulins, *MP* Mycoplasma pneumonia; *ADV* Adenovirus.

TABLE 2 The Laboratory values in 8 children with atypical pathogens pneumonia

Abbreviations: *N* Normal, *AN* Abnormality, *LDH* Lactate dehydrogenase.

TABLE 3 Additional examinations in 8 children with atypical pathogens pneumonia

Case number	Sex	Age	Past history	Hospital stay (days)	Febrile duration (days)	Pneumoslides IgM test	Initial manifestations	Macrolide antibiotics, MP, and IVIG duration (days)	Interval between onset and macrolide antibiotic treatment (days)
1	M	3Y	Eczema	9	7	MP	Fever, cough	ERM (4), AZM (3), IVIG (1)	4
2	F	4Y	nil	14	14	MP	Fever, cough	ERM (14)	14
3	M	6Y	nil	20	7	MP	Fever, cough	ERM (14), AZM (3), MP (7)	3
4	M	2Y	nil	14	8	MP	Fever, cough	ERM (10), MP (5)	8
5	M	8M	Eczema	10	1	ADV	Cough	Ganciclovir (10), MP (1)	15
6	M	2Y	nil	12	9	MP	Fever	ERM (12), MP (3)	4
7	F	7Y	Asthma	13	21	MP	Fever, cough	AZM (5), ERM (9), MP (10), IVIG (3)	14
8	M	8Y	nil	15	9	MP	Fever, cough	AZM (5), ERM (11), MP (10), P (12), IVIG (2)	16

Case number	C-reactive protein (≤ 10.0 mg/L)	Procalcitonin (≤ 0.5 ng/mL)	White blood cell count (≤ 10 × 10 ⁹ /L)	Neutrophil ratio (≤ 70%)	Elevated transaminase	LDH (u/L)	Myocardial enzymes
1	373.10	3.52	30.14	88.84	N	393	AN
2	35	□	13.05	75.09	AN	365	AN
3	36	□	3.48	68.10	AN	354	AN
4	0.60	□	8.38	32.54	N	584	AN
5	3.40	□	8.59	29.24	AN	326	N
6	6.00	0.35	12.88	42.74	N	376	□
7	26.30	0.22	8.47	87.64	AN	894	AN
8	30.60	0.082	8.07	78.74	N	274	AN

Case number	Chest radiograph	CT	ECG	Chest ultrasonography	Bronchoalveolar lavage fluid (BALF)	
					White blood cell count ($\times 10^6/L$)	Percentage of multiple nucleated cells (%)
1	PC	PC	AN	□	316.00	75.3
2	PC	PC	□	□	□	□
3	PC	PC	□	□	□	□
4	P	P	N	□	23255.00	84.3
5	P	P	□	□	3105.00	89.6
6	P	PC	AN	□	21469.00	88.1
7	P	PC	□	PE	10313.00	96.0
8	P	PC	N	N	1758.00	73.8

Abbreviations: *CT* Computerized tomography, *ECG* Electrocardiogram, *P* Pneumonia, *PC* [Pulmonary consolidation](#), *PE* Pleural effusion, *ADV-IgM* Adenovirus Immunoglobulin M, *MP-IgM* Mycoplasma pneumoniae Immunoglobulin M, *AN* Abnormality, *N* Normal; □: No test.

Figures

Figure 1

(A) Chest X-rays showed pneumonia of the right upper lobe (red arrow). Chest CT scan showed lobar pneumonia: (B) the left upper lobe (red arrow), (C) the left lower lobe (red arrow), (D) the right upper lobe (red arrow) and a right-sided small amount of pleural effusion (blue arrow), (E) the right upper lobe (red arrow). (F-G-H-I) Gross image of cast (black arrow) removed via bronchoscopy.

Figure 2

Patient 3 and 8. Bronchial biopsy detectable by hematoxylin-eosin staining (HES) showed fibrinous necrosis characterized by a large number of cellulose cells (red arrow), and inflammatory exudate characterized by a variety of neutrophils and lymphocytes (black arrow).