

Bronchoscopic Features and Correlative Factor Analysis of Severe *Mycoplasma pneumoniae* Pneumonia in Children.

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May 20, 2021

Abstract

Objectives: We aimed to determine the bronchoscopic features of children with severe *Mycoplasma pneumoniae* pneumonia (SMPP), and correlation with obliterative bronchitis (OB), so as to help early clinical evaluation and treatment of pediatric SMPP. **Methods:** 213 pediatric SMPP cases admitted to Beijing Children's Hospital were included. Medical records and bronchoscopic manifestations at different SMPP stages were retrospectively analyzed. **Results:** Of 213 acute-stage pediatric SMPP patients, bronchoscopy revealed 22 cases (10.3%) with subacute-stage or recovery-stage OB, for an OB incidence rate in cases with mucous embolus of 48.8% (22/47), a significantly higher rate than the rate without mucous embolus (0/166, 0%) ($P < 0.001$). Notably, the OB incidence rate for children undergoing bronchoscopy within 10 days (9/142, 6.3%) of SMPP onset was significantly lower than in children undergoing bronchoscopy 10 days post-disease onset (13/71, 76.5%) ($P < 0.007$). **Conclusions:** In pediatric SMPP patients, airway mucus and debris from epithelial necrosis and exfoliation can block airway subbranches, readily leading to OB.

INTRODUCTION

Mycoplasma pneumoniae pneumonia (MPP) is one of the most common types of community-acquired pneumonia (CAP) in children.¹ Macrolide antibiotics are effective treatments for most patients, but in some cases MPP may progress to severe MPP (SMPP). SMPP patients exhibit poor responses to single macrolide antibiotics and progression of disease that is accompanied by persistent high fever, aggravation of pulmonary lesions, and additional complications, such as necrotizing pneumonia, atelectasis, bronchiectasis, obliterative bronchiolitis (OB), and other disorders. SMPP complications can lead to repeated infections and decreased quality of life for afflicted children.^{2,3}

The pathogenesis of SMPP likely involves many processes, such as excessive immune inflammatory reactions, mixed infections, and so on. Therefore, the abovementioned factors should be considered during SMPP treatment to reduce the development of pulmonary sequelae. Notably, using bronchoscopy we have found that MPP is associated with specific manifestations such as airway mucus blockage and mucosal necrosis as main findings that cannot be completely eliminated by conservative treatments such as antibiotics and glucocorticoids. Indeed, airway blockage is of particular concern in that it can occur within a short period of time and progress to permanent atelectasis. Therefore, avoidance of OB should be an early treatment priority for practitioners caring for pediatric MPP patients in China, especially in the northern region.⁴ Consequently, a better understanding of the effects of early abnormal dynamic inflamed airway changes on later incidence of airway occlusions and their implications for MPP treatment have not yet been reported. Such information may be acquired via bronchoscopy, which can facilitate SMPP diagnosis during acute-phase MPP by providing bronchial lavage fluid for pathogen detection and information pertaining to microscopic disease manifestations. Also, bronchoscopy can reveal complete membranous obstructions within subsegmental bronchi of OB cases.

In this retrospective study, we analyzed bronchoscopic findings of pediatric SMPP patients admitted to Beijing Children’s Hospital affiliated with Capital Medical University from October 2017 to January 2019 to reveal correlations between bronchoscopically determined disease manifestations and SMPP prognosis.

METHODS

Subjects

This study was a retrospective analysis of pediatric patients afflicted with SMPP and admitted to the hospital from June 2017 to January 2019. Diagnostic criteria of MPP were as follows: (1) fever, cough, and other clinical manifestations; (2) chest image findings indicative of pneumonia; (3) MPP-specific IgM antibody titer persisting at a level $\geq 1:320$, or an antibody level that increased 4-fold during convalescent and acute SMPP phases (passive agglutination method, Fujirebio Inc., Japan). Based on MPP diagnosis combined with the latest diagnostic criteria for severe CAP in China, any one of the following criteria was used as a reference for the diagnosis of SMPP:^{5,6} obvious shortness of breath or tachycardia (criteria: 1-5 years old, RR ≥ 40 times/min; >5 years old, RR ≥ 30 times/min, respectively); hypoxemia during inhalation and pulse oximetry-based oxygen saturation (SaO_2) less than 0.93; chest images demonstrating multi-lobe or segment involvement or pulmonary area involvement of greater than 2/3 of the total lung area; pleural effusion, atelectasis, pulmonary necrosis, pulmonary abscess, and other pulmonary complications; complications associated with severe damage of other systems, such as central nervous system infection, heart failure, myocarditis, gastrointestinal hemorrhage, obvious electrolyte/acid-base balance disorder, etc. Exclusion criteria included previous congenital or secondary immunosuppression or defect, chronic pulmonary disease, kidney or cardiovascular disease, and connective tissue disorders, etc. Patients were also excluded if they were infected with other pathogens within 7 days post-admission or did not receive bronchoscopy at admission. All recruited children had received treatment with macrolide antibiotics for one week without noticeable improvement.

Bronchoscopy

Bronchoscopy was performed under the following conditions: decreased respiratory sounds corresponding to the lesion site during auscultation; ineffective anti-infection treatment; chest image showing large area of pulmonary consolidation. Bronchoscopic reexamination was conducted when chest imaging showed poor absorption of lung lesions and the airway still harbored a mucous embolus one week after bronchoscopy had been conducted in spite of systemic hormone and anti-MP treatment.

Bronchoscopic procedures were as follows: for each patient, the nasal cavity and pharynx were locally anesthetized with 1% lidocaine prior to the procedure. After sedation via intravenous injection of 0.1-0.3 ml/kg midazolam, bronchoscopy was performed using either an Olympus BFXP-260F model (outer diameter 2.8 mm) or Olympus BF P-260F model (outer diameter 4.0 mm) bronchoscope via entry through the nostril. Changes in mucosa of the nasal cavity, pharynx, trachea, bronchus, and subsegmental mucosa were observed in turn. If the mesh foreign body basket was blocked by mucous plugs or the cell brush removed mucus plugs from the airway, deep subsegmental bronchi lumens were infused with not more than 5 ml/kg 0.9% sodium chloride according to patient body weight. Routine examination of lavage fluid was conducted to determine etiology.

The study was approved by the ethics committee of Beijing Children’s Hospital. All parents or legal guardians provided written informed consent before conducting the study and any study-related procedures.

Data Collection

Bronchoscopic manifestations, time between disease onset and bronchoscopy, lung images, serum C-reactive protein (CRP), and body temperature changes were analyzed retrospectively. The following data were assessed: bronchoscopic manifestations of pediatric SMPP patients with different imaging findings; lavage fluid pathogen detection; time of body temperature recovery to normal, and total fever course after bronchoscopy; OB incidence, time to OB onset, and disease characteristics; pulmonary imaging results, including lesion

site, type, imaging findings, and therapeutic outcome; duration of fever during disease course and after bronchoscopy; inflammatory indexes, such as routine blood and CRP test results.

Statistical Analysis

SPSS statistics Version 22.0 (International Business Machines (IBM) Corporation) was employed for data analysis. Enumeration data were expressed as percentages and the χ^2 test was used for comparisons between groups. Measurement data conforming to the normal distribution were expressed as the mean \pm standard deviation (SD) and the t-test was used to make comparisons between two groups. The median [interquartile range (IQR) M(P₂₅-P₇₅)] was used for measurements of data not conforming to the normal distribution and the rank-sum test was used to make comparisons between two groups. Count data were expressed by rate or constituent ratio and chi-squared testing was performed. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

A total of 248 cases were diagnosed with SMPP, of which 213 cases met the enrollment criteria. The average time period that elapsed from disease onset to first bronchoscopy was 8.9 ± 2.4 days, with the average number of prior bronchoscopies found to be 2.2 ± 1.8 . Of the enrolled cases, 142 cases (142/213, 66.7%) had their first bronchoscopy within 10 days post-disease onset, while 71 cases (71/213, 33.3%) had their first bronchoscopy 10 days post-onset of disease. 183 cases (183/213, 85.9%) underwent bronchoscopy no more than twice, while 30 cases (30/213, 14.0%) underwent bronchoscopy at least three times (Table 1).

Clinical and Bronchoscopic Manifestations

In this study, disease course was assessed based on clinical manifestations, lung imaging, and bronchoscopic findings then was classified into three disease course categories: acute-stage, subacute-stage, and recovery-stage.

Symptoms during acute-stage SMPP included fever, elevated CRP, and large areas of consolidation detected via lung imaging. Generally, detection of bronchial mucosal congestion with or without airway mucosal follicular hyperplasia and bronchial secretions increased with use of bronchoscopy. Symptoms of subacute-stage SMPP were characterized by decreased or normal fever peak, improved signs as assessed via lung imaging, increased blood CRP, and decreased bronchial secretions and airway blockages accompanied by mucous membrane necrosis and exfoliation found via bronchoscopy. Symptoms of recovery-stage SMPP included normal body temperature, normal blood CRP, and either improved findings via lung imaging or atelectasis.

Bronchoscopic manifestations of acute-stage SMPP: all cases exhibited different degrees of congestion and roughness of tracheal and bronchial mucosa, mucosal longitudinal fold changes, and mucinous secretion. During the first bronchoscopy, follicular hyperplasia of airway mucosa was found in 162 cases (162/213, 76%), with lung lesions located in grade I and grade II trachea. Erosion of airway mucosa was found in 105 cases (49.2%), with lesions located in grade III or lower grade bronchi. Mucous plug blockages involving grade III or lower bronchi were found in 47 cases (47/213, 22.0%). The mean disappearance time of mucous plugs was 15 ± 1.7 days. The mean number of previous bronchoscopies was 2.6 ± 3.5 . Of cases with mucous plugs, 8 cases (8/213, 3.8%) had severe mucous plug obstruction (with tree-like bronchial-shaped changes). Locations of lesions were as follows: lesions of 11 cases (11/213, 10.5%) were in the left upper lung, of 15 cases were in the left lingual lobe (15/213, 14.3%), of 48 cases were in the left lower basal segment (48/213, 45.7%), of 13 cases (13/213, 12.4%) were in the right upper lobe, of 10 cases (10/213, 9.5%) were in the right middle lobe, of 64 cases (64/213, 60.9%) were in the right lower basal segment, of 63 cases (63/213, 60%) were in one lobe, of 32 cases (32/213, 30.5%) were in two lobes, of 7 cases (7/213, 6.7%) were in three lobes, of 3 cases (3/213, 2.8%) were in four lobes; no cases involved five lobes.

Bronchoscopic manifestations in subacute and recovery stages: 22 cases (22/213, 10.3%) had OB, including

13 males (13/22, 59%) and 9 females (9/22, 41%). The median time to diagnosis of Sub-bronchial stenosis was 15 days [IQR 12-18]. The initial obstruction was a thin film that was easily broken with biopsy forceps in order to reopen the airway. With time, the untreated occluded airway section gradually thickened and the center became concave and became associated with a peripheral radial hyperplasia-like obstruction. Proximal tracheal examination revealed the presence of fishbone-like bronchiectases that were difficult to reopen using biopsy forceps (Figures 1 and 2).

Analysis of Factors Associated with SMPP Progression to OB

Of 47 (46.8%) pediatric SMPP patients with mucous emboli, 22 patients developed OB and no OB was found in children without mucous emboli; thus, OB incidence in children with mucous emboli was significantly higher than in children without mucous emboli ($P < 0.001$). All 8 cases (100%) with plastic bronchitis determined via bronchoscopy exhibited different degrees of OB. During the convalescent stage, OB occurred in 4 of 183 cases (2.2%) reporting two or fewer prior bronchoscopies and 18 of 30 cases (60%) with at least 3 prior bronchoscopies. The incidence of OB in children with two or fewer bronchoscopies was significantly lower than OB incidence in children with at least three prior bronchoscopies ($P < 0.001$). Importantly, of 142 children (6.3%) who had the first bronchoscopy within 10 days of disease onset, 9 developed OB (6.3%); of 71 children who had their first bronchoscopy on or after 10 days of disease onset, 13 (76.5%) developed OB. Therefore, OB incidence of children undergoing bronchoscopy within 10 days of disease onset was significantly lower than that of children undergoing bronchoscopy at or after 10 days post-disease onset ($P < 0.007$). Moreover, the average chest CT number for children with acute stage obstructive bronchitis was 26 u, while the average CT number for children without OB was 19 u. Thus, chest CT values of children with OB were significantly higher than those of children without OB, with the difference between groups reaching statistical significance ($P < 0.05$). Notably, OB was found in all 6 cases afflicted with necrotizing pneumonia (100%), as detected via pulmonary imaging (Table 2, Figure 3).

Adverse Events

No massive hemorrhage occurred. However, during acute-stage SMPP some bronchoalveolar lavage or cell brush interventions caused a small amount of bleeding. In such cases, a local application of 1:10000-diluted adrenaline may help. No case of pneumothorax was detected.

Discussion

Children afflicted with SMPP have severe clinical symptoms and more complications than those with MPP, including necrotizing pneumonia, atelectasis, bronchiectasis, OB, and permanent airway structural damage. As a result, lung function declines and repeated infections can impact quality of life for these patients. According to previous studies, main clinical manifestations of pediatric SMPP include continuous high fever and the presence of large areas of lung consolidation detected via pulmonary imaging. These findings reflect an overactive immune response that often requires hormone therapy for suppression of harmful inflammatory processes.⁷⁻⁹

The clinicalClinical manifestations of MPP in China differ from those reported in other countries, with symptoms more serious in China, especially in northern areas.⁴ In recent years, the widespread application of pediatric bronchoscopy for SMPP diagnosis and treatment has led to great progress in treating this disorder in China. Although some practitioners doubt the value of bronchoscopic findings for MPP prognosis, the value of bronchoscopy has been demonstrated for pediatric SMPP prognosis in China. In this study, congestion and swelling of airway mucosa were obvious in acute-stage cases examined via bronchoscopy, with some of these findings accompanied by follicular hyperplasia, a relatively specific MPP-associated manifestation. Meanwhile, during bronchoscopy bronchoalveolar lavage fluid is readily collected for use in MPP pathogen detection as a direct and effective method for achieving differential MPP diagnosis and treatment. Importantly, acute-stage SMPP mucous plug obstructions should be cleared bronchoscopically in a timely manner in order to maintain unobstructed airway subbranches and subsequently control infection. In subacute-stage SMPP, bronchoscopy can be used to monitor recovery from airway inflammation and detect OB sequelae for use in guiding treatment and respiratory rehabilitation planning. Therefore, bronchoscopic examination

and intervention can benefit children with SMMP, with no significant adverse effects of bronchoscopy found in this study.

OB, a type of chronic airflow obstruction syndrome, mainly involves small and medium bronchi and is associated with proliferation of fibrous tissue. The main manifestations of OB are atelectasis and lobar collapse. Under bronchoscopic examination, the distal obliterans of some subsegmental and subsubsegmental bronchi of OB patients is accompanied by atrophy of proximal mucosa, appearance of obvious cartilage rings, and lumen expansion. OB often occurs secondary to severe pneumonia and has gradually gained recognition as a common SMPP-associated sequela,¹⁰ although few studies in China or abroad have described OB caused by *M. pneumoniae* infection. With increasing research attention paid to SMPP airway damage, OB detection rates have significantly increased and highlight OB as an urgent clinical problem stemming from processes underlying SMPP development. Meanwhile, studies have shown that MP infection can result in cellular and humoral immune dysfunction and disturbances of cytokine networks. Moreover, an excessive inflammatory reaction causes airway mucosal epithelial damage followed by airway subbranch injury that leads to scar contracture and occlusion. In this study, it was observed that OB caused by SMPP mainly involved grade III bronchi or below. The OB developmental process could be outlined as follows: in acute-stage disease, diseased sub-bronchi begin to erode then mucous plugs develop and blockages form. Next, necrotic epithelium detaches and blocks the airway in the subacute stage. Afterwards, subsegmental bronchi gradually became narrower, leading to poor ventilation, insufficient local blood supply surrounding lesions, then gradual formation of obliterans. The obliterans formation process supports the conclusion that obliterans are caused by airway injury. Meanwhile, initial obliterans lesions first appear as a thin film that is easily reopened using biopsy forceps. Next, the occluded part gradually thickens to form a barrier that biopsy forceps cannot reopen in most cases. It has been suggested that it may be possible to reopen airway branches after choosing the appropriate timing for bronchoscopic intervention, with further study needed to optimize interventional timing for improved treatment outcomes.

In this study, the timing of bronchoalveolar lavage was also investigated to detect correlations with OB incidence during late-stage SMPP. Specifically, the incidence of OB in pediatric patients who received first bronchoalveolar lavage at 10 days post-SMPP onset was significantly higher than that of children receiving their first bronchoscopies within 10 days post-disease onset. It has been suggested that for pediatric patients with persistent fever and large lung consolidations, atelectasis, and other pulmonary pathological changes detected via imaging within 10 days of onset, timely bronchoalveolar lavage is recommended to avoid complications such as OB.

The main components of bronchial mucous plugs include a mixture of mucin and cellular debris combined with a large number of infiltrating inflammatory cells that make this mixture extremely viscous. At present, it is widely recognized that hyperimmune inflammation is one of the main pathogenic mechanisms underlying SMPP.^{3,11} MP infection tends to lead to mucosal necrosis and mucus hypersecretion via a mechanism that may involve direct damage and release of infection-triggered toxic metabolites that ultimately damage bronchial epithelial cells and cilia. Such pathological damage may further impair mucociliary system function and weaken ciliary discharge capacity and clearance of secretions. Afterwards, tethered secretions that form within the local airway can trigger airway obstruction, with local obstruction of the proximal bronchus and various sizes of mucous plugs occurring within deep subsegmental bronchi in some serious cases. This study demonstrated that pediatric SMPP patients who also developed OB during late-stage disease exhibited different degrees of mucous plug development during acute-stage SMPP that were detected via bronchoscopy. Therefore, for patients with mixed lesions that are associated mainly with mucous plugs, mucus necrosis, and particularly with successive mucus plug development detected upon bronchoscopic reexamination, localization of mucous plugs should be done as early as possible in conjunction with administration of systemic treatment. Moreover, regular bronchoalveolar lavage treatment would facilitate the timely removal of mucous plugs in order to improve ventilation and secretion clearance at lesion sites and promote inflammatory absorption.

This study demonstrated that the density of large consolidation areas was significantly increased during

acute-stage SMPP, suggesting that subbranches can be severely blocked by mucous embolisms. Thus, bronchoscopy should be performed as soon as possible to remove airway secretions that in such cases consist of thick viscous mucus that is difficult to clear away. For conducting a first bronchoscopic examination of patients with this type of lesion, a bronchoscope with a larger diameter (such as 4.0 mm) is recommended; because the diameter of the suction duct is large, it can loosen and brush mucous plugs to the depth of subsegmental bronchi and can effectively remove mucous plugs from deeper airways with the help of a cell brush. Due to acute-stage mucosal damage and congestion, adrenaline can be applied locally to shrink blood vessels while plugs are slowly and gently brushed to minimize bleeding during plug removal. During late-stage SMPP recovery characterized by improved lung imaging findings, the 2.8-mm diameter bronchoscope could be selected for subsequent inspection and clearance of deep subsegmental bronchial mucous plugs.

Due to the risk of pneumothorax that may occur during bronchoscopic examination and treatment of necrotic pediatric SMPP, the use of bronchoscopy for such cases is still controversial at present. However, it is worth noting that of 6 patients with late-stage necrotic pneumonia receiving treatment in this study, all of these patients developed OB even though they had different degrees of bronchoscopically detected airway blockage due to mucous plugs and mucinous necrosis. Notably, no pneumothorax occurred as a result of bronchoscopic treatment. Nevertheless, owing to the small sample size of this study, it is impossible to judge the advantages and disadvantages of bronchoscopy for necrotic SMPP based solely on results of this study.

In summary, pediatric SMPP patients exhibit certain characteristics during different disease stages that can facilitate diagnosis. However, airway mucus and mucosal epithelial necrosis and detachment could lead to clogging of subbranches and subsequent OB. Thus, it is recommended that pediatric SMPP patients with mucous plugs undergo timely bronchoscopy in addition to customary antibiotic treatment. Because this study did not comprehensively summarize and analyze factors associated with OB in pediatric SMPP patients, predictive factors predisposing patients to OB development were not definitively identified. Therefore, collection of additional clinical data is needed to further evaluate possible predictors of later OB occurrence that would be used to inform future clinical practice.

Acknowledgements: We thank the children and families who graciously consented to participate in the bronchoscopy of SMPP children in this study.

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Table 1: General informations

Age(years old)	Male/Total cases(%)	Female /Total cases(%)	Pulmonary consolidation cases/Total cases(%)	Atelectasis cases/Total cases(%)	Pulmonary necrosis(cases)/Total cases(%)	Extrapulmonary complications(cases)/Total cases(%)	Average fever time (days)	Average postoperative fever time (days)
4.2 ± 2.6	114/213(53.5)	99/213(46.4)	213/213(100)	189/213(88.7)	6/213(2.8)	192/213(90.1)	8.8±1.2	1.8±4.4

Table 2: Main factors of influencing obliterative bronchiolitis: comparison between children with and without obliterans

	Time of first bronchoscopy since the onset of the disease Within 10 days	Time of first bronchoscopy since the onset of the disease After 10 days
Cases	142	71
Obliterans cases	9	13
P value	P _i 0.007	P _i 0.007

Figures and Legends

Figure 1: Chest X-ray and high-resolution CT showed large consolidation shadow in the left lower lung(A,B,C). Obvious hyperemia of bronchial mucosa and nodular protrusion on the surface of mucosa (D). Longitudinal fold change of subbronchiolar mucosa and mucus plug obstruction in the lesion site of bronchial subbranch (E). The subbronchiolar mucosa looked pale, and necrotic detachment of bronchial epithelial mucosa blocked lumen opening(F). The subbronchiolar mucosa were pale in color and occluded with concave center and peripheral radial hyperplasia in the occluded part(G,H). Plastic mucus plug taken by cell brush under bronchoscope(I).

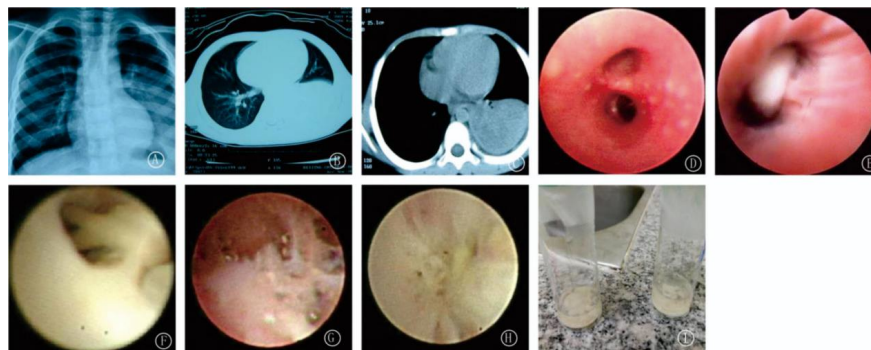


Figure 2: Chest high-resolution CT showed atelectasis in the left lower lung three weeks after the onset of the disease(A). The color of subbronchiolar mucosa was pale and the lumen was occluded(B). Biopsy forceps were used to recanalize the subbranch occlusion under bronchoscope(C) and the recanalized airway subbranch(D). Chest high-resolution CT scan showed that atelectasis in the left lower lung got better one month after bronchoscopy(E).

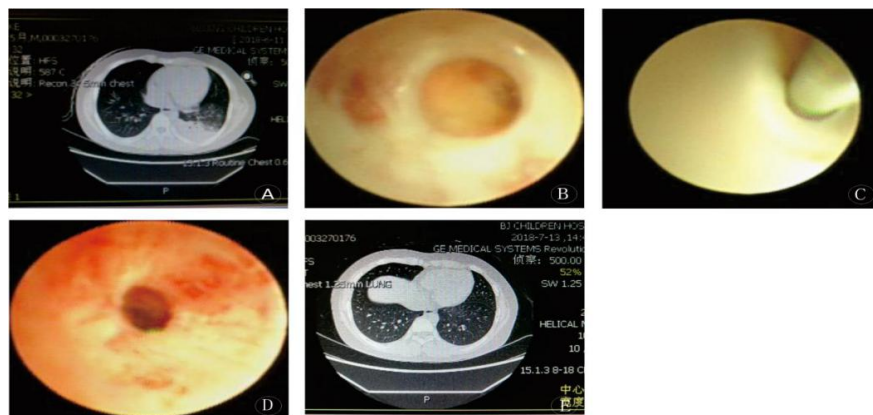


Figure 3: *Chest X-ray and high-resolution CT discovered large consolidation shadow with liquefactive necrosis and cavity in right lung (A,B,C). Extensive occlusion in left lower pulmonary bronchus under bronchoscope(D).*

