Original Article
Pulmonary sequestration in children: a clinical analysis of 48 cases

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Abstract: Background: This study aimed to explore clinical features, diagnosis, treatment, and outcomes of children’s pulmonary sequestration (PS) to reduce misdiagnosis. Methods: Clinical records of 48 children with PS in Children’s Hospital of Chongqing Medical University between April 1994 and April 2013 were retrieved, and the literature was reviewed. Results: 48 cases were collected, 30 cases confirmed (Group A) and 18 suspicious cases (Group B). In Group A, 16 cases were confirmed before operation by 64-row enhanced CT (4 cases), enhanced CT combined with three-dimensional reconstruction (9 cases), and digital subtraction angiography (3 cases). Misdiagnosis rate was 36.7%, while missed diagnosis rate 10%. 26 cases received surgery and were confirmed finally. Aberrant arterial supply mainly originated from thoracic aorta (22 cases) and abdominal aorta (5 cases). Hypoplasia and chronic inflammation were shown by postoperative histopathological examinations in all children with surgery. There was no operative mortality. Encapsulated pleural effusion occurred in one patient as only post-operation complication. All were discharged after successful treatment. Conclusion: Chest X-ray and color Doppler ultrasound can be used for routine screening for PS. Technique of choice for confirmation is three-dimensional chest CT. Identifying anomalous systemic artery is key for confirmed diagnosis. Surgery is recommended as early as possible. X-ray plus ultrasound as routine screening combined with three-dimensional CT for definitive diagnosis and video-assisted thoracoscopic surgery might be best choice for PS in future.

Keywords: Children, pulmonary sequestration, diagnosis, treatment

Introduction
Pulmonary sequestration (PS) is a rare congenital broncho-pulmonary malformation and belongs to one of congenital cystic lung lesions, accounting for 0.15%~6.4% of all congenital pulmonary malformations [1, 2]. The main feature of this disease is that partial lung tissues separate from the main lung during the embryonic period, grow separately to generate cystic mass without lung function and receive blood supply from systemic circulation arteries (mainly including thoracic aorta and aorta abdominalis). Its pathogenesis is not clear, and categorized into congenital and acquired PS. Most of the scholars supported congenital origin. Traction theory (Pryce) was once commonly accepted [3], but an increasing number of studies support that PS was formed by the growth of the primitive foregut ventral side lung bud during embryonic development period [4]. Pulmonary sequestration is classified into intralobar sequestration (ILS) and extralobar sequestration (ELS) according to the absence or presence of independent visceral pleura encase in abnormal lung tissues. In addition, the mixed sequestration is rarely seen [5]. For ILS, the sequestration lung and normal lung lobe are wrapped in the same visceral pleura, and its intracystic lesions communicate with normal bronchus or not, which easily leads to repeated infection; and this type accounts for 83.95% [6]. For ELS, sequestration lung is outside the lung lobe and has its own independent visceral pleura. Moreover, its intracystic lesions do not communicate with normal bronchial tree at all. It may be asymptomatic for a long time, and this type is rarely seen.

In recent years, children with protracted pneumonia and chronic pneumonia were increasing year by year, in addition to considering simple
Pulmonary sequestration in children

l lung infections, the combined underlying disease should be noticed at the same time, especially congenital lung abnormalities and some other diseases which were easy to be ignored. Clinically, the main manifestations of PS are recurrent respiratory tract infection or asymptomatic condition combined with other malformations. The symptoms of this disease are atypical, and it tends to be misdiagnosed or missed [7]. Sameh et al [8] reported that the misdiagnosis rate of PS was up to 71%, therefore, the treatment was easily delayed, affecting the therapeutic effect and the quality of life. Clinical screening and diagnosis of PS often occurs after recurrent respiratory tract infections when lung damage was wider and adhesions were heavier, and thus significantly increased the risk of surgery. If the disease was undiagnosed or not considered before operation, it may cause abnormal vascular rupture and then lead to massive hemorrhage during operation. At the same time, PS has the possibility of causing fungal or tuberculosis infections, fatal hemoptysis, hemothorax, cardiovascular diseases and even malignancy [2]. Clinicians, especially pediatricians need to raise awareness of pulmonary sequestration urgently.

Multiple cases of PS were reported in literatures in our country except for Tibet, Qinghai, Chongqing, Taiwan, Hong Kong and Macau. But pulmonary sequestration from a single children’s institute is rarely reported in literature. The number of the reported cases from Fudan University in Shanghai in China and Bologna University at abroad was the highest (only 22 cases). No abundant literature about the disease has been found in either adults or children in Chongqing city. This study is intended to explore and summarize the clinical data, then propose the best way of diagnosis and treatment, causing the attention of clinicians to the importance of the disease, thus early diagnosis and treatment, reducing the misdiagnosis, at the same time finding clues between PS and gene mutation.

Material and methods

All data of 48 children who were diagnosed with pulmonary sequestration when they discharged from hospital between April 1994 and April 2013 in Children’s Hospital of Chongqing Medical University were retrospectively analyzed. The follow-up records were reviewed or the follow-up visits were performed through telephone. All the children were divided into group A (confirmed) and group B (suspected). In group A, the age, gender, course of disease, symptoms, signs, diagnosis and treatment outside the hospital, image examination, types, misdiagnose or missed diagnosis, merged abnormality types, therapeutic methods and length of stay were recorded. Meanwhile, the operation methods, operation records, postoperative thoracic closed drainage time, postoperative complications and pathological examination results of the children receiving the operation needed to be recorded. All the data were made into Microsoft excel to calculate the age distribution, mean age, sex ratio, mean course of disease and mean time of postoperative closed thoracic drainage. A large number of related documents were referred to and the results were analyzed. The main diagnosis means and their manifestations of the suspected patients in group B were recorded, and the children were followed-up for prognosis.

Results

Gender and age

A total of 30 cases (12 males and 18 females; gender ratio: 1:1.5) were enrolled in group A during the period mentioned above in this hospital. The ages ranged from 13 days + 1 hour to 14-year-old (average age: about 4.37 year-old). Among them, 1 case (3.3%) aged ~ 28 days, 6 cases (20%) aged ~ 1-year-old, 10 cases (33.3%) aged ~ 3-year-old, 4 cases (13.3%) aged 6-year-old, 8 cases (26.7%) aged ~ 13-year-old, and 1 case (3.3%) aged ~ 14-year-old.

Clinical manifestation

Symptoms: Twenty-seven patients (90%) showed nonspecific symptoms: fever (21 cases, 70%), cough (20 cases, 66.7%), expectoration/phlegm sound in the throat (13 cases, 43.3%), anhelation (7 cases), cyanosis (6 cases), dyspnea (5 cases), vomit/milk regurgitation (4 cases), chest pain (3 cases), wheezing (2 cases), milk chocking (1 case) and hemoptysis (1 case). The following symptoms were also showed: fever + cough (16 cases, 53.5%), fever + expectoration/phlegm sound in the throat (12 cases, 40%) and fever + cough + expecto-
Pulmonary sequestration in children

ruration/phlegm sound in the throat (10 cases, 33.3%). Most of patients exhibited moderate or high fever and white mucus sputum (occasionally yellow purulent sputum and even purulent blood sputum). Repeated attack of the symptoms may appear in patients with longer history. 3 PS patients (10%) absence of symptoms were found during physical examination, including 2 patients with ILS and 1 patient with ELS. The course of disease lasted for 14 days – over 2 years with a mean course of 5 months.

Findings on physical examinations

Decreased breath sound was found on their affected side of 16 patients (53.3%). A few moist rales coarse were heard in 6 patients (20%). Dull resonance was heard after percussion in 2 patients because of combined pleural effusion on the affected side, in which, 1 patient with reduced cry fibrillation. 1 patient showed hyperresonance with reduced cry fibrillation after percussion (once misdiagnosed as pulmonary bullae), and 8 patients (26.7%) did not exhibit positive signs.

Findings on image studies

In group A, chest radiography, chest color Doppler ultrasound, chest CT plain scan, CT-enhanced scan, CT-enhanced + three-dimensional reconstruction, retrograde aortography and bronchofibroscope were performed in 19, 13, 26, 6, 9, 3 and 1 patient, respectively.

Chest radiography

Seven patients showed cystic shadow on the lower lung lobe, and some edge was not clear. 1 patient exhibited multiple bullae of lung. 2 patients showed mass shadow. 9 patients showed floculent/patchy compact shadow, and gas-fluid levels and round or quasi-circular bright shadow were seen in some patients.

Chest CT (plain scan/enhanced scan/enhanced scan + three-dimensional reconstruction)

A total of 8 patients showed cystic or solid mass. 11 patients exhibited single or multiple cystic shadows with varying sizes. Gas-fluid levels, separation and bright zone (round/quasi-circular) were seen in some patients. Strip, sheet or triangle compact shadows were found in 5 patients, and the density of the compact shadows was uneven, in which quasi-circular/round bright shadow was visible. 1 patient showed lung bullae shadow. 1 patient exhibited lung consolidation accompanied with pulmonary atelectasis change. After enhancing, the capsule wall and separation of the lesions could be intensified, and the thickened and warped blood vessel shadows in the lesions increased, among them, it was found definitely that exact abnormal blood vessel entered the lesions which was confirmed before operation among 4 cases. 9 patients were diagnosed with suspected PS by enhanced-CT scan and then was given three-dimensional reconstruction, both of which showed that abnormal blood vessels entered the lesions, thus this condition was confirmed before operation. Meanwhile, venous return deformation was displayed clearly in 4 patients (Figures 1 and 2).

Bronchofibroscopy

From bronchofibroscopy, chronic tracheal and bronchus intimitis was indicated, and no obvious endobronchial space-occupying lesions were found.

Digital subtraction angiography (DSA)

All the patients were given a definite diagnosis by angiocardiography because of combined patent ductus arteriosus (PDA), among them, 2 patients received PDA closure and collateral vessels closure, and another 1 patient received thoracotomy.

Chest color Doppler ultrasound

Three patients had mixed cystic and solid structure. 1 patient showed tiny collateral vessels. 1 patient was found to have abnormal echo area, of whom no echo area was found in partial area. 1 patient showed sheet compact shadow. 3 patients were accompanied by PDA, and 1 patient was accompanied by ASD.

Incorrect preoperative diagnosis

Sixteen patients (53.3%) were confirmed before operation in group A, among them, 9, 4 and 3 patients were confirmed by enhanced-CT scan + three-dimensional reconstruction, enhanced-CT scan and DSA, respectively. 3 patients (10%) were not diagnosed before operation and then were found during pulmonary lobectomy because they were accompanied by pulmonary
Figure 1. Lower left pulmonary sequestration (ELS). Bulk soft tissue shadow was seen on the left lower lobe (black arrow in A and B). An about 1.2 mm wide vessel from the left wall of thoracic aorta at about the level of 10th thoracic vertebra stretched into the lower left lung lesion for blood supply (red arrow in B-E). The lesion was confirmed to be extralobar sequestration during operation.
Figure 2. Lower right lobe PS (ILS) associated with gastro-bronchial fistula and mediastinal cyst. Sheet compact shadow was seen on the lower right lung (black arrow in A and D). An about 3.8 mm*4.7 mm wide abnormal blood vessel shadow (black arrow in A-C) from about the level of 7th thoracic vertebra went through to the lower right lung for blood supply, and drained back to the left atrium through the lower right pulmonary vein (A and D). The combined gastro-bronchial fistula and mediastinal cyst (red arrow in B and E) were found, and the postoperative findings confirmed that the disease was intralobar PS associated with bronchogenic cysts.
Table 1. Pulmonary sequestration complicated with other malformations

<table>
<thead>
<tr>
<th>Complicated malformations</th>
<th>Intrapulmonary sequestration</th>
<th>Extrapulmonary sequestration</th>
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</thead>
<tbody>
<tr>
<td>Pulmonary cyst</td>
<td>34.8%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funnel chest</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>21 trisome + PDA</td>
<td>1</td>
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</tr>
<tr>
<td>ASD + bronchiactia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mediastinal cyst + Bronchial gastric fistula + ASD</td>
<td>1</td>
<td></td>
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<tr>
<td>Esophagotraheal fistula</td>
<td>1</td>
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</tr>
<tr>
<td>PDA + funnel chest</td>
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<tr>
<td>Pulmonary cyst + ASD + funnel chest</td>
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Footnotes: PDA: patent ductus arteriosus; ASD: atrial septal defect.

cyst. 11 patients (36.7%) were misdiagnosed before operation. In the past, 9 and 6 patients were misdiagnosed with pulmonary cyst and pneumonia, respectively; moreover, 1 case of tumor, lung abscess, bullae of lung and lung consolidation with atelectasis each were misdiagnosed. Suspected pulmonary cyst, tumor, pulmonary abscess, paragonimiasis, pulmonary atelectasis and phthisis occurred in 2, 4, 2, 2, 1 and 4 patients, respectively.

Classification and complicated malformations

The classification of group A was based mainly on operation findings. Another 4 children receiving conservative treatment were diagnosed definitely by chest three-dimensional CT, and the findings showed deformation of draining vein clearly. These 4 patients were diagnosed with ILS according to lesion site, trend of venous drainage, clinical manifestation and complicated malformation. Therefore, 23 cases (76.7%) of ILS, 7 cases (23.3%) of ELS and 12 cases (40%) of complicated malformations were found in group A. See Table 1 for details.

Treatment and prognosis

In group A, 24 patients received excision, and 2 patients were given intervention closure, and 4 patients underwent conservative treatment. Table 2 lists operation methods. Length of stay after operation was 7-14 days (10 days on average) for the surgical children and were 4 days and 14 days for the two patients receiving intervention therapy. Closed thoracic drainage time after surgery was 2-7 days (3.8 days on average).

No surgical children died due to operation. After operation, thoracentesis drainage was carried out in 1 patient because of encapsulated pleural effusion. All surgical children were cured and discharged after closed thoracic drainage and anti-infective therapy. Among the patients receiving the intervention therapy, 1 patient was given complete closure, and 1 patient was found to have residue of tiny collateral vessels. No complications were observed during post-operation follow-up of 4 months to 5 years (3.2 years on average). 4 children did not receive operation, in which, 2 patients lost to follow-up after discharge from hospital when they got better through anti-infective therapy and symptomatic treatment; 1 patient died after her parents gave up treatment due to the concurrent congenital heart disease (partial anomalous pulmonary venous drainage and PDA), severe pulmonary hypertension and severe pneumonia; and 1 patient only received NUSS thoracoplasty due to the concurrent funnel chest and then did not show any specific symptoms, therefore, this patient did not receive surgery later.

Lesion site, source and branch of abnormal supplying arteries and venous drainage

The maximum diameter of the lesion in group A was 2.5~15 cm (7.7 cm on average). Diameters of supplying arteries were 0.8~10.6 mm (5.4 mm on average). See Table 3 for details.

Pathological examination

Postoperative pathological examination showed that the main manifestations were pulmonary hypoplasia and chronic inflammation. No concurrent fungal infection, atypical hyperplasia, precancerous lesions or canceration were found in the whole group. 1 patient was found to have mycobacterium tuberculosis by acid-fast staining and then was diagnosed as combined tuberculosis.
Patients with suspected PS (group B)

Among a total of 18 patients, 12, 12 and 6 patients were given color Doppler sonography, chest radiography and CT scan/enhanced scan (3 cases by enhanced-CT), respectively. Major imaging manifestations for suspected diagnosis include tiny collateral vessels formation or abnormal echo block mass with blood flow signal by color Doppler sonography of 12 patients (100%), inflammation changes, consolidation with atelectasis or mass shadows or strip and floc shadow by chest radiography (100%) of 12 patients and block mass shadow or cystic shadow on the lower lobe by CT scan/enhanced scan of 6 patients (100%). Regrettably, only 3 patients with suspected PS were followed-up successfully, and among them, 1 patient died due to severe pneumonia, and 2 patients were vulnerable to repeated respiratory tract infection.

Discussion

The number of ILS was significantly more than that of ELS in group A. ELS were all located at costophrenic angle, which was the same as that reported in literature [6]. No ELS locating at mediastinum, pericardium and subphrenic space was found [9]. Generally, PS occurred more easily in the left lung (73.6%) compared with the right lung (26.4%) [6], but this disease was more likely to be found on the right lung in this group (43.3%) compared with the findings in literature [6]. Wei et al [6] found that there was no significant difference in gender, clinical manifestation and abnormal artery between children and adult with PS. However, ILS/ELS ratio (106/44) in children was lower than that in adult (116/16), and this conclusion was supported by this ratio of 23/7 in this study (Table 3).

ILS’s clinical manifestations were relatively more common than those of ELS, and they involve respiratory system and cardiovascular system most frequently. The clinical manifestations were fever, cough, expectoration, anhilation, cyanosis and even expectoration of purulent blood sputum. Therefore, these patients were often misdiagnosed with pneumonia, pulmonary cyst, lung abscess, pulmonary tumor...
etc. Due to attaching great importance to this disease, the sum of missed diagnosis and misdiagnosis rate was up to 46.7%, lower than that reported in literature [10].

Although ELS could be asymptomatic for a long time, severe acute respiratory distress syndrome [11] may happen in infancy. Over 60% of this disease were associated with congenital deformity [12, 13], in which congenital heart disease and diaphragmatic hernia were most common [8], and funnel chest, congenital pulmonary cyst, bronchial gastric/esophageal fistula were also common. In group A, it was found that the malformation combination rate was 40% (see Table 1 for details). Though ELS (57.1%) may more easily combine with malformations than ILS (34.8%), in this study, ILS showed a higher combined ratio with malformations compared with that reported in literatures [1] and often combined with multiple malformations. Bronchiactia was common in PS [14], and only 1 case was found in this group. As we know, no other similar literature report has been found.

Although there were PS combined chromosomal abnormalities and a variety of other malformations reported in 2001 and 2002 [15, 16], our hospital also found one case of trisomy 21 children with PS merger and PDA, while Staebler M et al [17] found no chromosomal abnormalities after karyotype analysis of fetus with PS but not combined with other malformations. In recent years, several studies have shown relationship between genomic copy number variations (CNVs) and a variety of lung diseases, such as lung cancer, bronchial asthma [18, 19] and so on. The literature also speculated that CNVs may be involved in the pathogenesis of multiple lung diseases [20], and the large fragment of CNV can affect two or more adjacent genes which lead to multi-gene defects, thereby causing syndrome type of disease or complex diseases. Things above provide evidence that PS easily combined with other malformations from the genetic level. We suspect that the occurrence of PS has nothing to do with abnormal chromosome number or structure, but a certain degree of correlation with some congenital genetic disorders, although its related genes and gene mutation form still needs further research.

ELS with symptoms (85.7%) in group A were significantly more than that reported in literature, which was considered to be related to factors such as lesion site, size and combined malformations. Therefore, it is necessary to perform gastrointestinal barium, cardiac color ultrasound and other examinations to exclude the possibility of combined malformations for the children who had been confirmed.

There is often single supplying artery (89.3%), which mainly originates from thoracic aorta (73.3%) and aorta abdominalis (16.7%). Abnormal blood vessel coming from other arteries such as intercostal artery, arcus aortae, arteria subclavia, coronary artery, arterial aneurysm artery and other arteries were rare [21, 22].

Finding abnormal feeding artery from systemic circulation is the key to confirm PS. The confirmation rate of CT-enhanced scan in group A was only 26.7%, which is not consistent with the result that CT-enhanced scan was enough to diagnose the disease by Franco et al [23]. CT-enhanced scan plus three-dimensional reconstruction could display feeding artery clearly with a 100% precision, therefore, it is preferred for confirmation. Its typical sign is connection of funicular blood vessel shadow in lesions with systemic circulation arteries.

Non-absorbing stationary shadow for a long time on the chest film is the characteristic performance of PS. However, the feature is non-specific. It can be only used for finding and locating the lesions, but could not be used to make a definite diagnosis. From ultrasonic examination of 18 patients (72%) in the whole group, lesions were prompted, and the combined PDA, ASD and others were found. However, these conditions were not confirmed, and the negative results could not be completely ruled out, therefore, ultrasonic examination for diagnosing this disease has certain limitations. Bronchofibroscopy cannot provide evidence for diagnosis of this disease, but whether there is bronchial stenosis and others deformity can be observed. The patients in group B were diagnosed suspectedly mainly with color Doppler ultrasound and chest radiography because their family refused to receive examination for definite diagnosis. There more patients were lost to follow up in this group, but the findings of 3 patients receiving the follow-up indicated that the prognosis is poor after conservative treatment.
Pulmonary sequestration in children

Therapeutically, surgical resection is still preferred. Although 10% PS children were asymptomatic, many experts [24] recommended that patients should receive operative treatment positively once a definite diagnosis was made, and infected patients should receive surgery 1-2 weeks after infection was controlled. The reasons are analyzed as follows: a) PS may develop into fungus/tuberculosis infection, fateful hemoptysis, hemotherax, angiocardiopathy and even canceration [2, 25]; b) PS has the feature of recurrent infection in the local region, and thus may cause change of hemodynamics, abnormal blood oxygenation, pulmonary venous pleonaeemia and pulmonary fibrosis. Moreover, the condition may aggravate with age, thus resulting in massive hemoptysis and even death by suffocation; c) a poor prognosis may appear if the patients with PS was associated with other malformations; d) early surgery was more conducive to the compensatory growth of lung tissues, thereby, reducing complications; e) the safety of the current operation during infancy stage has increased greatly.

Pulmonary lobectomy was mainly used for ILS, while the lesions can only be removed for ELS. Veins in ILS patients usually return to pulmonary vein (90.7%), especially the lower pulmonary vein [6], while over 50% draining veins in ELS patients were azygos vein and hemiazygous vein [26]. The difference of draining vein is the key to preoperative classification. However, in this group, only 9 patients displayed clearly abnormal artery, and 4 patients showed the trend of venous return. No classification was performed before operation. Meanwhile, no abnormal bleeding occurred during operation. Therefore, it was not the absolute contraindication that no classification was performed before operation or the trend of artery/vein was unclearly displayed. Careful operation techniques could avoid abnormal bleeding. Other malformations combined, could be treated together during operation. In this group, simple resection for pulmonary sequestration was performed in 4 ILS children because their conditions allow (located on the surface of the lung lobe, less-severe pleural adhesions and good compliance of the attached lung lobe) and in 1 ILS child because this patient had other malformations at the same time and may cause larger surgical trauma. Moreover, other malformations were combined in 6 patients and were treated during operation together (see Table 2 for details). The key of operation was the treatment of abnormal blood vessels and the separation of adhesion, avoiding fateful massive hemorrhage. In this group, 5 abnormal arteries were seen at most, so we could not be satisfied with finding single supplying vessel. The period of intrathoracic drainage tube placement after operation was different in different literatures, and 3.8 days on average was adopted in this group, which was consistent with that reported in the literature [27] (both of them were longer than that of 1.2 days [28] in VATS). Patients were followed up for 3.2 years on average after operation. No possible complications such as recurrent lung infection, gastroesophageal reflux, funnel chest and pyloric stenosis were found [29].

VATS [30] and intervention closure [31, 32] are the important supplement means of excision. VATS is safe and reliable for infants. This operation is still feasible even for the < 6-month infants by experienced surgeons [30]. Moreover, this surgery would lead to fewer postoperative complications and is more conducive for the recovery of patients. Preoperative pneumonia (severe adhesion) may be the only independent risk factor of transferring into thoracotomy [33]. The operation was not carried out in this group because the unilateral lung/single lung ventilation and thoracoscopic technique were immature, but the author thought that the minimally invasive therapy prospect of VATS was very bright. Intervention closure is mainly used for newborn and children, and was still the preferred therapy for PS patients in whom cardinal symptom is hemoptysis and CT showed limited pulmonary multi-vessel syndrome or those who cannot tolerate surgery and are asymptomatic in clinic. However, this method is not suitable for infected patients with pulmonary sequestration [31] or < 3-month infants [32]. In group A, 2 patients received intervention closure and showed definite short-term effect, but the long-term effect remains to be studied further.

Postoperative histopathological examination is performed mainly to exclude whether other lesions (e.g. fungus, tuberculosis infection and even malignant change, etc.) are combined. Pathological examination of group A shows that PS is combined with phthisis in 1 patient. This patient was given antituberculosis therapy and exhibited favourable prognosis.
In conclusion, chest radiography plus chest color Doppler ultrasound for routine screening and chest three-dimensional CT for confirmation and VATS are gradually becoming the preferred treatment mode for pulmonary sequestration.

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Disclosure of conflict of interest

None.

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References


Pulmonary sequestration in children


