Original Article

Mycoplasma pneumoniae pneumonia complicated with pulmonary embolism: a systematic analysis of published case reports

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Abstract: Objective: To analyze the clinical manifestations, laboratory values and treatment process of mycoplasma pneumoniae pneumonia (MPP) complicated with pulmonary embolism (PE) and provide a reference for the clinical diagnosis and management. Methods: We searched the electronic databases systematically to retrieve the relevant literatures. Results: A total of 17 articles about MPP complicated with PE were involved in our study. Most of cases had dyspnea, cough and fever. D-dimer examination was all positive. Ten were diagnosed by computed tomographic angiography. Seven of them occurred in bilateral pulmonary arteries; five cases occurred in right pulmonary artery, two cases occurred in left pulmonary artery and one case occurred in pulmonary vein. Five patients were treated with methylprednisolone and fifteen patients had anticoagulant therapy. Conclusion: PE should be ruled out in patients with MPP if the symptoms are aggravated after MPP treatment.

Keywords: Mycoplasma pneumoniae, pneumonia, mycoplasma pneumoniae pneumonia, pulmonary embolism, diagnosis, systematic analysis

Introduction

Mycoplasma pneumoniae (MP) is a common pathogen of respiratory tract infection in children and adolescents, accounting for about 10-40% of community acquired pneumonia (CAP) [1, 2]. MP infection is a generally self-limited process, which occurs pandemically every 3-7 years [3]. The clinical manifestations of mycoplasma pneumoniae pneumonia (MPP) vary greatly, ranging from a mild pneumonia to severe pulmonary or extra-pulmonary complications. In general, the clinical features also vary with patients’ ages [4]. The pulmonary complications include pulmonary abscess, pleural effusion, empyema, atelectasis, pneumothorax, etc. In recent years, there have been many case reports of MPP complicated with pulmonary embolism (PE). PE and MPP present similarly, thus often leading to misdiagnoses. So, we searched the electronic databases systematically to retrieve the relevant literatures and analyzed the clinical manifestations, laboratory values and treatment process to provide a reference for the clinical diagnosis and management.

Materials and methods

Cases selection

The relevant literatures for the present meta-analysis were searched from the following electronic databases: PubMed, Embase, Wanfang Data and China National Knowledge Infrastructure databases. The following search terms were used: (“mycoplasma” or “mycoplasma pneumoniae” or “mycoplasma pneumoniae pneumonia” or “M pneumoniae” or “MP” or “MPP”) and (“embolism” or “pulmonary embolism” or “pulmonary thromboembolism” or “PE”). The corresponding Chinese search terms were used to search the Chinese electronic databases. We also checked the references of the relevant papers carefully to minimize the
omissions. The last search was updated on April 5, 2015.

**Inclusion and exclusion standards**

Literatures included in this meta-analysis must meet all the following criteria: (a) must be published data; (b) must have clear clinical data for the cases; (c) must present MPP complicated with PE. Duplicated cases were excluded. There was no limitation in language.

**Data extraction**

We designed a standard form to record the original data for each case, which were extracted independently by two authors (Huang ZY and Cheng BJ) and were checked by the third author (Zhang BF). The following data were extracted from each study: first author’s name, year of publication, age, gender, country and ethnicity, symptoms, history and physical examination, auxiliary examinations and treatment.

**Results**

**Case selection process**

A total of 47 literatures were screened in the initial search. After reading the title and full text, we excluded 30 articles, in which 27 articles were not related to PE, two articles were reviews and one article was a repeated study. The flow diagram of articles selection process is listed in Figure 1. Finally, 17 articles met the inclusion criteria [5-21]. Among them, seven articles were written in Chinese, nine articles in English and one article in Spanish; eleven Asian case reports, three Europeans case reports.
Table 1. Characteristics of the included cases

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Gender</th>
<th>Age (y)</th>
<th>D-dimer</th>
<th>aLP</th>
<th>Protein C activity</th>
<th>Method of definite diagnosis</th>
<th>Location of emboli</th>
<th>Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiménez D [8]</td>
<td>1999</td>
<td>Spain</td>
<td>European</td>
<td>F</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>LVPS</td>
<td>NA</td>
<td>UH + warfarin</td>
</tr>
<tr>
<td>Chow-Quan [9]</td>
<td>2005</td>
<td>Spain</td>
<td>European</td>
<td>M</td>
<td>42</td>
<td>+</td>
<td>ACA (+), β2GPI (+)</td>
<td>decreased</td>
<td>CTA</td>
<td>bilateral</td>
<td>anticoagulant</td>
</tr>
<tr>
<td>Bakshi M [10]</td>
<td>2006</td>
<td>India</td>
<td>Asian</td>
<td>M</td>
<td>4</td>
<td>NA</td>
<td>aLP (+), LA (-)</td>
<td>NA</td>
<td>cardiac ultrasound</td>
<td>left</td>
<td>anticoagulant</td>
</tr>
<tr>
<td>Graw-Panzer KD</td>
<td>2009</td>
<td>American</td>
<td>African American</td>
<td>M</td>
<td>13</td>
<td>+</td>
<td>ACA (+), LA (+)</td>
<td>normal</td>
<td>CTA</td>
<td>right</td>
<td>UH + warfarin</td>
</tr>
<tr>
<td>Ascer E [14]</td>
<td>2011</td>
<td>Brazil</td>
<td>American</td>
<td>F</td>
<td>28</td>
<td>+</td>
<td>ACA (+), LA (+)</td>
<td>NA</td>
<td>CTA</td>
<td>right</td>
<td>UH + warfarin + aspirin</td>
</tr>
<tr>
<td>Su HY [16]</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>ACA (+)</td>
<td>decreased</td>
<td>CTA</td>
<td>left</td>
<td>LMWH + warfarin</td>
</tr>
<tr>
<td>Xin Y [17]</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>M</td>
<td>7</td>
<td>+</td>
<td>ACA (+), β2GPI (+), LA (+)</td>
<td>NA</td>
<td>CTA</td>
<td>bilateral</td>
<td>UH + warfarin</td>
</tr>
<tr>
<td>Liu Y [18]</td>
<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>aLP (+), LA (-)</td>
<td>decreased</td>
<td>CTA</td>
<td>bilateral</td>
<td>LMWH + warfarin</td>
</tr>
<tr>
<td>Chen Y [19]</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>F</td>
<td>12</td>
<td>+</td>
<td>ACA (+)</td>
<td>NA</td>
<td>LVPS</td>
<td>bilateral</td>
<td>LMWH + warfarin + aspirin</td>
</tr>
<tr>
<td>Wei HL [20]</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>F</td>
<td>9</td>
<td>+</td>
<td>ACA (+), β2GPI (+)</td>
<td>normal</td>
<td>CTA</td>
<td>right</td>
<td>LMWH + warfarin</td>
</tr>
<tr>
<td>Zhuo ZH [21]</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>M</td>
<td>9</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>CTA</td>
<td>bilateral</td>
<td>LMWH + warfarin</td>
</tr>
</tbody>
</table>

M, male; F, female; aLP, antiphospholipid antibody; ACA, anticardiolipin antibody; LA, lupus anticoagulant; β2GPI, anti-β2-glycoprotein I; CTA, computed tomographic angiography; LVPS, lung ventilation/perfusion scan; NA, non-available; UH, unfractionated heparin; LMWH, low molecular weight heparin.
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and three American case reports, by patient ethnicity.

Patient clinical data

Of the 17 patients, nine were males and eight were females; the age ranged from 4 years to 48 years old. Nine patients were children and eight patients were adults; fifteen patients had dyspnea, fifteen patients presented with cough, fourteen cases had fever, eight patients complained of chest pain, two patients experienced chest tightness, one patient had hemoptysis, one patient had expectoration and one patient had syncope. Only one patient had typical “pulmonary infarction triad” (chest pain, hemoptysis and dyspnea). The basic data are listed in Table 1.

Laboratory and auxiliary examination

Ten studies included D-dimer examination and the results were all positive. Eight studies included the arterial blood gas analysis and the hypoxemia rate was 87.5% (7/8); the positive rate of cold agglutination test was 91.7% (11/12). For the antiphospholipid (aLP) antibodies test, two studies included total aLP antibody; four cases included anti-β2-glycoprotein I (β2GPI) antibody; nine studies included anticyclophilin antibody (ACA); all of them were positive. The lupus anticoagulant (LA) in four out of six cases tested was positive (66.7%). Six studies included the protein C activity tests and four of them decreased significantly. Nine studies included electrocardiogram (ECG). Four ECG results were normal; three results showed sinus tachycardia and two results were of ST segment changes. None of the cases had typical “S I Q T III” which was considered as the specific ECG findings of PE [22].

Diagnosis of MPP complicated with PE

All of seventeen articles described the methods used to determine the MP pathogen. In which, fifteen cases were determined by serum antibody of MP, one by cultivation of MP and one by sputum examination.

The diagnostic methods of MPP complicated with PE were described in sixteen cases, in which ten were diagnosed by computed tomographic angiography (CTA), three by lung ventilation/perfusion scan (LVPS), two by autopsy and one by cardiac ultrasound. All of the ten cases diagnosed by CTA were published after 2005.

Fifteen cases described the location of embolus. Seven of them occurred in bilateral pulmonary arteries; five cases occurred in right pulmonary artery, two cases occurred in left pulmonary artery and one case occurred in pulmonary vein. A total of four cases combined with femoral vein embolism. Seven cases had pleural perfusion.

Management

Five patients were treated with methylprednisolone. One patient received fibrinolytic therapy with recombinant tissue plasminogen activator (r-tPA). Fifteen patients had anticoagulant therapy and twelve cases provided the details of anticoagulant therapy. The initial anticoagulants were unfractionated heparin in six patients and low molecular weight heparin (LMWH) in another six patients; ten patients received the oral sequential therapy with warfarin, and the longest follow-up time was seven months. After treatment, the results of abnormal aLP antibodies, protein C activity and cold agglutination test in nine cases returned to normal.

Discussion

To our knowledge, the current meta-analysis was the first systematical study to analyze the clinical manifestations, management of MPP cases complicated with PE.

Epidemiological data show that the annual incidence of PE in United States is more than 0.06% and the annual incidence of PE in China is about 0.1% [23, 24]. Recently, the incidence of PE has increased greatly and about thirty percent of mortality. PE is the third common clinical cause of mortality in MPP. It declines significantly with prompt diagnosis and proper treatment. The risk factors for PE include long-term immobilization, malignant tumor, pregnancy, infection, etc. The Virchow’s triad of vascular thrombosis is vascular endothelial damage, venous stasis and blood hyper-coagulable state [25]. There have been many case reports of MPP complicated with PE in the world in recent years. After a careful search, in our study, we included a total of seventeen cases meeting all
the inclusion standards. The mechanisms of MP infection complicated with PE are still unclear. It may be related to both direct and indirect effects [21]. The direct effects are: through hematogenous spread, MP arrives in the pulmonary artery and induces cytokines, such as interleukin-8, tumor necrosis factor-α and chemotactic factors, which may damage the pulmonary vascular wall function. The indirect effects are: (a) parts of the membrane proteins and glycolipids in MP have the same antigen as human organs, such as heart, lung and vascular smooth muscle. When MP infects, antibodies are generated and then immune complexes form, which induce leukocytes to migrate to pulmonary artery and release a large number of inflammatory mediators and lysosomal enzymes, leading to the injury of vascular endothelial cells. (b) the damaged endothelial cell expresses and releases procoagulant and anti-fibrinolytic substances, promoting thrombosis. (c) the lipopolysaccharide in MP can induce the procoagulant activity of human mononuclear cells, by increasing the titer of ACA and aLP antibodies (these antibodies may simulate the antigen of post-infection MP) and the levels of D-dimer. The above reasons may interact to cause PE (Figure 2).

The common clinical manifestations of PE are dyspnea, chest pain, cough and hemoptysis, similar to MPP. The typical PE triad (chest pain, hemoptysis and dyspnea) is relatively rare. In our study, most of cases had dyspnea (15/17), cough (15/17) and chest pain (8/17). One case presented with hemoptysis and only one case had the typical PE triad. The clinical manifestations of PE vary and lack of specificity. In addition, the history from children selves is unreliable, which may also lead to mis-diagnosis and under-diagnosis of this complication. When the symptoms of dyspnea and chest pain continue or even worse after proper anti-infection treatment, we should rule out MPP complicated with PE.

Research has shown that PE might occur bilaterally or in multi sites and acute PE usually
occurs in the right pulmonary artery [26]. In our study, PE was in bilateral pulmonary arteries in seven cases and on the right side in five cases. Only two cases presented with left-sided PE, consisted with previous study. In addition, seven cases were complicated with pleural effusion. The location of pleural effusion in six cases on the same side of the emboli. It has been discovered that pleural effusion secondary to pulmonary embolism is always exudates and often hemorrhagic. But the precise mechanism still remains unclear [27].

D-dimer is the metabolite of specific cross-linking protein, a soluble marker for fibrinolytic system, which reflects in the secondary hyper fibrinolysis. D-dimer plays an increasingly important role in PE diagnosis. Research has shown that D-dimer had high sensitivity but low specificity in acute PE diagnosis [28]. If the D-dimer is negative, the PE will be ruled out [29]. Another study showed that D-dimer in children with MPP significantly increased, which indicated that patients with MPP had hyper-coagulation state and an increasing risk of thrombosis. In this study, a total of ten cases mentioned D-dimer test and the results were all positive. If the D-dimer was positive in patients with MPP, we should be cautious of the possibility of PE. D-dimer should be considered as an important PE screening tool. If necessary, we should consider also CTA or LVPS.

Recent studies have found that aLP antibodies were closely associated with PE [30]. aLP antibodies include ACA, LA and β2GPI. In our study, two cases included unspecified aLP detection, nine cases included ACA detection and four cases included β2GPI antibody. All of the results were positive. However, the results of LA in four out of six cases were positive. After treatment, the aLP antibodies became negative as the symptoms improved. This indicates that aLP may contribute to PE in MPP. The possible mechanisms are listed as follows: (a) When the acute infection happens, the ACA, mainly targeting the cardiolipin on platelets and endothelial cell membranes, increases significantly and injures the vascular endothelial cell, which releases pro-coagulant substance; (b) The injured vascular endothelial cells and the interaction between aLP and protein C decrease the synthesis of endothelial protein C. The protein C system cannot play its proper role, thus increasing the risk of thrombosis. In our study, the activity of protein C in four of six cases decreased. However, the aLP in all cases was positive, suggesting that aLP induced PE not only by inhibiting protein C activity, but also by other mechanisms.

As a simple and fast noninvasive procedure, LVPS has some advantages in the detecting PE and used to be important in detecting subsegment PE. Pulmonary angiography has become the “gold standard” for PE diagnosis. Both its the sensitivity and specificity are above 95%. It can detect vascular lesions above 0.5 mm diameter. But because the method is an invasive procedure, its clinical use has limitations. It is currently mainly used for interventional therapy. The sensitivity and specificity of CTA in diagnosing PE are also high, which mainly detects PE proximal to subsegment pulmonary artery. This technique has become the preferred method in diagnosis of acute PE at present. An American cross-sectional study indicated that the diagnosis of PE increased significantly from 2001 to 2010 (odds ratio: 1.091, 95% confidence interval: 1.034-1.152, \( P=0.002 \)), partly because CTA has become more available [31]. A total of ten patients (10/13, 76.9%) with PE were diagnosed by CTA in this study. Before 2005, none of the patients accepted CTA examination. After 2005, ten out of thirteen cases were diagnosed by CTA, maybe due to the wider clinical use of CTA in recent years.

Once PE diagnosed, the anticoagulant therapy should be initiated immediately [32]. If necessary, the thrombolytic therapy is required. In our study, only one case received thrombolytic therapy with r-tPA. Fifteen patients received anticoagulant therapy and the longest follow-up time of oral anticoagulation was seven months [12]. As for secondary PE, the time of anticoagulant therapy is at least three months when risk factors can be released [33]. For the anticoagulant drug, a total of ten cases have been reported to use heparin followed by warfarin treatment. Interestingly, six out of seven Chinese patients received low molecular weight heparin (LMWH) as the first anticoagulant and all of these cases were reported after 2012. However, five cases in other countries treated with the intravenous unfractionated heparin. The increased use of LMWH in Chinese patients may be related to the fact that the safety and effectiveness of the LMWH have been con-
firmed in Chinese antithrombotic guideline in recent years.

In our study, five cases included methylprednisolone therapy. Researcher has suggested that inflammatory immune response induced by MP was one of the important causes of PE [34]. Glucocorticoids, having immunosuppressive effects, can suppress the production of cytokines and chemokines, which can significantly reduce both inflammatory reaction and target organ damage [3]. Whether the use of corticosteroid is necessary in patients with MPP complicated with PE, there is still lack of high quality research in this area.

Conclusions

In conclusion, because the clinical manifestations of MPP complicated with PE are not specific, PE should be ruled out in patients with MPP if the symptoms are aggravated after MPP treatment.

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Disclosure of conflict of interest

None.

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References

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