Author's response to reviews

Title: Spontaneous pneumothorax from cryptococcal pneumonia in systemic sclerosis: a case report

Authors:

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Author's response to reviews: see over
Dear Sir/Madam:

Re: Manuscript 8690019434357491 entitled “Spontaneous pneumothorax from cryptococcal pneumonia in systemic sclerosis: a case report”

Thank you for your letter dated November 24, 2010. We appreciated the comments and have made changes as advised. We have highlighted yellow the areas where changes have been made and used “Track changes” to show what was changed.

Reviewer: 1
Comments to the Author

1. This article was very interesting and shows a rare disease course. However, very little has been written about spontaneous pneumothorax, the progress and the complication of the disease. Also, should the authors explain how the treatment was done in daily practice.

Response: The details of the disease progression, the complication, and the treatment have been added as below

The patient was admitted in May, 2010, because of a low-grade fever with pleuritic chest pain, progressive shortness of breath, and having had a productive cough for 5 days. On physical examination, the patient had tachypnea (28 breaths/minute) and a body temperature of 38.2°C. Lung examination revealed decreased breath sounds and vocal resonance of the right lung with a midline trachea position. The oxygen saturation of the room air at admission was 92%.

The complete blood count indicated: hemoglobin 14.2 g/dl, white blood cell count 8,800 cell/mm³, and platelet count 247,000 cell/mm³. The chest radiograph revealed pneumothorax of the right lung (Figure 5).

Cloudy yellow-colored fluid was found after a chest tube was inserted. The exudative profile of the pleural fluid included: red blood cells 890 cell/mm³ and white blood cells 1,890 cell/mm³ (polymorphonuclear cells 64%, eosinophils 30% and lymphocytes 6%). Indian ink, gram stain and acid fast stain of the pleural fluid and sputum were negative; however, the
pleural fluid was positive for cryptococcal antigen. The respective culture of the pleural fluid and serum was positive for Cryptococcus neoformans, while the cerebrospinal fluid was negative.

Due to desaturation and large air leakage, oxygen supplementation and drainage of the chest were performed immediately. Oral fluconazole 400 mg per day was prescribed after the presence of cryptococcal was confirmed (3 days after pneumothorax) and continued for 6 months. The fever, pleuritic chest pain and cough symptoms improved and the lung was re-expanded the third day after chest tube insertion without any complications. The oxygen line was removed 7 days after treatment. A chest radiograph indicated improvement of pulmonary infiltration two weeks after treatment (Figure 6) and 4 weeks after treatment the serum cryptococcal antigen test and hemoculture for Cryptococci were negative. No recurrent pneumothorax was detected after antifungal therapy was discontinued.

2. Literature is not enough current (only 2 articles were published 5 years ago). It is necessary to find the current literature and include in the article. So I think it is necessary to revise the article in detail.

Response: The literature has been extensive reviewed and added into the discussion part with rearranged reference as below. However, there is no many recent report of spontaneous pneumothorax in connective tissue disease, pathophysiologic of disease, or secondary spontaneous pneumothorax therapy. According to author guideline, the references should not be more than 15, so we have added only 6 references (total 21 references).

Spontaneous pneumothorax can be a complication of infection from anaerobic bacteria (5), Staphylococcus (6), tuberculosis (7), aspergillosis (8), or Pneumocystis jiroveci (9) or be associated with pre-existing lung disease such as chronic obstructive pulmonary disease (5), status asthmaticus (5), cystic fibrosis (5), cancer (10), thoracic endometriosis (11) or connective tissue disease (5). All of the above would be termed secondary spontaneous pneumothorax.

Secondary spontaneous pneumothorax (SSP) in connective tissue disease has been reported in SSC (2,3), polymyositis (10), ankylosing spondylitis (13), and rheumatoid arthritis (14); particularly in persons with a pre-existing lung disease associated with an underlying connective tissue disease. Spontaneous pneumothorax in SSC has been reported in patients with subpleural blebs or lung cysts, which are perhaps due to abnormal collagen in the pulmonary tissue as a result of SSC (2,3,15). An enlarged subpleural cyst—particularly >1 cm—might be a risk for spontaneous pneumothorax in patients with SSC (2).

Our patient had pre-existing pulmonary fibrosis related to his underlying SSC. A HRCT chest revealed only subpleural emphysema and he developed spontaneous pneumothorax after pulmonary infection. We conclude that even though subpleural bleb(s) occur in SSC in
association with spontaneous pneumothorax, infection can exacerbate symptoms in patients with subpleural emphysema thereby triggering spontaneous pneumothorax.

Spontaneous pneumothorax related to cryptococcal pneumonia has been reported, but mostly in underlying acquired immunodeficiency syndrome (AIDS) (16). There is one report in a healthy young woman (17). There are no reports of spontaneous pneumothorax related to cryptococcal pneumonia in persons with SSC. The pathophysiology of spontaneous pneumothorax could be a result of lung tissue necrosis due to infection (5), and the pulmonary complications of SSC could be a predisposing factor for pneumothorax in cases where there is a thinning subpleural bleb or bullae.

The objectives of treatment in both primary spontaneous pneumothorax (PSP) and SSP are to remove air from the pleural space and to prevent recurrent pneumothorax. Importantly, recurrence is higher and the treatment more difficult in SSP than in PSP (18); therefore, the management in SSP needs to be more aggressive. However, it is more difficult to make observations without any hospital-based treatment as is often the case among patients with PSP over against those with SSP, and, problematically, there is a higher morbidity and mortality among the latter (19). Moreover, because the chest symptoms in the secondary spontaneous pneumothorax are out of proportion with the degree of pneumothorax (20), the intervention must be prompt in those who cannot tolerate pneumothorax even if there is only a low volume of leakage into the pleural space. As for the patient with symptomatic SSP, the treatment should include oxygen supplementation to correct any arterial hypoxemia and air drainage (19). The treatment options of air drainage in SSP depend on the patient’s condition and the size of the air leak into the pleural space.

Our treatment of pneumothorax in daily practice follows The British Thoracic Society (BTS) Pneumothorax Guideline (19). Accordingly, aspiration can be performed with a 16-18G canula for patients with SSP if the size of the air leakage into pleural space is between 1-2 cm whereas a chest tube drainage should be inserted if the size is >2 cm (19). Our patient presented with severe chest symptoms with hypoxemia and air leakage into pleural space >2 cm (19), thus there was no doubt about the treatment option. Chest tube drainage and oxygen therapy were immediately performed on our patient. As per the BTS guideline, no pleurodesis was performed on our patient because the lung was re-expanded, the air leak was resolved and there was no recurrence of the pneumothorax (after chest tube drainage).

In most cases, lung re-expansion will lead to rapid recovery; however, re-expansion may be delayed in the patient with SSP (21) or even in SSC (3). Pneumothorax has been known to recur in cases of SSC (2,15); thus, pleurodesis will be the final treatment in most cases of SSC. Slow lung re-expansion and recurrent pneumothorax in SSC may be explained by poor lung compliance, multiple subpleural cysts and pleural-thickening and fibrosis (2,3).

In contrast to previous reports, our patient had full lung re-expansion within 3 days of chest tube insertion and anti-fungal therapy. The rapid recovery of the lung after re-expansion might be related to early anti-fungal treatment and early chest tube drainage. Thus, the prognosis of lung re-expansion in secondary spontaneous pneumothorax due to
infection might be better than pneumothorax due to ruptured subpleural bleb in the patient with underlying SSC.

In general, pleural effusion will not be detected in the ipsilateral lung of pneumothorax because the pressure in the pleural space will obscure the hydrostatic pressure of the interstitial fluid and there is, therefore, no movement of interstitial fluid into the pleural space (5). Our patient had pleural fluid after chest tube insertion and the specific cause of pneumothorax came from pleural fluid analysis. Thus, the pleural fluid can be a clue of a pre-existing pulmonary infection in cases of spontaneous pneumothorax.

References

**Reviewer: 2**

Comments to the Author

1. This is a case report of cryptococcal infection associated with pneumothorax in a patient with systemic sclerosis. While there is an elevated chance of pneumothorax with pulmonary fibrosis in systemic sclerosis, the authors hypothesis that cryptococcus contributed to this is entirely possible, especially as cryptococcus was detected from the pleural space. I think the authors should include details of the crypto Ag testing (titers and if cultures were also done).

Response: Our institute has a limitation to test for the titer of crypto Ag testing, the report would be presented only positive or negative result. The detail of the crypto Ag testing and cultures were added as follow

Cloudy yellow-colored fluid was found after a chest tube was inserted. The exudative profile of the pleural fluid included: red blood cells 890 cell/mm$^3$ and white blood cells 1,890 cell/mm$^3$ (polymorphonuclear cells 64%, eosinophils 30% and lymphocytes 6%). Indian ink, gram stain and acid fast stain of the pleural fluid and sputum were negative; however, the pleural fluid was positive for cryptococcal antigen. The respective culture of the pleural fluid and serum was positive for *Cryptococcus neoformans*, while the cerebrospinal fluid was negative.

2. Finally, some areas related to quality of English need to be cleaned up.

Example:

Abstract: Spontaneous pneumothorax is mostly found in systemic sclerosis patients who had an extensive pulmonary fibrosis with enlarged subpleural bleb. Had should be have

Abstract: We report spontaneous pneumothorax from cryptococcal pneumonia in systemic sclerosis with minimal subpleural emphysema. Should be … in a patient with systemic sclerosis

Pleural fluid which should not be found in ipsilateral lung of pneumothorax could be a clue of a pre-existing pulmonary infection. This should be changed. I think the authors are says that
pleural fluid that is present but not initially seen because of pneumothorax could clue of a pre-existing pulmonary infection.

**Response:** The language has been reviewed entire document.

This completes the responses to the peer reviewers. Should there be any omissions or other concerns, please let us know.

Sincerely,

Chingching Foocharoen