Author’s response to reviews

Title: Metaplastic ossification in the cartilage of the bronchus of a chronic multi-drug resistant tuberculosis patient: a case report

Authors:

Seok-Yong Eum (syeumkr@gmail.com)
Ji-Hye Kong (jhkong@itrc.re.kr)
Bo-Young Jeon (bojeon87@gmail.com)
Sang-Nae Cho (raycho@yonsei.ac.kr)
Jhingook Kim (jkimsmc@skku.edu)
Laura E Via (lvia@niaid.nih.gov)
Clifton E Barry (cbarry@niaid.nih.gov)
Won-Jung Koh (wjkoh@skku.edu)

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Author’s response to reviews: see over
Dear Editor,

This cover letter accompanies our submission of the revised version of MS ID 6688014212383746 entitled “Metaplastic ossification in the cartilage of the bronchus of a chronic multi-drug resistant tuberculosis patient”. We are very appreciative of both the editors’ and reviewers’ helpful comments and we believe that the revision is a substantial improvement over the original as a result.

Below follows a point-by-point summary of our edits based upon the reviewers’ suggestions and the accompanying files represent a version with the changes tracked as well as a clean, final version of the manuscript text. We thank the reviewers for their efforts.

We hope that you find the revised manuscript suitable for publication in the Journal.

Sincerely,

Seok-Yong Eum, DVM, Ph.D.
Division of Immunopathology and Cellular Immunology
Since there is no question from Reviewer #1, we answered the comments of Reviewer #2:

1) In your abstract, I might not be so bold as saying that this is the "first time in a chronic tuberculosis" patient, since as you mentioned in your conclusion, there are at least 2 other case reports in patients with TB--and the issue of "chronic" TB might be debatable.

We have modified the sentences and added on page 2, line 3 and 4 as “We report here a metaplastic ossification in the bronchial cartilage of a multi-drug resistant (MDR) tuberculosis (TB) patient.

2) What is the clinical significance of pulmonary ossification?

Pulmonary ossification could be defined as the histologic presence of mature bone in the pulmonary parenchyma. Patients are generally asymptomatic, but when symptomatic, it is usually associated with other pulmonary diseases such as interstitial pneumonia, fibrosis, or bronchiectasis (Chan et al. Am J Respir Crit Care Med. 2002;165:1654-1669). Diagnosis of this disease is usually made on postmortem examination, not clinically. Therefore treatment options are not well established, largely due to the lack of clinical diagnosis.

This above paragraph was added on page 5, line 1 - 11.

What are the thoughts of the clinical significance in the replacement of cartilagenous with bone?

Metaplastic ossification happens as part of aging process in thyroid cartilage (Mupparapu M et al, Angle Orthod. 2002;72:576-578). Poor perfusion of cartilage, resulting in reduced blood supply to airways and reduced ability to control airway infection is reported to be one cause for bronchial cartilage alterations in lung transplantation patients (Yousem SA et al. Chest. 1990;98:1121-1124). Other reports have suggested that cystic fibrosis-associated bacterial infection, metaplastic bone replacement along with destruction and elimination of bronchial cartilage (Ogring et al. Hum Pathol. 1998;29:65-73). Given these observations, our present report suggests that stimulations by either aging or inflammation affect the bronchial cartilage and metaplastic transformation.

Most part of the above paragraph was added on page 5, line 16 - 21.
**Are there any means of early detection (other than in postmortem analyses)?**

Pulmonary ossification is not usually visible in chest x-ray. Consequently, the disease is usually discovered by chance during autopsy. High resolution computed tomography (HRCT) might be of some help in finding calcification but histopathological confirmation must is required (Kim et al. Eur Radiol. 2005;15:1581-1585).

This paragraph was added on page 5, line 6 - 11.

**3) How much of the inflamed area was affected?**

As shown in the photo, the bronchus was so severely infected and inflamed and lost almost all epithelia. Without some epithelia left, it could be considered as a cavity. The other part with lesion in chest X-ray showed heavy fibrosis and also inflammation.

*When you say "metaplastic ossification with fatty marrow replaced a portion of the cartilage plate," was this rather diffuse around the granulomas? Or just a focal spot? If just focal, any ideas why just one spot?*

That was just a focal spot of cartilage limited to this severely inflamed bronchus. This bronchus was directly adjacent to a large cavity that apparently drained caseum into the bronchial lumen and wall. The stimulation caused by this chronic inflammation might have led the metaplastic transformation of the cartilage.

Above paragraph was added on page 6, line 6 – 10.