Author's response to reviews

Title: Histologic continuity in pulmonary mucinous cystic neoplasia: in support of the adenoma-carcinoma sequence.

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Christine Wynveen, Behnaz Behmaram, George Haasler and Nagarjun Rao

Responses to reviewers’ comments:

Reviewer 1:

Although the case report is well written and illustrated, I don't think that it represents a cystic mucinous neoplasm. The imaging shows a solid mass, the gross picture shows a mucinous tumor but it is not cystic enough to be called a cystic and solid neoplasm (although there are microcysts). The 2004 WHO classification of lung tumors is not used (rather the authors chose to reference the 1999 one). Based on the images and description provided, I would call this a mucinous adenocarcinoma. Thus this case report only adds to the confusion in terminology.

Response to reviewer 1:

We agree with the reviewer that the visual impression from the radiologic image is that of a solid mass. However, on comparison, the attenuation within the mass (now marked with a white arrow) was measured at approximately 24 Hounsfield Units (HU), which is lesser than blood within the aorta (approximately 35 HU) and skeletal muscle (46 HU approximately). This is radiologically consistent with a cystic rather than a solid lesion. The attenuations are now annotated in Figure 1A, for ease of comparison. The text is changed to include the above, as is the legend for Figure 1A.

The gross photographs also show a predominantly cystic mass with micro and macrocysts, best seen in Figure 1C, where the cysts have a translucent appearance due to their abundant mucin content. The microphotographs have also been changed to show the mucinous cystic character of the neoplasm more favorably.

The reviewer’s comment regarding using the 1999 reference for the WHO classification is well taken and we have now changed it to the 2004 WHO classification. The description of mucinous cystadenocarcinoma in the 2004 WHO “blue book” appears to relate to the features of our case quite well – “A circumscribed tumor that may have a partial fibrous capsule. Centrally there is cystic change with mucin pooling and the neoplastic mucinous epithelium grows along alveolar walls”. Mucinous “colloid” adenocarcinoma is on the other hand described as a “lesion identical to their counterparts in the gastrointestinal tract, with dissecting pools of mucin containing islands of neoplastic epithelium. The epithelium in such cases may be extremely well differentiated and sometimes tumor cells float within the pools of mucin”. While agreeing that the morphologic descriptions appear to overlap to an extent, we do believe that the features in our case best fit with a mucinous cystadenocarcinoma which, as the reviewer states, is frequently incorrectly characterized. We expect that the new microphotographs will reflect the morphologic features well.
Reviewer 2:

Reviewer’s comment: This is a report of a rare pulmonary cystic mucinous tumour showing 'borderline' malignant features. Although previously reported, these are extremely rare lesions and the comment regarding sampling of the lesion is well made.

Response to comment: We thank the reviewer for their comment.

Reviewer’s comment: Working on the assumption that these are slowly growing lesions (?), it seems odd that this lesion should 'appear' in such a short time, if the patient was really having annual chest x-ray examination.

Response to comment: The history of “annual chest x-ray examination” was obtained from the patient and was found on review of the patient’s charts. There is no other documentation to prove it. Whether she was genuinely having annual chest x-ray examinations is conjectural. We therefore agree with the reviewer’s comment, and have replaced the word “annual” with “routine” in the case presentation.

Reviewer’s comment: Page 8.....B-RAS.....is this correct?
I am not sure that the details of the Kurman classification of ovarian neoplasms is really needed in such detail in this report.

Response to comment: We agree with the reviewer and have removed the entire comment regarding the Kurman classification, including the comment on B-Ras.

Reviewer’s comment: pg 8, para2, line 10.....'consists of' or 'comprises'.....

Response to comment: Changed to ‘consisted of’.

Reviewer’s comment: I agree that CK20 expression is unusual in usual-type pulmonary adenocarcinomas but it is not unusual in pulmonary mucinous lesions.

Response to comment: We agree with the reviewer, and have changed the text (page 8, para 2, lines 13-14) to read as follows:
“In addition, CK20 positivity has been described in some types of primary pulmonary mucinous lesions”.

Reviewer’s comment:
Figs 1....OK
Fig2.....OK
Fig 3....problems. A and B are the same image. Image C is less than convincing and it could be that the TTF1 positivity is actually present in adjacent type 2 pneumocytes. I am not convinced that it is demonstrated in tumor cells in this image.

Response to comment: Figures 3A and 3B are not the same image, but show CK7 and CK20 staining in the same microscopic field, in the same group of tumor cells, presented
for ease of comparison. We have anyway, now provided a photograph of a different field with CK20 positivity. We agree with the reviewer that TTF1 positivity is questionable at best, owing to the very focal nuclear positivity in tumor cells. We have now provided a microphotograph at high magnification (60x) showing isolated tumor cells with nuclear positivity (black arrow) in contradistinction to neighboring pneumocytes with TTF1 positivity (white arrow).

Reviewer’s comment: The case is, in of itself, rare and therefore of interest. I am not sure how much further it takes us and care should be used in describing this as an example of the adenoma carcinoma sequence in the lung. This terminology usually applies to the AAH-BAC-invasive adenocarcinoma progression. We do not have any real follow up data on this case to determine whether or not this was a ‘malignant’ case.

Response to comment: Although we agree with the reviewer’s comment regarding lack of clinical follow up in this patient, the evidence which in our opinion makes this case a malignancy at the present time, is the lepidic spread by lesional cells into adjacent alveoli (Figure 2D), indicative of a bronchioloalveolar carcinoma-pattern involvement of the parenchyma. This pattern fits with the description of mucinous cystadenocarcinoma in the 2004 WHO classification.