Author's response to reviews

Title: Idiopathic Pleuroparenchymal Fibroelastosis: Consideration of a Clinicopathological Entity in a Series of Japanese Patients

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Author's response to reviews: see over
RESPONSE TO REVIEWER #1 (Dr. Matthew Jankowich)

MAJOR COMMENTS

1. Were the cases collected here diagnosed with IPPFE only in retrospective review, or was this the actual pathological diagnosis at the time of the open lung biopsy?

Thank you for pointing out the important issue. In 4 out of 5 cases had been initially diagnosed with IPPFE, and it had been confirmed by Dr. Colby, but in one case, he had been diagnosed with unclassifiable interstitial pneumonia at the time of the surgical lung biopsy, but finally diagnosed with IPPFE by Dr. Colby.

2. In the results, the authors state that “In all cases in this study, the histopathological findings fitted those previously described for IPPFE.” The Methods state that the “subject included 5 patients fulfilling criteria PPFE” and reference the paper by Frankel et al. While the authors adopt wording similar to that of Frankel et al in the description of pathology on page 6 of the Results, I think that all the criteria used for the diagnosis of IPPFE should be delineated in the Methods.

As reviewer 1 suggested, we delineated the phrase regarding the criteria. Thank you for your comment.

3. Case 5 seems to have significant lower lobe involvement based on the CT Images presented. In the text of the Results on page 5, case 5 is described as Having “somewhat more prominent involvement of the lower lobes rather than other cases”. Yet in the Discussion on page 7, the authors write that “The upper lobes were ALWAYS (emphasis mine) more severely involved, with involvement of the lower lobes being absent or less marked.” I think the lower lobe cystic and/or bronchiectatic changes shown in Figure 1 are significant and arguably more pronounced than the upper lobe disease, since the lower lobe disease in case 5, in the image presented, seems to involve more than 50% of the lung area.

As the reviewer 1 pointed out, the former CT image of lower lobe in case 5 made readers more complicated. We wrongly showed the image after having pneumonia. OP like shadow may enhance the lesion, furthermore repeated infection might make some cystic lesion. But initially there were no cysts in the lower lobe. We changed it to the appropriate one which is from just before surgical lung biopsy. We are sorry for presenting inappropriate figures. We need to clarify radiological course of the patients and how lower lobe were affected in future study.

4. I disagree with the authors’ statement in the Discussion that “Our data indicate that serum SP-D may also be useful indicator for diagnosis and prediction of disease progression of PPFE”. The data as presented do not indicate how SP-D levels are different in IPPEF from other forms of interstitial lung disease, and do not indicate how they are a prognostic marker in IPPFE.

As reviewer 1 suggested, we could not show any data regarding prognosis and SP-D in this IPPFE case series. Hence we changed the phrase. “Our data suggest that those epithelial cells may play a role in the fibrotic process of the disease.”
Minor comments

1. The authors sometimes use the abbreviation “IPPFE” for idiopathic pleuroparenchymal fibroelastosis, and at other times use the abbreviation “PPFE”. These terms should be reconciled.

Thank you for pointing out the important issue. We used the term IPPFE as “Idiopathic” PPFE. We tried to reconcile it. (p3, line11, p4, line20, p8, line12, 17, 18)

2. The authors state in the Abstract that 4/5 patients had an impairment in DLCO, but in the Results, page 5, state that “In addition, three cases had impairment of DLCO (Table2).” Table 2 seems to indicate that 4/5 had impaired DLCO (if DLCO/VA <80% predicted is considered impaired), while 3/5 have impaired DLCO/VA. This should be clarified.

We are sorry about writing a mistake. We considered DLCO/VA<80% predicted is impaired. So we have correct wrong description.

3. On page 7, there is a minor wording issue. “Among those cases, four case had treatment with BMT, and thoses cases presented with histological evidence of obliterative bronchiolitis, which was not a feature in THAT with idiopathic presentation of PPFE…” I think the authors mean THOSE. There are some other minor wording issues throughout.

Thank you for pointing out our wording issue. We sincerely corrected, according to reviewer 1’ suggestion.

4. There are some minor formatting issues with Tables 1 and 2 that I assume will be corrected in the proof, such as a value for RV(L) and RV % predicted being on the same line.

We reformatted it, according to reviewer 1’s suggestion. Thank you again.
RESPONSE TO REVIEWER #2 (Dr. Keith C. Meyer)
MAJOR COMPULSORY REVISIONS

1. Abstract: Conclusions: “Unifomity and largely overlapping with…” This sentence needs revision (suggest…”owing to its relatively distinct features.”). I recommend removing “largely overlapping with previously described idiopathic upper lobe fibrosis (IPUF) or change the sentence to state that IPPFE has some features in common with IPUF.

Thank you for your wonderful suggestion.

2. Abstract: Conclusions: “…(IPPFE should be clearly distinguished from other types of interstitial lung desease, because it is highly progressive.” I recommend softening this to “our limited experience with a cohort of 5 subjects suggests that IPPFE can be rapidly progressive.” Other forms of ILD can progress rapidly (e.g. IPF), and a larger number of patients would be needed to make firm conclusions concerning the natural history of the disease.

Thank you again for your comments. We changed the phrase according to reviewer’s suggestion.

3. Discussion: First paragraph, page 6: It is stated that “our study was an attempt to identify common features between these two entities…” This is not mentioned in the abstract as an objective of the study, although IPUF is mentioned in the Conclusion.

We added it in the abstract.

4. Discussion & Conclusions: It is mentioned that IPPFE is a distinct clinicopathological syndrome that largely overlaps with previously described IPUF. However, the similarities and differences of “IPUF” as compared to IPPFE are not well described. What are the pathologic manifestations of IPUF? Is fibroelastosis present in IPUF? It is only the radiologic features/regional distribution of the disease that are similar? The histopathology of IPFU should be described and compared to the features of the IPPFE case. A goal of the study given in the “Background” section on Page 4 is to “clarify its relationship with IPUF,” but the reader is left wondering what the histopathologic changes are in subjects with IPUF (is fibroelastosis present in the cited reports of cases of IPUF?)

Although IPUF patients with surgical lung biopsy or autopsy were reported in some Japanese literature, there are no pathological criterias as IPUF. But in all those cases, intraalveolar fibrosis and subpleural elastosis were noted. Those findings are same to the pathological findings with IPPFE. Interestingly, the specimens from some patients shows UIP like pattern in the lower lobe. Amitani9 et al strictly defined the lesion is in the upper lobe, but other reports includes the patients with UIP like lesion. Reddy10 also mentioned patients with PPFE had the fibrosis in the lower lobe. Further studies are needed how those patients should be categorized. We added this point in Discussion section.
RESPONSE TO REVIEWER #3 (Dr. Sara Piciucchi)
MINOR ESSENTIAL REVISIONS

1. Authors may add some information regarding each case in the section of radiological features.

Thank you for your suggestion. We added some information regarding each case in the section of radiological features.

2. Case 5: how do they define “cystic changes” in the right lower lobe? Did they consider honeycombing? Moreover they should add more comments on the marked ipoexpansion of right hemythorax on chest X Rays, particularly they may add differential diagnosis.

In case 5, we wrongly showed the image after having pneumonia. OP like shadow may enhance the lesion, furthermore repeated infection might make some cystic lesion. But initially there were no cysts in the lower lobe. We changed it to the appropriate one which is from just before surgical lung biopsy. We are sorry for presenting inappropriate figures. We need to clarify radiological course of the patients and how lower lobe were affected in future study.

3. Quality of radiological images should be improved, particularly for case 4: what does the image in left lower lobe represent? If it must represent the normality of lower lobe, please select another slice.

We are sorry for providing inappropriate image. As suggested by the Reviewer, we have replaced the image.

4. A panel of histological findings for the cases, similar to the radiological findings may be recommended.

We changed the figures regarding histopathological findings to the one which is more similar to the radiological findings.