Author's response to reviews

Title: Development of microscopic polyangiitis-related pulmonary fibrosis in a patient with autoimmune pulmonary alveolar proteinosis

Authors:

Yuhei Kinehara (s58530@yahoo.co.jp)
Hiroshi Kida (hiroshi.kida@imed3.med.osaka-u.ac.jp)
Yoshikazu Inoue (giichi@kch.hosp.go.jp)
Masaki Hirose (mhirose@kch.hosp.go.jp)
Akihiko Nakabayashi (akihiko25252001@yahoo.co.jp)
Yoshiko Takeuchi (reed_bamboo@hotmail.com)
Yoshitomo Hayama (kokyukisenntaku@yahoo.co.jp)
Kiyoharu Fukushima (kiyoharufukushima@hotmail.co.jp)
Haruhiko Hirata (charhirata@imed3.med.osaka-u.ac.jp)
Koji Inoue (kojinoue@imed3.med.osaka-u.ac.jp)
Toshiyuki Minami (toshiyuki0319@hotmail.co.jp)
Izumi Nagatomo (iznagatomo@imed3.med.osaka-u.ac.jp)
Yoshito Takeda (yoshito@imed3.med.osaka-u.ac.jp)
Toshiki Funakoshi (tfunakoshi@senri.saiseikai.or.jp)
Takashi Kijima (tkijima@imed3.med.osaka-u.ac.jp)
Atsushi Kumanogoh (kumanogo@imed3.med.osaka-u.ac.jp)

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Author's response to reviews: see over
Dear Editors,

Enclosed please find the revised manuscript (MS: 2099119729137060) entitled “Development of microscopic polyangitis-related pulmonary fibrosis in a patient with autoimmune pulmonary alveolar proteinosis” by Kinehara et al.

First of all, we’d like to thank for the favorable comments of two reviewers on this study. They also gave us helpful comments to improve the manuscript. We therefore revised our manuscript accordingly. We believe that the manuscript has been much improved by the revision suggested by the reviewer. Point-by-point replies to the comments are enclosed.

We hope that the revised manuscript is now suitable for publication in BMC Pulmonary Medicine. Thank you for your kind consideration of the revised manuscript.

(Change in reference 8) The paper by Lang et al. was replaced by the one by Xing et al. (page 3, line 93-page 4, line 96; page 11, line 282-285).

(Change in acknowledgements) The grant to YI and MH and the one to YI and HK were added (page 10, line 241-244).

Sincerely yours,

Hiroshi Kida, M.D., Ph.D.
Department of Respiratory Medicine, Allergy and Rheumatic Diseases
Osaka University Graduate School of Medicine
Reviewer #1

Minor comments

1) The patient presented in this case report is 75 years old, not a typical age for autoimmune PAP, according to the most recent papers (Campo 2013; Bonella 2011; Inoue 2008). Moreover, after 70 years old the prevalences of haematological diseases like CML, MDS or MGUS increases. It is known that during haematological diseases GM-CSF autoantibodies can be also found at a low titer. Did the author exclude any malignancy with subclinical presentation in this patient? What about the GM-CSF autoantibody titer in follow-up?

The reviewer asked the comorbidity of hematological diseases in this case. The reviewer also asked the time course of GM-CSF autoantibody titer. Regarding the comorbidity of hematological diseases, we found no peripheral blood cell abnormality during all the period, except for the low-grade anemia caused by the chronic inflammation. The concentration of serum IgG slightly increased. However, serum protein electrophoresis did not show M spike. As the reviewer suggested, it is important to exclude secondary PAP in this case. Accordingly, we stated this in the revised manuscript (page 5, line 126-128). Regarding the time course of GM-CSF autoantibody titer, we additionally measured GM-CSF autoantibody in two other serum samples (9 and 25 months), and found that the concentrations were 23.5 and 52.9 µg/mL, respectively. These data are of significance in our study. Accordingly, we revised manuscript and figure (page 5, line 137; page 8, line 204-209; Figure 1B in revised figure).

2) The patient presented at the hospital with respiratory symptoms. When was the onset of symptoms? It would be interesting to know the duration of disease.

The patient started to cough 2 months before the first visit to our hospital. As requested, we stated this in the revised manuscript (page 4, line 108-109).
3) Which was the occupation of this patient before he retired? Please insert this important information, if available.

The patient was an owner of a liquor shop. As requested, we stated this in the revised manuscript (page 4, line 109-110).

4) MPO-ANCA testing at diagnosis was negative. What about the rest of the rheumatology lab screening? ANA titer, for example?

At diagnosis, ANA titer was 1:40 (normal range, < 1:40). As requested, we stated this in the revised manuscript (page 4, line 116-page 5, 117).

5) PAP has been diagnosed also on the basis of BAL (PAS positivity). It is known from the literature that BAL can show a marked lymphocytosis (up to 90%). Eosinophilic changes or alveolar haemorrhage are seen in lung vasculitis. Dis the authors note some of these BAL changes in the first BAL?

The reviewer asked the differential cell profile in the first BAL. As requested, we provided the data in the revised manuscript (page 5, line 121-123).

6) In the discussion the authors reported an opinion of Prof. Luisetti (page 6, line 148). Is this a personal communication or do the author know an appropriate reference? Please quote.
We quoted Prof. Luisetti’s opinion from the reference 7. The reference was reminded in the revised manuscript (page 6, line 160).

7) *The figure 1 is not reported/reminded in the text.*

The figure 1 was reminded in the revised manuscript (page 5, line 119; page 5, line 135; page 5, line 139; page 6, line 140). According to the appearance in the text, we replaced figure 1A by figure 1B, figure 1B by figure 1A in the revised figure.

Reviewer #2

Major concerns

1) *The course of GM-CSF autoantibodies must be indicated in addition to that of ANCA. In particular as the level was not so high at diagnosis it would be interesting to see current level. Best add to figure 1A.*

We agree that this is critical for the significance of our study. Accordingly, we additionally measured GM-CSF autoantibody in two other serum samples (9 and 25 months), and found that the concentrations were 23.5 and 52.9 µg/mL, respectively. We revised manuscript and figure (page 5, line 137; page 8, line 204-209; Figure 1B in revised figure).

2) *In background the absolute number and references of all patients reported so far should be indicated. This information is scattered a little bit over the discussion. For example at the end of para 1, the authors could state, “…so far xy cases have been reported.”*
So far as we could access, there have been five case reports, including two case reports, which we quoted in the submitted manuscript. We agree that these case reports were highly suggestive. Accordingly, in the revised manuscript, we state this and quoted all 5 case reports as references (page 3, line 85-89; page 10, line 261-page 11, line 280). Because of the insertion of these references, the numbers of references were shifted in the revised manuscript.