Author’s response to reviews

Title: Anti-glomerular basement membrane glomerulonephritis following nintedanib for idiopathic pulmonary fibrosis: A case report

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Author’s response to reviews:

Many thanks for taking time to write such a detailed, constructive feedback and we have taken it onboard and made necessary changes.

Reviewer #1: Relevance of Article

We thank this reviewer for his very detailed and positive review of this case report.

1) While they mention the importance of VEGF in the developing glomerulus, they only make a brief comment on its hypothesised significance in regulating and maintaining the fully developed glomerular capillary endothelial cells and consequently microvascular permeability

--> See line 146 - 150

2) Platelet derived growth factor (PDGF) and fibroblast growth factor (FGF) are involved in the evolution of crescentic glomerulonephritis and scar formation, which has not been explore

--> It certainly have been documented. Thus, following from beneficial effect of pirfenidone I have included a line to comment on this observation

3) Grammar and structure
Lines 47-48: "She had been diagnosed with idiopathic pulmonary fibrosis ___ years earlier, on the basis of typical radiological and clinical features, and was managed by the respiratory department. She had begun treatment with the novel tyrosine kinase inhibitor nintedanib for the last four months"

Lines 103-104: Confusing sentence construct. Unsure of the statement you are trying to make, and cannot find evidence to support statement in references 2-4.

Lines 117-119: "Some of the reported adverse nephrological reactions following the use of other protein kinase inhibitors, especially with older generation agents, include hypertension, proteinuria, and electrolyte disturbances."

Lines 126-127: "Hence, it has been the subject of substantial research to explore therapeutic targets to decrease symptom burden and improve overall survival" Note, have already mentioned high mortality in preceding sentence (median survival 2-3yrs) so no need to repeat in follow-up statement

Lines 139-140: "Given these patients have coexisting chronic co-morbidities…"

Lines 150-151: "Interestingly, pirfenidone, an antifibrotic agent approved for use in idiopathic pulmonary fibrosis, has been explored…"

--> many thanks for your detailed review ...these have been rectified

4) The structure of the article into subheadings gives it clear organisation in which the reader can organise their thoughts. However, the discussion needs first to address the therapeutic drug in question (nintedanib), potential applications and molecular targets related to this drug. Subsequently the discussion should give a background on Anti-GBM antibody disease and IPF, followed by the exploration of the postulated causation link.

--> The discussion is now based on reviewers feedback with paragraphs and content as above

Reviewer #2

1). 110-111: "There were no clinical, radiological or biopsy findings of any these associated causes in our patient." This sentence leads no additional information in this case.

--> Added extra information see line 126 - 128
2). 159-161: "There is a growing body of evidence that suggest multi-kinase inhibitors not only heavily impact on the immune system but also new evidence has emerged implicating its role in the regulation of renal vascular endothelium dysfunction." This sentence is contradictory to the point you are trying to make. Do you mean - its role in renal vascular endothelium dysfunction? Please correct.

--> thank you done

3). 165-166: "It is possible the change in the glomeruli architecture is enough to expose glomerular basement membrane to circulating anti-GBM antibodies." This sentence implies that there is already the presence of anti-GBM antibodies and nintedanib only exposes GBM to the already present antibodies. Please correct (e.g expose GBM antigens and consequently, antibody formation).

--> thank you we have done that

4). This is obviously not a necessity but it would be interesting to know if this patient was tested for the anti-glomerular basement membrane susceptibility allele HLA-DRB1-15? I ask this as a previously reported drug induced cause of anti-GBM nephritis confirmed this allele in 2 patients. (Anti-Glomerular Basement Membrane Disease after Alemtuzumab. Menna R. Clatworthy, Elizabeth F. Wallin, M.B., B.Chir, David R. Jayne, M.D. http://www.nejm.org/doi/full/10.1056/NEJMc0800484#article

--> Thank for highlighting this, I have not included this as it was not performed.

5). Was her breast cancer active? What was her CA-153 level? Can it account for the anti-GBM nephritis? See Maes B et al. IgA antiglomerular basement membrane disease associated with bronchial carcinoma and monoclonal gammopathy.

--> Her breast cancer was certainly not active, no a CA 15-2 level was not performed. The case report you mentioned was for bronchial carcinoma and not for breast cancer.

6). Anti-GBM has also been reported in patients with pulmonary fibrosis. Please see. https://link.springer.com/article/10.1007/s10157-010-0390-0

--> Thank you, there is a double positivity for ANCA and AntiGBM in these cases. ANCA was negative in our case - please see line 127.
7). I would like to see one or two lines about other possible triggers (breast cancer, pulmonary fibrosis) and why they are more unlikely to have caused this patient's anti-GBM disease compared to nintedanib.

--> I have included that

Reviewer #3: The case is well written and clear. However, i ve got some concerns before considering for publication.

1/r Whether the tyrosine kinase inhibitor is the primary cause of the Anti-GBM is still speculative. In order to convince the reader, the authors should discussed the possible role of lung as the primary triggers for Auto-antiboby response. The authors claim that "It is possible the change in the glomeruli architecture is enough to expose glomerular basement membrane to circulating anti-GBM antibodies". Did they detect AntiGBM Ab prior to admission?

--> We have added further explanation according to reviewer #1 which should address this concern. And no anti-GBM was not checked prior

2/ Did the patient had Bronchoalveolar Lavage to eliminate concomitant infection as a cause of triggering.

--> Patient did not have a bronchoalveolar lavage performed at the same admission but clinically she did show signs or symptoms of infection. Neither radiologically it was apparent.

3/ i will moderate their statement that anti-GBM disease is a potential complication of nintedanib. it is still speculative.

--> Thank you, I have moderated that statement