Reviewer’s report

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

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Reviewer: David Mackintosh

Reviewer's report:

Relevance of Article

The authors describe a unique case in which a novel tyrosine kinase receptor blocker (Nintedanib) prescribed for radiologically diagnosed Idiopathic Pulmonary Fibrosis is presumed to have caused anti-GBM disease. The link of causation has been established via the temporal profile of both drug treatment and subsequent symptom onset of nephritic syndrome. There are attempts to further consolidate this link through the exploration of the molecular mechanisms of nintedanib, specifically suppression of VEGF activity leading to the development of abnormal glomeruli, and a plausible trigger with subsequently exposed glomerular basement membranes. 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[1], a fact which would be important in explaining the pathogenesis of Anti-GBM disease in this case. Specifically, animal studies in mice with anti-GBM glomerulonephritis, demonstrated low tissue VEGF, VEGFR-2, Ang-1, and Tie2 expression, and treatment with VEGF165 led to improvement of renal function and proteinuria through recovery of crescentic lesions, proliferation of endothelial cells and capillary repair[2].

The authors also rest their argument of pathogenic plausibility on the effect of VEGF on animal models with developing glomeruli, not mentioning that their patient in fact had fully developed glomeruli at the commencement of treatment with nintedanib. Further exploration of the effects of VEGF on the developed kidney, as mentioned above, may lend more support to the discussion of their case.

There is evidence that both 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 explored[3]. This would create good discussion given that depletion of these factors should in theory be protective against the formation of glomerular crescents, whereas this patient presented with established necrotising crescentic glomerulonephritis.

Reporting of possible adverse reactions of novel therapies is important given that there has been limited clinical exposure to these treatments to date. Therefore this case report is essential in
expanding the knowledge base of those who use tyrosine kinase inhibitors in the treatment of disease. The above points should be noted and expanded on in the final draft of this submission.

Article Structure & Grammar

Overall the grammatical standard is sound, but could be improved in several areas and not currently at the level expected for a final submission. Some basic sentence structures are lacking. Sentences which are especially confusing and require revision are noted below, with suggested new sentence 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…"

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.

This article should be accepted after revision.

References:
1. Schrijvers BF, Flyvbjerg A, De Vriese AS. The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. Kid Intl (2004); 65:2003-17


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