Author's response to reviews

Title: A case of podocytic infolding glomerulopathy with multiple myeloma

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Author's response to reviews:

Hayley Henderson, Executive Editor, BMC Nephrology

Dear Dr. Henderson,

Thank you very much for accepting our manuscript, entitled “A case of podocytic infolding glomerulopathy with multiple myeloma”.

We removed our PBP response from the manuscript as an additional file, and included it in this new cover letter.

Our response to each of the comments is given below.

Please inform me when there is a trouble in proceeding process of acceptance.

Thank you for your considerations.

With best regards,

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Responses to the comments of the Editor

(1) The authors need to report the tubulo-interstitial and vascular findings in the biopsy. And explain why the GFR was reduced.

These details have been added to the Case presentation section of the revised manuscript, as follows (page 7, line 16 to page 8, line 6).

“Although marked hyalinosis and severe intimal thickening of the renal interlobular arteries were not observed, there were focal tubulointerstitial lesions accompanied by tubular atrophy, as well as interstitial fibrosis and inflammatory
cell infiltration, suggesting focal renal ischemic changes. However, there were no changes indicating cast nephropathy or amyloidosis, which are often associated with myeloma. The patient had many risk factors for atherosclerosis such as advanced age, hypertension, diabetes mellitus, hyperlipidemia, and hyperuricemia. Therefore, we considered that the increasing kidney dysfunction resulted from glomerular dysfunction due to PIG superimposed on underlying chronic renal ischemia.

(2) 8 authors are far too many. Four will be quite enough for a paper that contains no new research information such as complement studies.

We tried to reduce the number of authors, but request permission to include six authors. The revised manuscript reports the results of additional immunofluorescence staining for C4d and C1q (Dr. H. Shimojo), and of discussion of the pathological findings with renal pathologists (Prof. T. Ehara and Prof. H. Shigematsu). Dr. M. Harada and Dr. Y. Kamijo contributed equally to the care of the patient. Dr. M. Higuchi was the chief physician directing the therapeutic plan.

Responses to the comments of Reviewer 1

(1) PIG has not been described anywhere other than Japan. The original paper describing these glomerular changes by Joh et al, is a review of 25 cases in Japan published in 2008. Since then, a series of case studies from Japan have described similar changes in glomeruli but no further characterisation or exploration of the possible underlying pathology has been described by any of the authors of the original review. Is this truly a new disease?

This is the first reported case of PIG in a patient with multiple myeloma, and we believe that accumulation and discussion of case reports are important for increasing our understanding of the pathogenesis of PIG. Further discussion of the classification of PIG and the importance of presenting this case has been added to the Background section of the revised manuscript, as follows (page 5, lines 8–17).

“PIG is not included in the current World Health Organization classification of glomerular diseases. Only a small number of cases of PIG have been reported to date, and these have all been in Japan. These reports show that PIG tends to be associated with autoimmune abnormalities, such as systemic lupus erythematosus (SLE). Although some specialists consider that PIG should be classified as a new disease entity, it is also possible that PIG reflects a transient morphological change in patients with conditions such as SLE and membranous nephropathy. In addition, the clinical features and pathogenesis of PIG are still unclear. To elucidate these issues, it is important to accumulate information from reported cases. We present here the first reported case of PIG in a patient with multiple myeloma.”

(2) This case also does not add anything new to our understanding of this possible new glomerular disease. The authors suggest that complement overactivity could be responsible. Immunohistochemical evidence of that, e.g in
the form of staining for C4d, would be a useful addition and strengthen the suggestion that complement has a role in this.

We performed additional immunofluorescence staining for C4d and C1q, which showed no glomerular deposition of these complement components. We concluded that hyperactivation of the complement pathway may not have played a significant role in the development of PIG in the current case. Description and discussion of this information has been added to the revised manuscript as follows.

The case presentation and conclusion of the Abstract has been changed as follows (page 4, lines 4-6, 8–9)

“There were no electron-dense deposits in the GBM, while various findings indicating podocyte injury were detected.”

“The mechanisms underlying the development of PIG in multiple myeloma are unknown, but may be associated with podocyte injury.”

Case presentation (page 7, lines 9–10)

“complement (C3)” has been changed to “complement components (C3, C4d, C1q)”

Discussion (page 10, lines 10-14)

“…there was no glomerular deposition of complement components (C3, C4d, C1q). It is therefore possible that hyperactivation of the complement pathway did not play a significant role in the development of PIG in the current case, and that PIG may also result from other mechanisms.”

Discussion (page 10, line 15 to page 11, line 4)

“Matsuo et al. reported a patient with podocytic infolding lesions associated with focal segmental glomerulosclerosis secondary to vesicoureteral reflux, suggesting that the podocytic infolding lesions were a reaction to podocyte injury [9]. They reported similar changes to those found in our patient, with various pathological changes in the foot process structures such as flattening, formation of microvilli, and increased actin filaments, suggesting podocyte injury. This suggests that podocyte injury may result in the development of PIG irrespective of complement activation. This new information may help to increase our understanding of the pathogenesis of PIG.”

The Conclusion has been changed as follows (page 13, lines 3–5).

“Although the pathogenesis of PIG is still unclear, our findings suggest that podocyte injury may result in PIG. Further case reports should be accumulated to increase our understanding of PIG.”

(3) Podocyte foot process effacement and formation of microvilli are features of podocyte injury irrespective of the insult. It is not clear in the discussion if the authors are suggesting these are features of PIG.

We do not consider podocyte injury to be a lesion specific to PIG. However, we
think that podocyte injury may result in PIG. This has been clarified in the Discussion section of the revised manuscript.

Responses to the comments of Reviewer 2

(1) I see no way to specifically link the patient’s plasma cell dyscrasia with the findings in the renal biopsy: Membranous nephropathy with microspherical particles termed in this manuscript podocytic infolding glomerulopathy (term coined by Joh et al). The absence of monotypical light chain staining in the lesion is clear evidence of a direct connection. To me, the two conditions are totally unrelated. Essentially, a patient with myeloma who develops a membranous nephropathy with microspherical particles, an entity referred to by some as PIG.

We considered the possibility that PIG is an unusual type of membranous nephropathy associated with microspherical particles that developed after resolution of immune complex deposition in the GBM. This is discussed further in the response to Question 4 below.

As you point out, direct evidence explaining specifically link between plasma cell dyscrasia and PIG may be insufficient, therefore we changed the title and text, as follows.

Title (page 1, line 2)
“A case of podocytic infolding glomerulopathy with multiple myeloma”

Background (page 3, line 9-10; page 5, line 16-17)
“We present here the first reported case of PIG in a patient with multiple myeloma.”

(2) The proposed pathogenesis is weak.

In the previous manuscript, we described the possibility that hyperactivation of the complement system may have played an important role in the pathogenesis of PIG in the current case, because many previous studies reported that such hyperactivation is often detected in multiple myeloma patients. However, immunofluorescence staining for C4d and C1q was negative in this case. The following text has been added to Discussion section (page 10, line 8 to page 11, line 4).

“In the current case, however, we did not detect any autoimmune abnormalities or hypocomplementemia by routine laboratory examinations, and there was no glomerular deposition of complement components (C3, C4d, C1q). It is therefore possible that hyperactivation of the complement pathway did not play a significant role in the development of PIG in the current case, and that PIG may also result from other mechanisms. Matsuo et al. reported a patient with podocytic infolding lesions associated with focal segmental glomerulosclerosis secondary to vesicoureteral reflux, suggesting that the podocytic infolding lesions were a reaction to podocyte injury [9]. They reported similar changes to those found in our patient, with various pathological changes in the foot process structures such as flattening, formation of microvilli, and increased actin
filaments, suggesting podocyte injury. This suggests that podocyte injury may result in the development of PIG irrespective of complement activation. This new information may help to increase our understanding of the pathogenesis of PIG.”

(3) I believe that publication of this case report adds no useful information to the already existing on PIG (podocytic infolding glomerulopathy).

The revised manuscript discusses the possibility that podocyte injury may result in the development of PIG even without hyperactivation of the complement pathway. The new information presented may help to increase our understanding of the pathogenesis of PIG, as described in the Discussion section of the revised manuscript (page 11, lines 2-4).

(4) Comparison of the entity (PIG) with garden variety of membranous nephropathy has shown similar response to therapeutic interventions, clinical course and prognosis, placing doubts as to the real clinical significance of establishing a new entity such as PIG.

A comparison of clinical characteristics between patients with PIG and idiopathic membranous nephropathy (IMN) has been added to the Discussion section of the revised manuscript, as follows (page 11, line 5 to page 12, line 6).

“We considered the possibility that PIG is an unusual type of membranous nephropathy associated with microspherical particles that developed after resolution of immune complex deposition in the GBM. To evaluate this possibility, we compared the clinical characteristics of patients with PIG and idiopathic membranous nephropathy (IMN) in previously reported Japanese studies. We found that these two groups of patients had different background characteristics. The mean age at the time of diagnosis was 41.8 years in patients with PIG and 59 years in patients with IMN [1,11]. The male-to-female ratio was almost 1:3 in patients with PIG and almost 1:1 in patients with IMN [1,11]. The mean urinary protein excretion was 2.2 g/day in patients with PIG and 7.9 g/day in patients with IMN [1,11]. The therapeutic responses also appeared to vary between these two groups of patients. All reported cases of nephrotic PIG associated with autoimmune disease achieved complete remission with corticosteroid therapy, whereas only 66.7% of cases of nephrotic IMN achieved complete or incomplete remission with corticosteroid therapy [1,12]. Although spontaneous remission may occur in some cases of IMN, complete or incomplete remission did not occur in any of the reported cases of nephrotic PIG not associated with autoimmune disease and not treated with corticosteroids [1]. These findings suggest that PIG is strongly influenced by corticosteroid therapy and by associated autoimmune disease, and that the response to therapeutic intervention differs between patients with PIG and IMN. We consider these findings to indicate that PIG is a new disease entity that differs from IMN.”

The term “Idiopathic membranous nephropathy (IMN)” has also been added to the list of abbreviations, and references #11 and #12 have been added.