June 23, 2018
Dr. Journal Metrics
Editor-in-Chief
World Journal of Nephrology

Re: 40003

Dear Dr. Metrics:

Your letter dated June 8, 2018 regarding our manuscript entitled, "A case of human immunodeficiency virus infection presenting as a tip variant of focal segmental glomerulosclerosis successfully treated by corticosteroid monotherapy," encouraged us to address the concerns raised by Reviewers, and resubmit our paper for publication. We appreciate this opportunity to resubmit our revised manuscript. We have carefully considered all the comments provided by Reviewers, and have revised the manuscript in accordance with the suggestions. We hope that the manuscript is now suitable for publication in *World Journal of Nephrology*.

Thank you very much for your kind attention to this matter.

Yours sincerely,
Naro

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Response to Reviewer #1 (00503179)

We thank you for your helpful comments. The manuscript has been revised in accordance with your suggestions. Our responses to the questions and issues raised are as follows:

1. The diagnostic classification of tip variant of focal segmental glomerulosclerosis (FSGS)

As indicated in the manuscript, only one glomerulus showed epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet was observed in a total of 35 glomeruli. Certainly, the frequency of damaged glomeruli was low. However, as kindly indicated by Reviewer #1, the histological change coincides with the definition of tip variant of FSGS. In addition, neither changes of the glomerular capillaries such as spike formation and bubbling appearance nor glomerular nodular lesions were found in the light microscopic findings. Immunofluorescent microscopic examination showed the absence of immunoglobulins and complements and no thickness of glomerular basement membrane was observed in electron microscopic findings. These findings exclude diabetic nephropathy and membranous nephropathy and confirm the diagnosis of tip variant of FSGS. We have added these contents in the Case (page 6 3rd paragraph to page 7, 1st paragraph) and Discussion sections (page 8, 2nd paragraph to page 9, 1st paragraph).

Response to Reviewer #2 (00503176)

We thank that Reviewer #2 reviewed our manuscript and permitted to publish this manuscript.

Response to Reviewer #3 (00503014)

We thank you for your helpful comments and have revised our manuscript in accordance with your suggestions. Our responses to the questions and issues raised are as follows:

1. Difference between minimal change disease and FSGS.

Just one glomerulus revealed the findings of tip variant of FSGS. This fact indicates that this diagnosis of renal biopsy is a minimal change disease. However, tip variant of FSGS diagnosis according to the Columbia classification requires at least one glomerulus with a segmental lesion involving the tip domain of the glomerular capillary tuft. Therefore, the tip variant of FSGS but not minimal change disease, was

diagnosed in this case.

2. Possibility of trigger factors such as heart failure or obesity

As Reviewer #3 suggested, steroid treatment immediately ameliorated nephrotic syndrome, and this response when compared with the common response to the treatment of FSGS, could have led to the diagnosis of minimal change disease. However, because several papers report that tip variant of FSGS responds well to steroid therapy in contrast to other variants of FSGS, this rapid response to steroid therapy may be an indicator of tip variant of FSGS.

In addition, as kindly suggested by Reviewer #3, it is possible that heart failure or obesity caused this massive proteinuria and renal dysfunction. However, no symptoms of heart failure were found during the clinical course. Moreover, this patient is remarkably obese (body mass index: 31.3 kg/m^2) and obesity-associated FSGS was suspected as a differential diagnosis. However, this patient's clinical features were considerably different than those of the obesity-associated FSGS based on the following evidences:

(1) Although obesity was not improved, urinary protein levels were dramatically decreased by steroid treatment.

(2) Praga et al. reported that the levels of proteinuria in obesity-associated FSGS are lower and that the incidences of hypoalbuminemia and edema are less frequent than in patients with idiopathic FSGS. In addition, they indicated that glomerular hyperfiltration is more frequently found in renal biopsy specimens of patients with obesity-associated FSGS than in renal biopsy specimens of patients with idiopathic FSGS. Therefore, this case was unlikely to be of obesity-associated FSGS. We have added this information in the revised manuscript (page 6, 1st, 2nd and 3rd paragraphs and page 9, 2nd paragraph).

Response to Reviewer #4 (00502999)

We thank you for your helpful comments and have revised our manuscript in accordance with your suggestions. Our responses to the questions and issues raised are as follows:

1. The association between HIV infection and tip variant of FSGS

As rightly suggested by Reviewer #4, it cannot be completely denied that this case indicates a patient with HIV infection and tip variant of FSGS. However, Lescure et al. indicated that HIV-associated nephropathy (HIVAN) decreased from 75% in 1995-2000

to 29% in 2004-2007 because of the introduction of antiretroviral therapy (ART), and that FSGS other than HIVAN conversely increased from 11.1% in 1995-2000 to 46.9% in the 2004-2007. The incidence of FSGS with HIV infection in both periods is much higher (86.1% in 1995-2000 and 75.9% in 2004-2007) than that of black patients without HIV infection (49%). These results indicate that HIV infection is associated with the FSGS pathogenesis with or without adequate quantity of HIV. Additionally, some pathogeneses of kidney diseases such as immunodeficiency and dysregulation of immunoglobulin synthetic responses and T-cell function are increased in HIV-infected patients. Thus, the FSGS pathogenesis associated with HIV infection and idiopathic FSGS might be different. Probably, the corticosteroid therapy corrected the dysregulation of the immune system caused by HIV infection in this tip variant of FSGS. Therefore, further study to clarify the FSGS pathogenesis without HIV RNA in HIV-infected patients who were effectively treated with ART should be conducted. This information has been added in the revised manuscript (page 9, 3rd paragraph). We hope that Reviewer #4 permits our concepts.

2. Renal damage due to atazanavir

As suggested by Reviewer #4, the presence of atazanavir-induced progressive renal insufficiency and nephrotic-ranged proteinuria cannot be completely denied. Certainly, we also suspected atazanavir induced nephropathy at first. However, progressive renal insufficiency and nephrotic-ranged proteinuria did not improve after the discontinuation of atazanavir. Moreover, to the best of our knowledge, atazanavir induced tip variant of FSGS has yet to be reported in scientific literature. Therefore, we believe that atazanavir did not cause the massive progressive renal insufficiency and nephrotic-ranged proteinuria. These comments were added in the revised manuscript (page 10, 1st paragraph).

3. Native check of English

Our manuscript was checked by a native English speaker before submission. However, because of the comments pointed out by reviewers, and extensive corrections of our manuscript, we have had a native English speaker review it again. We hope that Reviewer #4 finds satisfaction in our revised manuscript.

4. Creation of Table to shorten the clinical case

According to Reviewer #4's suggestion, Table 1 is created to show the laboratory data.

Response to Reviewer #5 (00503199)

We thank you for your helpful comments and have revised our manuscript in accordance with your suggestions. Our responses to the questions and issues raised are as follows:

1. Relationship between HIV infection and tip variant of FSGS

As suggested by Reviewer #5, it cannot be completely denied that this case indicates a patient with HIV infection and tip variant of FSGS. However, Lescure et al. indicated that HIV-associated nephropathy (HIVAN) decreased from 75% in 1995-2000 to 29% in 2004-2007 because of the introduction of antiretroviral therapy (ART), and that FSGS other than HIVAN conversely increased from 11.1% in 1995-2000 to 46.9% in the 2004-2007. The incidence of FSGS with HIV infection in both periods is much higher (86.1% in 1995-2000 and 75.9% in 2004-2007) than that of black patients without HIV infection (49%). These results indicate that HIV infection is associated with the FSGS pathogenesis with or without adequate quantity of HIV. Additionally, some pathogeneses of kidney diseases such as immunodeficiency and dysregulation of immunoglobulin synthetic responses and T-cell function are increased in HIV-infected patients. Thus, the FSGS pathogenesis associated with HIV infection and idiopathic FSGS might be different. Probably, the corticosteroid therapy corrected the dysregulation of the immune system caused by HIV infection in this tip variant of FSGS. Therefore, further study to clarify the FSGS pathogenesis without HIV RNA in HIV-infected patients who were effectively treated with ART should be conducted.

However, as suggested by Reviewer #5, it is possible that this case indicates a patient with HIV infection and tip variant of FSGS. Therefore, we have revised some sentences in Abstract (page 4) and Core tip (page 4), Discussion (page 7, 3rd paragraph) and Conclusion (page 10, 3rd paragraph) accordingly. In the near future, further study to clarify the pathogenesis of FSGS without HIV RNA in HIV infected patient who were effectively treated with ART should be conducted. We have added these sentences in the revised manuscript (page 9, 3rd paragraph). We hope that Reviewer #5 permits our concepts.