Author’s response to reviews

Title: Predominant but Silent C1q Deposits in Mesangium on Transplanted Kidneys - Long-Term Observational Study -

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Author’s response to reviews:

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Editors-in-Chief Dr. Hayley Henderson,

BMC Nephrology

Dear Dr. Hayley Henderson,

Thank you for your suggestive advices to improve our manuscript. We much appreciate them.

We revised our manuscript following the reviewers’ advices.
Editor comments

Suggestion 1. If written informed consents were not obtained, you must remove all potential clinical identifiers (age, sex etc) from this manuscript.

Reply. Thank you for your careful suggestions. We much appreciate it.

The written informed consents could not be obtained from them, because they have left away from our hospital. So their ages and sexes were removed from Table 1.

This study complies with the Declaration of Helsinki, and was approved by the Ethics Committee of Tokyo Women’s Medical University. The written informed consents from each participate are not required for this study. To let the patients to notice this study, we have put an announcement on our web site: http://www.twmu.ac.jp/TWMU/Medicine/RinshoKouza/093/shinryou_kenkyu.html#isyoku_c1g since September 2016.

Reviewer (Dr. Alenka Vizjak)

To Dr. Alenka Vizjak,

Thank you for your valuable comments. We much appreciate them.

Comments 1-1. Use the word of “transplanted kidney” instead of “donated kidney.”

Reply. The words of “donated kidney” are changed to “transplanted kidney” in the title and through this manuscript.

Comments 1-2. The term of normal proteinuria is not used. And proteinuria in studied patients should be measured quantitatively.
Reply. The term of “normal proteinuria” is changed to “negative proteinuria” through this manuscript.

It is true that proteinuria in studied patients should have been measured quantitatively. This retrospective study does not allow us to re-analyze them.

Comments 1-3. Patients with mild proteinuria cannot be defined as cases with silent C1q deposits.

Reply. It is true especially if they are not renal recipient patients.

But this is a study of renal recipient patients. Amer et al. reported that 45% of renal transplanted patients in general were found to have proteinuria (>150mg/day). (Am J Transplat 2007;7:2748-2756). And, as we stated, during the follow-up period, no cases presented with persistent proteinuria and/or hematuria greater than or equal to 2+ by dip stick test.

So I believe mild proteinuria only does not always indicate renal dysfunction in the cases of renal recipient patients.

Comments 1-4. In the Abstract, mild proteinuria is defined as 1+ by dipstick and in the Materials and Methods as less than 1+ by dipstick.

Reply. The definition is “less than or equal to 1+ by dipstick” through this manuscript.

Comments 2-1. The characterization of C1qN is incorrect in Abstract line 3.

Reply. The characterization of C1qN in Abstract was changed as follow; “C1q nephropathy was first described as glomerular disease characterized by predominant mesangial C1q deposits in patients with proteinuria and no evidence of systemic lupus erythematosus.”
Comments 2-2. In abstract line 8, the word of “two” should be “some.”

Reply. The word of “two” was changed to “some.”

Comments 2-3. In Abstract, the phrase in line 28-30 is repeated.

Reply. The repeated phrase was deleted.

Comments 2-4. In Abstract, line 35-38. These data are not the results and are inappropriately cited in the Abstract.

Reply. Line 35-38 in Abstract was deleted. Then, the precise clinical and immunopathological results at the diagnosis of C1q deposition and in the follow-up period is stated: “At the time when predominant mesangial C1q deposits were detected, 2 cases presented with mild proteinuria without hematuria, but the other 3 cases showed normal urinalysis. Light microscopy revealed minor glomerular abnormality in all the cases. Immunofluorescent study showed predominant mesangial C1q deposits with IgG, IgM and C3 in all cases. All selected specimens presented electron dense-depos in the mesangium. 10 years later from the detection, 2 cases continued to be normal urinalysis and 3 cases had mild proteinuria without hematuria. During this follow-up period, no cases presented with persistent proteinuria and/or hematuria greater than or equal to 2+ by dip stick test. And no cases developed systemic lupus erythematosus. Follow-up renal graft biopsies were performed in 2 cases 8 years later from the detection. They showed minor glomerular abnormalities. C1q deposit disappeared in one case.”

Comments 3-1. Material and Methods, line 50. Clarify whether 18-year-old patient is classed as adult or child.

Reply. The phrase was changed to a following sentence; “The cases consisted of 334 adults aged 19 years old or older, and 80 children aged 2 to less than or equal to 18 years.”

Reply. The following sentence has been changed, and the citation has been deleted due to the criteria of transplant glomeruropathy (Remport A, et al. NDT 2015, 30: 1825-1833);

“We excluded cases with morphologic features of membranoproliferative glomerulonephritis type I [1, 6] or that fulfilled the diagnostic criteria for SLE [7], and had chronic rejection findings (duplication of glomerular basement membrane and arterial intimal hypertrophy with inflammatory cell infiltration) because they transplant glomerulopathy accompanied by chronic rejection occasionally shows mesangial C1q deposits with proteinuria and renal dysfunction [8].”

Comments 4-1. Results, page 7, line 52-54. “less intensity in other components” can be omitted.

Reply. “less intensity in other components” has been omitted.

Comments 4-2. Results, page 8, line 28-35. “how many repeated biopsies were performed.”

Comments 4-3. Results, page 6, line 35-38: Renal graft-biopsies were carried out an average of 2.2 times…” It is unclear.

Replies. To clarify the times and timings of renal graft biopsies, we put the Fig 1. It will help readers understand them. Additionally, we added some words to make them clear; in Results, page 8, “In Case 1 and 3, follow-up renal graft biopsies after C1q detection on mesangium were performed once 8 years later in each case.”

Comments 5. Discussion is superficial.

Reply. To emphasize the concept that C1q deposition may be a coincidental findings with no pathologic significance, we put following sentences in Discussion; “Said et al. reported that patients who had predominant mesangial C1q deposits with MGA on their transplanted kidneys, had maintained no proteinuria for a mean follow-up of 1 year [10]. Moreover, our study
demonstrated that patients who had predominant mesangial C1q deposits with MGA on their transplanted kidneys, had maintained negative to mild proteinuria without hematuria even for 10 years follow-up.”

Comments 6. English language is poor and should be improved.

Reply. This manuscript has already been edited by “San Francisco Edit http://www.sfedit.net/.” I attach the certification. If this manuscript need much improvement, please let me know. I will ask the editing service company.

Reviewer Dr. Anthony M. Valeri

To Dr. Anthony M. Valeri.

Thank you for your suggestive advices to improve our manuscript. We much appreciate them.

Comments 1. A quantitation of the amount of proteinuria.

Reply. The amount of proteinuria should have been quantified. This retrospective study does not allow us to re-analyze them.

Comments 2. What was the timing of prior biopsy that did not show C1q deposition in relation to the time from transplantation and to the follow-up biopsy that showed C1q deposition?

Reply. To clarify the times and timings of renal graft biopsies, we put the Fig 1. It will help readers understand them.

And to clarify them, we add the word of “Protocol” in Result part.
Comments 3. Did the patient have a follow-up biopsy that showed resolution of the C1q deposition, and the timing relative to the index biopsy showing C1q deposition.

Reply. To clarify the times and timings of renal graft-biopsies, we put the Fig 1. It will help readers understand them.

And to clarify them, we add the some words as follows; “In Cases 1 and 3, follow-up renal graft biopsies after C1q detection on mesangium were performed once 8 years later in each case.”

As stated in Result, “The IF study in Case 3 was negative for C1q, IgG, IgM, IgA and C3 (table 2, Fig. 2d and 2e)”

Comments 4. Were the biopsies stained for C4d especially in the peri-tubular capillaries to suggest a related acute or choronic antibody-mediated rejection (AMR)?

Reply. When predominant mesangial C1q deposits were detected, only case 4 showed very weak positive C4d staining on peri-tubular capillaries. Other 4 cases did not show C4d staining on peri-tubular capillaries. So the possibility is quite low that there was any relation between AMR and mesangial C1q deposits.

Comments 5. Did any of these patients have AMR previously or afterwards?

Reply. After 8 years later from C1q deposition was found, Case 1 did not show positive C4d staining on peri-tubular capillaries. On the other hand, after 8 years later from C1q deposition was found, Case 3 showed positive C4d staining on peri-tubular capillaries, with slight increase of serum creatinine level from 1.2 mg/dL to 1.78 mg/dL. However, Case 3 showed negative C1q staining at that time. So the possibility is quite low that there was any relation between AMR and mesangial C1q deposits.

Comments 6. The discussion should focus on the concept that C1q deposition may be just a coincidental findings with no pathologic significance.
Reply. To emphasize the concept that C1q deposition may be just a coincidental findings with no pathologic significance, we put following sentences in Discussion: “Said et al. reported that patients who had predominant mesangial C1q deposits with MGA on their transplanted kidneys, had maintained no proteinuria for a mean follow-up of 1 year [10]. Moreover, our study demonstrated that patients who had predominant mesangial C1q deposits with MGA on their transplanted kidneys, had maintained negative to mild proteinuria without hematuria even for 10 years follow-up.”

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