Author’s response to reviews

Title: Thrombospondin type-1 domain-containing 7A-associated membranous nephropathy after resection of rectal cancer: a case report

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Author’s response to reviews:

Dear Antonello Pani,

We greatly appreciate your review of our manuscript and the helpful suggestions. Below are our responses to the reviewers’ comments, with a description of the changes made to the manuscript. After incorporating the reviewer’s suggestions, the revised manuscript has become slightly longer. We sincerely apologize for this issue.

Response to Reviewer 1

We greatly appreciate your helpful comments and suggestion.

In accordance with your suggestions, we have revised our figures to improve their quality.

Response to Reviewer 2
We greatly appreciate your helpful comments and suggestions. In accordance with your suggestions, we have revised the manuscript.

Answer to comment 1):

We did not test for circulating antibodies to THSD7A because the patient’s consent was not obtained for economic reasons. However, it is reported that there is no significant difference in sensitivity and specificity between THSD7A tissue staining and serum antibody testing (Shree G Sharma, et al. Modern Pathology. 2017; 31; 616-22), and we believe that testing for THSD7A antibody is not necessarily needed.

Answer to comments 2) and 3):

Based on your suggestion, we have added the following description: “Regarding the pathogenesis of MN, it is suggested that idiopathic MN develops based on the concept of in situ immune complex formation, in which the antigens responsible are present in glomerular podocytes and immune complexes are formed in situ [23]. Moreover, the discovery of PLA2R and THSD7A supports this hypothesis [3, 4]. In cancer-related MN, it is assumed that antibodies against tumor antigens are produced and form immune complexes with similar structural endogenous antigens on the podocytes in situ, or immune complexes formed in the circulation are trapped in the capillary wall, but the details are unclear [24]. In THSD7A-associated MN, it is suggested that an antibody against THSD7A, a tumor antigen, is produced and forms an immune complex in situ with THSD7A as an endogenous antigen in podocytes, resulting in the development of MN [8]. As it became clear that THSD7A-associated MN and tumor are related, the concept of in situ immune complex formation might be the major pathological condition in tumor-associated MN as with idiopathic MN. In this case, although there is no obvious recurrence, there is a possibility that lymph node metastasis may remain because postoperative chemotherapy has not been performed. Antibodies against the THSD7A antigen expressed in the remaining tumor may have been produced, which may have led to MN .” on page 9, lines 158-172, in the discussion section.

Answer to comment 4):

Although this case has no evidence of recurrent cancer, secondary MN, which is not necessarily tumor-associated MN, is more likely because of negative staining for PLA2R, positive staining for IgG1 and IgG2, and positive staining for THSD7A in both renal and tumor tissue. In secondary MN, the effect of steroid therapy is limited and treatment for the cause is the first choice (Glassock RJ, et al. Nephrol Dial Transplant. 1992;7 Suppl 1:64-71). Therefore, in this
case, after consultation with the patient and his family, steroid therapy was not performed and he was kept on observation with supportive therapy.

Answer to comment 5):

As a cause of MN in this case, HCV infection cannot be completely ruled out. Because there have been only few cases of HCV-related MN (Rihova Z, et al. Ren Fail. 2005;27(4):397-402), there is no report on the staining for PLA2R or THSD7A in HCV-related MN. Therefore, though the possibility that HCV infection is related to MN in this case cannot be completely denied; THSD7A-positive staining in both the kidney and tumor tissues suggests that the association between rectal cancer and MN is highly certain.