Author’s response to reviews

Title: Membranoproliferative glomerulonephritis related to a Streptococcal infection in a girl with IgA deficiency: A case report

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Reviewer reports:

Claire Harris (Reviewer 1): The authors present a case which seems rare enough in the pediatric literature to present but the hypothesis/uniqueness of the case needs to be weighed against the question of the diagnosis in this case.

The authors mention that this could be a case of SIRN which seems most likely to me but fail to give enough details regarding

I am grateful for the important comments on my manuscript.
I have responded to your comments below.

1) the indication for renal biopsy given the non-severe presentation and high likelihood of improvement with supportive management for suspected PIGN/PSGN.
Response: We do not have enough information for the indication to perform the renal biopsy for non-severe case with SIRN. In this case, it has not been established as a general treatment; multidrug combination therapy may have been an overtreatment.

2) The clinical features or course that led them to pursue aggressive immunosuppressive treatment i.e. was the serum creatinine worsening?, were there any other worrisome signs.
Response: Serum creatinine did not worsen, and no other signs were observed.

3) what was the authors thoughts on SIRN vs alternate diagnoses - how would the path findings differ as C3/IgG would be expected in PIGN/SIRN so why does IgAD matter, this could be flushed out more
Response: Please elaborate, as the meaning of your comment is not clear to me.
4) why was the patient re-biopsied 4 years later?
Response: This procedure is not routine. In general, long term treatment is required for MPGN. We performed a re-biopsy to decide whether PSL should be continued or not. The time for taking this decision is about 4 years at our institution.

The authors should additionally provide rationale for the choice of their treatments, why not PSL alone if immunosuppression is going to be used, why add MZR? What is the reason that warfarin was used? We need more clinical data and rationale to better explain the management in this case. I would also be interested in more details on how quickly the patient improved.
Response: In fact, MPGN treatment regimen has not yet been established and may vary between institutions. As mentioned by you, therapy with PSL alone may have been adequate for this patient. However, multidrug therapy including continuous use of MZR yielded good outcome in this case.

The writing style and language is good.

Pasquale Esposito (Reviewer 2): This case is well presented and documented, describing a rare and interesting condition.

However, some points should be clarified.

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1. I'd like to know how the authors chose the treatment (e.g. what were the reasons to use mizoribine and warfarin?).
Response: As mentioned by you, treatment with PSL alone is generally used for MPGN. However, we had encountered MPGN cases that did not improve with PSL alone and required multidrug therapy including immunosuppressive agents and warfarin. Actually, this combination therapy, as in this case, is usually used for MPGN at our institution.

2. I think there is space to discuss deeper the differential diagnosis.
Response: In this case, the most relevant diseases are streptococcus infection-related nephritis and secondary MPGN. Especially, secondary MPGN with SLE is important because development of autoimmune diseases in IgAD is well known. However, in this case, elevation of the ASO titer, characteristic findings on IF staining, and hump formation, but no EDD on EM provided supportive evidence of a streptococcus infection-related nephritis although NAPIr was negative.

3. There are possible pathogenetic mechanisms linking glomerulopathy to IgAD?
Response: I have not described the mechanisms relating IgAD and glomerulopathy because I do not believe that it is specific to IgAD. However, CIC are detected in 50% to 60% of patients with selective IgAD and may be involved in the immunopathogenesis of vasculitis and glomerulonephritis. The presence of CIC for streptococcus antigen and antibody possibly induced MPGN in our patient.
4. It could be useful to add a graph on the clinical course of the patient in relation to the treatment. Response: I have added the graph of clinical course as Figure 2.

5. What was the indication of the second biopsy? Response: We performed a re-biopsy to decide whether PSL should be continued or not. The time for this decision is about 4 years at our institution. I have added the explanation in paragraph 4 of the case presentation.