Author's response to reviews

Title: Progressive and deleterious multifocal cerebral infarction in a young kidney transplant recipient due to thrombotic microangiopathy

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Author's response to reviews: see over
We thank both Reviewers for their valuable suggestions and comments that certainly helped to improve the manuscript.

Response to Reviewer 1:

1. ‘End-stage renal failure of unknown cause’. The key question here is ‘could he have had atypical Haemolytic-Uremic Syndrome (aHUS) as his primary disease’? There may be some information which makes this very unlikely or, conversely, possible. We need to know his ethnicity, details of his family history (FH), eg siblings, anything to suggest HUS in the family? The most common cause of ESRD would be renal dysplasia – any suggestion he had unequal sized kidneys at presentation?

We were able to retrieve very early medical files of this patient from the children's hospital which contained a report on a renal histology: end-stage renal failure was focal segmental glomerulosclerosis.

We added this information in the the Summary of the Case:

“His medical history comprised a kidney transplantation 12 years earlier for end-stage renal failure due to focal and segmental glomerulosclerosis…”

His ethnicity was Caucasian. We have added this information in the Summary of the Case:

“A 25-year-old male caucasian patient presented….”

The patient had no history of aHUS and no family history of any kidney diseases. We have added this information in the Discussion:

“Also, in our patient there was no clue for TMA in the former history with regard to his original renal disease, in an allograft biopsy performed two years before his death, or in his family.”

2. He was receiving erythropoietin with a creatinine of 156 µmol/l. Was he small (wt.?) was his eGFR lower than one might guess for a creatinine of 156. Was he chronically haemolysing? Best test for this in HUS is haptoglobin; was this ever measured? why do the authors think he needed Epo?

The corresponding eGFR to the S-creatinine of 156 µmol/l was 47 ml/min which may not explain the need for EPO treatment. However, we report in the Summary of Case that the patient suffered from hypoplastic bone marrow of unknown cause as diagnosed by bone marrow biopsy. In our opinion, this explains the necessity of the EPO treatment with moderate dosage (40 µg darbepoetin alfa every two weeks).

We have included information on the eGFR in the Summary of the Case:

“The serum creatinine concentration was 156 µmol/l (equaling an eGFR of 47 ml/min) which…”
3. ‘Vasculitis was excluded…’; presumably ANCA performed?

Yes, indeed, ANCA was in the laboratory workup. We added this information in the Summary of the Case:

„... excluded by negative results for anti-nuclear antibodies, ANCA anti-mitochondrial antibodies, anti-cardiolipin antibodies cryoglobulins/HCV and HIV status…”

4. What is ASS?

We have changed the abbreviation to: “acetyl salicylic acid” in the Summary of the Case.

5. ‘undulant avolition’ is a wonderful expression : is this exactly the correct English phrase that the authors mean?

By this phrase we meant ‘listlessness’. We replaced the term by “listlessness” in the Summary of Case.

6. What does tsd/µl mean?

We meant thousand/µl. We changed this in the Summary of Case.

7. Cyclosporine levels - please mention method briefly (e.g. whole blood).

Cyclosporine levels were measured by mass spectrometry (LC-MS/MS) in the serum. We added this information in the Summary of Case.

8. ‘loss of vigilance’: is this the correct English phrase? Do you not always lose vigilance when you are blind?

By this phrase we intended to describe the impaired conscious state. To put it more precisely we now describe the condition with by the use of the Glasgow coma scale which was 8 at that particular time:

“At the 5th day, he was discovered having bilateral blindness accompanied by moderate to severe loss of conscious (Glasgow coma scale of 8)…”

9. Virology: was Hepatitis C excluded. Hep C and cryoglobulinaemia commonly causes a TMA/HUS syndrome.

And

10. Virology: was HIV excluded?

We performed a number of virology tests, including Hepatitis C and HIV, which both were negative.

We have added this information in the Summary of Case:

“Vasculitis was further excluded by negative results for anti-nuclear
antibodies, ANCA, anti-mitochondrial antibodies, anti-cardiolipin antibodies, cryoglobulins/HCV and HIV status.”

11. To be added: Table of lab data; something like this:
X months earlier Admission 4 weeks later xx
Hb
Wbc
Plates
Creatinine
CyA level
etc

We added a table containing the course of the most relevant lab data as suggested.

12. High quality image(s) of thrombotic microangiopathy histology – preferably from kidney. Was any previous renal histology performed?

We thank the reviewer for this advice and provided post-mortem histological images form different organs displaying sings of thrombotic microangiopathy (Figure 3). A renal allograft biopsy had been performed two years before the patient’s death, which showed only interstitial fibrosis and tubular atrophy but no specific lesions which indicated prior thrombotic microangiopathy.

We have added information to the previous renal biopsy in the Discussion and have included a new Figure 3, which shows TMA in the different organs:

“Also, in our patient there was no clue for TMA in the former history with regard to his original renal disease, in an allograft biopsy performed two years before his death, or in his family.”

13. The current fig 2 can be omitted.

If possible we would like to keep this figure as it convincingly shows the progression of brain damage within a short period of time.

Response to Reviewer 2:

1. The case presentation is well described; unfortunately, in my opinion several data are lacking: concerning the pre-transplantation period, what kidney disease was suspected, have you got histology? can we suppose that this patient present an abnormality of the alternative pathway of the complement?

We were able to retrieve very early medical files of this patient from the children’s hospital which contained a report on a renal histology: end-stage renal failure was focal segmental glomerulosclerosis.

We added this information in the Summary of the Case:

“His medical history comprised a kidney transplantation 12 years earlier for
end-stage renal failure due to focal and segmental glomerulosclerosis...”

We do not have information about complement abnormalities in this patient from the history. Complement titers were normal, when we suspected TMA. We were not able to perform a gene analysis.

We have included this information in the Summary of the Case and in the Discussion:

“Unfortunately, we could not perform thorough complement gene analysis in this short disease course. Nevertheless, C3c, C4 and CH50 complement titers were normal at the time of presentation.“

2. Concerning the post transplant period, do you have previous biopsy? does it show signs of TMA? what about the kidney function during the transplant period? and in the first day after the transplantation did you have noted datas for TMA after ciclo A introduction?

The patient had been transplanted for 12 years. A biopsy was performed two years before his death because of a moderate chronic loss of graft function showing only interstitial fibrosis and tubular atrophy but no specific lesions which indicated prior thrombotic microangiopathy.
We have added this information in the Discussion:

“Also, in our patient there was no clue for TMA in the former history with regard to his original renal disease, in an allograft biopsy performed two years before his death, or in his family.”

3. Concerning infectious tests: do you have realized HIV tests, and PCR for CMV? the presence of diarrhea and Shiga toxin?

We performed a number of virology tests, including Hepatitis C and HIV and PCR for CMV which all negative.
As diarrhoea was not present at any time we did not test for Shiga toxin.
We included these points in the Summary of the Case and in the Discussion:

“Vasculitits was further excluded by negative results for anti-nuclear antibodies, ANCA, anti-mitochondrial antibodies, anti-cardiolipin antibodies, cryoglobulins/HCV and HIV status.”
“As diarrhoea was not present at any time we did not include infectious haemolytic uremic syndrome in our differential diagnosis.”

4. Do you have looking for haematological disease such as lymphoma?

As reported in the Summary of the Case, bone marrow biopsies were performed in this patients without evidence for lymphoma. Differential blood count was not revealing. We also performed abdominal sonography without evidence of suspicious lymph masses. As the post-mortem examination did not reveal lymphoma we believe that this differential diagnosis does not need more consideration in the Summary of the Case.

5. Concerning the discussion, I'm not sure that you can conclude that ciclo A is
responsible for this presentation, due to the long period between the graft surgery and the introduction of CNI and the TMA; it would be very interesting and in my opinion necessary to analyse precisely the complement and particularly the alternative pathway of the complement... and all the cause reported with occurrence of TMA

We agree that we can not conclude that cyclosporine A was causative in this case. Therefore, we stated in our Discussion: “Nevertheless, this does not completely argue against cyclosporine A-induced vascular injury...”. In fact, TMA in association with cyclosporine A has been reported after years of cyclosporine A treatment. To make this point clearer, we have added in the Discussion:

“Onset of TMA was highly variable with 4 days to 2190 days post-transplantation, suggesting that other precipitating factors besides cyclosporine A may have been present in some patients.”

6. Minor revisions
It would be interesting to discuss about essential treatments for TMA in 2013, and particularly plasma exchanges and eculizumab, please discuss

At the end of the Discussion, we have discussed the most recent work to plasmapheresis and eculizumab and we have included two new references to this topic:

“Plasmapheresis has been the mainstay in the treatment of TMA. Improved allograft outcomes have been reported particularly with pre-emptive plasmapheresis therapy in patients with known risk for atypical haemolytic uremic syndrome. More recently, eculizumab has emerged as an efficacious therapy in such patients, either with or without plasmapheresis treatment.”
