Author's response to reviews

Title: Identical twins: one with anti-glomerular basement membrane glomerulonephritis and the other with systemic lupus erythematosus

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Author's response to reviews: see over
Dear Editor,

I am sorry to submit the revised edition so late. We also thank you for the postponements of the deadline of revision. We took too much time to contact the twins. We really appreciate your and reviewers` comments. We have revised the manuscript according to these comments. We hope that the revised manuscript is suitable for publication in BMC Nephrology.

Sincerely yours,

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For reviewer 1 (Zhao Cui)

Major revisions

1. For the first case of anti-GBM disease, since renal biopsy was not performed, the diagnosis of disease depended on the serology test alone. The detection method and result should be described in more detail with fluorescent figure shown up, aiming to make the disease diagnosis more reliable.

Reply

We rechecked the detection method of anti-GBM antibody and found that we made the mistake. We used enzyme immunoassays (ELISA, EA 1251-9601 G, EUROIMMUN Medical Laboratory Diagnostics Co., Ltd) to detect anti-GBM antibody, not multianalysis fluorescent detection. We are so sorry about the mistake. We have corrected this part. Because it is an ELISA method, we cannot provide the fluorescent figure.

2. For the second case with SLE, the medical history is too simple. The photos of malar erythema should be shown in the case report. Was any other system affected on the time of admission, except hematologic and renal system? During the follow up for more than 2 years, did she undergo the remission and relapse course of SLE? What were her clinical features and treatment during this period? Did she get renal involvement later on and was there any biopsy performed to her? How about the immunological system? Did she present anti-dsDNA antibodies and lower complement during the disease course? Since the
coexistence of SLE and anti-GBM disease has been reported, did this case present anti-GBM disease as well?

Reply

Thanks for your advice. We added many data about the second patient including follow-up and detailed treatment. Unfortunately, we did not take photos of malar erythema when the lesions were obvious. Recently we contacted the patient. However, her malar erythema almost disappeared. Therefore, we cannot provide this photo. This patient showed positive ANA and Smith antibody, arthralgia and malar erythema, based on which, lupus can be diagnosed.

The second patient only presented symptom and sign of skin and joint without evidence of involvement of other organs. During the next two years, this patient experienced relapse of malar erythema with mild lowered serum C3. Anti-dsDNA antibody had been still negative.

During follow-up, the patient has not shown any evidence of renal injury and serum anti-GBM antibody has been in normal range.

All above has been added in the revised manuscript.

3. The authors mentioned that the environment may be the reason for the twins to have different types of autoimmune disease. It should be discussed further. Did they live in the same environment? Have the common environmental etiologies for anti-GBM disease and SLE been detected for them? What are the results and the suggestion?
Reply

These twins lived in the same environment. However, they developed to 2 distinct diseases respectively. It is hard to figure out the triggering step. We discussed the relationship between lupus and anti-GBM glomerulonephritis. We guess that some unknown factors triggered the differentiation. Unfortunately, we cannot figure them out till now.

For reviewer 2 (Masayuki Iyoda)

Minor revision

1. What kinds of epigenetic factors are suggested in previous papers in anti-GBM glomerulonephritis and SLE?

Reply

Thanks for your advice. In fact, there are many epigenetic factors suggested to play an important role in pathogenesis of lupus. However, there are few studies of anti-GBM glomerulonephritis in this field. We briefly discussed the epigenetic role in the revision.

2. You should cite Li's paper in Scand J Rheumatol (Li CH et al. Scand J Rheumatol 2006 May;35(3):201-8) that also indicates the relationship between anti-GBM glomerulonephritis and SLE in Chinese patients.

Reply
3. Please give us more information about how important HLA-DRB1*1501 is in the development of anti-GBM glomerulonephritis and SLE.

Reply

We have revised these part and added the information about the function of HLA-DRB1*1501 as below.

Human leukocyte antigen (HLA), which plays an important role in immune responses, consists of the class I and class II molecules. Class II molecules are required for the presentation of antigens to T cell receptors and contribute to the production of specific antibodies. Genetic defects in self-tolerance can be triggered by reduced or altered expression of HLA molecules, which may aggravate the progression of different autoimmune diseases[9]. Genes in the HLA complex are among the strongest predisposing genetic factors. HLA-DRB1*1501 has been associated with susceptibility to anti-GBM disease. The frequency of HLA-DRB1*1501 in anti-GBM antibody-positive Japanese and Chinese patients was significantly higher than controls (36/88 vs 64/400, P=1.597×10^{-7}, in China) [10, 11]. HLA-DRB1*1501 alleles were also significant risk factors for SLE [9, 12]. DRB1*1501/DQB1*0602 was identified as one of three
microsatellite-inferred risk haplotypes in European lupus families[13]. HLA-DRB1*1501 allele are strongly associated with multiple sclerosis in African-American[14]. The mechanism underlying HLA association with autoimmune diseases is not clearly understood until now.

4. Citation is needed for the statement in Page 9 Lines 14-15 ‘The concordance rate of lupus in identical twins is greater than in the general population, but it is still incomplete.’

Reply

We have added the references of this sentence as below.

The concordance rate of lupus in identical twins is greater than in the general population, but it is still incomplete [21-23].
