Reply to the comments on manuscript (NO.: 61330, Case Report) " Systemic Lupus Erythematosus Combined with Primary Hyperfibrinolysis and Protein C and Protein S Deficiency：A case report”

Dear Mr. Ma:

Thank you very much for your reply of our manuscript, NO.: 61330, Case Report, entitled " Systemic Lupus Erythematosus Combined with Primary Hyperfibrinolysis and Protein C and Protein S Deficiency：A case report”. Thanks for the reviewer's comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our paper. We have studied the reviewer's comments carefully and have made corrections which we hope to meet with your approval. We are sending the revised manuscript according to the comments of the reviewer. Revised portion are underlined in red.

For Reviewer #1's comments，our replies are as follows.

Comment 1.1: I understand that the patient had secondary protein S and C deficiency due to SLE. Thus, what kind of autoantibodies are responsible for this issue? Please clarify and if possible, sequential changes of the titer of such autoantibodies after immunosuppressive treatment.

Reply 1.1：

We added the changes of PS, PC, AT-III, ANA, dsDNA, ACL, aβ2GPI, C3 and C4 at 3 months, 7months and 10 months of treatment in “OUTCOME AND FOLLOW-UP” part of the revised manuscript on page 7, line 12. We Added the following contents: “After 3 months of systematic treatment of SLE, the amount of pleural effusion decreased but Fib did not improve with no bleeding events. PS, PC, AT-III, dsDNA, ACL and aβ2GPI returned to normal with ANA 1:100 and C3 and C4 slightly decreased at 3 months, 7 months and 10 months of treatment.”

While the PS, PC returned to normal, ACL and aβ2GPI was normal at the same time, after 3 months of immunosuppressive treatment of SLE. ACL and aβ2GPI maybe responsible for PS and PC deficiency. We have explained the mechanism of how APL affect PC in the following paragraph. If we could retest the autoantibodies earlier at 1 months or 2 months after immunosuppressive treatment, we might be better to see the sequential changes of the titer of the autoantibodies. More clinical and basic trials are needed to verify the association between PC, PS and APL in patients with SLE. We added the reason in "DISCUSSION" part of the revised manuscript on page 9, line 18. We Added the following contents:"We considered a diagnosis of acquired PC and PS deficiency, and the decline of PC and PS might be related to ACL and aβ2GPI due to PC, PS, ACL and aβ2GPI all returned to normal after 3 months of systematic immunosuppressive treatment of SLE."

Comment 1.2: Extensive literature search regarding similar cases should be needed. Then, in-more-depth discussion should be needed.

Reply 1.2：

We added more literature regarding similar cases of PS and PC deficiency in patients with SLE and did the disucussion in "DISCUSSION" part of the revised manuscript on page 10, line 8. We Added the following contents and 9 references:"In N. Belfeki 's study, APL were positive in 32.1% patients with SLE (LA 16.9%，ACL 13.2%，aβ2GPI 7.5%) and PS deficiency was noted in 32.1% patients with SLE. PC deficiency and acquired APCA showed no significant difference between the SLE patients and controls[18]. A case of SLE presenting with positive APL, acquired APCR and autoimmune hemolytic anemia was reported[19]. However, in Giuseppe A. Ramirez's study, anti-PC are associated with APCR in patients with SLE, independently of aPL[20]. Studies showed an association between reduced PS levels and APL in patients with SLE[21,22], but another study found no association of decreased PS levels and ACL[23]. Two

cases of PS deficiency in patients with SLE with no APL was reported[24,25]. The PS deficiency was possibly aggravated by the presence of C4b-binding protein which may increase in SLE and result in a decrease in free PS levels in one case[24], and was caused by oral anticoagulant therapy or deep vein thrombosis in another case[25]. The results of studies of associations of deficiencies in PC, PS and APL in patients with SLE were conflicting[26]. More clinical and basic trials are needed to verify the association between PC, PS and APL, and explore more mechanisms of PC and PS deficiency in patients with SLE except for the influence of APL."

We didn't find any cases of primary hyperfibrinolysis in patients with SLE, and had explained that hyperfibrinogenemia and impaired fibrinolysis were existed in patient with SLE and pointed the contradiction of this case in manuscript.

The language of the manuscript has been polished. We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper and were marked in red in revised paper. We appreciate for Editors and Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Yan-fei Guo