[Manuscript NO: 68480]

Subject: Submission of revised paper Anticoagulant treatment for pulmonary embolism in patient with cerebral hemorrhage secondary to mechanical thrombectomy: A case report

Dear Editor:

Thanks very much for taking your time to review our manuscript [Manuscript NO: 68480] and allow us to resubmit a revised copy of the manuscript. We really appreciate all your comments and suggestions! These suggestions have enabled us to improve our work. We have carefully reviewed the comments and revised the manuscript accordingly, and the changes we have made are highlighted with yellow background in the marked revised manuscript. The following part is the point-by-point responses to the editor.

Furthermore, we have revised the format of the abbreviations by checking the entire manuscript and provided the original and decomposable figures, organize them into a single PowerPoint file, and add the PMID and DOI in the reference list to meet your direct publishing needs. We hope you will find this revised version satisfactory and be very grateful if the manuscript could be published in World Journal of Clinical Cases.

Yours sincerely,

Dr. Zhou

To question 1: Please correct grammatical errors - few examples as below - Abstract - mixed aphasia of 2.5 hours duration. According to her continuous follow-up brain computed tomography (CT), we observed changes in cerebral hemorrhage - we observed changes in cerebral hemorrhage on serial monitoring of brain computed tomography (CT) Case presentation - 2 months instead of 2 mo.

Response: Thank you for the grammatical suggestions, and we have carefully and thoroughly checked the manuscript throughout and also revised the grammatical errors according to the reviewer's comments.

Abstract - According to her continuous follow-up brain computed tomography (CT), we observed changes in cerebral hemorrhage - we observed changes in cerebral hemorrhage on serial monitoring of brain computed tomography (CT) and adjusted the dose of anticoagulant drugs. (Line 14-15, page 3).

Part of the grammatical errors is automatically generated by the F6 publishing system and cannot be modified by itself - few examples as below - 1. Abstract - mixed aphasia of 2.5 h; 2. Abstract - 3 wk-3

weeks; 3. Case presentation - 2 mo; 4. Case presentation - 2.5 h; 5. Outcome and follow-up - 6 months.

To question 2: Is there any family history in particular of clotting disorders.

Response: Thank you for the suggestion. We have verified that this patient has no relevant family history in particular of clotting disorders, and it has been added to our manuscript (Line 8, page 5).

To question 3: Laboratory examination - I see that hypercoagulable workup was done - please mention the results of Factor V Leiden, Prothrombin gene mutation as well as B2 glycoprotein antibodies which is done as a part of hypercoagulable workup.

Response: Thank you for underlining this deficiency. After verification, we found that the patient's factor V Leiden, Prothrombin gene mutation as well as anti-β2-glycoprotein-1 antibodies were within normal limits, and it has been stated in the manuscript (Line 22-24, page 5).

To question 4: Was the patient discharged on oral anticoagulation - as cerebral hemorrhage resolved.

Response: Thank you very much for raising this point. The effect of

anticoagulation therapy on patients in the hospital is good. Continuous follow-up brain CT shows no new evidence of cerebral infarction or hemorrhage, and her neurological and respiratory symptoms are significantly improved. In order to facilitate patient treatment outside the hospital, she was discharged to an oral anticoagulant, namely warfarin, and no recurrence of cerebral infarction or cerebral hemorrhage was found after 6 months of follow-up (Line 15-17, page 7).

To question 5: Role of IVC Filter in these settings.

Response: Thanks for your great suggestion on improving the accessibility of our manuscript. Ultrasound of the patient's lower extremity revealed the left muscle calf venous thrombosis (MCVT), so we considered the possibility of MCVT fall off and cause PE and cerebral embolism[1,2]. Although there is no strong evidence-based medical evidence to guide MCVT standardized treatment, we still recommend the use of inferior vena cava filters (IVCF) to prevent PE again[3,4]. Because the patient's family refused, we did not carry out IVCF (Line 12-27, page 8).

To question 6: What could be the cause of Cerebral embolism and pulmonary embolism at the same time in patient without any risk

factors. As this patient has Pulmonary HTN - could she have chronic PE causing pulmonary HTN.

Response: We are grateful for the suggestion. We searched the literature comprehensively and considered the patient was diagnosed with "pulmonary hypertension" in the outer hospital, we think she is likely to have pulmonary hypertension caused by chronic PE. The patient had cerebral embolism and PE, and both the venous system and arterial system were affected at the same time. Because this patient Protein C, protein S, antithrombin III, lupus anticoagulant, and factor V Leiden, Prothrombin gene mutation as well as anti-β2-glycoprotein-1 antibodies were within normal limits, we ruled out chronic pulmonary embolism caused by common causes. Therefore, the patient may be due to rare causes of the hypercoagulable state of blood and MCVT, leading to chronic PE and further pulmonary hypertension. And pulmonary hypertension may cause a short right-to-left shunt and emboli from pulmonary arteries to enter the left heart system, finally causing paradoxical cerebral embolism[5]. Although the patient's cardiac examination showed no abnormal passage between the right heart and the left heart, abnormal passages such as patent foramen ovale (PFO) may be closed or healed as the PE improves, according to the previous research[6]. This may be related to the pressure change between the

right atrium and the left atrium. The above considerations have been explained in the manuscript (Line 4-11, page 8).

REFERENCES

1. **Kret MR**, Liem TK, Mitchell EL, Landry GJ, Moneta GL. Isolated calf muscular vein thrombosis is associated with pulmonary embolism and a high incidence of additional ipsilateral and contralateral deep venous thrombosis. *Journal of vascular surgery. Venous and lymphatic disorders.* Jan 2013;1(1):33-38.[PMID:26993891 doi:10.1016/j.jvsv.2012.04.001]
2. **Su H**, Liu H, Liu J, Wang X. Elderly patients with intertrochanteric fractures after intramedullary fixation : Analysis of risk factors for calf muscular vein thrombosis. *Der Orthopade.* Apr 2018;47(4):341-346.[PMID:29556746 doi:10.1007/s00132-018-3552-5]
3. **Turner TE**, Saeed MJ, Novak E, Brown DL. Association of Inferior Vena Cava Filter Placement for Venous Thromboembolic Disease and a Contraindication to Anticoagulation With 30-Day Mortality. *JAMA network open.* Jul 6 2018;1(3):e180452.[PMID:30646021 doi:10.1001/jamanetworkopen.2018.0452]

4. **Kaufman JA**, Barnes GD, Chaer RA, Cuschieri J, Eberhardt RT, Johnson MS, Kuo WT, Murin S, Patel S, Rajasekhar A, Weinberg I, Gillespie DL. Society of Interventional Radiology Clinical Practice Guideline for Inferior Vena Cava Filters in the Treatment of Patients with Venous Thromboembolic Disease: Developed in collaboration with the American College of Cardiology, American College of Chest Physicians, American College of Surgeons Committee on Trauma, American Heart Association, Society for Vascular Surgery, and Society for Vascular Medicine. *Journal of vascular and interventional radiology : JVIR.* Oct 2020;31(10):1529-1544.[PMID:32919823 doi:10.1016/j.jvir.2020.06.014]

5. **Schäbitz WR**, Köhrmann M, Schellinger PD, Minnerup J, Fisher M. Embolic Stroke of Undetermined Source: Gateway to a New Stroke Entity? *The American journal of medicine.* Jul 2020;133(7):795-801.[PMID:32247819 doi:10.1016/j.amjmed.2020.03.005]

6. **Ryoo S**, Chung JW, Lee MJ, Kim SJ, Lee JS, Kim GM, Chung CS, Lee KH, Hong JM, Bang OY. An Approach to Working Up Cases of Embolic Stroke of Undetermined Source. *Journal of the American Heart Association.* Mar 22 2016;5(3):e002975.[PMID:27006118

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