Author’s response to reviews

Title: Mixed cerebrovascular disease in an elderly man with mixed vascular risk factors: a case report

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Author’s response to reviews:

Dear Professor Benjamin Ragen,

We have carefully considered each comment presented by the reviewers, and made the corresponding amendments. Our detailed responses to the comments are listed in red below. The newly revised contents were marked in blue in the revised manuscript. We do hope this new revision will obtain your approval and acceptance. Thank you very much for your attention and consideration. Looking forward to your decision.

Sincerely,

Dian He
Reviewer reports:

Svetlana Lorenzano (Reviewer 1): The Authors have replied satisfactorily to most comments.

In the description of the case report, the Author stated "The degree of WMH was steady at Grade II on the Fazekas scale, and the mRS score maintained at 2 during the follow-up, with a stable status of cognition", however, for the sake of completeness, it should be specified that neurocognitive tests were not performed. In any case, it is known that neurocognitive tests are able to identify also mild cognitive impairment that may be not immediately clinically apparent.

At the end of the Discussion, the Authors made some final speculations on the possible etiopathogenetic mechanisms underlying the occurrence of multiple strokes in this patient. It is generally agreed that, due to the important familiarity of cardiovascular diseases and thrombotic events, hereditary protein S deficiency probably along with some undiagnosed specific genetic alterations and uncontrolled vascular risk factors may have played an important role in the development of both thrombotic and hemorrhagic cerebrovascular events in this patient. However, during the general discussion on the potential causes underlying the mixed cerebrovascular disease, the Authors should also briefly include the hypothesis of a potential association with occult cancer. It is known that cancer is associated with hypercoagulability but also with an increased risk of bleeding. It could be also possible that alterations of the immune system associated with an impairment of coagulation system could lead not only to recurrent cerebrovascular and systemic vascular events, including hemorrhagic and ischemic strokes and DVT, but also (in particular immune system abnormalities) to cancer development that not necessarily should be immediately detectable on regular diagnostic imaging.

Thanks for the suggestions. We specified that “neurocognitive tests were not performed” in the second paragraph of “Case presentation” (Marked in blue), and replaced “with a stable status of cognition” with “with no clinically apparent cognitive impairment” in the last paragraph of “Case presentation’(Marked in blue).

We totally agreed with the speculation on the occult cancer as a possible cause. We made a detailed description regarding the discovering process of the lung cancer: He suffered hoarseness from the age of 66 years, at that time, laryngoscope was performed but no abnormality was found. About one year later, he had dry cough and received a chest CT study due to a episode of hemoptysis, a mass in the left upper lobe of lung was discovered. Subsequently, he was further
diagnosed with lung cancer and died of the disease at the age of 68 years. (See the last paragraph of “Case presentation”, marked in blue).

In Discussion, we added the speculation on the existence of occult lung cancer at the onset of stroke and discussed the possible etiological contribution via increasing hypercoagulability: Besides PSD, the patient had other risk factors for thrombophilia: hyperhomocysteinemia, and occult lung cancer that had possibly been in existence at the onset of stroke despite of the normal results of lung CT plain scans at that time. These factors, alone or in combination, can result in a hypercoagulable state, which is a recognized etiology for both venous and arterial thrombosis. (See the third paragraph in the Discussion, marked in blue).

In the fourth paragraph of Discussion, we discussed the association of cancer with risk of ICH and added a reference: Hypercholesterolemia, hyperhomocysteinemia and systemic cancer have also been identified to be clinically associated with an increased risk of ICH[7, 9, 10]. (Marked in blue in the fourth paragraph of Discussion).


In the fifth paragraph of Discussion, we summarized the possible role of the underlying occult lung cancer and discussed the association of occult cancer and immune system abnormalities, and three references were added: PSD and the underlying occult lung cancer add insult to injury by promotions of hypercoagulability, as well as alterations of the immune system associated with an impairment of coagulation system[12]. Immune system abnormalities could lead not only to recurrent cerebrovascular and systemic vascular events, including hemorrhagic and ischemic strokes and DVT[13], but also in turn, along with hypercoagulability, to the development of occult cancer[14], which is not necessarily immediately detectable on regular diagnostic imaging. (Marked in blue in the fifth paragraph of Discussion).


Mark Fisher (Reviewer 3): The authors have been responsive to the critique and the manuscript is improved. The conclusions in Abstract and Discussion regarding hemodynamic/hemorheologic stroke mechanisms are difficult to follow and appear too speculative. Please consider an alternative explanation: Hyperhomocysteinemia has shown some association with intracerebral hemorrhage clinically (https://www.ncbi.nlm.nih.gov/pubmed/29416106) and is associated with altered autoregulation experimentally (https://www.ncbi.nlm.nih.gov/pubmed/29611066). The patient's hyperhomocysteinemia was substantial, and focusing on the patient's hypertension and hyperhomocysteinemia may provide a better basis to explain the stroke syndrome.

Thanks for the suggestions. We totally agreed with the point of view. In the fourth paragraph of Discussion, we discussed the associations of hyperhomocysteinemia with the risk of ICH and the autoregulation of cerebral blood flow, and the above two references were added: Hypercholesterolemia, hyperhomocysteinemia and systemic cancer have also been identified to be clinically associated with an increased risk of ICH[7, 9, 10]. Among them, hyperhomocysteinemia has been shown to be experimentally associated with endothelial link dysfunction in the autoregulation of cerebral blood flow[11]. (Marked in blue in the fourth paragraph of Discussion).


In the Conclusion and Abstract, we removed the speculation that hemodynamic changes and hemorheologic changes could cause another stroke. We modified the last sentence of the “Case presentation” in the Abstract as follows: After excluding coagulopathy, endocarditis, atrial
fibrillation, patent foramen ovale, brain tumors, cerebral venous thrombosis, cerebral vascular malformation, cerebral amyloid angiopathy and vasculitis, hypertension, hereditary protein S deficiency, hypercholesteremia and hyperhomocysteinemia are identified as contributing etiologies in this case. (Marked in blue in the last sentence of the “Case presentation” in the Abstract).

In the Conclusion and Abstract, We redescribed the conclusions as follows: This case presents complex underlying mechanisms of mixed cerebrovascular disease, in which hypertension and hyperhomocysteinemia are considered to play a central role. (Marked in blue in the last sentence of the “Conclusion” in the Abstract and the last paragraph of the “Discussion and Conclusions”).