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. We supplemented the medical histories that were omitted in the first manuscript to avoid producing confusion, including the history of hypertension, drug use in the past, the execution time of MRI and DSA, the burden of WMH, the results of serum tumor markers and chest CT scans, and the score of the modified Rankin Scale. The revised manuscript was more readable, with full information of the case.

Our detailed responses to the comments are listed below. We do hope this 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 reported on a clinical case of a 63-year-old man, with a history of multiple deep venous thrombosis related events in the lower limbs, for which no secondary prophylaxis was taken over, and Raynaud's phenomenon in the hands. He had a 30-year history of smoking and alcohol intake (50 g/day) and also a family history of ICH which both parents died for, hypertension (three sisters), arteriopathy and thrombophilia.

The patient had a sudden onset of weakness in his right limbs followed by an episode of focal seizure. NIHSS was 2. Neuroimaging, including plain CT, DWI-, T1w-, T2w-, SWI, and Gd-enhanced MRI showed bilateral intracerebral hemorrhagic lesions in the parietal lobe and an hemorrhagic infarction in the left frontal lobe. MR-Angiography and digital subtraction angiography were normal. Routine laboratory tests showed high values of total and LDL cholesterol, homocysteine, and D-dimer and a decreased activity of plasma protein S. CSF was substantially negative. A leptomeningeal and cortical biopsy was also negative for inflammatory changes and amyloid deposition in blood vessel.

A diagnosis of mixed cerebrovascular disease (MCVD) was made. Vascular risk factors were taken under control with secondary prevention treatments. In particular, warfarin was prescribed for the DVT prophylaxis but it was unsuccessful due to the scarce patient compliance with consequent occurrence of recurrent DVT events during the five-year follow-up. The patient died at the age of 68 years for lung cancer.

The clinical case is interesting also because the patient underwent to extensive diagnostic work-up and was followed-up for long time. However, there are some observations as follows:

1. It is not clear if the patients was taking some medications prior to the index stroke, and if so, which medications.

Thanks for the suggestions. At the time when the patient had the first-lifetime symptomatic DVT in the left lower limb, he received 3-month warfarin therapy. Since then no secondary prophylaxis was applied, as a result, he experienced multiple recurrences of lower limb DVT. He had a five-year history of hypertension, but with no antihypertensive therapy.

We added these past medical histories in the revised manuscript (See the fist paragraph in the “Case presentation”).
2. It is not possible to fully evaluate the extent of the white matter hyperintensity (WMH) based on the slices of neuroimaging reported in the Figure. The Authors should provide at least a visual (if semi- or quantitative assessment is not possible) assessment of the WMH, for example by using the Fazekas or modified Fazekas scale, possibly performed on FLAIR imaging.

Thanks for the suggestions. The degree of white matter hyperintensity (WMH) was moderate (Grade II on the Fazekas scale). We added the grade of WMH in the revised manuscript (See the third paragraph in the “Case presentation”).

3. It should be specified whether neurocognitive tests were performed and the patient was also followed-up for these aspects?

Thanks for the suggestions. Neurocognitive tests were not performed since the patient had no complaints and signs of cognitive impairment after the onset of strokes, even during follow-up. We added this in the second paragraph and last paragraph of “Case presentation”.

4. Was specific tests for detecting potential viral, bacterial or fungal infection performed on peripheral blood and CSF?

Thanks for the suggestions. The results of CSF analysis were described in the third paragraph of “Case presentation” in the manuscript: The results of cerebrospinal fluid analysis were within normal limits. We added additional descriptions regarding infections: with no evidence on viral, bacterial or fungal infections (See the third paragraph of “Case presentation” in the revised manuscript).

5. The Authors should clarify after how many days from the onset of index strokes, anticoagulant treatment was started and the reason why the patients continued to be treated with warfarin despite his scarce compliance and he was not switched to one of the direct oral anticoagulants.

Thanks for the suggestions. We added the start time of warfarin treatment in the revised manuscript. We added the therapeutic schedule after the failure to adhere to warfarin treatment (See the last paragraph of “Case presentation” in the revised manuscript): Warfarin was
administered as secondary prophylaxis for venous thromboembolism two months after the onset of strokes, however, he did not adhere to the schemes of monitoring of blood coagulation function. So antiplatelet therapy with clopidogrel was given as an alternative due to his refusal to other oral anticoagulants.

6. Was folic acid used in combination with vitamin B12 for the treatment of hyperhomocysteinemia?

Thanks for the suggestions. Yes, the patient received a combination therapy with folic acid and vitamin B12. We described the specific drugs for lowering homocysteine in the last paragraph of “Case presentation” in the revised manuscript: Following treatments with antihypertensive drugs, folic acid, vitamin B12 and statins, the levels of blood pressure, serum homocysteine and cholesterol were controlled in the normal range.

7. Were some genetic tests performed, for example for MTHFR, given the high levels of homocysteine, or Fabry disease, also considering the potential impairment of renal function (serum creatinine at admission 152.18 micromol/L), or NOTCH3 for CADASIL, despite the fact that the extent and degree of WMH is not clear, or other specific test?

Thanks for the suggestions. Genetic tests for hyperhomocysteinemia, Fabry disease and CADASIL were not done. During the disease course, hyperhomocysteinemia in this case was not considered hereditary because a normal level of homocysteine was persistently observed after long-time discontinuation of folic acid and vitamin B12. The occurrence of impairment of renal function was probably related with uncontrolled hypertension. A diagnosis of CADASIL was less likely due to a lack of cerebral microbleeds on the follow-up SWI and the moderate degree of WMH, which was steady at Grade II on the Fazekas scale during the follow-up.

We added the follow-up findings of WMH on FLAIR imaging in the last paragraph of “Case presentation” in the revised manuscript.

8. The Authors should clarify if the patients recovered from the index strokes and report the modified Rankin Scale score at discharge and at follow-up.
Thanks for the suggestions. We added the modified Rankin Scale score at discharge and at follow-up. The mRS score was 2 at discharge and maintained at 2 during the follow-up.

9. Patient died after 5 years of lung cancer. It is not known if the lung cancer was already starting at the time of the index stroke occurrence. Did the Authors think about the possibility that the index strokes were related to a non-classic "paraneoplastic" syndrome? It is known that cancer is associated with hypercoagulability but also with an increased risk of bleeding. It could be also possible that this patients had an impairment of immune system; in fact, he had a history of Raynaud's phenomenon in his hands which could be potentially even a sign of a paraneoplastic syndrome in some cases. Alterations of the immune system associated with an impairment of coagulation system could have led 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. The Authors should elaborate on this other potential hypothesis on the etiopathogenesis of the index strokes.

Thanks for the suggestions. Chest CT scans and screening of serum tumor markers were performed after admission to hospital for excluding brain metastatic tumor. The results showed no lesion in the lung, and serum tumor markers were negative. Four years after the onset of strokes, the patient received a chest CT examination. The result revealed a nodule in the superior lobe of left lung. Moreover, brain MRI was performed repeatedly during follow-up, brain tumor could be excluded based on the results. Thus, it was unlikely that the brain lesions and the Raynaud's phenomenon were associated with lung cancer. After all, the emergence of Raynaud's phenomenon in his hands was not frequent. This more likely to be attributable to protein S deficiency due to the involvement of impaired fibrinolysis in the pathogenesis of Raynaud's phenomenon by predisposing towards fibrin deposition and vascular obstruction.

We added the above information and made in-depth discussions regarding Raynaud's phenomenon in the revised manuscript.

Georgios Tsivgoulis (Reviewer 2): The coexistence of multiple cerebral infarcts and parenchymal hemorrhages is an expected manifestation in patients with occult cancer. Therefore the novelty of the present case report and presented figures is very limited.

Thanks for the comments. Indeed, an association between strokes and cancer should be suspected. However, chest CT scans and screening of serum tumor markers were performed after admission, and no abnormalities were found. Lung cancer was found four years after the onset of
strokes. Pathological results of the brain lesion biopsy and follow-up MRI excluded brain metastatic tumor. There was no evidence to show an association between strokes and lung cancer in this case.

Mark Fisher (Reviewer 3): The manuscript describes an interesting patient with mixed cerebrovascular disease, with concurrent ischemic and hemorrhagic processes. The manuscript would benefit by some additional information: The history strongly suggests cerebral venous thrombosis, with recurrent peripheral DVT, low protein S, hyperhomocysteinemia, and family history of thrombophilia. Perhaps this is cerebral venous thrombosis with negative MRV? It would be helpful to see examples of the cerebral venous imaging studies, including MRV and venous imaging if obtained with DSA, in order to demonstrate convincingly that venous thrombosis was ruled-out. Was the MRV performed with contrast? When was MRV performed in relation to the patient's presentation? Could there have been venous thrombosis that cleared spontaneously by the time that imaging studies were performed?

Thanks for the suggestions. Regarding brain MRA and MRV, they were performed on the day of the onset of strokes, with no contrast. Venous thrombosis could be ruled out by the DSA examination, which was done on the second day after onset of strokes. The results showed no abnormality in arterial phase, venous phase and venous sinus phase. From the perspective of strokes, the lesions were located in different distributions of veins, so it was unlikely that thrombosis occurred in several veins simultaneously.

We added the execution time of these examination in the revised manuscript.