Reviewer's report

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

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Reviewer: Svetlana Lorenzano

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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.
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.

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

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

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.

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

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?

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.

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.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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Not relevant to this manuscript

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Dr. Svetlana Lorenzano served as expert consultant for Boehringer Ingelheim from 2013 to 2014; she received two travel grants from Boehringer Ingelheim (one in 2016 one in 2017), one travel grant from Bayer (2014), Quintiles IMS (2017), Daichii Sankyo (in 2017).

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