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LETTER TO THE EDITORS

Thrombus hallmarks reveal atherothrombotic stroke aetiology

A. Semerano[1,2] · A. Genchi[1,2] · M. Callea[4] · F. Sanvito[4] · F. Simionato[3] · P. Panni[3] · F. Scomazzoni[3] · C. Doglioni[4] · G. Comi[2] · A. Falini[3] · M. Filippi[2] · L. Roveri[2] · Marco Bacigaluppi[1,2]

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Dear Sirs,

The occlusion of a large cerebral vessel can derive from various sources such as cardiac embolism, atheroembolism, local cerebral arterial thrombosis or paradox embolism. Establishing the aetiology of stroke is relevant for secondary stroke prevention. Unfortunately up to a third of ischemic strokes remain classified as cryptogenic, despite extensive clinical workup [1, 2]. Since the recent approval of mechanical thrombectomy, cerebral thrombotic material has become a valuable clinical specimen. While research studies are thriving about quantitative rates of main thrombus components as the signature of aetiology, qualitative histopathological examination remains an invaluable tool in the diagnostic workup [3]. We here report a case of acute middle cerebral artery (MCA) stroke treated with an endovascular procedure, in which histological analysis of the thrombus allowed the aetiological definition.

An 86-year-old man with a history of arterial hypertension was admitted to our emergency department for left-sided weakness that had started 1.5 h before. On admission, he presented mutism and moderate left-sided hemiparesis (NIHSS15). A non-contrast brain computed tomography (CT) scan showed moderate leukoaraiosis without signs of acute ischemia, or vascular hyperdensities. Multiphase computed tomography angiography (CTA) revealed a focal occlusion in the distal M1 segment of the right MCA (Fig. 1a, b, c). Thrombolytic treatment (0.6 mg/kg) with rtPA was started at 2.5 h from onset and the patient was transferred to the angiography suite for mechanical thrombectomy. An aspiration catheter was navigated to the proximal occlusion site, but two aspiration attempts resulted unsuccessfully. A 6 × 20-mm Solitaire FR stent retrieval system was then deployed within the distal right M1 MCA trunk, and finally, aspiration and stent retrieval performed simultaneously, achieved complete recanalization (TICI 3) at 5 h from onset (Fig. 1d). A single solid thrombus, brilliant yellow with a focal red spot, measuring 0.9 × 0.2 × 0.2 cm, was retrieved and immediately fixed in formaldehyde for paraffin embedding (Fig. 2a). Histopathological findings were consistent with atherosclerotic plaque characterized by an intima layer filled with foamy macrophages, scattered lymphocytes, extracellular matrix, smooth muscle cells, cholesterol clefts, focal hemorrhage and outer fibrin cap (Fig. 2b–f). Further, cardiac diagnostic workup did not reveal other concomitant aetiologies, so that the stroke was classified as atherothrombotic, and antiplatelet therapy started.

In the investigation of stroke aetiology, the difficulty to unequivocally differentiate occlusions due to intracranial atherosclerosis from those related to embolism is noteworthy [4, 5]. A local thrombosis superimposed on an intracranial atherosclerotic plaque as documented by histology (high amount of inflammatory macrophages, yellow colour, intraplaque haemorrhage [6]) represents the most likely stroke mechanism in our patient, rather than an athero-embolic aetiology. This is supported by the paucity of atherosclerotic alterations in the aortic arch and cervical vessels, by the angiographic characteristics of the cerebral vessel showing a focal truncal-type occlusion with distal anterograde repermeability [5], as well as by mechanical thrombectomy refractoriness [7–9]. An embolus superimposed on a local atherosclerotic plaque is, moreover, rather unlikely, due to the cohesion of the single retrieved thrombus and the negative cardiac investigations.

Recent histopathologic studies quantifying thrombus components showed, on large patient cohorts, that

✉ Marco Bacigaluppi
bacigaluppi.marco@hsr.it

1 Neuroimmunology Unit, Institute of Experimental Neurology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

2 Stroke Unit, Department of Neurology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

3 Department of Neuroradiology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

4 Department of Pathology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

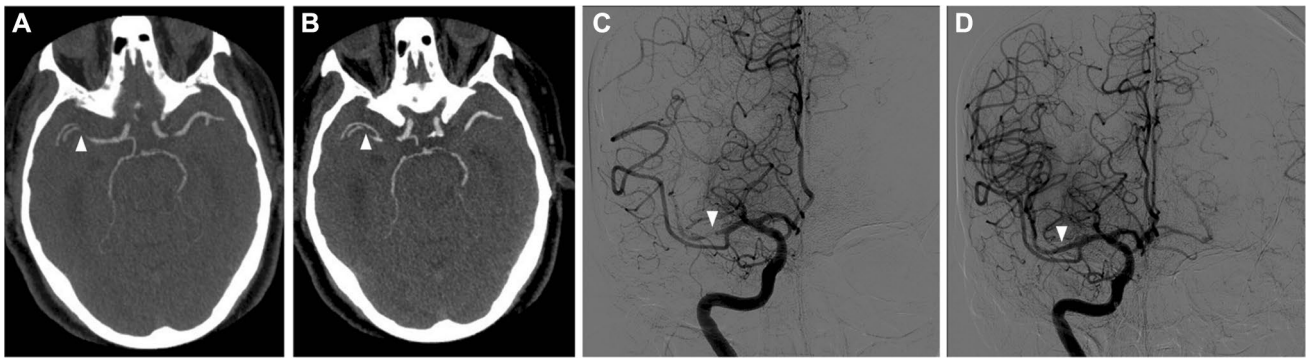

Fig. 1 **a b** Multiphase brain CTA showing a 5-mm-long focal occlusion of M1 segment (white arrowhead) of the right middle cerebral artery, after the release of the anterior temporal artery (ATA) just before the bifurcation. **c** First angiographic series, by catheterization of the right internal carotid artery, confirming the occlusion site (white arrowhead) and **d** final angiographic series showing complete recanalization (TICI3) at the end of the endovascular procedure (white arrowhead)

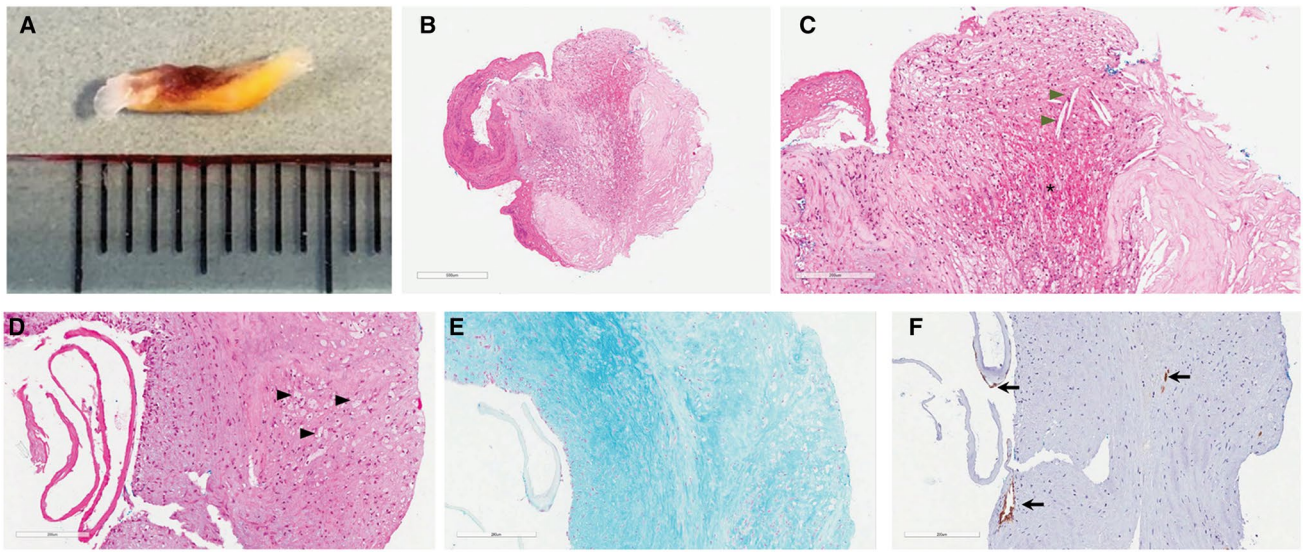

Fig. 2 **a** Thrombus gross appearance immediately after retrieval. **b–f** Representative sections of the specimens stained by haematoxylin and eosin (**b–d**), by Alcian blue (**e**) or immunostained with anti-CD34 antibody (**f**). **b–d** Fragments are represented mainly by numerous foamy macrophages (black arrowheads) and scattered lymphocytes interspersed within fibrin, extracellular matrix and cholesterol clefts (green arrowheads), with an area of focal hemorrhage (asterisk). **e, f** Scattered foamy macrophages embedded within the extracellular matrix (Alcian blue in **e**) with an accumulation of smooth muscle cells; intima layer is lined by endothelial cells (CD34-positive staining, arrows). Scale bar in **a** 12 mm, **b** 500 µm; **c–f** 200 µm

cardioembolic thrombi encompass higher proportions of fibrin to platelet ratio and lower proportions of red blood cells compared to non-cardioembolic thrombi [10–12]. Unfortunately, the predictive value of these quantifications in determining the single thrombus aetiology remains undefined, and still cannot classify single patients. Dissimilarly, in selected cases, qualitative analysis of thrombus characteristics might be straightforward. A recent report also underscored thrombus analysis as decisive in understanding the origin of embolization, in that case, amenable to an aortic wall fragment after transcatheter aortic valve implantation [3].

In conclusion, we here highlight that ordinary histological investigation should always be attempted on cerebral thrombi since in certain cases it can be of support to reveal stroke aetiology.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards Patients' consent to analyse, process clinical data and images and to publish anonymous data was obtained.

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