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COVID-19

Carotid free-floating thrombus in COVID-19: a cerebrovascular disorder of cytokine storm-related immunothrombosis

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Abstract

Backgrounds Several neurological manifestations, including stroke, have been reported in COVID-19 patients. The putative role of the COVID-19-related hyperinflammatory state in cerebrovascular disorders remains unclear.

Methods From March 2020 to September 2021, we searched for patients who exhibited an ischemic stroke related to carotid free-floating thrombus (CFFT) to investigate its incidence and relationship with COVID-19.

Results Of 853 ischemic strokes referred to our Stroke Centre during the study period, 5.7% ($n=49$) were positive for SARS-CoV-2. Six had CFFT, of which two tested positive for SARS-CoV-2 (2/49 = 4.1%), and four did not (4/802 = 0.5%). The former were two middle-aged men suffering from COVID-19 pneumonia. Floating thrombi were promptly extracted by endarterectomy and endovascular thrombectomy, respectively, with no early and long-term complications. Notably, our COVID-19 patients exhibited little or no atherosclerosis burden on CT angiography, markedly elevated D-dimer levels, and extensive thrombus length.

Conclusions COVID-19-induced immunothrombosis possibly played a significant pathogenic role in CFFT.

Keywords Ischemic stroke · Treatment · Atherosclerosis · Inflammation · SARS-CoV-2

Introduction

COVID-19 is a pandemic disease caused by SARS-CoV-2, which encompasses a broad spectrum of severity and clinical manifestations. Severe cases have been associated with an exaggerated systemic inflammatory state, namely cytokine storm, which may lead to multi-organ failure in a subset of patients [1]. Several neurological manifestations have been reported in COVID-19 patients, including encephalopathy and stroke [2]. While overwhelming evidence supports a putative role of the hyperinflammatory state in the former [1, 3–6], such relationship has remained less clear in cerebrovascular disorders. Notably, COVID-19 may result in a distinctive hypercoagulable condition characterized by elevated fibrin degradation products, such as D-dimer, yet relatively normal fibrinogen levels, coupled with endothelial dysfunction [7]. The complex interplay of these pathological alterations and inflammation is defined as immunothrombosis and is arguably accountable for the micro- and macrothrombotic manifestations frequently observed in COVID-19 patients [7, 8].

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Carotid free-floating thrombus (CFFT) is a rare cause of stroke, characterized by a thrombus attached to the carotid wall with the surrounding flow at its distal part. Here, we describe COVID-19 and non-COVID-19 patients with CFFT and investigate the pathogenetic role of immunothrombosis in this rare condition.

Methods

Data for these case reports were collected at the comprehensive Stroke Center, Maggiore Hospital, Bologna, Italy. From March 2020 to September 2021 (18 months), we searched for patients who exhibited an ischemic stroke related to CFFT to investigate its incidence and relationship with COVID-19. Patients who exhibited ischemic stroke related to CFFT were identified retrospectively (from March 2020 to February 2021) and prospectively (from March 2021 to September 2021). CFFT was defined as a mobile thrombus attached to the carotid wall with a complete circumferential blood flow at its end, confirmed by both CT angiography (CTA) and cervical duplex ultrasound.

Results

Collectively, 853 ischemic stroke patients were admitted to our Stroke Unit during the study period, of whom 5.7% ($n = 49$) had SARS-CoV-2 infection confirmed by molecular assays on a nasopharyngeal swab. Six cases affected by CFFT were found, among whom two patients tested positive for SARS-CoV-2 (2/49 = 4.1%) and four did not (4/802 = 0.5%). Both SARS-CoV-2-positive patients were not vaccinated.

Case report 1

A 50-year-old man presented with a sudden-onset left sensorimotor syndrome. Medical history was relevant for arterial hypertension, hypercholesterolemia, obesity, and a 1-week history of fever and cough related to SARS-CoV-2 infection. Neurological examination revealed left-sided hemianopia, hemianesthesia, hemiataxia, and mild hemiparesis (NIHSS = 6). CTA showed right MCA M2 occlusion and a subocclusive floating thrombus at the origin of the right internal carotid artery (ICA), extending within the vessels for 53 mm (Fig. 1). Since a large right frontoparietal ischemic core was already evident at the non-contrast head CT (ASPECTS = 6), no reperfusion strategies were attempted. Nonetheless, considering the high risk of stroke recurrence, an emergency carotid endarterectomy was performed within a few hours as early secondary prevention. Aspirin, dexamethasone (10 mg q8h), remdesivir, and heparin (4000 IU daily) were started. Serial cervical duplex ultrasounds confirmed the resolution of the carotid thrombus. The hypercoagulable panel, 24-h Holter monitor, and echocardiogram were unremarkable. Laboratory markers of inflammation and coagulation collected during the hospital showed elevated D-dimer levels (up to > 35 mg/dL) (Table 1). After 1 week since the cerebrovascular event, COVID-19 pneumonia was resolved, and a neurological examination revealed right sensory hemineglect associated with right pyramidal signs. After 3 months, no stroke recurrence was observed, and the modified Rankin Scale (mRS) was 2.

Case report 2

A diabetic 56-year-old African man hospitalized for COVID-19 pneumonia presented with left-sided weakness on awakening. He was receiving remdesevir, intravenous dexamethasone (10 mg q8h), heparin (6000 IU daily), and low-flow

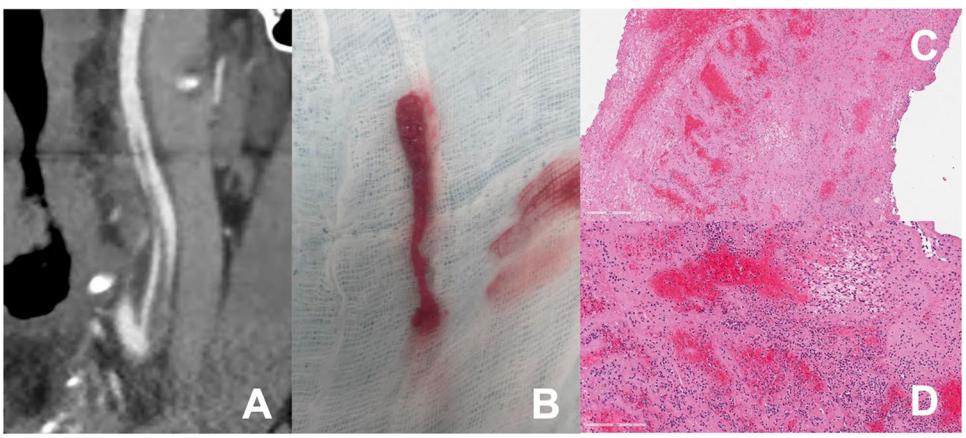

Fig. 1 Sagittal image of CT angiography reveals a long subocclusive floating thrombus at the origin of the right internal carotid artery (**A**). Macroscopic examination of the thrombus (**B**). Microscopic examination of the thrombus revealed an aggregate of fibrin, platelets, leukocytes, and erythrocytes in laminated layers that underwent organization and recanalization. Hematoxylin and eosin 100 × of magnification (**C** and **D**)

Table 1 Selected blood tests during the hospital stay

	Reference values	Patient 1			Patient 2	
		Day − 7	Day 0	Day + 10	Day 0	Day + 4
Hematology						
White-cell count (10^9/L)	3.6–10.5	4.72	16.8	9.5	4.72	3.47
Neutrophil count (10^9/L)	1.5–7.7	3.93	16.14	7.82	3.21	1.40
Lymphocyte count (10^9/L)	1.1–4	0.64	0.3	1.13	1.18	1.58
Hemoglobin (g/dL)	12.0–15.6	14.9	13.5	11.5	12.4	10.9
Platelet count (10^9/L)	160–370	148	170	427	604	514
Coagulation						
INR	< 1.2	1.01	1.1	1.04	1.08	1.06
aPTT	0.82–1.25	0.91	0.89	0.79	< 0.70	0.81
Fibrinogen (mg/dL)	150–400	542	584	533	909	515
D-dimer mg/L	< 0.55	0.79	14.05	-	12.19	> 35
Serum inflammatory proteins						
C-reactive protein (mg/dL)	< 0.5	1.54	11.16	1.16	1.59	2.41
IL-6 (pg/mL)	< 5.9	27.6	48.7	-	14.7	3.31
Procalcitonin (ng/mL)	< 0.5	0.2	0.3	< 0.1	0.2	0.1
Ferritin (ng/mL)	11–306	440	2808	694	-	-
LDH (U/L)	< 248	255	1182	480	270	253

We refer to ischemic stroke as day "0," while all data collected subsequently or precedingly as "plus day" and "minus day," respectively

oxygen therapy (Fig. 2). Neurological examination revealed dysarthria, left-sided hemianopia, sensory hemineglect, and severe hemiparesis (NIHSS = 15). Blood tests showed a dramatic increase in D-dimer level (14.05 mg/L) and a slight increase in inflammatory markers (Table 1). Multimodal CT assessment revealed a right early ischemic frontotemporal lesion with a favorable penumbra pattern. CTA showed a large vessel occlusion of the M2 segment of the right MCA and a fluctuating thrombus in the ipsilateral ICA (12 mm), partially attached to a small non-hemodynamic atherosclerotic plaque. Primary mechanic thrombectomy (contact aspiration plus stent retriever) successfully removed the fluctuating thrombus at the first attempt. Yet, endovascular recanalization of the right MCA was not achieved despite several attempts at the occlusion site; consistently, the neurological status of the patient did not significantly improve after that. The patient was treated with prophylactic heparin and aspirin. During the hospital stay, cervical duplex ultrasound confirmed the presence of a stable carotid plaque, while an extensive stroke workup, comprehensive of

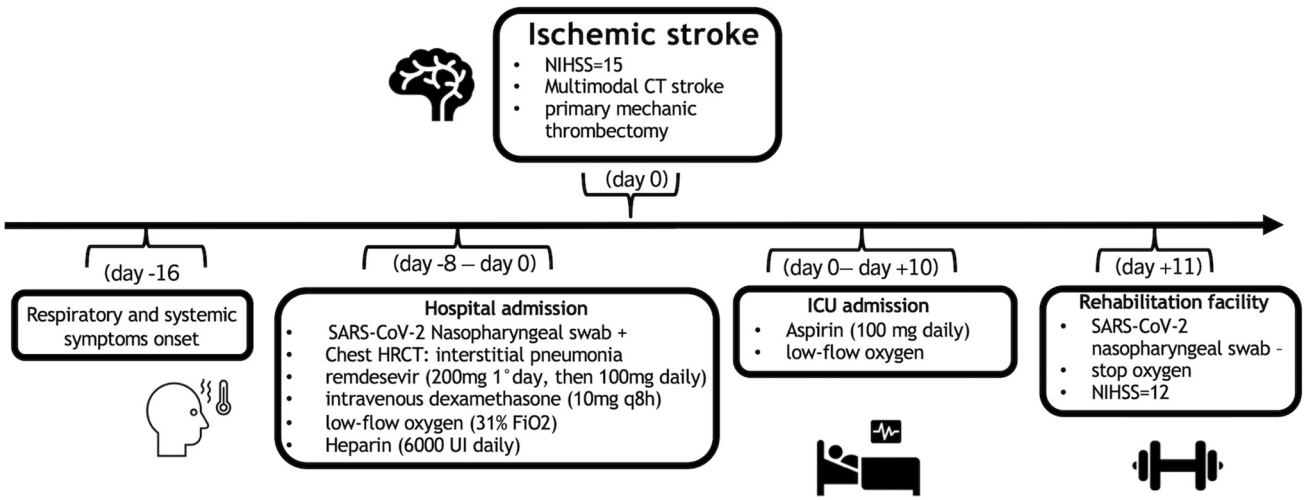

Fig. 2 Disease course in patient 2

a hypercoagulable panel, 24-h Holter monitor, and echocardiogram, was unremarkable. The patient was gradually weaned off oxygen, and 2 weeks after the stroke, COVID-19 pneumonia resolved. After 3 months, a severe neurological disability persisted (mRS = 4), yet no stroke recurrence was observed.

Case series (non-COVID-19)

Four patients presented CFFT non-concomitant with SARS-CoV-2 infection in our series (Table 2), among whom two patients were young with no significant cardiovascular risk factor. Three patients had the floating thrombus localized at the origin of the ICA, while in one patient, it was localized in the ICA cervical segment. The median thrombus length was 8 mm (range: 6–17 mm). The underlying stroke mechanism was artery-to-artery embolism in three patients and hemodynamic in one patient. As secondary prevention, three out of four patients underwent CEA.

Discussion

We described two middle-aged men with COVID-19 and related immunothrombosis who experienced ischemic stroke secondary to CFFT. Notably, comparisons between COVID-19 and non-COVID-19 patients revealed a consistently higher incidence of CFFT, as well as a tendency toward a more extensive median thrombus length and a younger age in the former group, suggesting a disease-modifying role of the SARS-CoV-2 infection.

Etiologies underlying CFFT are heterogeneous, including atherosclerosis, fibromuscular dysplasia, dissection, vasculitis, and prothrombotic conditions [9]. No evidence of carotid web or dissection was present in our patients and the hypercoagulable panels were negative, yet extensive diagnostic work-up to exclude paraneoplastic thrombophilia was not performed. Whereas our COVID-19 patients exhibited some cerebrovascular risk factors, their young age, little if no atherosclerosis burden detected on CTA, and the concomitant markedly elevated D-dimer, suggest COVID-19-induced immunothrombosis as the primary pathogenic mechanism. The term immunothrombosis defines the elaborate cross-talk between the innate immune system and coagulation system, where leucocyte activation and cytokine release promote the coagulation cascade and platelet activation [10, 11]. This has been considered an evolutionary conserved defensive response against pathogen dissemination. Yet, an exaggerated, namely maladaptive, response may lead to a pathological prothrombotic state, as in COVID-19 and other cytokine storm disorders [10, 11]. Notably, whereas patient 1 displayed elevated serum inflammatory levels, patient 2 did not. However, ferritin levels, which reflect the activation of the monocyte-macrophage system and better correlate with cytokine storm disorders, [12, 13] were not measured. Additionally, a recent systematic review investigating serum inflammatory and thrombotic markers in COVID-19 patients with thrombotic manifestations found that inflammatory markers were only modestly elevated in a subgroup of patients [14]. Likely, the cross-talk between the pro-inflammatory and pro-thrombotic actors may result in a spectrum of findings in cytokine storm disorders where the former or the latter may predominate.

In our cohort, an estimated incidence of 0.7% of CFFT among all ischemic stroke causes has been observed, in line with a recent systematic review where the reported patient-weighted frequency was 0.4–1.6% [9]. Interestingly, in a recent literature review investigating CFFT in COVID-19 patients ($n = 15$), a relatively young age at presentation (mean 59 years old) was reported, and histopathologic analysis of extracted floating thrombi revealed an organized clot with inflammatory infiltrates in the intima, in accordance with our findings [15]. Taken together, these data substantiate the concept that mild carotid atherosclerotic plaque may be susceptible to thrombus formation in the context of COVID-19-related immunothrombosis, potentially resulting in CFFT. Additionally, aortic arch mobile thrombi have been recurrently observed in COVID-19 patients with stroke, reinforcing the concept of a prothrombotic state as the underlying etiology [16, 17].

We acknowledge that the small number of incidental CFFT cases and the absence of D-dimer values in non-COVID-19 CFFT are potential limitations of our study. Additionally, the absence of pre-specified analysis to compare COVID-19 and non-COVID-19 groups, and the absence of adjustment for confounding variables do not allow for drawing definitive conclusions. Therefore, further studies are needed to corroborate this pathophysiological view.

In our patients, floating thrombi were promptly extracted by endarterectomy and endovascular thrombectomy, respectively, with no early and long-term complications. As a result of the infrequency of this condition, best management strategies, comprising both pharmacological and surgical treatment choices as well as timing, are still under debate [9].

Conclusions

Improving decision-making in CFFT will need continued parallel progress throughout underlying pathogenic mechanisms and investigation of treatment responses. Distinct populations with a higher risk of developing this uncommon cerebrovascular disorder, such as COVID-19 patients or other conditions related to immunothrombosis, may serve as a framework model to shed light on the underpinning biologics of CFFT and inform its treatment.

Table 2 Clinical and instrumental characteristics of CFFT in non-COVID-19 patients

Age, sex	Cardiovascular risk factors	NIHSS at admission	Etiological diagnostic work-up	Mechanism of stroke	Thrombus position	Thrombus length (mm)	Acute stroke treatment	Secondary prevention	Follow-up at 3 months
75 years, M	Arterial hypertension, obstructive sleep apnea	18	Standard work-up, trans-esophageal echocardiography, chest CT	Artery-to-artery embolism (right M2 occlusion)	Carotid bulb and ICA origin	9	IVT, EVT (TICI score 2a)	Aspirin + CEA	mRS = 4; no stroke recurrence
44 years, F	None	16	Standard work-up, trans-esophageal echocardiography, chest CT, hypercoagulable and vasculitis panel, serum tumor markers	Artery-to-artery embolism (left M2 occlusion)	ICA origin	6	IVT, EVT (TICI score 2b)	Aspirin	mRS = 1; no stroke recurrence
75 years, M	Arterial hypertension, dyslipidemia	9	Standard work-up, chest CT	Hemodynamic (sub-occlusive ICA stenosis + arterial hypotension)	ICA cervical segment	6	None	Aspirin + CEA	mRS = 1; no stroke recurrence
43 years, F	None	7	Standard work-up, hypercoagulable and vasculitis panel, serum tumor markers, whole-body CT with contrast and angio-CT	Artery-to-artery embolism (right M1 occlusion)	ICA origin	17	None	Aspirin + CEA	mRS = 2; no stroke recurrence

Standard work-up includes head and neck CT angiography, cervical Doppler ultrasound, trans-thoracic echocardiography, cardiac telemetry, and brain MRI

ICA internal carotid artery, *IVT* intravenous thrombolysis, *mRS* modified Rankin Scale, *EVT* endovascular treatment, *TICI* thrombolysis in cerebral infarction, *CEA* carotid endarterectomy

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Data availability The authors take full responsibility for the data, the analysis, and the interpretation of the research, and they have full access to all of the data.

Declarations

Ethics approval All investigations were carried out according to the Declaration of Helsinki.

Consent for publication All authors agreed with this final version.

Informed consent Informed consent was acquired from participants of the study.

Conflict of interest The authors declare no competing interests.

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