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BRIEF COMMUNICATION

Carotid free-floating thrombus during COVID-19 vaccine era: causality or not?

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Abstract

Carotid free-floating thrombus (FFT) is very rarely diagnosed in patients with acute ischemic stroke. It is a real clinical emergency due to the significant risk of death associated with thromboembolic complications. Herein, we present three patients with ischemic stroke caused by carotid FFT after less than 20 days from administration of mRNA vaccine BNT162b1 (Pfizer/BioNTech) for Severe Acute Respiratory Syndrome—CoronaVirus 2 (SARS-CoV-2). To our knowledge, these are the first cases reporting carotid FTT following SARS-CoV-2 vaccination.

Keywords Free-floating thrombus · SARS-CoV-2 · COVID-19 vaccine · mRNA vaccine BNT162b1 · Acute ischemic stroke

Introduction

A free-floating thrombus (FFT) is a very rare condition defined as elongated intraluminal thrombus attached to the arterial wall, which can move according to the blood flow [1].

FFT involves the cervical segment of internal carotid artery (ICA) in most cases, while the localization in common carotid artery (CCA) is unusual [2].

The reported incidence of carotid FFT (CFFT) is about 1.5% in acute ischemic stroke (AIS), affecting more commonly men in their 60 s [3].

The most common causes are atherosclerosis, complicated by ulcerated plaque, and cardioembolic disorders. Arterial dissection and hypercoagulability disorders are uncommon [4].

The carotid plaque instability can cause the complete occlusion of the vessel or distal embolism, due to plaque erosion and rupture. Crescendo transient ischemic attacks and AIS are the most frequent complications, with severe disabling symptoms and high risk of death.

Early diagnosis can reduce morbidity and mortality.

Standard stroke imaging studies, such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), and carotid duplex ultrasonography (CDUS), can detect CFFT.

Although digital subtraction angiogram (DSA) is considered the gold standard to evaluate carotid stenosis, CDUS can allow direct visualization of the "mobile thrombus" [1].

Adequate treatment entails FFT stabilization or disappearance. Lacking universal consensus on FFT management, medical treatment includes both antiplatelets and anticoagulants therapies. Surgical treatments, carotid stenting (CAS), or carotid endarterectomy (CEA) must be evaluated case by case, depending on morphological characteristics of the plaque and stenosis severity.

Herein, we present three patients with AIS and CFFT occurring less than 20 days from administration of

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mRNA vaccine BNT162b1 (Pfizer/BioNTech, BNT) for Severe Acute Respiratory Syndrome—CoronaVirus 2 (SARS-CoV-2).

Case reports

Case 1

An 85-year-old female with hypertension and a previous radio-treated breast cancer was admitted for severe headache, partial hemianopia, and mild left hemiparesis (NIHSS 4), occurring 5 days after an episode of similarly severe headache. The patient received BNT third dose 18 days before the hospitalization. Head and neck CTA showed AIS with FFT in the right ICA (Fig. 1A, B, C). CDUS after 24 h confirmed hypoechoic mobile thrombus (supplemental_Fig._2A). We started high-dose statin and antithrombotic treatment with cardioaspirin and heparin 100 UI/kg BID. After 6 days, we shifted to prophylactic heparin alone, because of hemorrhagic transformation. Twenty-day follow-up CTA demonstrated the complete FFT resolution (Fig. 1F). The patient was discharged without neurological deficits (NIHSS 0).

Case 2

A 74-year-old man with hypertension, coronary artery disease, and diabetes mellitus was admitted for the

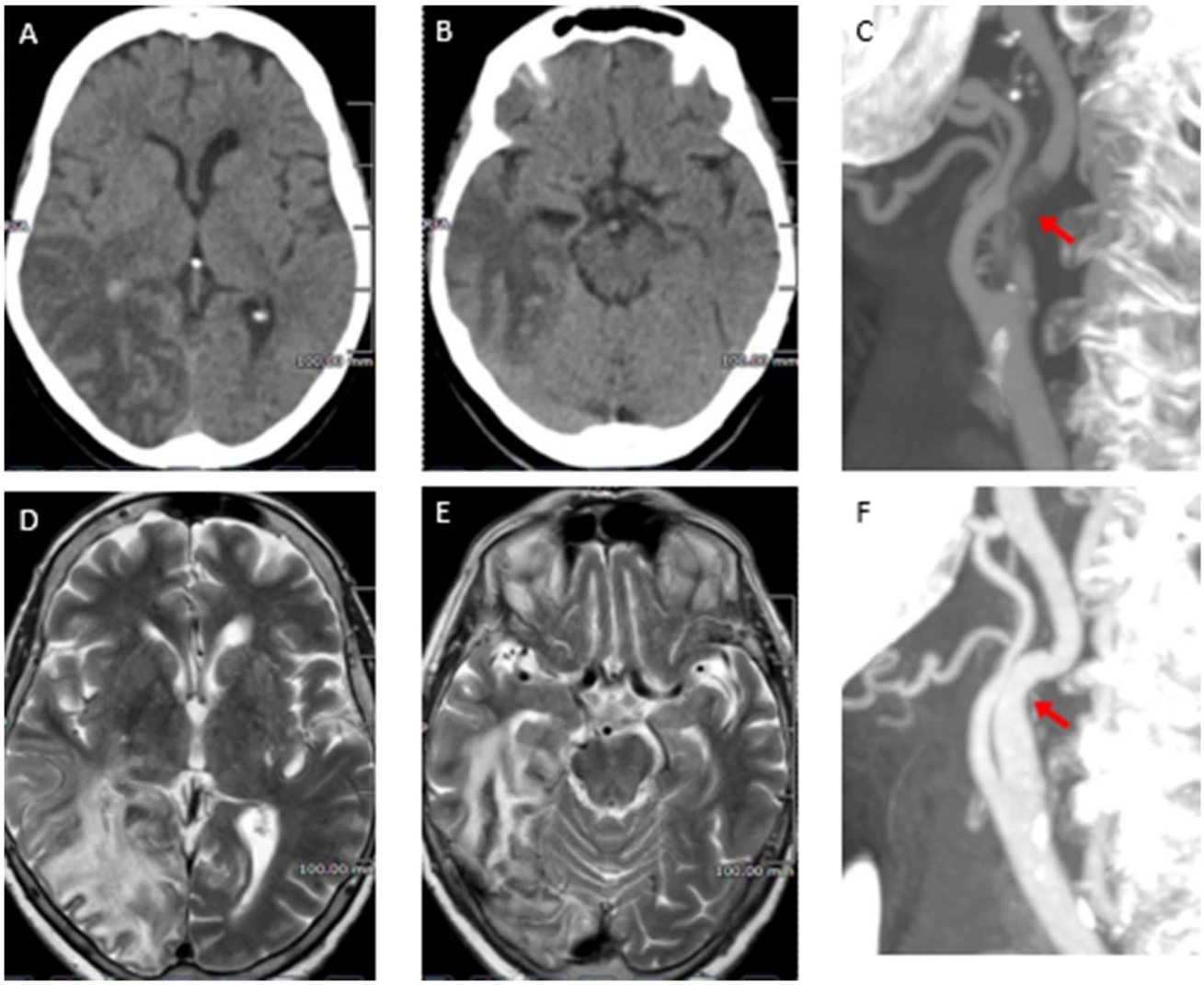

Fig. 1 *Case n. 1.* **A**, **B** Brain computed tomography (CT) revealing right occipito-temporal acute ischemic stroke (AIS). **C** Computed tomography angiography (CTA) showing a free-floating thrombus (FFT) in the right internal carotid artery (ICA) with severe plaque > 80% stenosis, measured with North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (red arrow). **D**, **E** Magnetic resonance imaging (MRI) showing stability of infarction in T2-weighted images. **F** Follow-up CTA demonstrating the complete resolution of FFT in the very same position (red arrow)

sudden onset of lethargy, global aphasia, and right hemiplegia (NIHSS 15). He received BNT first dose 10 days before stroke onset. MRA showed AIS without intracranial vessels occlusions (Fig. 2A-B). Early CDUS found FFT in the distal portion of the left CCA (supplemental_Fig._2B), confirmed by CTA (Fig. 2C). We started high-dose lipid-lowering therapy and double antiplatelet therapy (DAPT). The day after, brain MRI showed hypoperfusion in the left hemisphere, contextually with slight clinical worsening. DSA was immediately performed with carotid artery stenting (CAS) (Fig. 2D, E), showing an additional FFT in abdominal aorta, contextually. Heparin 100 UI/kg BID was started. After a week, abdomen CTA monitoring (Fig. 2F) revealed the complete FTT disappearance. The patient was discharged with dramatic neurological improvement (NIHSS 2). Three months after CAS, CDUS did not detected anomalies.

Case 3

An 87-year-old man with history of smoking, hypertension, and undefined thrombocytosis on hydroxyurea treatment was admitted for the onset of mild right hemiparesis (NIHSS 3). The patient presented the very same symptoms a few hours before, spontaneously resolved in 30 min. He received BNT third dose 20 days before stroke onset. MRA revealed AIS with hemorrhagic transformation (supplemental_Fig._1A-B). Neck CTA showed left ICA FFT (supplemental_Fig._1C-D), confirmed by CDUS (supplemental_Fig._2C-D). Recent ischemic lesions contraindicated CEA, and mild neurological deficits discouraged CAS. Hence, we started cardioaspirin and high-dose statin. Ten-day follow-up CDUS was unremarkable for changes. The patient improved (NIHSS 0) and was discharged after 2 weeks from admission with DAPT.

Data on coagulation parameters and inflammation markers are summarized for each case in Table, as Supplemental Material.

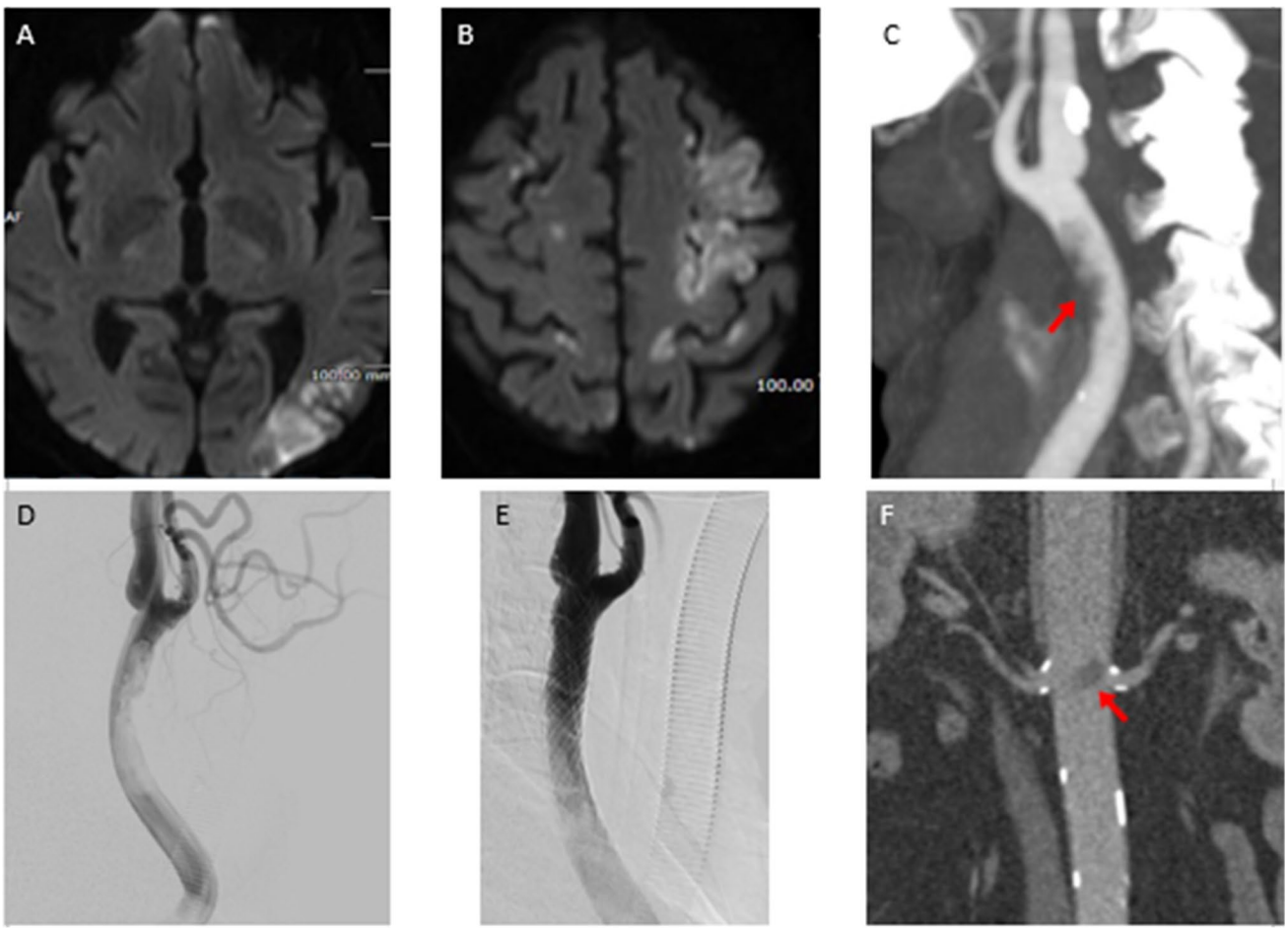

Fig. 2 *Case n. 2.* **A**, **B** MRI showing left fronto-parietal AIS on diffusion-weighted imaging (DWI). **C** CTA demonstrating hypodense plaque in left common carotid artery (CCA) with a NASCET stenosis of 70% (red arrow). **D**, **E** Digital subtraction angiography (DSA) performed after 24 h with carotid artery stenting (CAS) procedure. **F** Abdomen CTA showing additional FFT in abdominal aorta (red arrow)

Discussion

Since the beginning of the coronavirus pandemic, about 15 cases of FFT have been reported in patients with SARS-CoV-2, who manifested neurological symptoms approximately 10 days after infection [5]. However, no CFFT cases have been reported after SARS-CoV-2 vaccination.

Concerning case n.1, although the patient had cerebrovascular risk factors, none of them are closely related to FFT. However, the time elapsed from vaccine was more than 2 weeks and no adverse effects had been reported after the first two vaccine dose administrations. On the other hand, the time since vaccine dose administration was very short in case n.2, and two FFTs were found in two different sites. About case n.3, high platelet count might be related to CFFT, because hypercoagulability is one of the possible cause of FFT formation. Nevertheless, thrombocytosis was a chronic and stable condition, and therefore a correlation with vaccine dose administration could not be excluded. In addition, routine laboratory tests and procoagulant activity tests were unremarkable in all patients. Two patients received conservative medical treatment because of clinical stability, while case n.2 underwent combined medical and CAS approach with a good clinical evolution.

All patients had AIS due to CFFT, occurring within a month after BNT administration. Hence, both the timing and the absence of obvious risk factors for FFT raise the question about their correlation.

The risk of thrombotic events related to SARS-CoV-2 vaccination is extremely rare [6] and has been described after first or second dose administration of adenoviral vector-based vaccines (AVBV), related to vaccine-induced immune thrombotic thrombocytopenia (VITT) [7, 8].

However, cerebrovascular events have also been reported in association with BNT, considering multiple causal factors [9]. BNT was recently associated with arterial thromboembolism and increased risk for AIS 15–21 days after vaccination, but not with thrombocytopenia or venous thromboembolism. However, the risks of most of these events were substantially higher and more prolonged after SARS-CoV-2 infection than after vaccination in the same population [6, 10].

The underlying mechanism is still uncertain and too few cases have been described in order to understand a possible correlation between SARS-CoV-2 vaccination and such a rare pathology as FFT [10]. To date, case–control studies, comparing FFT cases with recent BNT use to controls without, have not been conducted yet. Recently, Cascio Rizzo et al. conducted a systematic review on ischemic stroke and VITT following ABVB [11]. They found a high prevalence of large intraluminal thrombi (7 patients) and FFT (3 patients) in extracranial vessels, such as the carotid artery, in the absence of underlying atherosclerotic disease, pointing out that, in addition to cerebral venous thrombosis, ABVB also appears to have a cerebral arterial thrombotic risk. Therefore, according to literature data available, an ad hoc study including FFT patients with/without recent BNT should consider also cases occurring in both ABVB-related VITT and SARS-CoV-2 infection, in order to compare baseline demographics, risk factors, clinical presentation, and any difference in prognoses and response to treatment.

Conclusion

The conditions predisposing to CFFT are very rare, and therefore the clinical management strategy and the best treatment options are still challenging.

In our cases, it is difficult to analyze the relationship between BNT and AIS because of concomitant comorbidities. Nevertheless, the short time elapsed from vaccine administration and the onset of neurological symptoms raises a strong suspicion of causal relationship.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-022-06307-1.

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Author contribution L.F., M.C., C.D., and P.L. contributed to the study design. M.C., C.D., F.Gr., and T.B. performed data collections. F.Gi., A.P., and S.L.V. performed imaging analysis. F.Gi. and R.F.M. revised the manuscript. P.L. supervised the research. L.F. and F.G. wrote the article.

Declarations

Ethics approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The paper does not report on primary research. Our analysis looked retrospectively at outcomes for a large cohort of patients treated. All data analyzed were collected as part of routine diagnosis and treatment.

Consent to participate Unfortunately, to account for the restrictive measures in place due to COVID-19, a handwritten signature is not possible. However, we obtained an audio recording of oral consent from the patient.

Consent for publication Informed consent was waived given to the retrospective anonymous collection of data, according to Italian regulations.

Conflict of interest The authors declare no competing interests.

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