

Endovascular mechanical thrombectomy in a child with COVID-19: Clot analysis reveals a novel pathway in the neuroinflammatory cascade resulting in large-vessel occlusion

Interventional Neuroradiology

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DOI: 10.1177/15910199221094758

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Abstract

Large-vessel occlusion is rare in children, but its results can be devastating and may lead to recurrent strokes, persistent neurological deficits, and decreased quality of life. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has yielded extrapulmonary effects and multiorgan diseases, many of which are neurological manifestations. There is a paucity of literature in pediatric patients about large-vessel occlusion in the setting of COVID-19 infection. We discuss a nine-year-old child who presented with a left middle cerebral artery occlusion and underwent revascularization with a Thrombolysis in Cerebral Infarction grade 3 reperfusion approximately three weeks after COVID-19 diagnosis. The patient harbored concerning signs and symptoms of multisystem inflammatory syndrome in children. This case emphasizes the importance of recognizing SARS-CoV-2 and the propensity for thrombosis in a delayed fashion, which can lead to severe stroke in young people.

Keywords

COVID-19, multisystem inflammatory syndrome in children, neutrophils, pediatrics, stroke, thrombectomy

Received 25 February 2022; final manuscript received March 24, 2022; accepted: 26 March 2022

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease commonly known as coronavirus disease 2019 (COVID-19) was initially acknowledged for its severe respiratory symptoms; however, subsequent reports of neurological manifestations, most notably venous and arterial thromboembolism manifesting in acute ischemic stroke (AIS), have come to light.^{1,2} The incidence of ischemic stroke in adult patients with COVID-19 is estimated between 1% and 3%, with a disparately elevated mortality rate at 30%.^{3,4} There have been several reports of AIS in the setting of COVID-19, including in patients younger than 50 years of age with SARS-CoV-2 infection.^{2,5} AIS is a rare event in children, occurring in 2.3 of 100,000 children;⁶ however, it can cause significant mortality, ranging from 3% to 6%, with a 70% morbidity rate.^{7,8} Furthermore, pediatric ischemic stroke attributed to COVID-19 is exceedingly rare.

The off-label use of mechanical thrombectomy in children has been widely reported and appears to be safe and efficacious in treating large-vessel occlusion (LVO).⁹⁻¹² The pathological composition of thrombus causing LVO includes neutrophils and neutrophil extracellular traps (NETs),¹³ but the composition of thrombus in the setting of pediatric LVO and COVID-19 is not well understood

and may further elucidate a different pathophysiologic mechanism in this setting.

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We report a case of a young patient with COVID-19 presenting with a left middle cerebral artery (MCA) syndrome from a left MCA M1 segment occlusion who underwent emergent revascularization via endovascular mechanical thrombectomy (EVT) three weeks after confirmed COVID-19 infection. In this report, we discuss the histopathological characteristics of the thrombus, delineating the potential differences in the setting of COVID-19.

Case report

This study was performed in compliance with Institutional Review Board (IRB) and Health Insurance Portability and Accountability Act regulations. A waiver of approval is provided by the institutional review board for single case reports. Consent for procedures, data collection, and publication was obtained based on institutional guidelines.

History and presentation

A previously healthy nine-year-old girl was infected with the SARS-CoV-2 virus during the COVID-19 pandemic; the infection was confirmed using PCR testing. She developed respiratory and constitutional symptoms that were managed with supportive care. She required no hospitalization, and her symptoms resolved within several days. Approximately three weeks after resolution of symptoms, she had witnessed onset of altered mental status, global aphasia, and right hemiplegia. She was taken emergently to a community hospital, where computed tomographic angiography demonstrated occlusion of the M1 segment of the left MCA. She was transferred to our tertiary care pediatric hospital for intervention. Her Pediatric National Institutes of Health Stroke Scale (PedNIHSS) score on presentation was 16. Upon arrival at the children's hospital, her neurological examination was unchanged. Given the LVO with persistent neurological symptoms, she was immediately referred for endovascular thrombectomy as per institutional stroke protocol.

Procedural characteristics

General endotracheal anesthesia was induced and maintained for the procedure. Using a standard Seldinger technique, right femoral arterial access was obtained, and a 5 French guide catheter was advanced into the left internal carotid artery. Angiography confirmed left M1 occlusion (Figure 1A,B). A microcatheter was advanced over a microwire beyond the clot. The microwire was withdrawn, and a 4 × 20-mm retrievable stent was advanced through the microcatheter, which was then withdrawn to deploy the stent retriever across the clot. Manual aspiration was applied to the guide catheter while the retrievable stent was retracted and removed from the patient's body. The microwire and microcatheter were removed, and manual aspiration was undertaken using a 20-ml syringe, leading to recanalization. The clot was isolated

intact from the retrievable stent after removal. Angiography confirmed complete recanalization of the vessel (Thrombolysis in Cerebral Infarction grade 3) (Figure 1C,D). The patient was aroused from anesthesia and transferred to the pediatric intensive care unit. The time elapsed from groin puncture to recanalization was 40 min.

Postprocedural work-up and recovery

Upon the patient's initial presentation, there was concern for cardiac and pulmonary involvement as she had pleuritic chest pain, but pulmonary embolus was ruled out. She was afebrile on arrival to our institution but had documented fever before arrival that persisted for more than 24 h. She met several of the laboratory criteria for inflammation: increased neutrophils (81.4%), decreased lymphocytes (14.4%), elevated C-reactive protein level (1.2 mg/dl), and elevated procalcitonin level (0.13 ng/ml). Her erythrocyte sedimentation rate was elevated at 24 one month after thrombectomy.

She made a good clinical recovery, with a PedNIHSS of 2 on postprocedural day one, with some weakness in the intrinsic muscles of the right hand and mild gait instability. Magnetic resonance imaging on postprocedural day one demonstrated areas of infarct in the left basal ganglia and additionally in peripheral cortical regions in the left MCA territory (Figure 2A,B).

No clear source of embolism was identified, and the diagnosis of multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) was made in the setting of fevers and elevated inflammatory markers and multisystem involvement.¹⁴ She underwent treatment with intravenous immunoglobulin and corticosteroids and is now maintained on 81 mg of aspirin. In the ensuing weeks, her neurological deficits resolved completely, and she has made a complete recovery with a modified Rankin Scale score of 1 at one and three months after discharge.

Histopathological/molecular analysis

Stroke thrombus was collected via endovascular thrombectomy as per institutional stroke protocol. Immediately after thrombectomy, clot specimens were washed in 0.9% saline and submitted for processing and embedding in paraffin. After rehydration and heat-induced antigen retrieval, slides were fixed in 4% paraformaldehyde and blocked in 3% donkey serum with 0.5% Tween20. As primary antibodies, we used goat anti-myeloperoxidase (MPO) (2 µg/mL, AF3667, R&D Systems), rabbit anti-human citrullinated Histone H3 (2 µg/mL, ab5103, Abcam), and mouse anti-GPIIb (2 µg/mL, MA5-11642, Invitrogen).¹⁵ As secondary antibodies, we used donkey anti-rabbit AF488, donkey anti-goat AF546, and donkey anti-mouse AF633. DAPI was used as a nuclear counterstain (Life Technologies). Secondary antibodies only served as a negative control. Images were acquired using a high-resolution, confocal reflection microscope (Olympus IX81, FV300).

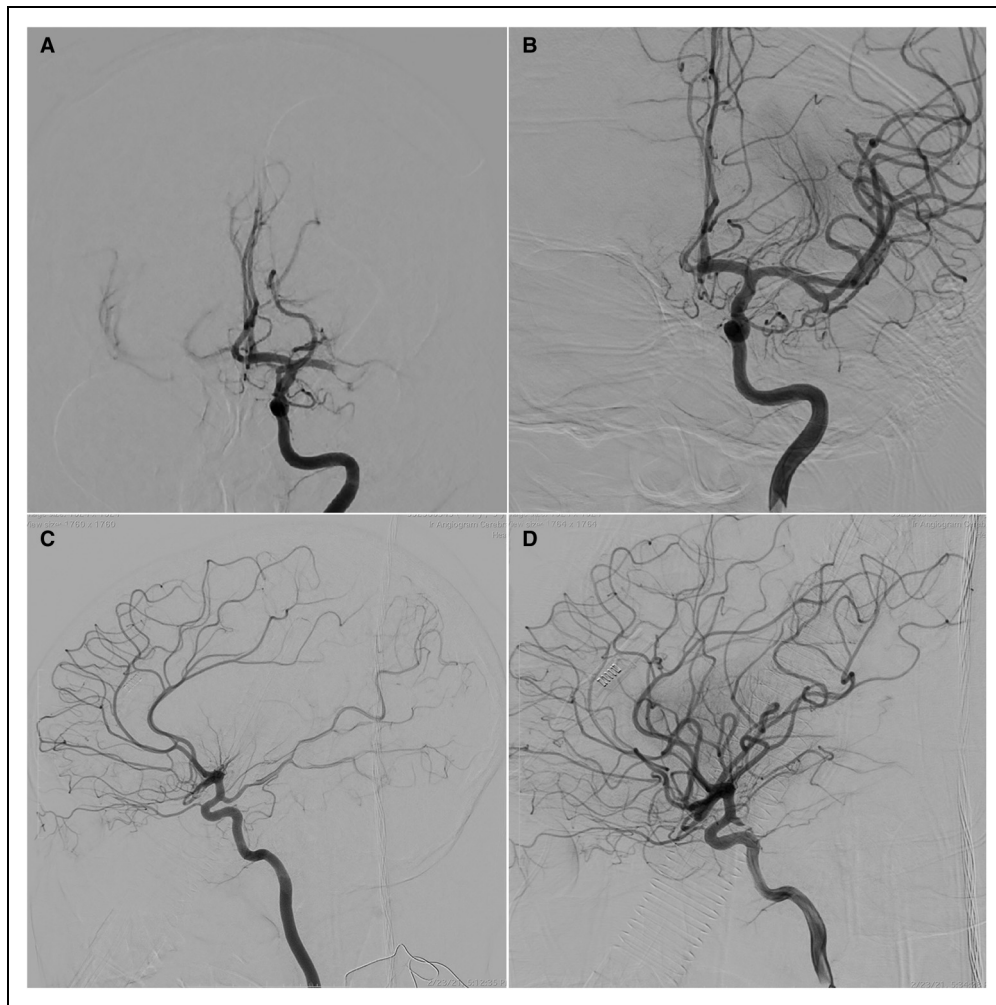


Figure 1. Anterior/posterior (A) pre- and (B) post- and lateral (C) pre- and (D) post-angiographic projection demonstrating left M1 occlusion and subsequent complete recanalization of the vessel (thrombolysis in cerebral infarction grade 3) after thrombectomy.

Polymerase chain reaction analysis did not reveal any viral RNA within the thrombus itself. Pathological analysis using hematoxylin-eosin was performed, as well as the immunostaining shown in Figures 3 and 4. The thrombus demonstrated a hyperacute appearance with thrombocytes and erythrocytes with minimal amounts of fibrin and fibrinogen. Immunofluorescence demonstrated an abundance of platelets (glycoprotein Ib) and neutrophils (MPO). In regions where neutrophils were present, many neutrophils were positive for citrullinated histone H3 (H3Cit), a marker for NET formation (Figure 3). Extensive evidence for extracellular NET formation was observed throughout the thrombus as indicated by the colocalization of DNA, MPO, and H3Cit (Figures 3 and 4).

Discussion

In this report, we describe a successful mechanical thrombectomy in the setting of an LVO of the left M1 segment with AIS in a pediatric patient presenting 3 weeks after diagnosis of COVID-19. The use of endovascular thrombectomy in pediatric ischemic stroke has

been described in several studies,^{9–12} although there are limitations to its widespread adoption, most notably variable therapeutic windows secondary to diagnostic delays.

SARS-CoV-2 infection and subsequent COVID-19 have been linked to hypercoagulability; the subsequent coagulopathy is the mechanism of thrombotic complications due to the disease process, including LVO and AIS. Stroke in the setting of COVID-19 in pediatric patients who lack the traditional risk factors highlights this process. Although a hypercoagulable state contributes to the risk of stroke, other mechanisms have been posited to play a role including focal arteriopathy. LaRovere et al. and others described the role of multisystemic inflammatory response due to COVID-19 in focal neurological processes such as LVO, cerebral sinus thrombosis, and focal cerebral arteriopathy.^{15–17}

There are several reports of pediatric AIS related to LVO attributed to COVID-19; however, with COVID-19 cases in children increasing, the incidence is likely to rise. Other cases of endovascular treatment for ischemic stroke in the pediatric population have been described (Table 1). Appavu and colleagues¹⁹ reported

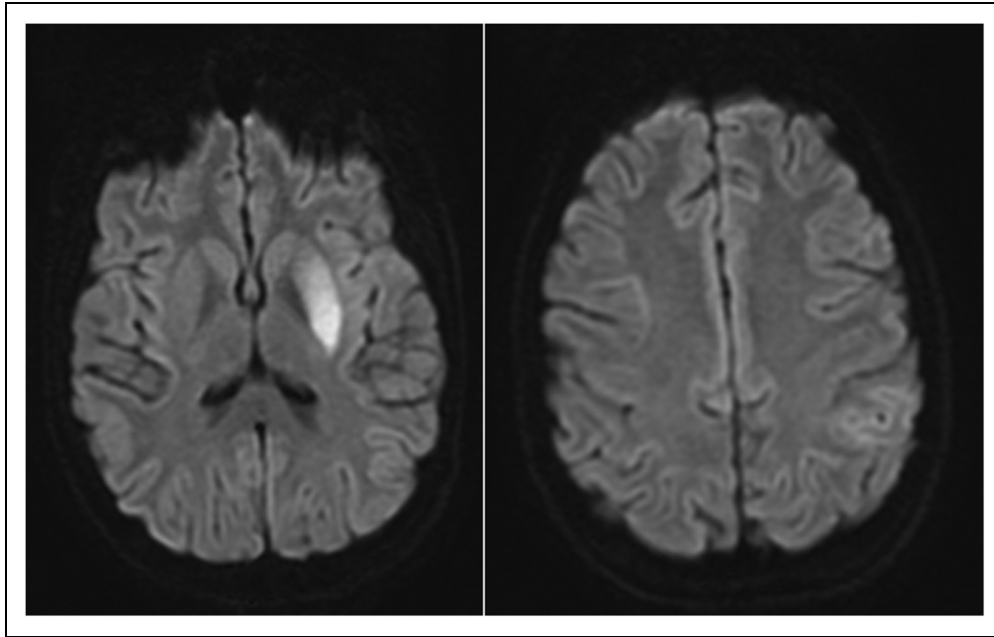


Figure 2. Magnetic resonance imaging on postoperative day one demonstrated areas of infarct in the (A) left basal ganglia and (B) peripheral cortical regions in the left MCA territory.

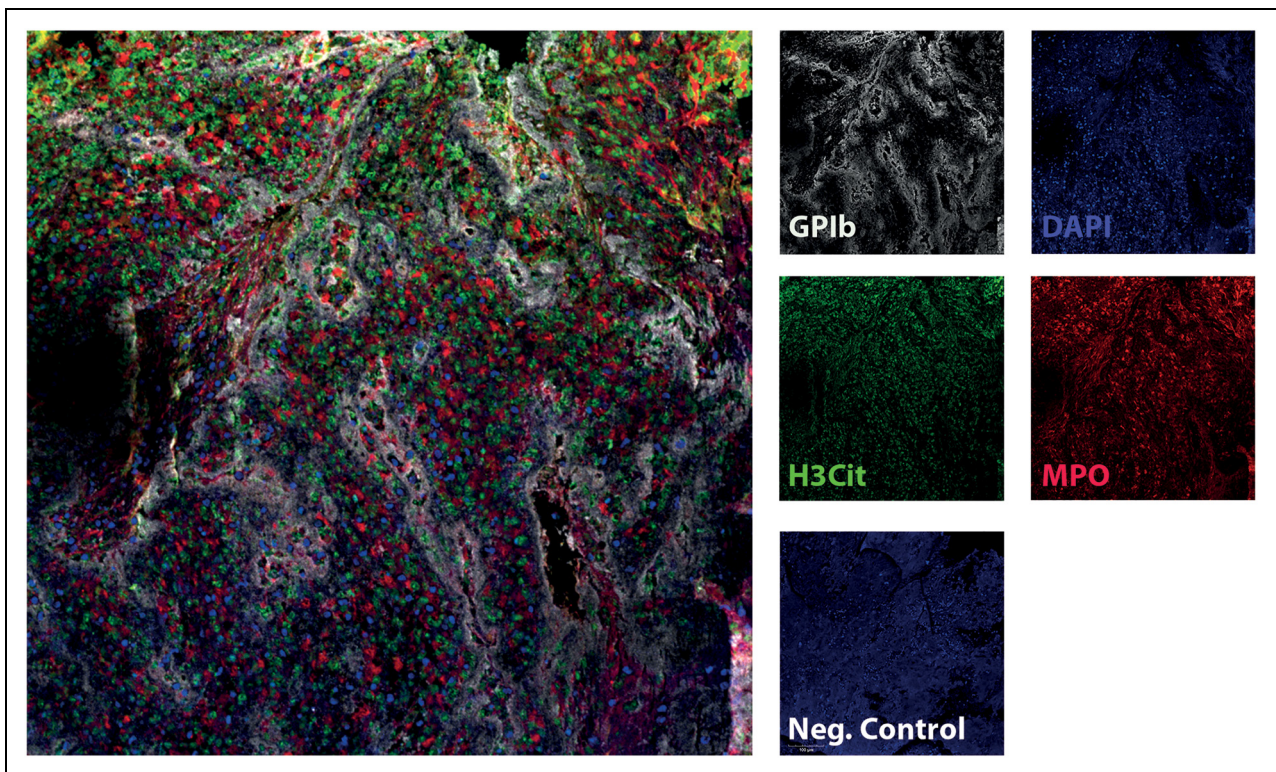


Figure 3. Histological specimen demonstrating that ischemic stroke thrombus in a patient with COVID-19 contains platelets, neutrophils, and NETs. Thrombus was collected via thrombectomy and processed for histology. Neutrophils were identified by myeloperoxidase (MPO). NETs were identified by colocalization of MPO (red), citrullinated histone H3 (H3Cit; green), and DNA (DAPI; blue). Platelets were stained with glycoprotein Ib (GPIb, white). See text for staining.

on two children who experienced LVO strokes, with both patients having their strokes within 3–4 weeks of COVID-19 infection. The authors posited that the underlying mechanism involved a systemic vascular

inflammatory process with involvement of the arteries of the central nervous system, either via direct viral entry of SARS-CoV-2 into vascular endothelial cells or secondary to an immunoglobulin G antibody-mediated response.

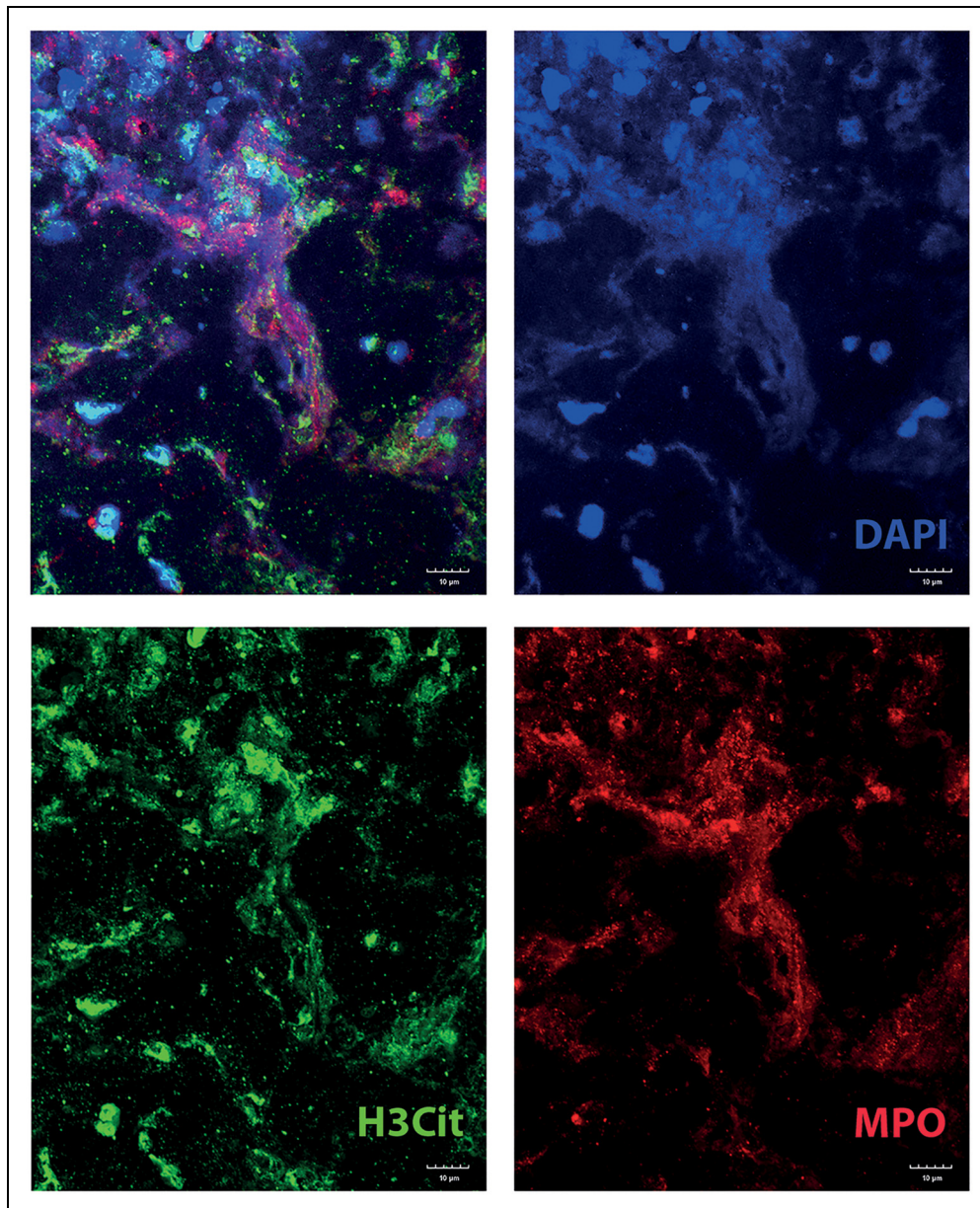


Figure 4. NETs are present in a thrombus from a pediatric stroke patient. Thrombus was collected via thrombectomy and processed for histology. Neutrophils were identified by myeloperoxidase (MPO). NETs were identified by colocalization of MPO (red), citrullinated histone H3 (H3Cit; green), and DNA (DAPI; blue). See text for staining.

In contrast, Jillella et al.²⁰ described a 12-year-old boy with concomitant COVID-19 infection with a left supraclinoid ICA occlusion.

As emerging variants of SARS-CoV-2 and subsequent COVID-19 come to light, the effects on children, specifically contributions to ischemic cerebrovascular disease, will be further elucidated. The role of vaccination may also become apparent on the incidence of thromboembolic complications in the pediatric population.

Cellular composition of thrombus

Previous studies of thrombectomy specimens causing LVO have demonstrated the presence and contribution of NETs to thrombus composition and stability.^{21,22} The

pathological feature of NET formation is the citrullination of histones, which leads to the decondensation of the nuclear chromatin.¹³ NETs are subsequently released as decondensed chromatin lined with granular components that yields fibrous structures that possess antimicrobial characteristics.²¹ This immunological reaction is thought to participate in the formation of venous and arterial thrombosis,²² because NETs serve as a framework for adherence by platelets and erythrocytes²³ and promote coagulation.²⁴ Laridan et al.¹³ found neutrophils extensively in ischemic stroke thrombi, with some of these neutrophils having formed NETs. Specifically, H3Cit, which is a hallmark of NETs, was observed in all 68 clot specimens they examined. Quantitative analysis demonstrated H3Cit presence ranging from 0.21% to 13.45% of the

Table 1. Endovascular treatment for ischemic stroke in pediatric patients with COVID-19.

Author	Age (years)/ sex	Timing of COVID-19 infection	Criteria met for MIS-C	Thrombectomy Method	Outcome (mRS)	Histopathological Findings
Appavu et al. ¹⁴	8 F	3 weeks earlier	No - absence of fever	Stent retriever-assisted contact aspiration	2 at discharge	Unorganized platelet- and fibrin-rich thrombus and sparse clusters of erythrocytes, degenerated histiocytes, few eosinophils, and rare neutrophils
Jillela et al. ¹⁸	16 M 12 M	4 weeks earlier Concurrent	No - absence of fever No - no elevation of inflammatory markers	N/A Stent retriever-assisted contact aspiration	3 at 2-mo f/u 1 at discharge	N/A N/A
Current case	9 F	3 weeks earlier	Yes	Stent retriever-assisted contact aspiration	1 at discharge	Abundance of neutrophils and NETs

MIS-C, multisystem inflammatory syndrome in children; mRS, modified Rankin Scale; N/A, not available; M, male; F, female; f/u, follow-up; NET, neutrophil extracellular trap.

section surface area.¹³ Several studies have recently confirmed these findings and detected the presence of NETs in ischemic stroke thrombi,^{13,25,26} and systemic evidence of NETs in plasma from patients who have experienced ischemic stroke was also reported.^{27–29} Boeckh-Behrens et al.³⁰ found considerable NET presence in the LVO of a 28-year-old patient, with 25% of thrombus neutrophils primed to produce NETs based on H3Cit staining. In adult patients, NET presence and activation in COVID-19 may be associated with or causative of the additional systemic effects of the disease.^{31,32} As demonstrated in the current case, there is now evidence of this phenomenon in children. Interestingly, we observed a large area of the thrombus that stained positively for H3Cit in our patient (Figures 3 and 4), suggesting NETs may be more common in ischemic stroke thrombi during COVID-19. However, we are limited in drawing further conclusions because this is a single case report and NETs in non-COVID-19 pediatric stroke have not been examined.

In one of two reported cases by Appavu et al.,¹⁹ the specimen was described as recently formed, unorganized platelet- and fibrin-rich thrombus with scattered clusters of erythrocytes, degenerated histiocytes, few eosinophils, and rare neutrophils. This sharply contrasts the present case in which there is an abundance of neutrophils and NETs. NETs are extracellular DNA lattices that are released upon neutrophil activation and function to trap pathogens, specifically blood-borne microorganisms.³³ However, NETs are critical regulators of thrombosis, including venous thrombosis,²³ ischemic stroke,¹³ and pulmonary thrombotic complications in COVID-19.¹⁸ Importantly, neutrophils are “first-responder” immune cells after ischemic stroke.³⁴ Given the propensity for COVID-19 to manifest with MIS-C, the pathogenesis of stroke and histopathological findings of LVO and COVID-19 as we describe in this report may suggest subsequent neutrophil/NET targeting as potential therapeutic options that require further rigorous study.

Conclusion

In this case, we have highlighted the use of endovascular intervention for LVO in a pediatric patient with COVID-19. We have demonstrated the histopathological presence of neutrophils and NETs in the specimen that may have been causative of LVO. The pathophysiology of stroke in the setting of COVID-19 represents a novel disease pattern and requires further large-scale study.

Acknowledgements

We thank Kristin Kraus, MSc, for editorial assistance.

Author disclaimer

“The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the

Department of the Navy, Department of Defense, nor the U.S. Government.”

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Grandhi is a consultant for Balt Neurovascular, Cerenovus, Integra, and Medtronic Neurovascular. The other authors have no conflicts of interest.

Ethical approval statement

This study was performed in compliance with Institutional Review Board (IRB) and Health Insurance Portability and Accountability Act regulations. A waiver of approval is provided by the institutional review board for single case reports. Consent for procedures, data collection, and publication was obtained based on institutional guidelines.





Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Institutes of Health (K01AG059892, R01HL163019, and Utah StrokeNET U24NS107228) and the American Heart Association (2021Post830138).

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