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Intracranial complications of hypercoagulability and superinfection in the setting of COVID-19: illustrative cases

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BACKGROUND Hypercoagulability with thrombosis and associated inflammation has been well-documented in COVID-19, and catastrophic cerebral venous sinus thromboses (CVSTs) have been described. Another COVID-19–related complication is bacterial superinfection, including sinusitis. Here, the authors reported three cases of COVID-19–associated sinusitis, meningitis, and CVST and summarized the literature about septic intracranial thrombotic events as a cause of headache and fever in COVID-19.

OBSERVATIONS The authors described three adolescent patients with no pertinent past medical history and no prior COVID-19 vaccinations who presented with subacute headaches, photosensitivity, nausea, and vomiting after testing positive for COVID-19. Imaging showed subdural collections, CVST, cerebral edema, and severe sinus disease. Two patients had decline in mental status and progression of neurological symptoms. In all three, emergency cranial and sinonasal washouts uncovered pus that grew polymicrobial cultures. After receiving broad-spectrum antimicrobials and various additional treatments, including two of three patients receiving anticoagulation, all patients eventually became neurologically intact with varying ongoing sequelae.

LESSONS These cases demonstrated similar original presentations among previously healthy adolescents with COVID-19 infections, concurrent sinusitis precipitating CVST, and subdural empyemas. Better recognition and understanding of the multisystem results of severe acute respiratory syndrome coronavirus 2 and the complicated sequelae allows for proper treatment.

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KEYWORDS COVID-19; hypercoagulability; superinfection; cerebral sinus thrombosis; empyema

COVID-19 is a disease caused by the novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can have a variety of clinical presentations ranging from asymptomatic to multisystem organ failure. The risk of both arterial and venous thromboembolic events with COVID-19 and their associated mortality has been well documented.[1] Neurologically, multiple studies have also documented young patients presenting with large vessel occlusions resulting in strokes.[2] SARS-CoV-2 is thought to cause a hypercoagulable state through immune dysfunction, widespread endothelial injury, complement-associated coagulopathy, and systemic microangiopathy.[3] Antiphospholipid antibodies (aPLs) have also been widely documented in hospitalized patients with COVID-19, particularly with severe disease progression, and have been hypothesized to play a role in hypercoagulability prompting thrombotic events.[4]

Immune dysregulation or permissive mucosa in COVID-19 also imposes risks for secondary infection.[5,6] Documented bacterial coinfection rates vary from 4% to 25%, reaching up to 50% in nonsurvivors.[5] Common bacterial pathogens include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus* species.[5] Data on fungal infections is more sparse, but *Candida* species appear to be the most common fungal pathogen encountered.[5] Superinfected pneumonias are well documented

ABBREVIATIONS aPL = antiphospholipid antibodies; CRP = C-reactive protein; CT = computed tomography; CVST = cerebral venous sinus thrombosis; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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in recent literature; however, reports of secondary infections of other organs in the presence of COVID-19 are lacking. In this series, we describe three cases of adolescents with similar presentations who were found to have both cerebral sinus thromboses and polymicrobial sinus and cerebral infections causing subdural and subarachnoid empyemas in the setting of COVID-19.

Illustrative Cases

Case 1

An adolescent boy with no pertinent past medical history and no prior COVID-19 immunization presented to an outside hospital in the summer of 2021 for subacute headaches and was found to be positive for COVID-19 via nasopharyngeal polymerase chain reaction (PCR) testing and was discharged home. He returned 3 days later for worsening headache with associated photosensitivity, nausea, and vomiting. He was found to be afebrile and neurologically intact. Laboratory tests were notable for a leukocyte count of 16.13 $\times$ 10^9/L. Head computed tomography (CT) was performed and raised suspicion for superior sagittal sinus thrombosis and possible cavernous sinus thrombosis (Fig. 1A) as well as a right-sided subdural collection, pneumocephalus, and severe opacification of the frontal, anterior ethmoid, and maxillary sinuses suggestive of a sinonasal source of the infection (Fig. 1B). He was transferred to our hospital for surgical care. In our emergency department, he was found to have a left hemisensory deficit. He then acutely became more somnolent and developed bradycardia and anisocoria. An urgent head CT demonstrated superior sagittal sinus thrombosis with cavernous sinus thrombosis, a large right subdural collection, diffuse cerebral edema with 10 mm of midline shift, and severe paranasal sinus disease (Fig. 1C). The patient was emergently taken to the operating room for right-sided hemicraniectomy and washout, at which time diffuse subdural and subarachnoid purulence was encountered (Fig. 1D). Intraoperative cultures grew *Streptoccocus constellatus* and *Parvimonas*. After urgent management of his herniation, the patient returned to the operating room the next day for endoscopic sinus surgery. Sinus cultures also grew *P. aeruginosa*, *S. aureus,* and *Staphylococcus epidermidis*. Hypercoagulability workup to investigate the cause of his sinus thromboses revealed the presence of the lupus anticoagulant. The patient required multiple cranial and sinonasal washouts for ongoing purulence. A sample from a later surgery grew *Candida dubliniensis* as well. He received placement of an external ventricular drain, tracheostomy, and gastrostomy tube. His sinus thromboses were treated with anticoagulation. He never required oxygen support for his COVID-19. Steroids were not indicated and were avoided because of severe superinfection, but he did receive remdesivir. His polymicrobial infection was managed with an extended course of broad-spectrum intravenous antimicrobials and a short course of intrathecal therapy. The patient was eventually discharged to a rehabilitation facility and has since been discharged home. Recent neurological examinations have demonstrated that he is alert and oriented. He is nonverbal but can communicate via writing and pointing. He maintains cognitive impairments and motor apraxia but can perform activities of daily living and ambulate with some supervision and assistance.

Case 2

An adolescent girl with no pertinent past medical history and no prior COVID-19 immunization (not approved for her age group at the time) presented to an outside hospital in the summer of 2021 for subacute headaches and was found to be positive for COVID-19 via rapid testing and was discharged home. She returned 4 days later for worsening headache with associated photosensitivity, neck stiffness, nausea, vomiting, and left-sided weakness. COVID-19 nasopharyngeal PCR was positive. CT was notable for epidural and subdural abscess with midline shift and possible venous sinus thromboses. She was started on ceftriaxone and was sent to our hospital for further management. In our emergency department, she was afebrile and neurologically intact. Laboratory tests were notable for a leukocyte count of 23.66 $\times$ 10^9/L and C-reactive protein (CRP) $>$300 mg/L. Magnetic resonance imaging (MRI) showed right subdural collection and severe sinus disease suggestive of sinonasal source of infection (Fig. 2A and C). She had worsening pain, her mental status began to decline, and she had a fever of 39.7°C. She had an acute decompensation episode, with pupils becoming fixed and dilated, and she had associated systolic blood pressures in the 200s and electrocardiography showing idioventricular rhythm. She was urgently taken to the operating room with neurosurgery and otolaryngology for decompressive hemicraniectomy and functional endoscopic sinus surgery. Intraoperative cultures grew *Fusobacterium necrophorum* and methicillin-susceptible *S. aureus*. Her polymicrobial infection was managed with an extended course of broad-spectrum intravenous antibiotics. Subsequent MR venography showed small, nonocclusive superior sagittal sinus thrombosis (Fig. 2B), and she was not started on anticoagulation because of risks of postoperative bleeding. Later imaging showed a right anterior frontal lobe intraparenchymal abscess. She was given broad-spectrum antibiotics, and the abscess improved without surgery. She did not require any additional treatments for COVID-19. During her inpatient stay, she returned to her

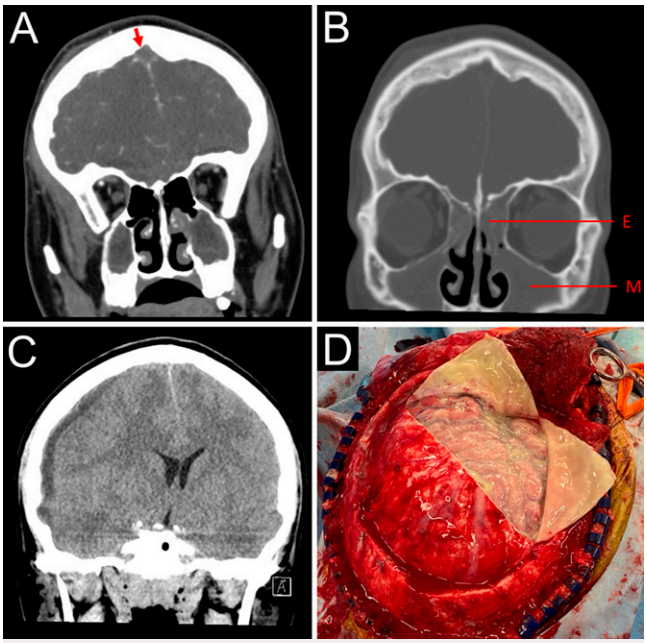

FIG. 1. A: CT venogram demonstrating large, expanded filling defect within the anterior aspect of the superior sagittal sinus (*arrow*), consistent with venous sinus thrombosis. **B:** Noncontrast head CT demonstrating opacification of ethmoid (*E*) and maxillary (*M*) sinuses, suggesting sinonasal disease. **C:** Noncontrast head CT demonstrating 6-mm hypodense subdural fluid collection along the right cerebral hemisphere with global cerebral edema and 9 mm of leftward midline shift. **D:** Intraoperative hemicraniectomy view of diffuse subdural and subarachnoid purulent fluid.

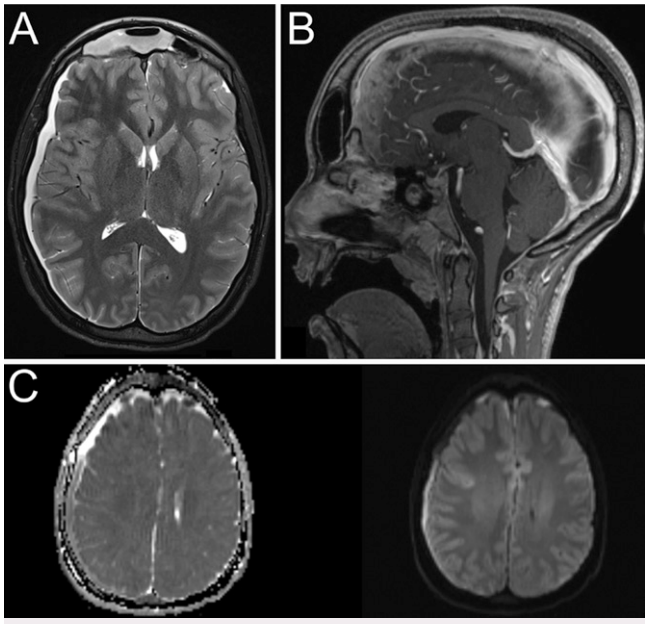

FIG. 2. A: T2-weighted MRI demonstrating right-sided subdural collection and extensive opacification of the right sinus, suggesting sinonasal disease. **B:** MR venography demonstrating small, nonocclusive superior sagittal sinus thrombosis. **C:** Apparent diffusion coefficient (ADC; *left*) and diffusion-weighted imaging (DWI; *right*) demonstrating right subdural collection.

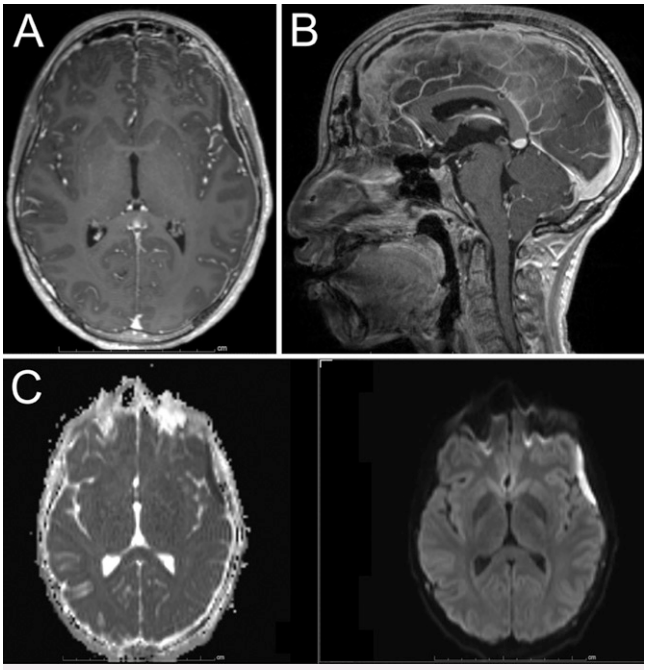

FIG. 3. A: T1-weighted MRI demonstrating left frontotemporal and anterior left frontal subdural collection with surrounding leptomeningeal enhancement and sinus disease. **B:** MR venography demonstrating nonocclusive superior sagittal sinus thrombosis. **C:** ADC (*left*) and DWI (*right*) demonstrating a left frontotemporal subdural collection.

neurological baseline. After 3.5 months from her original presentation, she had a cranioplasty for bone flap replacement with native bone. Her drain has since been removed without complications, she was discharged home, and she continues to remain at her baseline.

Case 3

An adolescent boy with no pertinent past medical history and no prior COVID-19 immunization presented in the winter of 2022 to an outside hospital emergency department for subacute headaches, fevers, photophobia, nausea, vomiting, and diarrhea. He was neurologically intact with horizontal nystagmus. Laboratory tests were notable for a leukocyte count of 14 $\times$ 10^9/L and CRP $>$300 mg/L. CT showed frontal sinus mucosal thickening, left-sided frontotemporal subdural collections, and extensive dural venous sinus thrombus. He was started on ceftriaxone and metronidazole and sent to our hospital for further management. In our emergency department, he was afebrile and neurologically intact. MRI demonstrated left subdural collections, left frontal and ethmoidal sinus disease suggestive of sinonasal source of infection, and superior sagittal sinus thrombosis (Fig. 3). He was taken to the operating room with neurosurgery and otolaryngology for left craniotomy for evacuation of subdural empyema and functional endoscopic sinus surgery. Extensive subdural pus was encountered, with minimal purulence expressed from the sinuses. Preliminary intraoperative cultures grew *Streptococcus intermedius* and *Parvimonas micra*, and the Gram stain additionally showed gram-positive rods. Outside hospital blood cultures were positive for *S. intermedius*. Postoperative MRI demonstrated interval posterior propagation of thrombus, and he was started on prophylactic anticoagulation. Imaging also demonstrated new frontal cerebritis with small right frontal abscess and frontal bone osteomyelitis, and the patient underwent an additional left craniotomy and right burr hole for new sites of empyema formation. He was managed with broad-spectrum intravenous antibiotics as well as therapeutic anticoagulation, was discharged home, and continues to remain at his neurological baseline.

Discussion

Observations

Hypercoagulability in the setting of COVID-19 has been well documented.[3] The incidence of cerebral venous sinus thrombosis (CVST) in patients with laboratory-confirmed SARS-CoV-2 infection has been reported at 0.02%.[7] Previous COVID-19 reports have presented patients with headaches due to CVST.[8] Mechanisms suggested include systemic inflammation, postinfectious immune-mediated responses, and virus-induced endotheliitis or endotheliopathy.[9] aPLs, as seen in Case 1, have also been a proposed contributor to COVID-19–associated hypercoagulability. aPLs can appear during other viral infections and may be transient and nonpathogenic. However, interpretation of positivity may be difficult in critically ill patients due to inflammation and anticoagulant treatments, which can interfere with correct results.[10] Although there is a proposed role of lupus anticoagulant increasing thrombotic risk with COVID-19, the association between its presence and thrombotic events is still inconsistently supported, with some studies failing to find a significant correlation.[4]

Separately, the systemic effects of SARS-CoV-2 infection may have also played a role in the vulnerability to a more severe superinfection seen, in this case, through immune system dysfunction and interruption in mucosal integrity. The virus has been found to cause both lymphopenia and decreased lymphocyte function, including CD4+ and CD8+ T cells, B cells, and natural killer cells.[11] Studies have also found cell markers of immunosuppression and T-cell

exhaustion.[11] However, T-cell–mediated immunity does not usually play a major role in sinusitis and bacterial infections. The virus may have also allowed for invasiveness of bacteria through breakdown of epithelial barrier functions.[6] One case series described 6 patients with COVID-19 who developed primary spinal epidural abscesses. The authors suggested that they may have developed due to the coexistence of initially asymptomatic bacterial contamination, with COVID-related endotheliitis allowing for retrograde bacterial invasion into the epidural space.[12] SARS-CoV-2 infection triggers a systemic inflammatory response with massive release of cytokines, chemokines, and other inflammation signals, which leads to substantial breakdown of the blood–brain barrier.[13] These conditions may have allowed for the development of a severe superinfection with the intracranial, subdural, and subarachnoid expansion seen in our case.

It is important to note that outside of COVID-19, viral infections are known predecessors to bacteria sinusitis and potentially associated complications, such as sinus thrombosis. These sequelae, however, have not been well described in the setting of COVID-19. The complex features of COVID-19 may create the perfect storm for sinusitis-related complications. One case study discussed a patient with a history of chronic sinusitis who developed symptoms of subdural empyema 19 days after recovery from COVID-19.[14] Subdural empyema is a well-described sinusitis-associated intracranial infection that may be associated with venous sinus thrombosis or septic thrombophlebitis and can spread from the sinonasal region through retrograde septic thrombophlebitis of valveless emissary veins.[15] In the cases presented, hypercoagulability-induced thromboses and superinfection-induced thrombophlebitis may have played a compounding role in development of a severe empyema.

Lessons

As the COVID-19 pandemic continues to evolve, clinicians must be aware of the complex presentations and complications in patients with this disease. Our cases suggest a complex interplay of mechanisms contributing to a rare but life-threatening case of COVID-19 in a teenager. In these cases, COVID-19 was associated with septic venous thrombosis, subdural empyemas, and herniation. We hypothesize that it was the result of several processes, including hypercoagulability with sinus thromboses as well as immune/endothelial dysfunction and superinfection. Because this series involved just three patients, it is limited in definitively proving causality. Subdural empyema is a neurosurgical emergency that must be addressed immediately due to its high risk of status epilepticus, spreading cortical venous and corticovenous sinus thrombosis, fulminating cerebritis, brain swelling, herniation, and death. Clinicians should be aware of this complication because such cases must be treated with timely surgical intervention and appropriate antimicrobial therapy and anticoagulation.

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Disclosures

Dr. Chen is a founder and holds equity in Verge Genomics and holds equity in Gravity Medical Technology. No other disclosures were reported.

Author Contributions

Conception and design: McMahon, Blitz, Chalif, Jarvis, Segar, Chen, Arnaout. Acquisition of data: McMahon, Chalif, Jarvis, Northam, Chen, Arnaout. Analysis and interpretation of data: McMahon, Chalif, Chen, Bergmark, Arnaout. Drafting the article: McMahon, Blitz, Chalif. Critically revising the article: McMahon, Blitz, Chalif, Segar, Northam, Chen, Bergmark, Davis, Yawetz, Arnaout. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: McMahon. Administrative/technical/material support: Chalif, Arnaout. Study supervision: McMahon, Chalif, Yawetz.

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