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HEMATOLOGY: BRIEF REPORT

Pulmonary embolism in pediatric and adolescent patients with COVID-19 infection during the SARS-CoV-2 delta wave

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Abstract

Coronavirus disease 2019 (COVID-19) infection in children has been associated with thrombosis, though few cases of COVID-associated pulmonary embolism (PE) have been described. We performed a retrospective review of the nine cases of COVID-19-associated PE during the B.1617.2 variant surge at Texas Children's Hospital. The patient cohort largely contained unvaccinated obese adolescents. All patients were critically ill with two requiring catheter-directed thrombolysis in addition to anticoagulation. Eight of the nine patients had COVID pneumonia along with PE. This report stresses the importance of maintaining a high index of suspicion for PE in pediatric COVID-19 infection and vaccinating obese adolescent patients.

KEYWORDS
anticoagulation, COVID-19, pulmonary embolism

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection has been associated with the development of micro- and macrovascular thrombosis due to inflammation-driven endothelial dysfunction and a hypercoagulable state.[1,2] Children and adolescents have increased markers of inflammation and coagulopathy (elevated D-dimer, fibrinogen, and prothrombin time) and rates of thrombosis in acute COVID-19 infection.[3–5] Clinicians caring for critically ill children hospitalized with COVID-19 or those with underlying thrombotic risk factors should consider thromboprophylaxis to prevent the thrombotic complications of COVID infection.[6–9] Hospitalized older children (12 years and over) have the highest risk of COVID-associated thrombosis, with an incidence of 2.1%.[3] This study was undertaken to review the clinical characteristics of pediatric COVID-19-associated pulmonary embolism (PE) diagnosed and treated at Texas Children's Hospital (TCH) during the B.1617.2 delta variant wave.

Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; PE, pulmonary embolism; TCH, Texas Children's Hospital.

2 | STUDY METHODS

We report a case series of patients admitted to TCH with COVID-19 infection and PE between July 1, 2021 and September 22, 2021. Patients were identified via a patient reporting tool within the TCH electronic medical record system, including patients under 21 years with the inpatient ICD-10 codes of COVID-19 infection and PE. The total number of patients admitted to TCH with acute COVID-19 during the same study period were identified using the inpatient ICD-10 code of COVID-19 alone. Patients with multisystem inflammatory syndrome in children (MIS-C), identified from our rheumatology division, were excluded from the patient cohort. Cases of acute COVID-related (non-PE) deep vein thrombosis (DVT) were identified from the total patient cohort with acute DVT ICD-10 codes and individual patient record screening. Patients who did not have a positive COVID polymerase chain reaction (PCR) test during their hospitalization were excluded from the study. See Supporting Information for clinical and laboratory data collected.

PE severity was stratified based on cardiac dysfunction and hemodynamic stability: acute PE was defined as PE without evidence of

right ventricular dysfunction or hemodynamic instability; submassive PE was defined as PE with evidence of right ventricular dysfunction and no evidence of hemodynamic instability; and massive PE was defined as PE with evidence of right ventricular dysfunction and hemodynamic instability. Microsoft Excel was used to calculate mean and median values of extracted data. See Supporting Information for our institutional guidelines for anticoagulation prophylaxis in COVID-19 infection during the study period and institutional diagnostic imaging practices. This study was approved by the Baylor College of Medicine institutional review board.

3 | RESULTS

3.1 | Patient characteristics

Nine out of 543 (1.7%) patients admitted with COVID-19 infection during the study period were identified as having PE at TCH. An additional five patients were identified as having a COVID-related DVT, making the incidence of COVID-related venous thromboembolism in the study period 2.6% (14 out of 543). Obese adolescents made up the majority of the cohort, with eight (88.9%) being over 12 years of age and six (66.7%) having a body mass index (BMI) over 30 (median of 40.8, range 12.6–48.6). Sickle cell disease was another thrombotic risk factor identified in the cohort, present in two (22.2%) patients and was the only identified risk factor in the patients under 12 years of age. Six (66.7%) of the patients were diagnosed with acute COVID infection prior to their admission, with a median length of diagnosis 10 days prior to presentation (range 3–16). No patients in the cohort were fully vaccinated against COVID-19, and only one adolescent patient had received the first of the series of two COVID mRNA vaccines. Of note, the 6-year-old patient was not yet eligible to receive the COVID vaccine at the time of the study. Demographic information for each patient is presented in Table 1. See Supporting Information for the cohort laboratory characteristics.

3.2 | Pulmonary embolism presentation and treatment course

All patients were critically ill requiring intensive care admission, with eight (88.9%) presenting with hypoxia, and three (33.3%) requiring invasive mechanical ventilation. Hypoxia was considered multifactorial from PE, COVID-19 pneumonia, and possible pulmonary infarction. The median number of days from COVID-19 diagnosis to PE diagnosis, and admission to PE diagnosis was 9 (range 0–16), and 0 (range 0–8), respectively. The median length of intensive care admission was 4 days (range 1–15). Anticoagulation was administered to all patients following PE diagnosis, though only one patient was receiving prophylactic anticoagulation prior to PE diagnosis. See Supporting Information for further details of thromboprophylaxis in this cohort.

Four patients had evidence of myocardial dysfunction, as evidenced by echocardiography findings and elevations in myocardial enzymes. Two of the four patients had evidence of severe right ventricular heart dysfunction with hemodynamic instability and inotropic requirement, therefore undergoing catheter-directed thrombolysis (0.5–1 mg/h for 12 hours) for management of massive PE. An example of the computed tomography (CT) and echocardiogram findings in a 14-year-old patient with heart dysfunction secondary to PE is demonstrated in Figure 1.

Two patients had extremity thrombi in addition to their PE. Five of the seven who were not diagnosed with extremity DVT had screening Doppler sonograms of their extremities, while two did not. There were no deaths in the cohort. Two clinically relevant, nonmajor bleeding events (episodes of hemoptysis and epistaxis) occurred in two patients while receiving anticoagulation, though neither received thrombolysis. COVID-19 pneumonia, in addition to PE, was diagnosed via imaging in eight (88.9%) of the patients. A breakdown of each patient's presentation, PE, and treatment course is demonstrated in Table 1. Follow-up and PE outcome information is presented in Supporting Information.

4 | DISCUSSION

The surge caused by the delta variant of SARS-CoV-2 was associated with increased occurrence of PE at TCH. Our center has treated ~77 patients with acute PE between 2016 and 2021, with 25 in the year 2021. Nine of the 25 represent our cohort with COVID-19 and PE. The PE frequency in our cohort may be an underestimation as all children admitted with COVID-19 did not undergo imaging to evaluate for PE. Though most patients in our cohort were diagnosed with acute PE needing only anticoagulation, two patients did undergo thrombolysis for massive PE as the patients were hemodynamically unstable requiring vasoactive support and had evidence of right ventricular dysfunction on echocardiography with elevated troponin and B-type natriuretic peptide (BNP). One of the four patients with evidence of myocardial dysfunction was felt to have acute myocarditis secondary to COVID-19. Overweight and obese adolescent patients made up the majority of our cohort, suggesting that this patient population is at the highest risk of developing COVID-19-related PE, adding to the existing evidence that obesity is a risk factor for poor outcomes in COVID-19.[10,11] Additionally, no patient in our cohort was fully vaccinated against COVID-19, with only one receiving the initial mRNA vaccine dose. The combination of these findings highlights the critical importance of vaccinating obese adolescents to prevent severe COVID-19 clinical outcomes.

All but one patient in the cohort were diagnosed with COVID-19 pneumonia in addition to PE on imaging studies, both likely contributing to the hypoxia observed in our patients. This cohort demonstrates the importance of having a high index of suspicion for PE in pediatric patients ill with COVID-19 and cardiovascular or respiratory symptoms. Though outside of the scope of this study, we hypothesize that the patients in this cohort were more severely ill secondary to increased pulmonary vasculature involvement (PE) in addition to the lung parenchymal disease of their COVID-19 infection. Diagnostic testing for PE should be performed in acutely ill pediatric patients with COVID-19 in the setting of dyspnea or hypoxia

TABLE 1 PE presentation and treatment summary

	Patient								
	1	2	3	4	5	6	7	8	9
Gender	F	F	M	M	M	M	M	F	M
Age (years)	6	13	20	16	12	16	13	16	14
Race/ethnicity	AA/hispanic	AA/not hispanic	Caucasian/hispanic	AA/not hispanic	Caucasian/not hispanic	Caucasian/hispanic	AA/not-hispanic	AA/not-hispanic	AA/not-hispanic
BMI	12.6	40.8	41.1	31.7	43.3	40.9	27.7	48.6	20.5
COVID vaccination status	Unvaccinated[a]	Partial[b]	Unvaccinated	Unvaccinated	Unvaccinated	Unvaccinated	Unvaccinated	Unvaccinated	Unvaccinated
Comorbidities	SCD	Obesity	Obesity	Obesity	Obesity	Obesity	None	Obesity	SCD
PE location	Unilateral Segmental	Unilateral Segmental	Unilateral Main/lobar	Unilateral Subsegmental	Bilateral Segmental Subsegmental	Unilateral Segmental	Bilateral Segmental Subsegmental	Unilateral Main/lobar Segmental	Bilateral Main/lateral Segmental Subsegmental
PE severity	Acute PE	Acute PE	Acute PE	Acute PE	Acute PE	Massive	Acute PE	Acute PE	Massive
COVID pneumonia (Y/N)	Y	Y	Y	N	Y	Y	Y	Y	Y
Time from COVID dx to PE dx (days)	15	5	4	8	0	0	15	16	14
Time from admission to PE dx (days)	8	5	0	0	0	0	0	0	2
ICU (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Length of stay (days)	6	9	11	1	2	15	4	3	4
Hypoxic (Y/N)[c]	Y	Y	Y	Y	Y	Y	Y	N	Y
IMV (Y/N)	Y	N	Y	N	N	Y	N	N	N
NIV (Y/N)	Y	Y	Y	N	N	Y	Y	N	Y
Presence of other DVT (Y/N)	N	N	Y	N[d]	N	N[d]	N	N	Y
Anticoagulant(s) used	UFH enoxaparin	Enoxaparin	UFH enoxaparin	UFH enoxaparin	UFH enoxaparin	UFH enoxaparin	UFH enoxaparin	UFH enoxaparin	UFH enoxaparin
Thrombolysis (Y/N)	N	N	N	N	N	Y	N	N	Y

(Continues)

TABLE 1 (Continued)

	Patient								
	1	2	3	4	5	6	7	8	9
D-dimer at PE Dx (μg/ml)	>20	>20	>20	3.52	2.48	8.2	9.2	1.11	>20
RV strain/function Elevated BNP (Y/N)	N	Y	N	N	N	Y	N	N	Y
Elevated troponin (Y/N)	N	Y	Y	N	N	Y	N	N	Y
RV function	Mild depressed function	Mild depressed function	N	N	N	Moderate–severe depressed function	N	N	Severe depressed function
Bleeding sequelae (Y/N)	N	Y	Y	N	N	N	N	N	N
Type	N/A	Hemoptysis	Epistaxis	N/A	N/A	N/A	N/A	N/A	N/A

Note: Massive PE: PE + evidence of right ventricular dysfunction and hemodynamic instability. Submassive PE: PE + evidence of right ventricular dysfunction. Acute PE: evidence of PE without right ventricular dysfunction.

Abbreviations: AA, African American; BMI, body mass index; BNP, brain-type natriuretic peptide; DVT, deep vein thrombosis; IMV, invasive mechanical ventilation; N, no; NIV, noninvasive mechanical ventilation; PE, pulmonary embolism; RV, right ventricle; SCD, sickle cell disease; UFH, unfractionated heparin; Y, yes.

[a]Patient ineligible to receive COVID-19 vaccine at the time of admission due to age.

[b]Patient had received the initial mRNA vaccine though not the second dose.

[c]Hypoxia was defined as the inability to maintain oxygen saturations above 94% without supplemental oxygen.

[d]Extremity Doppler ultrasounds were not obtained to evaluate for extremity DVT.

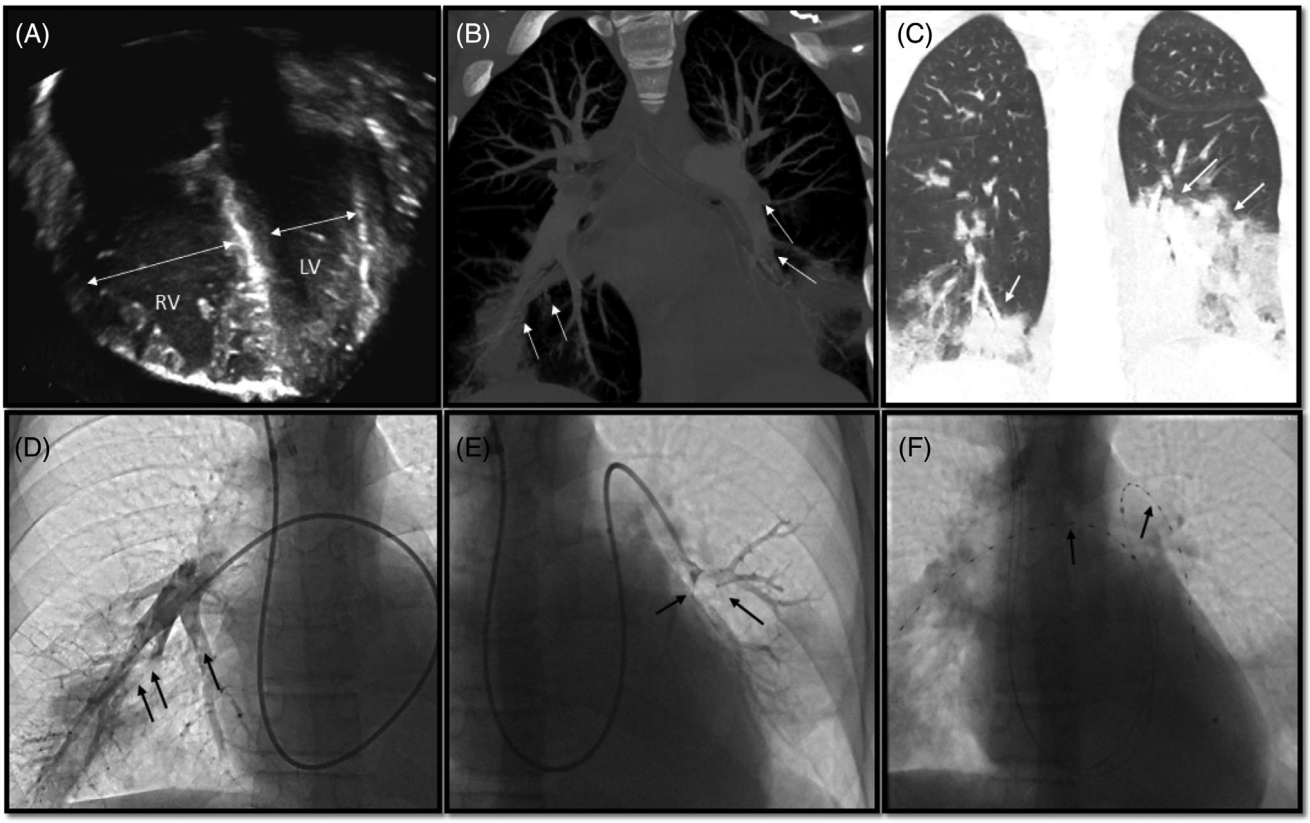

FIGURE 1 Fourteen-year-old male with acute pulmonary embolism (PE). (A) Echocardiogram illustrates dilated right ventricle. (B) CT demonstrates bilateral segmental and subsegmental thrombi (white arrows) and (C) bilateral consolidation and ground-glass opacities (white arrows). (D and E) Angiograms demonstrated negative contrast opacities in the bilateral lobes (black arrows). (F) Bilateral EKOS catheters placed for local tissue plasminogen activator (tPA) infusion

that cannot be explained by chest x-ray alone or other concerning cardiorespiratory signs to allow for timely diagnosis and initiation of medical and interventional therapy if needed. Routine prophylactic anticoagulation should be considered in critically ill children secondary to COVID-19 and those with underlying thrombotic risk factors with acute infection.[6]

It is our practice at TCH to administer prophylactic anticoagulation to pediatric and adolescent patients admitted to the hospital with COVID-19 who are critically ill or over 12 years of age with additional thrombotic risk factors if not critically ill. Sickle cell disease has since been added as a risk factor in our institutional guidelines for thromboprophylaxis in children and adolescents hospitalized with COVID-19 infection (as it was not at the time of the study). Our study raises the question if more aggressive upfront anticoagulation should be administered for obese adolescents with COVID-19 pneumonia at the time of diagnosis to avoid the development of life-threatening PE. This is a challenging question, as six of the eight adolescent patients were diagnosed with an acute COVID-19 infection prior to their hospitalization for management of PE. Further studies are needed to determine if prophylactic anticoagulation is an appropriate strategy for preventing COVID-19-associated PE in the obese adolescent population being managed on an outpatient basis. Though universal guidelines for outpatient anticoagulation prophylaxis in acute COVID-19 infection are not discernable from this study, heightened provider awareness and counseling of high-risk patients (obese and unvaccinated adolescents) on the signs and symptoms of PE and thrombosis is critical for timely diagnosis and intervention.

In conclusion, the recent wave of COVID-19 admissions secondary to the delta variant was associated with a high frequency of COVID-19-associated PE in obese, unvaccinated adolescents, stressing the importance of administering the COVID vaccine to this high-risk population. Though subsequent COVID-19 variants are likely to have different thrombotic and inflammatory responses in children when compared to the delta and previous variants, it is critical for clinicians to remain vigilant of the potential life-threatening thrombotic complications of pediatric and adolescent COVID-19 infections.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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