# PULMONARY EMBOLISM AS THE INITIAL PRESENTATION OF CORONAVIRUS DISEASE 2019 IN ADOLESCENTS

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**Abstract:** The current coronavirus disease 2019 pandemic has been particularly challenging for the clinician because of the unclear nature of the underlying disease mechanisms. One of the hallmarks of the disease involves an increased risk of thrombosis and hypercoagulable state. Here, we describe 2 cases of patients admitted with submassive pulmonary embolism in the setting of positive tests for severe acute respiratory syndrome coronavirus 2.

**Key Words:** severe acute respiratory syndrome coronavirus 2, hypercoagulable state, deep vein thrombosis, venous thromboembolism, coronavirus, pediatric, children

Accepted for publication January 19, 2021
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The authors have no funding or conflicts of interest to disclose.
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DOI: 10.1097/INF.0000000000003106



The current coronavirus disease 2019 (COVID-19) pandemic bears witness to devastating morbidity and mortality associated with this illness, at upwards of 95.54 million global cases and 2.04 million deaths at the time of this writing.[1] Of its many manifestations, hypercoagulability and venous thromboembolisms (VTE) often lead to dire complications such as pulmonary embolism (PE).[2] In adult case series, 20–30% of critically ill patients manifested PE despite thromboprophylaxis[3–5] at a rate higher than that seen in controls identified before the pandemic. In contrast, PE as an initial finding in the pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patient has not been previously reported.[6] This report identifies 2 adolescent patients presenting with PE, and whether their cases illustrate mechanisms leading to PE in pediatric patients with SARS-CoV-2 remain to be determined.

## CASE REPORT 1

A 15-year-old female with obesity (body mass index 46.6) presented to the emergency department with sudden onset of nonradiating chest pain and associated shortness of breath of 1-hour duration. The patient denied fever, cough, dizziness, sick contacts, palpitations or paresthesias. She denied a history of thrombi or any recent prolonged immobility. There was no family history of hypercoagulable disorders or known COVID-19 exposures. Of note, the patient had taken oral contraceptives (OCPs) for 3 months but discontinued these 1 month before presentation.

Vital signs revealed tachycardia with slightly increased respiratory rate (heart rate 124 bpm, respiratory rate at 24 breaths/min, oxygen saturation at 94% on room air). On examination, the patient had no respiratory distress. Laboratories revealed an elevated D-dimer of 5.1 with normal prothrombin time (13.6 seconds), aPTT (26.3 seconds) and international normalized ratio (1.04). A rapid nasopharyngeal antigenic test for SARS-CoV-2 was also positive. Cardiac enzymes were elevated (troponin-I 0.92 ng/mL). A comprehensive metabolic panel, complete blood count with differential, urine drug screen, lower extremity ultrasound and electrocardiogram were normal. A computed tomography (CT) and angiography of the chest (Fig. 1A) revealed moderate thrombus in the distal left and right pulmonary artery extending into the upper and lower lobes bilaterally, with right heart strain. There was a mild opacity in the right lower lobe consistent with developing pneumonia or atelectasis. An echocardiogram demonstrated mildly depressed right ventricular systolic function. The patient received a heparin infusion that was titrated to an aPTT goal of 60–90 seconds. She also received nasal cannula oxygen at 2 L/min and was transferred to the pediatric intensive care unit for monitoring.

Adult interventional cardiology was consulted for potential thrombectomy and recommended continuing medical management. Mechanical thrombectomy or catheter-directed thrombolysis was deferred because of the distal locations of the thrombi and mild symptoms. Her cardiac enzyme elevation improved over 2 days, and her symptoms manifest only as chest pain on exertion. An echocardiogram on hospital day 2 showed improvement to normal right ventricular systolic function and size, although a repeat CT and angiography of the chest showed persistent significant PE burden. Given her improved heart function and clinical stability, she transitioned to enoxaparin on day 3. The patient improved and was transferred to the hospital floor on day 6 of admission. She demonstrated a hepatic transaminitis (alanine aminotransferase 112, aspartate aminotransferase 52) but was otherwise asymptomatic from an abdominal standpoint. Hypercoagulability evaluations for systemic lupus erythematosus, antiphospholipid antibody syndrome, factor V Leiden thrombophilia and prothrombin gene mutation were negative. Levels of protein C, S and antithrombin III were deferred to follow-up because of the effect of heparin on these anticoagulants and are not available at the time of this report.

She initially tested positive for SARS-CoV-2 infection via nasopharyngeal PCR and demonstrated IgG antibodies to the virus upon admission. Daily multisystem inflammatory syndrome in children (MIS-C) screening was performed using lactate dehydrogenase, ferritin, fibrinogen and procalcitonin, and these values were normal. C-reactive protein was elevated at 26.9 mg/L as well as sedimentation rate at 35 mm/h. She received 5 days of dexamethasone, and remdesivir was deferred. From a respiratory standpoint, the patient transitioned to room air on day 3 and maintained normal oxygen saturations. She remained afebrile and without any respiratory, inflammatory or gastrointestinal symptoms of COVID-19 throughout her hospital stay. She was discharged 10 days after admission, receiving enoxaparin with planned 3-month hematology follow-up. No new COVID-19 cases among her contacts were reported to her care team.

## CASE REPORT 2

A 16-year-old female with obesity (body mass index 42.7) and a history of uncontrolled diabetes mellitus (HgbA1C 11.6%) presented with 2 weeks of fatigue leading to bedrest, several days of shortness of breath with productive cough presented to the emergency department with hypoxia and tachycardia (heart rate 127 bpm, respiratory rate 29 bpm, weight 125.6 kg). She described "feeling bad" and was largely bed-bound aside from eating and hygienic self-care. At hospital admission, she became syncopal while receiving a delivery. She was found by a bystander and was brought to the emergency department. Although her glucose level was elevated at 358 mg/dL, she did not demonstrate acidosis, an anion gap or ketosis.

Given her hypoxia to 86% saturation on room air, a chest CT was obtained and showed a significant pulmonary saddle embolus, as well as distal branch pulmonary emboli and right ventricular/left

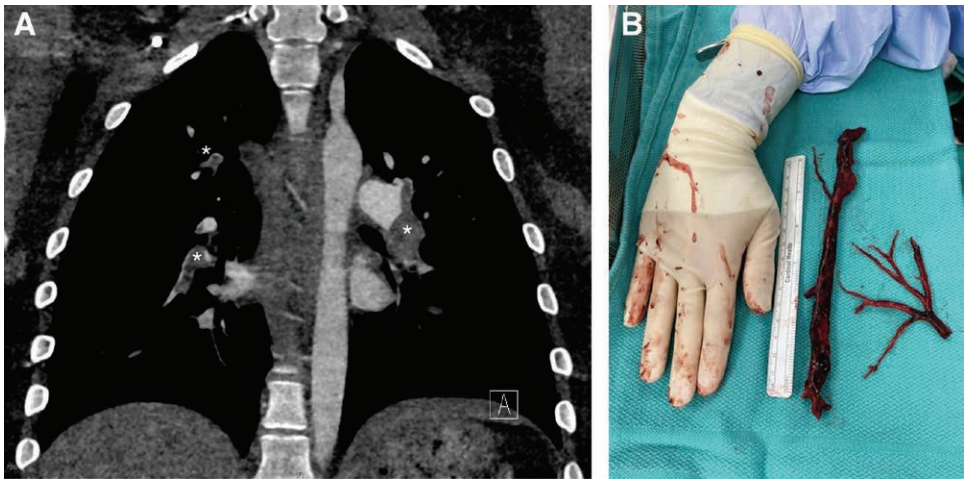


**FIGURE 1.** Imaging obtained during patient course. A: Coronal view of admission CT angiography for Case Report 1 through the distal branch pulmonary arteries. Significant embolism burden noted bilaterally marked by asterisk (*). B: Image of pulmonary embolism removed from patient in Case Report 2, surgeon's hand and ruler to provide scale.

ventricular ratio diameter ratio > 1.0 indicating right ventricular strain. She did not endorse the recent use of regular OCPs. There were patchy ground glass opacities in the right upper and bilateral lower lobes consistent with viral infection or pulmonary edema.

Based on her symptomatology, right heart strain and proximal pulmonary emboli burden, she underwent pulmonary embolectomy via median sternotomy under cardiopulmonary bypass. Two emboli were removed, the larger being 8.3 × 5.1 × 1.2 cm (Fig. 1B). A postoperative transesophageal echocardiogram revealed no additional emboli and moderately depressed right ventricular systolic function. After this, she recovered in the pediatric ICU, was extubated by postoperative day 1 and progressively weaned from noninvasive positive pressure ventilation to room air by the time of discharge. No deep vein thrombosis was discovered on ultrasound imaging on postoperative day 0. Serial echocardiographic assessments of right ventricular function proved too technically difficult. A predischarge cardiac CT was obtained and revealed resolution of right ventricular dilatation and otherwise no clear evidence of persistent thrombosis or right ventricular dysfunction.

During her stay, rapid COVID-19 antigen tests were performed however returned negative, and a COVID-19 IgG assay was positive on postoperative day 2 however. She remained afebrile through her stay and improved from a pulmonary standpoint. MIS-C screening was performed although on postoperative day 3 and demonstrated elevated levels of fibrinogen ranging from 619 to 748 mg/dL, interleukin 6 at 22.57 pg/mL, lactate dehydrogenase at 302 units/L, ferritin at 520 ng/mL, erythrocyte sedimentation rate of 97 mm/h, C-reactive protein at 209 mg/L and procalcitonin of 0.39 ng/mL. In light of a lack of symptoms, MIS-C specific immunomodulatory therapies were not initiated. An admission blood culture remained negative, and a urine culture revealed *Escherichia coli* for which she was treated with ceftriaxone and transitioned to cephalexin on day 2 of a 7-day course.

From a thrombophilia standpoint, her functional protein S level was low at 36 m, and antithrombin III level was depressed at 67 consistent with consumption because of extensive thrombosis and heparin use, respectively. Protein C activity was normal at 82 as well as total protein S at 114%. D-dimer at admission was elevated 0.76 µg/mL. Lupus anticoagulant, factor V Leiden and prothrombin gene mutation were not measured and were to be evaluated at hematology follow-up 3 months after discharge which is not available at the time of this writing. Anticardiolipin and β-2 glycoprotein assays were normal. She was initially managed with heparin infusion titrated to an activated coagulation time of 160–180 and then transitioned to apixaban on postoperative day 3. She was discharged 11 days after admission, and no new COVID-19 cases among her contacts were reported to her care team.

## DISCUSSION

This is the first report of pediatric patients presenting with submassive PE as primary issues in the setting of concomitant SARS-CoV-2 infection without MIS-C. One previous report[7] describes the case of a 15-year-old female who demonstrated SARS-CoV-2 IgG antibodies after manifesting massive PE and cardiopulmonary failure while recovering from a laparoscopic appendectomy. In contrast to the patient in Case 1, the patient described by Kotula et al[8] consistently demonstrated negative rapid SARS-CoV-2 antigen tests, and she also demonstrated MIS-C which the patient in Case 1 did not. With regard to her OCP history, antithrombin III and fibrinogen levels normalize within 2–6 weeks after discontinuation of OCPs. There is a case report of a 61-year-old man who was found to have died from fatal saddle PE in the absence of SARS-CoV-2 symptoms or rapid COVID-19 assay positivity 5 and 3 days before death although there were 2 sick contacts who demonstrated positivity.[9] This suggests that this phenomenon is not isolated to children.

Neither patient manifested classic symptoms of MIS-C: fever, gastrointestinal symptoms, neurologic symptoms, rash, conjunctivitis, oral mucosal changes, extremity erythema or swelling or cervical lymphadenopathy. While inflammatory biomarkers were elevated, they were not diagnostic of MIS-C. Their lack of symptoms and inflammation contrasted starkly to the severity of their VTE.

It is unclear as to what thrombosis prophylaxis is warranted in children exposed to SARS-CoV-2 given a dearth of evidence. Given that 31% of hospitalized adults with infection demonstrate evidence of VTE in some series,[4,10] considering older adolescents' risk for COVID-19–related comorbidities including PE seems reasonable. Current recommendations on thrombosis prevention in pediatric patients with COVID-19 infection[11] are based on a strong family/personal history of VTE or presence of a central venous catheter with 2 risk factors or 4 or more total risk factors. These risk factors include postpubertal age, decreased motility, burns, malignancy, venous stasis or low cardiac output state, estrogen therapy, active systemic infection, inflammatory disease flare, obesity, severe dehydration or recent surgery/trauma. Considering

these risk factors, these patients were postpubertal and obese. It is unclear how nuances in the OCP history of the patient in Case 1 or bedrest of the patient in Case 2 influenced development of deep vein thrombosis; however, the severity of VTE symptoms they experienced appear disproportionate to those factors.

This case illustrates the potential for bilateral symptomatic submassive PE in functional adolescents with concurrent SARS-CoV-2 infection. Clinicians caring for such populations benefit from recognizing this risk and should consider adult management guidelines for patients with these clinical features.

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# PARENT-COLLECTED NASAL SWAB FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 TESTING IN CHILDREN

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**Abstract:** This cross-sectional study, including children hospitalized for severe acute respiratory syndrome coronavirus 2 infection, demonstrates for the first time that nonhealthcare worker parents perform similarly to healthcare workers in the administration to their children of an unsupervised nasal swab for severe acute respiratory syndrome coronavirus 2 detection by following written instructions and video tutorials.

**Key Words:** swab, coronavirus disease 2019, pediatrics, diagnosis

Accepted for publication January 21, 2021

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The authors have no funding or conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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DOI: 10.1097/INF.0000000000003103

Health and social policies geared to the containment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic have impacted dramatically children's access to education. The preservation of social interaction with peers and the attendance to schools is crucial for proper psychophysical development during childhood. The early identification of pediatric cases is thus essential for effective contact tracing and outbreaks containment. Moreover, especially during winter, children frequently develop infections that can clinically mimic coronavirus disease 2019 (COVID-19). For this reason, early and frequent access to SARS-CoV-2 testing is fundamental for the rapid reintegration of the symptomatic child into the community, thus minimizing the number of missed school days and the impact on family organization and parental work. However, nasopharyngeal or oropharyngeal swabbing performed by a healthcare worker (HCW) may be perceived by children as a traumatic experience, especially in certain age groups and if repeated several times. The World Health Organization acknowledges the existence of an increasing demand for simplified sampling procedures.[1] Expanding data is showing that properly instructed non-HCWs are capable to provide adequate self-collected samples (Ricci et al. submitted).[2] Nasal swabbing performed on children by parents has already proven to be efficient for influenza diagnosis and is now contemplated in the United Kingdom government testing guidance as a feasible option for SARS-CoV-2.[3,4] Nevertheless, evidence about diagnostic performance of nasal swabbing for SARS-CoV-2 administered to children by parents is lacking.

The aim of the present study was to assess whether parents perform similarly to HCWs in the administration of an unsupervised nasal swab to their children by following simple instructions and a video tutorial.

## MATERIALS AND METHODS

This cross-sectional study included pediatric patients (0–18 years old) hospitalized for COVID-19 at the Meyer Children's University Hospital in Florence between September 1, 2020, and November 15, 2020. At admission, all the eligible children had a positive real-time reverse transcription-polymerase chain reaction SARS-CoV-2 test result on a swab performed by HCW. Children with HCW parents were excluded from the study. There were no other exclusion criteria. Each enrolled patient underwent first an unsupervised anterior nasal swab performed by the parent after following written instructions and a video tutorial. A second anterior nasal swab was performed by a trained HCW immediately after the first. The swabs were performed during the hospitalization, in addition to those routinely recommended by the Italian Ministry of Health.

The definition of clinical severity was based on the position paper of the Italian Society of Pediatric Infectious Disease.[5]

A flocked swab (ESwab Copan, Brescia, Italy) was used for the collection of all samples, which were analyzed using reverse