

Deep vein thrombosis and pulmonary embolism in pediatric COVID-19

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Abstract

Thrombotic complications of SARS-CoV-2 have been increasingly recognized as an important component of COVID-19 in adults; however, they have been less evident in children. We report a case of a teenager with positive SARS-CoV-2 RT-PCR and underlying prothrombotic risk factors, including aromatase inhibitor therapy, who developed deep vein thrombosis resulting in pulmonary embolism. Laboratory tests revealed deranged coagulation parameters (high D-dimers and Factor VIII and low antithrombin). The patient required intensive care and was managed with anticoagulants, dexamethasone and antithrombin concentrate. Clinical condition and hemostatic profile gradually improved. A review of the available literature for similar cases is presented.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has various extra-pulmonary manifestations, including venous thromboembolism (VTE)¹. Pediatric recommendations for hospital-associated VTE in COVID-19 have been provided^{2,3}, though data regarding VTE risk in non-hospitalized children are limited. We describe the case of an adolescent with a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) and underlying prothrombotic risk factors who developed deep vein thrombosis (DVT), resulting in pulmonary embolism (PE).

Case Description

A 15-year-old male was referred to our emergency department with a four-day history of gradually progressive pain and swelling of the right lower limb, in the absence of any recent history of injury. A magnetic resonance imaging (MRI) of the hip, undertaken previously in outpatient setting following orthopedic referral, demonstrated a thrombus in the external iliac vein (Figs. 1A and 1B). The patient also reported gastrointestinal symptoms two weeks earlier, i.e., diarrhea and vomiting, along with low-grade fever of 37.3°C, lasting for two days. With regards to his medical history, he was under anastrozole, an aromatase inhibitor (AI), over the last two years, as prescribed by his physician for short stature.

The adolescent was overweight with body mass index (BMI) of 25.2 kg/m². On admission, he had body temperature of 38.9°C and exhibited pain in the right hip with limited mobility of the joint and edema of the right knee. Triplex ultrasound of the right lower extremity depicted an extended DVT, from the external iliac vein down to the great saphenous and popliteal vein. Further laboratory investigations were

undertaken, including SARS-CoV-2 RT-PCR on nasopharyngeal sample. Initial management consisted of combined antibiotic therapy with intravenous (IV) ceftriaxone and teicoplanin and anticoagulation treatment with subcutaneous low molecular weight heparin (LMWH) i.e., tinzaparin in a therapeutic dose of 175 IU/kg body weight once daily.

Within the first hour, he developed hypotension with low diastolic blood pressure (25 mmHg), not responding to IV fluids, tachycardia (125 beats/min) and reduced urine output. Saturation of oxygen dropped to 94%, few hours later. Computed tomography pulmonary angiogram (CTPA) demonstrated embolus in the left pulmonary artery. (Figs. 1C and 1D), whereas the SARS-CoV-2 RT-PCR revealed high viral load.⁴

The patient was urgently transferred to the COVID-19 pediatric intensive care unit where IV dexamethasone 0.15 mg/kg (max 6 mg/day) was added to his treatment plan. Oxygen supply was maintained to 2-3 L/min without further need of intubation or mechanical ventilation. Subcutaneous tinzaparin was continued and a single dose of IV antithrombin concentrate was administered due to low levels, resulting in immediate response to 125%. Systematic thrombolysis was not required. High temperature subsided 24 hours later, oxygen was weaned off and antibiotic treatment was discontinued following negative blood cultures.

The patient stepped down to the COVID-19 pediatric ward after 72 hours where he gradually improved. A total of ten days of IV dexamethasone was completed and subcutaneous tinzaparin was substituted by oral warfarin, after completion of three weeks. Anastrozole was discontinued. He was discharged 34 days after admission under warfarin 5 mg once daily. Hemostatic parameters and SARS-CoV-2 RT-PCR were regularly evaluated during hospital stay and post discharge, as summarized in Table 1. Genetic testing for hereditary thrombophilia has been scheduled after the acute phase of thrombosis.

Discussion

Only few patients under 18 years with COVID-19 have been reported with PE⁵⁻⁷. The vast majority of literature data refers to critically ill adults⁸⁻¹⁰, where local pulmonary thrombotic microangiopathy appears to be the underlying pathophysiological mechanism¹¹. In contrast, our patient had mild COVID-19 prior to manifestation of VTE, without hyperinflammatory state, and PE was secondary to embolization from the lower limb.

Puberty and age above 12 years increase the thrombotic risk in children². Nevertheless, the adolescent had additional prothrombotic risk factors. Aromatase inhibitor (AI) therapies prevent the conversion of androgens to estrogens and are mainly used in estrogen receptor-positive breast cancer. In children with short stature, they are supposed to allow for greater height potential by delaying the epiphyseal maturation, given the fact that the ultimate fusion of the growth plates in both males and females is estrogen-dependent¹². Thromboembolism is an adverse effect of AI in female breast cancer patients and women receiving anastrozole are found to have greater risk for VTE compared to untreated, healthy women¹³. Such adverse effects have been poorly investigated in children. Therefore, the inhibition of the estrogens production through the inhibition of the aromatase may lead to increased testosterone concentration. In turn, the increased testosterone levels in pubertal boys could lead to erythrocytosis and thrombotic events, but further investigation is needed in this context¹⁴. Moreover, in our patient, the reported pre-existing symptoms from gastrointestinal system could induce hypercoagulability in view of dehydration and increased blood viscosity, as described in adults with COVID-19¹⁵. The patient also reported excessive screen time due to his tele-education over the last weeks and the resulting immobilization, i.e. being sedentary for many hours, could constitute an additional risk factor through circulatory stasis, as described under the term of e-thrombosis¹⁶.

COVID-19 as well induces per se a hypercoagulable state¹⁷. The suggested mechanism^{18,19} is that the disease leads to an immunothrombosis response through the interplay between inflammatory and coagulation pathways, resulting in cytokine storm, neutrophil and complement activation which propagate a pro-agulant state. Furthermore, the virus itself provokes a direct endothelial injury activating the coagulation cascade. The vascular endothelium is a key target-organ of SARS-Cov-2²⁰ this endotheliitis²¹ was evident in our case, as high levels of Factor VIII (FVIII) were persistent. FVIII is a blood-clotting protein associated with inflammation but also direct endothelial damage²² and it has been suggested as a predictive coagulation

biomarker in COVID-19, as reported in a cohort study of adult patients, where high levels at admission were linked to early-onset VTE²³.

Coagulopathy in COVID-19 has further laboratory features, overlapping with other coagulopathies but also differing^{24,25}. Similarly, our patient presented high fibrinogen, which normalized soon after the initiation of anticoagulation, and significantly increased levels of D-dimers, which gradually decreased but remained above normal limits even after six weeks. Such elevated D-dimers e.g., >5 times the upper limit of normal values, are suggested as a marker for introducing thromboprophylaxis in children hospitalized with COVID-19, independently of clinical risk factors for VTE². Moreover, prothrombin time (PT) was mildly prolonged, with subsequently low Factor VII, whereas activated partial thromboplastin time (aPTT) and platelets count were, unlike in disseminated intravascular coagulation, normal.

The patient, additionally, demonstrated persistent low levels of antithrombin even after supplementation. Interestingly, his mother -who had also a positive SARS-CoV2 RT-PCR but remained asymptomatic- was found with low antithrombin (59%). During her reevaluation one month later (with negative RT-PCR), levels were almost restored (78%). These findings support the correlation between the virus and acquired antithrombin deficiency, as seen in studies showing low antithrombin in a high proportion of patients with COVID-19²⁶. This should be taken into consideration when introducing anticoagulation to patients with COVID-19; antithrombin deficiency induces heparin resistance and higher heparin doses or antithrombin concentrate to correct values < 70%, like in our case, might be needed^{27,28}.

In conclusion, our case underlines the fact that pediatric patients with SARS-CoV-2 infection, even the non – hospitalized, could develop serious VTE in the co-existence of underlying prothrombotic risk factors and COVID-19 associated coagulopathy. Clinical suspicion should be high in specific age groups like adolescents, who may receive therapies like AI or are more sedentary during the pandemic. Therefore, there is a need for further recommendations regarding VTE risk assessment, hemostatic monitoring and application of anticoagulation in children and adolescents with COVID-19.

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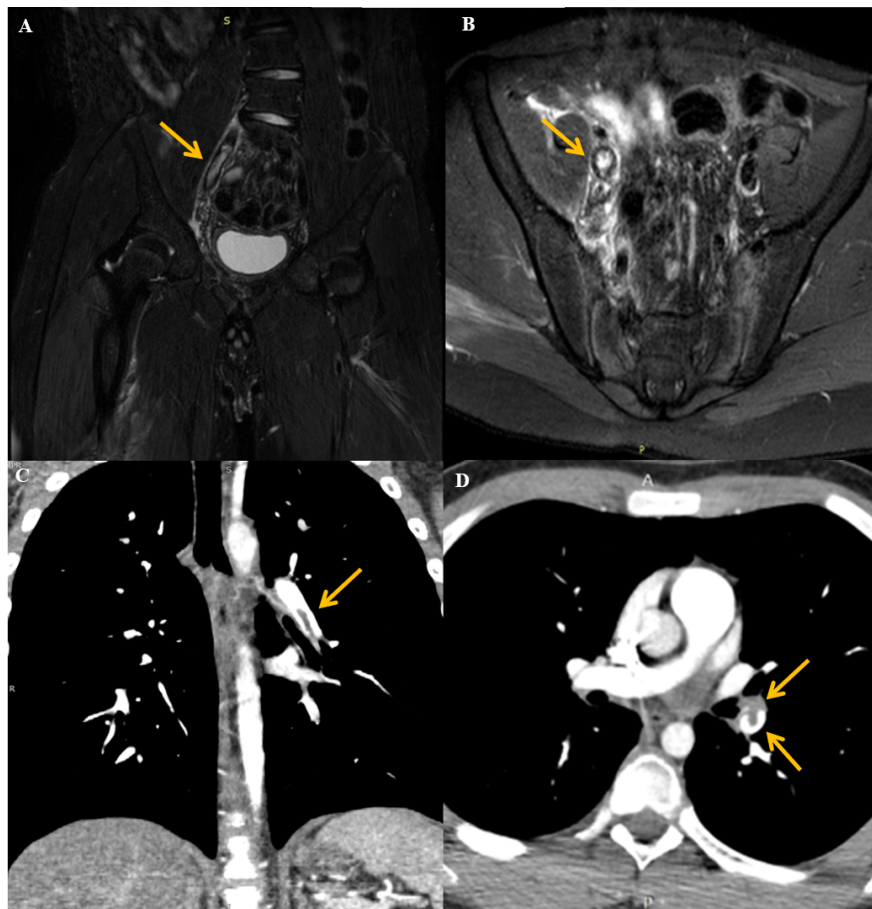
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FIGURE 1

Imaging confirmation of VTE. Coronal (A) and axial (B) fat-suppressed T2-weighted images of MRI scan of right hip joint, demonstrating a hyperintense clot in the right external iliac vein, and coronal (C) and axial (D) views of lung CTPA scan revealing a large pulmonary embolus of approximately 3 cm longitudinal diameter in left pulmonary artery's branch which supplies the left lower lobe.



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TABLE 1 Changes in laboratory parameters.docx available at <https://authorea.com/users/437900/articles/539238-deep-vein-thrombosis-and-pulmonary-embolism-in-pediatric-covid-19>