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CLINICAL CORRESPONDENCE

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Pulmonary embolism in adolescent with COVID-19 during aromatase inhibitor therapy

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To the Editor,

Thrombotic complications associated with SARS-CoV-2 infection have been quite uncommon in children and adolescents with COVID-19 who do not develop multisystem inflammatory syndrome.[1] We report a case of an adolescent boy with COVID-19 who presented with extended deep vein thrombosis (DVT) resulting in pulmonary embolism (PE), managed in intensive care unit, while he was on treatment with anastrozole, an aromatase inhibitor (AI), whose thromboembolic risk has not been thoroughly studied in pediatric populations.

The 15-year-old male presented to our emergency department with the diagnosis of right external iliac vein's DVT, as depicted in magnetic resonance imaging of the hip (Figure 1A,B, performed after orthopedic referral, due to a 4-day history of gradually progressive pain and swelling of the right lower limb. With regard to his medical history, the boy had short stature and was receiving anastrozole over the last 2 years for height increase. On admission, the adolescent exhibited pain in the right hip with limited mobility of the joint and edema of the right knee, while body temperature was 38.9°C and rest of vital signs were within normal range. A triplex ultrasound of the right lower extremity followed, demonstrating that the DVT was extending further down to great saphenous and popliteal vein. Initial anticoagulation treatment consisted of subcutaneous low molecular weight heparin (LMWH), that is, tinzaparin in therapeutic dose.

A few hours after admission, the boy developed hypotension with low diastolic blood pressure (25 mmHg), tachycardia (125 beats/min), and drop in oxygen saturation to 94%. Urgent computed tomography pulmonary angiogram revealed a big embolus of 3 cm longitudinal diameter in the left pulmonary artery, establishing the diagnosis of PE. (Figure 1C,D). Along with this finding, initial laboratory results were finalized (Table 1), including nasopharyngeal swab for SARS-CoV-2 RT-PCR, which was positive for COVID-19.

The boy was transferred to the COVID-19 pediatric intensive care unit where he received oxygen supply and intravenous (IV) dexamethasone 0.15 mg/kg (max 6 mg/day). He continued on subcutaneous tinzaparin and was supplemented with a single dose of IV antithrombin (AT) concentrate due to low AT levels, resulting in immediate response (values from 36% to 125%). There was no need for intubation or systematic thrombolysis. High temperature subsided 24 h later, oxygen was gradually weaned off and the patient stepped down to the COVID-19 pediatric ward after 72 h.

A total of 10 days of IV dexamethasone was completed and LMWH was substituted by oral warfarin after 3 weeks. The patient was discharged on Day 34 with oral therapeutic anticoagulation whereas anastrozole treatment was ceased. Hemostatic parameters were regularly monitored postdischarge, as summarized in Table 1. Further investigation with genetic testing for hereditary thrombophilia was negative and follow-up imaging showed radiographic thrombus resolution.

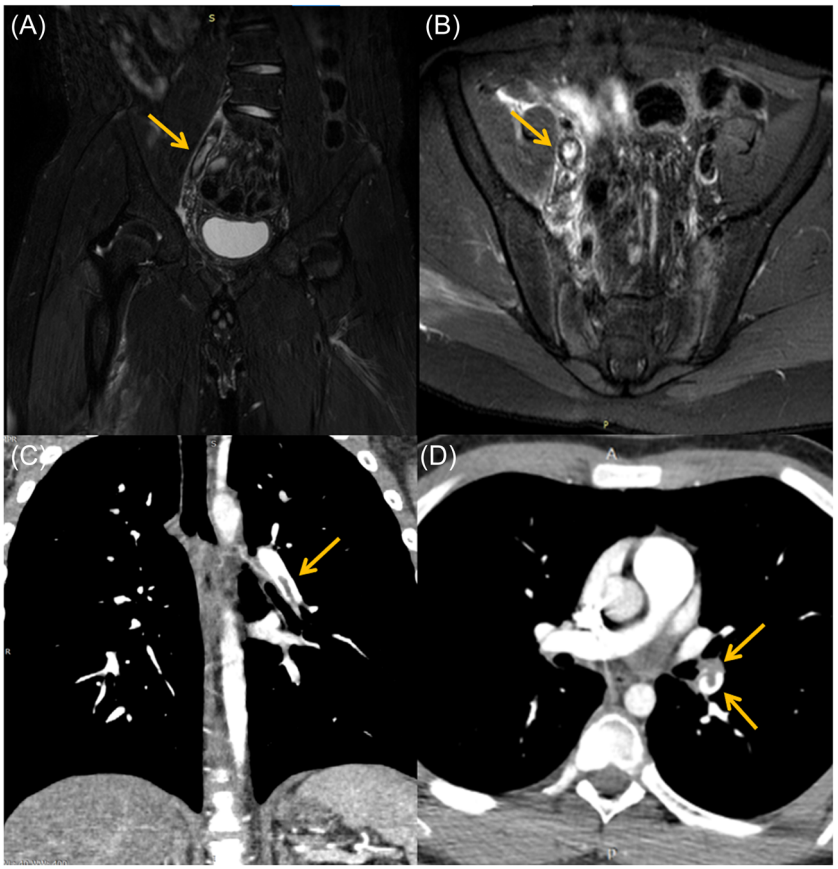

FIGURE 1 Imaging confirmation of VTE. Coronal (A) and axial (B) fat-suppressed T2-weighted images of MRI scan of right hip joint, demonstrating a hyperintense clot in the right external iliac vein, and coronal (C) and axial (D) views of lung CTPA scan revealing a large pulmonary embolus of approximately 3 cm longitudinal diameter in left pulmonary artery's branch which supplies the left lower lobe. CTPA, computed tomography pulmonary angiogram; MRI, magnetic resonance imaging; VTE, venous thromboembolism. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Changes in full blood count and hemostatic parameters

Laboratory parameter	Admission	Week 2	Week 4	Week 6	Week 9	Normal range
WBC (K/μl)	10.57	8.96	8.57	7.96	5.66	4.5–13.0
ALC (μl)	1210	2980	3630	3700	2600	1200–5200
Hg (g/dl)	13.0	13.9	13.8	13.5	14.6	14.5 (13.0)[a]
Plt (K/μl)	211	299	242	177	223	150–350
PT (s)	**16.3**	12.7	**27.4**[b]	**18.2**[b]	**20.4**[b]	10–14
aPTT (s)	30.4	32.2	27.5	18.2	20.4	20–39
FVII (%)	**43**	69	**13**[b]	NA	NA	60–120
FVIII (%)	**214**	**173**	**167**	**153**	**153**	50–150
Fibrinogen (mg/dl)	**440**	269	275	269	309	200–400
D-dimers (ng/ml)	**10**	**2.6**	**1.7**	**0.9**	0.2	<0.5
Antithrombin (%)	**36**	**56**	**67**	**75**	**76**	80–120
SARS-CoV-2 RT-PCR	**Positive**	**Positive**	**Positive**	**Positive**	Negative	Negative
Ct for ORF1ab target	**12.7**	**27.78**	**33.52**	**33.69**	>40	>40
Ct for N target	**11.8**	**29.11**	**31.3**	**31.93**	>40	>40

Note: Parameters outside the normal range for age are in bold.

Abbreviations: ALC, absolute lymphocyte count; aPTT, activated partial thromboplastin time; Ct, cycle threshold; FVII, Factor VII; FVIII, Factor VIII; Hb, hemoglobin; N, nucleocapsid protein; NA, not available; ORF, open reading frame; Plt, platelet count; PT, prothrombin time; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

[a]Data are mean (−2SD).

[b]Abnormal values due to oral Vitamin K antagonist treatment (warfarin).

PE in our patient was secondary to venous thromboembolism (VTE) affected the lower limb and was caused by the hypercoagulability state induced by the virus. Deranged hemostatic parameters, that is, prolongation in prothrombin time, elevated D-dimers, and high levels of factor VIII, confirmed the presence of COVID-19 associated coagulopathy, given that these hemostatic alterations are typical of the entity.[2] Systematic thrombolysis was not required in our case, despite the presence of initial hemodynamic instability. In addition to therapeutic anticoagulation and treatment with steroids, management as well included supplementation with IV antithrombin concentrate, due to patient's acquired antithrombin deficiency, a serious prothrombotic condition present in COVID-19.[3]

Nevertheless, apart from the procoagulant effect of COVID-19, treatment with anastrozole could further enhance the thrombotic risk. AI therapies block the aromatase-mediated synthesis of estrogens from androgens and are used in adolescent boys with short stature, aiming at greater height potential by delaying the epiphysial maturation, given the fact that the ultimate fusion of growth plates is estrogen-dependent. Although their adverse effects have been poorly assessed in pediatric populations, there have been suggestions that such therapies could cause VTE in pubertal boys.[4] The potential mechanism is that the mitigation of androgens' conversion to estrogens could result in increased testosterone concentration which, in turn, may lead to secondary erythrocytosis, increasing the risk of thromboembolic events.

Finally, there is an additional suggested mechanism through which AI potentializes SARS-CoV-2 complications. To date, there is wide evidence that one of the key factors of SARS-COV-2 susceptibility is the overexpression of transmembrane serine protease 2 (TMPRSS2), as the last facilitates SARS-COV-2 cell entry by priming the virus spikes for recognition by its cell receptor, the angiotensin-converting enzyme 2 receptor.[5] TMPRSS2 expression is positively regulated by androgens and, in this context, it has been postulated that the androgen accumulation occurring in patients receiving AI treatment could potentially promote SARS-CoV-2 infectivity and complications, through the androgen-driven upregulation of TMPRSS2.[6]

Our case underlines the fact that pediatric patients with COVID-19 could be at risk of developing severe VTE, including PE, especially in the presence of underlying risk factors that enhance the thrombotic mechanisms of SARS-CoV-2. Clinical suspicion should be high in specific age groups, like adolescents, and for certain therapies which are used in these populations. Further studies and updated recommendations regarding VTE risk assessment in children and adolescents are needed while COVID-19 is still on its ride.

AUTHOR CONTRIBUTIONS

Loukia Ioannidou: Writing–original draft (Lead); writing–review and editing (Equal). **Athina Dettoraki**: Conceptualization (equal); data curation–(equal); writing–review and editing (supporting). **Maria Noni**: Conceptualization (equal); data curation (equal); writing–review and editing (supporting). **Dimitra Koukou**: Data curation (Equal); writing–review and editing (supporting). **Aiketarini Michalopoulou**: Writing–review and editing (supporting). **Zoey Kapsimalli**: Data curation (equal); validation–(equal). **Evanthia Botsa**: writing–original draft (equal). **Athanasios Michos**: Conceptualization (equal); writing–review and editing (supporting). **Vana Spoulou**: Conceptualization (equal), writing–review and editing (supporting). **Helen Pergantou**: Conceptualization–(lead); writing–review and editing (equal). **Christina Kanaka-Gantenbein**: Conceptualization–(lead); writing–review and editing (equal funding source).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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