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Massive pulmonary thromboembolism in an adolescent with SARS-CoV-2 infection

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ABSTRACT

Thromboembolic events incidence is low in pediatrics; high suspicion and explicit management algorithms are essential.

We present a 12-year-old female patient with two weeks of dyspnea, orthopnea, and ankle edema. Tests showed metabolic acidosis, hyperlactatemia, elevated D-dimer, and positive SARS-CoV-2 CRP. The echocardiogram showed severe right ventricular dysfunction and supra-systemic pulmonary hypertension. Chest CT angiography showed extensive bilateral pulmonary thromboembolism. Anticoagulant therapy was started. She presented with hemodynamic instability. Adrenaline, norepinephrine, milrinone, and nitric oxide were started. The clinical picture was extremely severe in the first 24 hours. It was decided to perform systemic thrombolysis with alteplase, which led to an improvement.

Cardiorespiratory stabilization and anticoagulation are the mainstays of therapy in massive pulmonary thromboembolism. Fibrinolytic therapy is used in selected high-risk cases. In this patient, systemic reperfusion therapy with alteplase was performed with no significant complications.

Keywords: *SARS-CoV-2; pulmonary embolism; thrombolytic therapy; multiorgan failure.*

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INTRODUCTION

Coronavirus 2019 disease (COVID-19) in pediatrics can present with cardiovascular complications, such as myocardial injury, arrhythmias, and venous thromboembolism.

Pulmonary thromboembolism (PTE) is underdiagnosed in this population, with high morbidity and mortality, so it requires a high index of suspicion.[1] The prevalence is estimated to be increasing from 8.6 to 57 per 100 000 hospitalized,[1] mainly due to an increase in patients with severe pathologies and risk factors, such as the presence of central vascular access, obesity, or the use of hormone supplements.[2]

Virchow's triad plays a fundamental role in the PTE pathophysiology: endothelial injury, circulatory stasis, and hypercoagulability.[2] In SARS-CoV-2 infection, a hypercoagulable state has been described. Case reports in the SARS-CoV-2 delta wave inform up to 1.7% incidence of PTE in pediatric patients.[3]

CLINICAL CASE

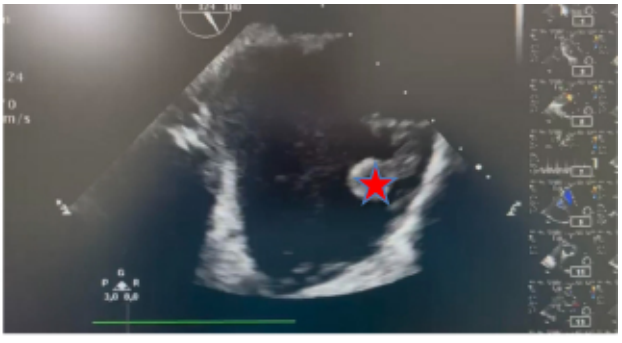
Female patient, 12 years old, with no history of morbidity or drug use, eutrophic (weight: 54 kilograms, height: 168 centimeters, body mass index: 19.1 kg/m^2), with two weeks of symptoms of weakening, dyspnea, orthopnea, dry cough, and ankle edema. At the emergency department, she presented with weakening, tachycardia, and dyspnea on minimal exertion. On physical examination, she presented slow capillary refill, decreased left basal pulmonary murmur, and hepatomegaly.

Tests showed metabolic acidosis, hyperlactatemia, leukocytosis, elevated D-dimer (DD), and positive SARS-CoV-2 CRP. The chest radiography showed bilateral pleural effusion and cardiomegaly. An abdominal ultrasound revealed ascites, hepatomegaly, and pericardial effusion.

She was admitted to intensive care (day 1) with the diagnoses of superinfected viral pneumonia, congestive heart failure, and pulmonary edema. Support was provided with noninvasive ventilation, furosemide, and ceftriaxone, achieving initial stabilization. The electrocardiogram showed nonspecific repolarization alteration and right bundle branch block. The transthoracic echocardiogram (*Figure 1*) was highly suggestive of pulmonary thromboembolism with severe right ventricular dysfunction, dilatation of right chambers, supra systemic pulmonary hypertension, and dilatation of pulmonary branches. Lower extremity ultrasound showed no deep vein thrombosis. Computed tomography angiography (CT angiography) of the chest (*Figure 2*) showed extensive bilateral pulmonary thromboembolism, right overload, pulmonary hypertension, atrial wall thrombus, and right basal pulmonary infarction. Anticoagulation therapy with low molecular weight heparin (LMWH) was initiated.

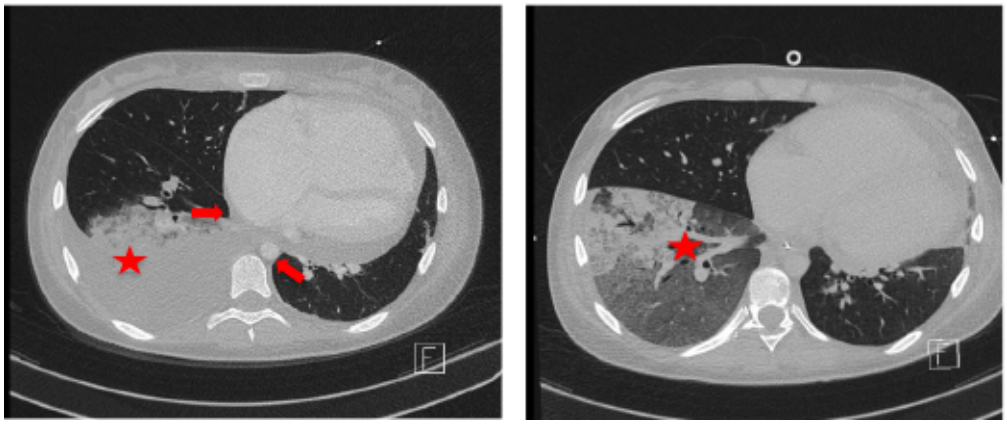
On day 2 of hospitalization, a transesophageal echocardiogram was performed under sedation, which confirmed the findings. The patient evolved with severe hemodynamic instability, cardiogenic shock, and ventricular arrhythmias. She was connected to mechanical ventilation and started on vasoactive support with adrenaline and norepinephrine in high doses, milrinone (0.75 ug/kg/min), and nitric oxide 20 parts per million (ppm). She progressed with extreme severity, with multiple organ failure. The brain natriuretic

Figure 1. Transesophageal echocardiogram



Evidence of a significant right atrial dilatation, with intracavitary thrombus (asterisk).

Figure 2. Chest computed tomography angiography evolution



The left image shows extensive bilateral right interlobar branch thromboembolism, bilateral segmental and subsegmental branches (arrows), right pleural effusion, and pulmonary infarction area (asterisk).
The right image, evolution after fibrinolysis, shows the hemorrhagic transformation zone (asterisk) without images suggesting thrombi in segmental or subsegmental branches.

peptide (pro-BNP) value was elevated.

It was decided to perform systemic thrombolysis (day 6) with alteplase 100 mg in a 6-hour infusion (0.25 mg/kg/h) and heparin in a continuous infusion (10 IU/kg/h). She underwent serial monitoring with examinations (hemogram, coagulation tests, fibrinogen, and DD). Post-procedure DD levels up to 99 800 ng/mL suggested effective thrombolysis (*Table 1*). She presented bleeding at vascular access insertion sites with no other adverse effects. On day 8 of hospitalization, an echocardiogram was performed, which showed severe right chamber dysfunction and pulmonary hypertension without thrombosis. Control CT angiography revealed a significant decrease of visible thrombi in pulmonary branches, with alveolar hemorrhage in the right lung's base.

Sildenafil was initiated on day 8, with an increase of progressive doses up to 4.5 mg/kg/day. Vasoactive agents were discontinued on day 10; nitric oxide was discontinued on day 14; mechanical ventilation was discontinued on day 16, and milrinone was discontinued on the 25th day of hospitalization. Carvedilol was initiated.

She progressed towards improvement, anticoagulation with LMWH in the therapeutic range, critical patient myopathy in resolution, and partial left tongue paresis in rehabilitation, with no other neurological deficit. Oxygen therapy was suspended, and she was transferred to the general ward one month after admission. The control echocardiogram (*Table 1*) on day 28

Table 1. Evolution of relevant tests according to days of hospitalization

Examination (baseline values)	Days of hospitalization					
	Day 1	Day 2	Day 6 (thrombolysis)	Day 9	Day 28	Day 41 (before discharge)
Troponin (up to 0.04 ng/mL)	0.770	0.260	0.130	0.045		
DD (up to 500 ng/mL)	18 730	16 800	99 800	3270		
Pro-BNP (up to 112 pg/nL)		14 367	11 088	8949		
EF (between 50-70%)	72	39	40	39	55	58
SF (over 30%)	12	14	19	17		
TAPSE (>16 mm)	10	10	10	10	28	33
PA (<0.5 Z-score)	+ 2.8				+ 2.74	+ 0.5

DD: D-dimer, EF: ejection fraction, PA: pulmonary artery diameter, pro-BNP: brain natriuretic peptide, SF: shortening fraction, TAPSE: tricuspid annular plane systolic excursion.

showed moderate right chamber dilatation and slightly improved right ventricular systolic and diastolic function, without left chamber dysfunction or images of thrombi. She was discharged on day 42 and maintained outpatient controls with satisfactory evolution.

DISCUSSION

We present a case of high-risk massive pulmonary thromboembolism (cardiogenic shock, intracavitary thrombus, supra-systemic pulmonary hypertension, elevated troponins, and pro-BNP) in the context of a SARS-CoV-2 infection in a pediatric patient who received satisfactory therapy with systemic thrombolysis.

Thromboembolic events incidence is low in pediatrics;[4] high suspicion is essential for timely diagnosis, with explicit algorithms for management and use of ancillary tests. The presentation in pediatrics is mainly with nonspecific symptoms, such as dyspnea and prechordalgia; the presentation as cardiogenic shock, as in our patient, is unusual (15% of the cases).[1] A mortality rate of up to 9% is described in the general population.[4] However, in cases of high-risk PTE, it could be as high as 31.8%, even 64% in case of cardiorespiratory arrest.[5]

The mainstays of therapy in PTE are cardiorespiratory stabilization and anticoagulation to prevent thrombus propagation, recurrence, and embolization.[4] In selected high-risk cases (massive PTE), fibrinolytic therapy is used, evaluating risks versus benefits. Reperfusion therapy has been increasing in recent years. However, there are still no guidelines with strong recommendations or studies of high methodological quality to guide administration in pediatrics, and they are mainly extrapolated from adults.

Reperfusion therapy is classified into systemic thrombolysis, catheter-directed thrombolysis, and surgical thrombectomy,[5] with no randomized studies comparing them. The choice depends on the type of patient, hemodynamic stability, bleeding risk, thrombus extension, and local experience. The former would be the therapy of choice in cases of PTE with hemodynamic compromise,[5,6] in patients without contraindications (active bleeding, thrombocytopenia less than 100 000/mm^3 or fibrinogen less than 100 mg/dL, recent trauma or surgery, intracranial hemorrhage, right-to-left shunts, extreme prematurity, cardiorespiratory arrest or asphyxia). Alteplase is the most used fibrinolytic, with pediatric literature extrapolated from case reports and observational studies.[7] It is a synthetic analog of tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin, promoting thrombus lysis by degrading fibrinogen. It has a short half-life (4 minutes) due to circulating inhibitors in plasma, with fibrinolytic activity up to 1 hour after infusion.[8] The optimal use is in the first 48 hours of presentation, but there are reports of use up to 14 days later.[9]

Regarding its dosage (extrapolated from adults), two dosage ranges are proposed: a) low dosage, 0.01-0.06 mg/kg/h (maximum of 2 mg/h) for 24 to 96 hours; and b) high dosage: 0.1-0.6 mg/kg/h in 2-6 hours,[10] which could be repeated in case of initial failure. Reports of this therapy show similar effectiveness and adverse effects rates, except for a retrospective observational study that shows more need for reintervention in the low-dose group (in patients with stable hemodynamics). Only one study in adult patients with PTE reports less risk of bleeding with low doses, but in the analysis by subgroups (massive PTE), this effect is lost.[11]

Meta-analysis in adults (2787 patients) shows lower mortality with alteplase compared to anticoagulation alone (odds ratio [OR]: 0.59), which is lost when analyzed by subgroups of patients with high-risk PTE. This meta-analysis also shows higher rates of bleeding (OR: 2.91) and intracerebral hemorrhage (OR: 3.18) with thrombolysis compared to anticoagulation alone. Alteplase is the thrombolytic with the lowest risk of bleeding (OR: 1.07) compared to tenecteplase.[5,12]

In pediatrics, there are retrospective case reports (46 patients) with lower mortality (33%) in the use of thrombolysis therapy over anticoagulation alone (47%) in high-risk PTE,[13] with an incidence of 1.5% for intracerebral hemorrhage and 17% for significant bleeding.[8] Reviews in pediatrics (observational studies, 320 patients) show in the thrombolysis group a mortality of 3.6%, a failure to resolve of 22.2%, a 5.7% risk of significant bleeding, and a 9.5% incidence of post-thrombotic syndrome compared to 0%, 50%, 0% and 28.6% with anticoagulation, respectively.[7]

Concomitant use of anticoagulation with fibrinolytic therapy is recommended. There is no clarity between LMWH and unfractionated heparin (UFH), the latter being the most effective described, with doses of 10 IU/kg/h.[8,13,14]

Although there is no high-quality pediatric

evidence, the guidelines for the adult population are clear and allow the extrapolation of doses and management. Consensus in pediatrics indicates thrombolysis for life-threatening cases,[15] so the risk of bleeding should always be considered against the benefit of reperfusion. Each unit should develop its management algorithms without clear protocols and high-quality studies. ■

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