Case Report

Pulmonary Embolism complicated Acute Chest Syndrome and suspected SARS-CoV-2 infection in adolescents with Sickle Cell Disease.

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Abstract

SARS-CoV-2 causes a hypercoagulable state that predisposes patients to thromboembolic events. We report two adolescents with sickle cell disease who developed pulmonary embolism during an acute chest syndrome episode associated with a possible SARS-CoV-2 infection. Both sickle cell disease and SARS-CoV-2 infection predispose to thromboembolic disease. Thromboprophylaxis with low molecular weight heparin should be considered in adolescent with acute chest syndrome, related or not to COVID-19 disease.

Introduction

Acute chest syndrome (ACS) can be a severe life-threatening condition and is defined as an acute illness characterized by fever and/or respiratory symptoms, with a new pulmonary infiltrate on chest X-ray (1). In addition to an infectious cause, microvascular injury, fat embolism, fluid overload and/or hypoventilation may trigger or worsen ACS. In adults with sickle cell disease (SCD), ACS is the main cause of death and may be complicated by pulmonary embolism (PE) (2).

On January 01, 2021, a total of 82 745 324 COVID-19 confirmed cases have been reported in the world with 1 805 521 deaths. In Belgium, 644 242 confirmed cases were associated with 19 441 deaths. SARS-CoV-2 virus mainly causes a respiratory distress syndrome but can also affect other organs and has been associated with cardiovascular complications (3).

SARS-CoV-2 binds to the cells expressing angiotensin-converting enzyme 2 (ACE-2) which is mainly expressed in alveolar cells but also in cardiac epithelial cells as well as in intestine, kidney and blood vessels (4). Through this binding, ACE-2 is less active and angiotensin II increases, provoking vasoconstriction, inflammation, and oxidative organ damage.

People over 65 years-old or with co-morbidities (such as obesity and high blood pressure) are more at risk of having a serious illness when they are infected by SARS-CoV-2 (4).

In SCD, SARS-CoV-2 (as other viruses) can trigger vaso-occlusive crises (VOC) and/or ACS through a major inflammatory cascade. SCD can probably be considered as an additional risk of having complications, but evidence is needed to confirm this hypothesis (5).

SARS-CoV-2 disease favors hypercoagulable status by endothelial inflammation, hypoxia, immobilization and diffuse intravascular coagulation that puts patients at a significant risk of venous thromboembolic events (VTE) (6).

We report here two Adolescents and Young Adults (AYA) with SCD who developed PE during ACS in a possible context of SARS-CoV-2 infection.

Case report 1

On April 04, 2020, a 17-years-old boy with SCD and autism chronically treated with hydroxyurea, folic acid, aripiprazole and zinc was hospitalized for ACS and managed accordingly (Table 1). He presented low oxygen saturation on pulse oximetry with hypoxia (partial pressure of arterial oxygen of 65mmHg). Oxygen support through non-rebreather mask was needed from day 1 to day 13. In addition, 2 top-up transfusions were required. SARS-CoV-2 infection was confirmed on day 1 by polymerase chain reaction (PCR) on nasopharyngeal swab (no serologies have been performed). No other pathogen was found in blood cultures and the film array respiratory panel on the nasopharyngeal swab was negative. On day 12, respiratory distress worsened, and the biological inflammatory syndrome increased. Computerized tomography (CT) pulmonary angiogram revealed right postero-basal segmental PE (as well as an infiltrate in the basal fields) (Fig. 1A and 1B). Treatment with low molecular weight heparin (LMWH) was started and the patient could be discharged on day 19. LMWH treatment was scheduled for 3 months. When last seen in June 2020, the adolescent was well.

Case report 2

On April 24, 2020, an 18-year-old boy with SCD chronically treated with hydroxyurea and folic acid was hospitalized for ACS and managed accordingly (Table1). He didn't present hypoxia at admission. Oxygen saturation and hypoxemia worsened at day 6, and non-invasive ventilation was required until day 9 in the Pediatric Intensive Care Unit. At admission, pulmonary CT-scan revealed ground glass opacities in both lungs (suggestive of COVID-19 disease). In addition to ventilation support, two top-up transfusions followed by one exchange transfusion for persistent hypoxemia were decided. Prophylactic LMWH was administered from day 9 to day 12 when information about the risk of thromboembolism associated with COVID-19 had emerged, but it was stopped after 4 negative SARS-CoV-2 PCRs on nasopharyngeal swabs, and due to unavailability of guidelines for the thromboprophylaxis in COVID-19 patients at this time. On day 15, the patient became dyspneic, febrile again and the biological inflammatory syndrome increased. PE in the lower left segment (Figs. 2A and 2B) was found on CT pulmonary angiogram. After initiation of therapeutic LMWH, the patient improved and could be discharged on day 21 with LMWH scheduled for 3 months. On day 19, IgG-antibodies for SARS-CoV2 were positive which suggested a possible COVID-19 disease. Other microorganisms could not be identified on blood cultures or with the film array respiratory panel on the nasopharyngeal swab. When last seen in August 2020, the patient was well.

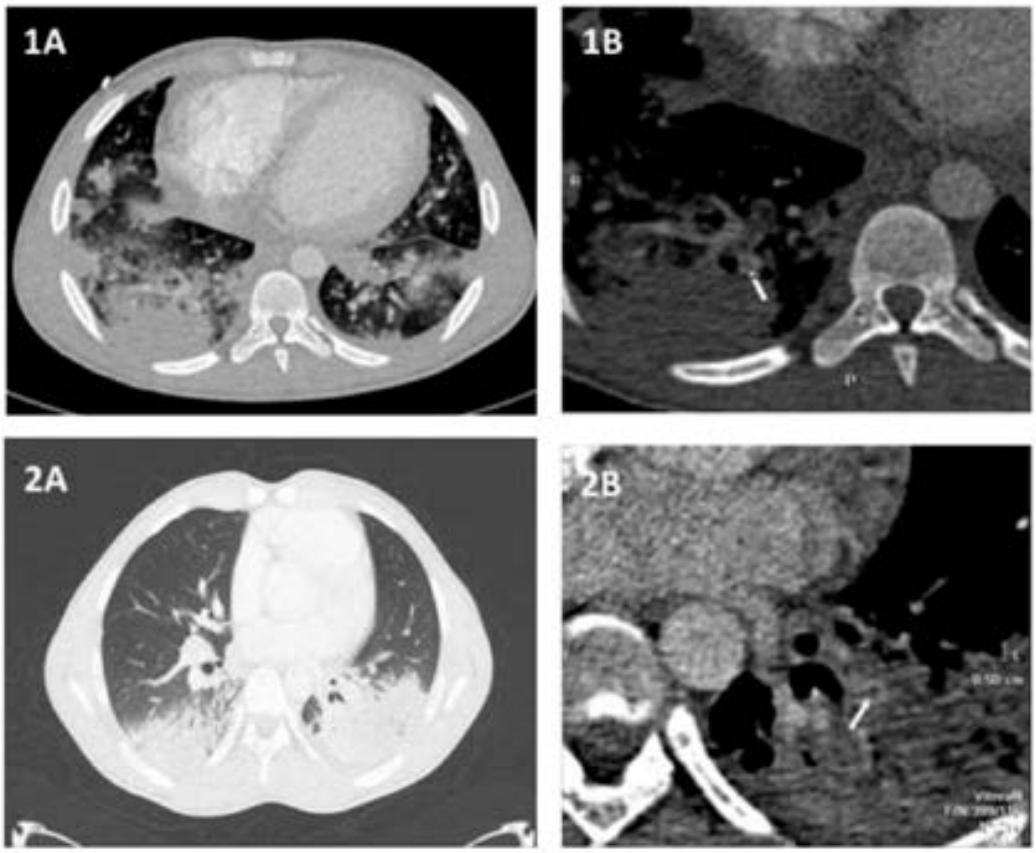
Discussion

The risk of VTE in the SCD adult population is high. In a cohort of 1523 SCD patients aged over 15 years, the Cooperative Study of SCD calculates a VTE

Table 1. *Patient characteristic*

	Patient 1	Patient 2
Sex	Male	Male
Age (years)	17	18
Body mass index	21.2	23.5
Medical History	Sickle Cell Anemia Autism spectrum disorder	Sickle Cell Anemia
Symptoms	Fever (39°C), cough, vomiting, fatigue, tachypnea (45 breath/minute)	Chest pain, chills, fever (38,5°C), tachypnea (40 breath/minute)
Laboratory values at admission Hemoglobin (g/l) White blood cell count (10E9/l) Lymphocytes (10E9/l) Neutrophils (10E9/l) Platelet Count (10 E9/l) CRP (mg/l)	 8.7 13.2 3.3 7.8 279 100	 7.4 18.9 2.2 14.9 300 150
Laboratory values at deterioration Hemoglobin (g/l) White blood cell count (10E9/l) Lymphocytes (10E9/l) Neutrophils (10E9/l) Platelet Count (10 E9/l) CRP (mg/l)	 8.2 12.5 1.6 7.8 800 340	 9.5 24.4 1.5 19.5 920 122
Respiratory support	Non-Rebreather-Mask (10L/min) for 13 days (day 1 to day 13)	Non-Invasive Ventilation for 4 days (day 6 to day 9)
Days in Pediatric Intensive Care Unit	0	3
Central venous catheter	No	No
Exchange transfusion	0	1 (day 8)
Prophylactic anticoagulation	None	Enoxaparin 3 days (day 9 to day 12)
Signs of deep venous thrombosis of the limbs	No	No
PCR on rhinopharyngeal swabs	Positive (day 1)	Negative (day 1,2, 8, 11)
Serology for SARS-CoV2	Not done	IgG 42UI/L – IgM 0 UI/L

Figure 1 : *CT pulmonary angiogram performed in Patient 1 on day 12 revealed consolidations and ground glass opacities in both lungs (Fig 1A) and right postero-basal segmental pulmonary embolism (Fig A2). In patient 2, CT pulmonary angiogram performed on day 15 confirmed the presence of consolidations in the lower lobes (Fig 2A) and right postero-basal segmental pulmonary embolism (Fig 2B).*



rate of 5.2 per 1000 person-years and the incidence of VTE was 11,3% by age of 40 years (7).

The American College of Chest Physicians recommends thromboprophylaxis for all SCD adults (> 18 years) who are admitted for an acute medical condition. There are no such recommendations for children. Our two patients were nearly adults and should have been treated as such. Recommendations for VTE prophylaxis in adults are usually not appropriate in children as their incidence of thrombosis is much lower. However certain factors are clearly associated with an increased risk of thrombosis: intensive care unit admission, the presence of central venous catheters, mechanical ventilation, postpubertal age, obesity, inflammatory disease. Our two patients had respectively 2 and 3 risk factors associated with an increased risk of VTE as indicated in the Branchford risk model which suggest pharmacological intervention in the presence of ≥ 3 risk factors (8).

The exact incidence and pathophysiology of PE in COVID-19 disease is not yet well known, but scientific data is increasing on this topic. SARS-CoV-2 causes an inflammatory cascade and a dysfunctional hemostatic system with high fibrinogen and D-dimers, leading to a hypercoagulable state and a risk for VTE. Hypoxemia further promotes vascular occlusion by decreasing blood flow by vasoconstriction (6).

On May 21, 2020, The American Society of Hematology recommended a pharmacologic thromboprophylaxis in all hospitalized adults with COVID-19, unless it is contraindicated. If this is the case, mechanical VTE prophylaxis (such as compression stockings) should be proposed (9). The Belgian Society on Thrombosis and Hemostasis (BSTH) adhered to this guideline in early June 2020. Our two patients were not treated according these recommendations due to their hospitalization in April 2020 and May 2020.

Compared to adults, SARS-CoV2 infections in pediatric population is less severe with frequent milder clinical courses or asymptomatic cases (10). Nevertheless, Feldstein reported presence of DVT/PE in children with multisystem inflammatory syndrome (MIS-C) (11).

Heilbronner and colleagues presented 12 SCD children (aged 5–17.5 years) admitted to the Pediatric Intensive Care Unit of the Necker Hospital in Paris for an ACS (12). All of them received thromboprophylaxis with Enoxaparin. Four patients had a PCR positive for SARS-CoV2 and they all required respiratory support with noninvasive ventilation. One of the patients aged 16 had a PE even under thromboprophylaxis. This data suggests that even pediatric SCD patients are at risk of PE and should be given antithrombotic prophylaxis. We tend to think that adolescents are more at risk than young children to evolve like adults, as is the case with our two patients.

Sars-CoV-2 infection in our second patient is suggested by the positive single point IgG serology but cannot be proven given the multiple negative PCRs on nasopharyngeal swabs. It could have been a previous exposure with no contribution to the existing respiratory illness.

Conclusion

Particular attention should be given to children and adolescents with SCD who are hospitalized during the COVID-19 epidemic and thromboprophylaxis with LMWH should be considered in adolescent with ACS in a context of COVID-19 disease or not. A high suspicion for PE should be kept in all circumstances in patient with SCD, and particularly in COVID-19 severe cases.

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