Pulmonary Embolism complicated Acute Chest Syndrome due to SARS-CoV-2 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 (SCD) who developed pulmonary embolism (PE) during acute chest syndrome (ACS) episode associated with a possible SARS-CoV-2 infection. Both SCD and SARS-CoV-2 infection predisposes to thromboembolic disease. Thromboprophylaxis with LMWH should be considered in adolescent with ACS, 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 infective cause, microvascular injury, fat embolism, fluid overload and/or hypoventilation may trigger or worsen ACS (2). In adults with SCD, ACS is the main cause of death and may be complicated by pulmonary embolism (PE) (3).

On October 05, 2020, a total of 35 330 119 COVID-19 confirmed cases have been reported in the world with 1 038 958 deaths. In Belgium, 130 235 confirmed cases were associated with 10 064 deaths. SARS-CoV-2 virus mainly causes a respiratory distress syndrome but can also affect other organs and has been associated with cardiovascular complications (4).

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 (5).

People above 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 (6) (7) (8).

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 (9).

SARS-CoV-2 disease favors hypercoagulable status by endothelial inflammatory, hypoxia, immobilization and diffuse intravascular coagulation that puts patients at a significant risk of venous thromboembolic events (VTE) (10).

We report here two AYA (Adolescents and Young Adults) with SCD who developed PE during ACS in a 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 PCR on nasopharyngeal swab (no serologies have been performed). No other pathogen was found on 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. CT pulmonary angiogram (CTPA) revealed right postero-basal segmental PE (as well as an infiltrate in the basal fields) (*Figs. 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 his admission. Oxygen saturation and hypoxemia worsened at day 6, and non-invasive ventilation was required until day 9. 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 has emerged, but it was stopped after 4 negative SARS-CoV-2 PCRs on nasopharyngeal swabs, and due to no guidelines available for the thromboprophylaxis in COVID-19 patients at this time. On day 15, the patient becomes dyspneic, febrile again and the biological inflammatory syndrome increased. PE in the lower left segment (*Figs. 2A and 2B*) was found on CTPA. 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 for SARS-CoV2 were positive which suggested a possible COVID-19 disease. Other germs could not be identified on blood cultures or with the FilmArray 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 (11). In a cohort of 1523 SCD patients aged over 15 years, the Cooperative Study of SCD calculates a VTE rate of 5.2 per 1000 person-years and the incidence of VTE was 11,3% by age of 40 years (12).

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.

Data of VTE in the children population with SCD are limited to case reports and the incidence is unknown (13) (14) (15). Kumar and colleagues accomplished a multicenter study over a 7-years period and showed an incidence of VTE (including 23,8% of PE) of 1,8%. The median age at VTE diagnosis was 15.9 years (16). The main risk factor in this population was the placement of central venous lines (CVL) but others risk factors have been demonstrated such as obesity, length of hospitalization, admission to ICU, older age, female sex, chronic renal disease and history of stroke. Studies on PE in SCD children are needed to develop evidence-based guidelines.

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 (17) (18).

On May 21, 2020, The American Society of Hematology published 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 (19) (20). The Belgian

Society on Thrombosis and Hemostasis (BSTH) joined the same guidelines 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 (21) (22). Among all COVID-19 pediatric cohort studies, no PE is described to our best knowledge.

Nevertheless, Heilbronner and colleagues presented 12 SCD children (aged 5–17.5 years) admitted to the PICU of the Necker Hospital in Paris for an ACS (23). 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.

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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Figure legend:

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, CTPA performed on day 15 confirmed the presence of consolidations in the lower lobes (Fig 2A) and right postero-basal segmental pulmonary embolism (Fig 2B).

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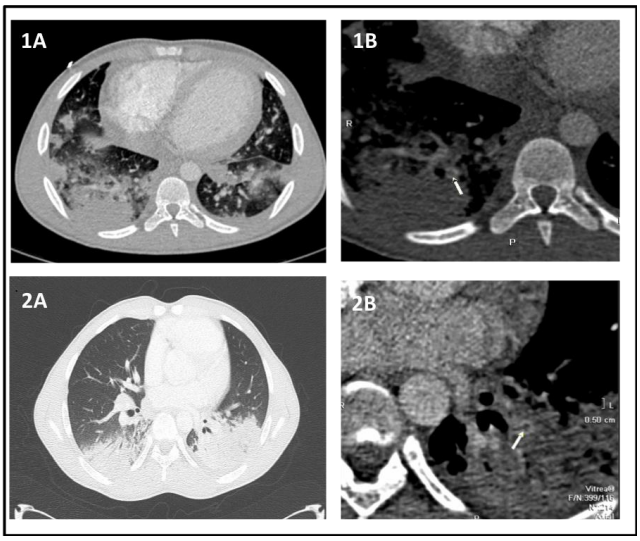
FIGURE 1: Chest imaging at deterioration



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