CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Man Wai Tang: data collection, data interpretation, literature search, writing; Erfan Nur: data interpretation, literature search, revising report; Bart J. Biemond: data interpretation, literature search, revising the report.

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SUPPORTING INFORMATION

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Dramatic improvement after tocilizumab of severe COVID-19 in a child with sickle cell disease and acute chest syndrome

To the Editor:

De Luna et al[1] recently reported a favorable outcome of an acute chest syndrome (ACS) related to a SARS-Cov-2 infection treated with tocilizumab (TCZ), in a 45-year-old male patient with homozygous sickle cell disease (SCD). Following this successful observation, TCZ was administered to a teenage girl with SCD who developed a severe COVID-19 associating ACS and pulmonary embolism.

This 16-year-old girl has a severe form of homozygous SCD with bilateral ischemic retinopathy. Given the recurrence of vaso-occlusive crises and abnormal transcranial doppler evaluations, she was treated with exchange transfusions from 5 to 11 years old, switched thereafter for hydroxyurea (22 mg/kg/day), with a favorable clinical outcome on vaso-occlusive events. She had no history of ACS or pulmonary hypertension, and her respiratory function and chest radiography were previously normal. As recommended by the French authorities, because of the COVID-19 outbreak, she was confined to her home with her parents. One week after her parents developed COVID-19 symptoms (cough, fever and anosmia), she presented with an isolated fever treated by acetaminophen (without non-steroidal anti-inflammatory drugs). Seven days later, she developed an ACS characterized by an acute chest pain associated with a respiratory distress syndrome (SpO_2 85%, superficial tachypnea 80/min, tachycardia 140/min). Real-time reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs confirmed the SARS-Cov-2 infection. Levels of C-reactive protein (355 mg/L), LDH (446 U/L) and D-dimer (23 611 ng/mL) were increased. Given the tachycardia and elevation of D-dimer in a SCD patient with COVID-19, a pulmonary embolism was suspected, which is assumed to be more frequent in this context. Indeed, the computed tomography pulmonary angiography (CTPA) showed a bilateral pulmonary embolism complicating the ACS, and was compatible with COVID-19 (bilateral consolidations with a halo sign on the right side, Figure S1). The patient was admitted to an intensive care unit (ICU) and required non-invasive ventilation, red blood cell exchange transfusion followed by simple transfusion (hemoglobin nadir 6.4 g/dL), and anticoagulation. Because of the severity of the disease, and based on the experience of COVID-19 in SCD adult patients,[1-3] she also received one pulse of intravenous

tocilizumab (TCZ, 8 mg/kg).[1] Plasma level of Interleukin (IL)-6 was extremely high (629 pg/mL; normal <8.5 pg/mL) and was even higher after TCZ (724 pg/mL), in line with IL-6 receptor blockade. To a much less extent, Tumor Necrosis Factor (TNF)-α level was also elevated (32.5 pg/mL; normal <20 pg/mL); and, on the contrary, IL-1β level was normal. The patient improved rapidly after TCZ treatment. Non-invasive ventilation was stopped 4 days after TCZ, with no oxygen requirement thereafter, allowing the discharge from ICU. She was then referred to a medical unit where CTPA was repeated 5 days after TCZ. A dramatic improvement occurred with a disappearance on the right, and a decrease on the left of both the pulmonary embolism and the consolidation opacities, as previously described by Cellina et al.[4] (Figure S1). She was finally discharged from the hospital 11 days after admission, with an oral anticoagulant treatment to be continued for a total of 6 weeks.

To our knowledge, this is the first reported use of TCZ in a COVID-19 pediatric SCD patient. A single injection of the treatment was followed by a rapid improvement of the patient's respiratory status, together with a dramatic improvement of CTPA images.

The etiology of ACS in children with SCD is often multifactorial, combining increased adhesion of sickle red cells to pulmonary microvasculature, pulmonary fat embolism, infarction, and infection, with an excessive inflammatory lung injury response in the presence of a damaged lung microvasculature. Infections are particularly common in children and frequent cause of ACS. The infectious microorganisms principally involved are *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, Respiratory Syncytial Virus, Influenza virus (notably the H1N1 strain), and Erythrovirus. Besides, monocyte activation has been reported in SCD and is responsible for an enhanced production of pro-inflammatory cytokines such as IL-6,IL-1β and TNF-α, which contributes to vaso-occlusion by promoting endothelial activation.[5] Many cytokines are elevated during steady-state in SCD, and some of them, especially IL-6, are further increased during vaso-occlusive crises.

To date, SARS-Cov-2 infection has been reported to cause ACS in four adult patients with SCD.[1-3] We recently managed two teenage SCD patients with ACS and COVID-19, including the presented case. Note, COVID-19 is characterized by an inflammatory storm enhanced by T cells and monocytes. Large amounts of IL-6 and TNF-α are found in the plasma of infected patients. Tocilizumab, that targets IL-6 receptors, was suggested to be effective on clinical evolution as well as on immune dysregulation.[6] After a single TCZ injection, serum IL-6 level first increases rapidly before decreasing. In the absence of significant clinical improvement with persistence of an elevated IL-6 level, a second and a third dose of TCZ can be administered after 12 and 24-36 hours respectively. A favorable CT evolution has been previously described in an adult patient 7 days after two TCZ injections at 12 hour intervals.[4] Cytopenia and increased transaminases have been reported and need to be monitored. No adverse effect of TCZ was observed in our patient.

In the context of the COVID-19 outbreak, this diagnosis has to be evoked in case of ACS in patients with SCD, as both ACS and COVID-19 pneumonia may present with similar features. The hyper-inflammatory state caused by the SARS-Cov-2 infection may be enhanced by the pro-inflammatory state of SCD. In such patients, TCZ seems to be safe and effective in adults as well as in children, in association with the usual treatment of severe ACS, including non-invasive ventilation and blood exchange transfusion.

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Glucose-6-phosphate dehydrogenase deficiency-associated hemolysis and methemoglobinemia in a COVID-19 patient treated with chloroquine

To the Editor:

Novel coronavirus disease (COVID-19) is spreading around the world and although clinical data are limited, immunomodulatory agents such as chloroquine and hydroxychloroquine are used as off-label treatment.[1] While these medications have an established clinical safety profile for their common use, (eg, malaria) their efficacy and safety in COVID-19 pneumonia remains unclear.[1] This is as most of the evidence to support use of chloroquine, or the less toxic hydroxychloroquine against the disease, comes from a small single arm trial.[2] As we demonstrate in this correspondence, the use of chloroquine for treatment of patients with COVID-19 infection is not without risks.

A 56-year-old man, with a medical history of diabetes mellitus type 2, presented to the emergency department with a 6-day history of myalgia and a dry cough. Oxygen saturation was 94% with room air and respiratory rate 24/min. There was no fever and his pulse and blood pressure were normal. So, COVID-19 was suspected which was confirmed by a real-time-PCR assay. A chest CT scan showed bilateral ground glass opacities. The patient was admitted for observation on a COVID-19 ward. During the following 2 days, his condition deteriorated with increasing need for oxygen administration. On the third day of admission his peripheral oxygen saturation dropped to 83% despite the use of a non-rebreathing mask with 15 L/min of oxygen. His respiratory rate was 30/minute. He was admitted to the intensive care unit (ICU) for initiation of mechanical ventilation. Treatment with chloroquine was started consisting of a first dose of 600 mg, followed by 300 mg twice a day (for 5 days).[1] Initial ICU laboratory results demonstrated a hemoglobin level of 11.4 g/dL (reference 13.7-17.7 g/dL), 12 hours later his hemoglobin level dropped to 8.9 g/dL and additional laboratory investigations demonstrated signs of severe hemolysis. A peripheral blood smear revealed findings consistent with hemolysis (Figure 1). Arterial blood gas results demonstrated increased levels of methemoglobin (9.1%; reference <1.5%). Given his ethnic background (African-Caribbean), glucose-6-phospate dehydrogenase (G6PD) deficiency was suspected and chloroquine was stopped.[3] He received 3 units of packed red blood cells in the following 48 hours. Although his methemoglobin level was relatively low, 1000 mg ascorbic acid (vitamin C) was administered intravenously four times a day for 2 days, to help optimize his oxygenation. His methemoglobin normalized within 6 days and laboratory testing for G6PD deficiency confirmed very low G6PD activity in the patient's red blood cells (Figure 1A,B). Genetic analysis demonstrated variant G6PD A- (the African variant).

Note, G6PD deficiency is an X-linked disease that affects 400 million people worldwide.[3] During a period of oxidative stress, intracellular levels of the reduced form of the nicotinamide adenine dinucleotide phosphate (NADPH) in these patients are depleted. This leads to the accumulation of oxidative damaged proteins and lipids in their red blood cells, resulting in hemolysis of deficient red blood cells. Chloroquine is on the list of oxidative drugs known to cause hemolysis in patients with G6PD deficiency.[3] The G6PD A- variant results in a moderate enzyme deficiency and clinically insignificant hemolysis. A short duration of chloroquine treatment at the above mentioned dose usually does not result in severe hemolysis, unless the antioxidant reserves are depleted by another (pre-existing) trigger, such as intensive systemic inflammation. In our patient, the ongoing inflammation due to the COVID-19 pneumonia had probably resulted in excessive consumption of intracellular antioxidants and thus NADPH. Under these circumstances, chloroquine possibly triggered a complete depletion of NADPH resulting in severe hemolysis. Our patient also suffered from a functional anemia due to methemoglobinemia. Hemoglobin is transformed to methemoglobin once ferrous iron (Fe^{2+}) of the heme group is oxidized to ferric iron (Fe^{3+}). Methemoglobin has such a high oxygen affinity that it virtually cannot release its oxygen in the tissues and this usually becomes clinically apparent at a level of 15% or more.[4] However, patients with severe anemia may have symptoms at lower levels. The most frequent cause of methemoglobinemia is exposure to oxidative drugs such as chloroquine.[5,6] Under normal circumstances methemoglobin is rapidly converted back to hemoglobin by the NADH-dependent cytochrome-b_5