5. Lin CI, Tsai CH, Sun YL, et al. Instillation of particulate matter 2.5 induced acute lung injury and attenuated the injury recovery in ACE2 knockout mice. *Int J Biol Sci*. 2018;14(3):253-265. https://doi.org/10.7150/ijbs.23489.
6. Watanabe T, Barker TA, Berk BC. Angiotensin II and the endothelium: diverse signals and effects. *Hypertension*. 2005;45(2):163-169. https://doi.org/10.1161/01.HYP.0000153321.13792.b9.
7. Gant NF, Daley GL, Chand S, Whalley PJ, MacDonald PC. A study of angiotensin II pressor response throughout primigravid pregnancy. *J Clin Invest*. 1973;52(11):2682-2689. https://doi.org/10.1172/JCI107462.
8. Dimmeler S, Rippmann V, Weiland U, Haendeler J, Zeiher AM. Angiotensin II induces apoptosis of human endothelial cells. Protective effect of nitric oxide. *Circ Res*. 1997;81(6):970-976. https://doi.org/10.1161/01.res.81.6.970.
9. Verlohren S, Stepan H, Dechend R. Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. *Clin Sci (Lond)*. 2012;122(2):43-52. https://doi.org/10.1042/CS20110097.
10. Zhou CC, Ahmad S, Mi T, et al. Angiotensin II induces soluble fms-Like tyrosine kinase-1 release via calcineurin signaling pathway in pregnancy. *Circ Res*. 2007;100(1):88-95. https://doi.org/10.1161/01.RES.0000254703.11154.18.
11. Murphy SR, Cockrell K. Regulation of soluble fms-like tyrosine kinase-1 production in response to placental ischemia/hypoxia: role of angiotensin II. *Physiol Rep*. 2015;3(2):e12310. https://doi.org/10.14814/phy2.12310.
12. Pickkers P, Sprong T, Eijk L, et al. Vascular endothelial growth factor is increased during the first 48 hours of human septic shock and correlates with vascular permeability. *Shock*. 2005;24(6):508-512. https://doi.org/10.1097/01.shk.0000190827.36406.6e.
13. Li C, Raikwar NS, Santillan MK, Santillan DA, Thomas CP. Aspirin inhibits expression of sFLT1 from human cytotrophoblasts induced by hypoxia, via cyclo-oxygenase 1. *Placenta*. 2015;36(4):446-453. https://doi.org/10.1016/j.placenta.2015.01.004.
14. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417-1418. https://doi.org/10.1016/S0140-6736(20)30937-5.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Received: 17 May 2020 | Revised: 18 May 2020 | Accepted: 19 May 2020

DOI: 10.1002/ajh.25877

Immune thrombocytopenia due to COVID-19 during pregnancy

To the Editor:

In April 2020, during the 2019 novel coronavirus disease (COVID-19) pandemic caused by the virus SARS-CoV-2, a pregnant patient was diagnosed with immune thrombocytopenia (ITP) triggered by COVID-19.

The 41-weeks-pregnant woman, with no significant past medical history, presented to the obstetric physician due to contractions. She had a sore throat but no other flu-like symptoms. She had no signs of easy bruising or bleeding. Her vitals at presentation were a temperature of 36·4°C, respiration rate of 16/min, peripheral oxygen saturation (SpO_2) of 98%, blood pressure of 115/80 mmHg, and pulse of 93/min. General laboratory examinations were performed, which showed a platelet count of 16 × 10E09/L. Two weeks earlier, the platelet counts were 98 × 10E09/L. The patient was suspected to have immune thrombocytopenia (ITP). Additional test with direct monoclonal antibody immobilization of platelet antigens (MAIPA) showed platelet auto-antibodies against glycoprotein V. Throat and nose swabs were positive for SARS-CoV-2.

The patient was diagnosed with a first presentation of ITP, most likely triggered by COVID-19. Treatment with intravenous immunoglobulin (IVIG) for 2 days was initiated. In order to be able to safely perform epidural anesthesia for the labor, 2 units of donor thrombocytes were administered. Her platelet counts increased to 80 × 10E09/L. Epidural anesthesia was complicated by hypotension with a suboptimal cardiotocography. Therefore, an urgent caesarian section was performed and a healthy daughter was born. Few hours later, she became hypoxic with a peripheral oxygen saturation of 91% without dyspnea. A chest CT showed infiltrates in the left lower lobe with ground-glass opacities, typical of COVID-19 (Figure S1). Within 24 hours, the peripheral oxygen saturation increased to 100% while breathing room air. Four days later, she was discharged without flu-like symptoms and with stable platelet counts of 82 × 10E09/L that normalized 3 weeks later (315 × 10E09/L). Her newborn daughter did not develop any symptoms of COVID-19. The newborn's platelets were 158 × 10E9/L at birth, but decreased to 41 × 10E09/L 5 days after birth. However, her platelets increased spontaneously thereafter, reaching 198 × 10E09/L at 3 weeks.

About 80% of patients infected with SARS-CoV-2 are asymptomatic or have mild flu-like symptoms.[1] While mainly a respiratory disease, COVID-19 can trigger widespread systemic pathology, ranging from thrombo-embolism, cardiovascular injury, hyper-inflammatory syndrome, immune-mediated pathology, and multi-organ failure.[2,3] Interestingly, COVID-19 has some unique aspects interfering with the immune system which are rarely observed in other respiratory viral infections.[4] Lymphopenia and, at the same time, a cytokine storm, which is reflected by elevated levels of acute phase reactants, show an affected innate and adaptive immune system and are thought to predict disease severity. Similar to other viral infections,[5] SARS-CoV-2 can also trigger ITP and probably autoimmune hemolytic anemia.[6] Our patient developed a COVID-19 induced ITP that was confirmed by a positive MAIPA. This case-report shows that COVID-19 can induce ITP even in patients with mild symptoms. Recently, Zulfiqar et al. reported a case of suspected ITP in a patient admitted due to COVID-19.[7] The patient had normal platelet counts at admission, but dropped gradually to 1 × 10E09/L in 8 days. However, no auto-antibodies against glycoproteins were found and no response to IVIG was observed in that patient.

As SARS-CoV-2 is now very widespread, we suggest testing for SARS-CoV-2 in patients suspected of a (relapsed) ITP, even in the absence of respiratory symptoms.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

FUNDING INFORMATION

This report was not funded by any grant. The corresponding author has full access to all the data.

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.

M.W. Tang, Erfan Nur, B.J. Biemond

Department of Clinical Hematology, Amsterdam University Medical Center, Amsterdam, The Netherlands

Correspondence

M.W. Tang, Department of Clinical Hematology, Amsterdam University Medical Center, Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands.

Email: m.w.tang@amsterdamumc.nl

DOI 10.1002/ajh.25877

ORCID

M.W. Tang https://orcid.org/0000-0001-9726-9943

REFERENCES

1. Thomas-Ruddel D, Winning J, Dickmann P, et al. Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020. *Anaesthesist*. 2020;69(4):225-235.
2. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med*. 2020;382:2012-2022.
3. Levi MT, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7(6):e438-e440.
4. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020. https://doi.org/10.1111/all.14364. Online ahead of print.
5. Goeijenbier M, van Wissen M, van de Weg C, et al. Review: viral infections and mechanisms of thrombosis and bleeding. *J Med Virol*. 2012;84(10):1680-1696.
6. Lazarian G, Quinquenel A, Bellal M, et al. Autoimmune hemolytic anemia associated with Covid-19 infection. *Br J Haematol*. 2020. https://doi.org/10.1111/bjh.16794. Online ahead of print.
7. Zulfiqar AA, Lorenzo-Villalba N, Hassler P, Andres E. Immune thrombocytopenic purpura in a patient with Covid-19. *N Engl J Med*. 2020;382(18):e43.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Received: 21 April 2020 | Accepted: 27 April 2020

DOI: 10.1002/ajh.25855

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