Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Update 3 (2021) 100047

Contents lists available at ScienceDirect

Thrombosis Update

journal homepage: www.journals.elsevier.com/thrombosis-update

COVID-19 as a trigger for splenic infarction in a patient with sickle cell trait: A case report

Álvaro Alejandre-de-Oña [a], Jaime Alonso-Muñoz [a], Pablo Demelo-Rodríguez [a,b,c,*], Jorge del-Toro-Cervera [a,b,c], Francisco Galeano-Valle [a,b,c]

[a] Venous Thromboembolism Unit, Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[b] Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Spain
[c] Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

ARTICLE INFO

Keywords:
Sickle cell trait
COVID-19
SARS-CoV-2
Splenic infarction
Epilepsy

ABSTRACT

Sickle cell trait (SCT) is the carrier state for sickle cell disease (SCD) and is usually perceived as a mild condition; however, previous studies have shown that hypoxemia may trigger sickle-cell related complications in these patients, including splenic infarction. Hypoxemia is a common finding in patients with COVID-19 pneumonia.

We present the case of a 19-year-old male with a history of epilepsy who presented to the emergency room due to abdominal pain in the left flank that appeared after presenting generalized tonic-clonic seizures and fever. SARS-CoV-2 RT-PCR testing in nasopharyngeal swab was positive and an abdominal computerized tomography (CT) revealed a massive splenic infarction. Hemoglobinopathy study using high-efficiency liquid chromatography demonstrated the presence of 39.7% HbS, thus confirming the diagnosis of SCT.

Hypoxemia, endothelial dysfunction and hypercoagulability caused by SARS-CoV-2 infection could lead to complement activation and microangiopathy, triggering the vaso-occlusive crisis that led to splenic infarction.

1. Introduction

Sickle cell trait (SCT) is the carrier state for sickle cell disease (SCD), which is an autosomal recessive disorder [1]. SCD is a serious condition caused by the presence of two sickle (S) genes leading to the production of abnormal hemoglobin (HbS). In patients with SCT red blood cells have one copy of the S gene and one copy of a normal gene, thereby showing an attenuate phenotype which reduces the likelihood of polymer formation [1,2]. For this reason, SCT is usually perceived as a mild condition; however, previous studies have shown that hypoxia may trigger sickle-related complications, including splenic infarction [1].

On the other hand, splenic infarction is a rare condition that classically presents as acute pain and tenderness in the left upper quadrant [3]. SCD and its variants are the cause of splenic infarction in 6% of cases. Splenectomy is a rare outcome and the risk of death associated to splenic infarction is very low [2].

COVID-19, the infection caused by SARS-CoV-2 virus, has a great variety of clinical manifestations, ranging from asymptomatic infection to severe pneumonia and need for orotracheal intubation [1]. Hypoxemia, a well-known trigger for SCD complications is a common finding in patients with COVID-19 pneumonia.

2. Case report

We present the case of a 19-year-old male from Dominican Republic with a medical history of epilepsy since childhood who received treatment with levetiracetam. The patient presented to the Emergency Room for abdominal pain in the left flank that appeared after presenting four episodes of generalized tonic-clonic seizures in a period of approximately 4 h. At physical examination, the patient was hemodynamically stable, his oxygen saturation was 98% while breathing room air and temperature was 38.3 °C. Physical examination revealed pain on deep palpation in the left flank, without signs of peritoneal irritation. The rest of the physical examination, including the neurological examination, was normal.

Blood exam showed hemoglobin 14 g/dL, platelets 91000/μL, leukocytes 14800/μL, INR 1.32, D-dimer 1065 ng/mL, ALT 44 U/L, LDH 320 U/L, CK 600 U/L, C-reactive protein 1.2 mg/dL, high sensitivity troponin

* Corresponding author. Venous Thromboembolism Unit, Internal Medicine, Hospital General Universitario Gregorio Marañón, C/. Doctor Esquerdo, 46, 28007, Madrid, Spain.
E-mail address: pbdemelo@hotmail.com (P. Demelo-Rodríguez).

https://doi.org/10.1016/j.tru.2021.100047
Received 3 December 2020; Received in revised form 20 February 2021; Accepted 18 March 2021

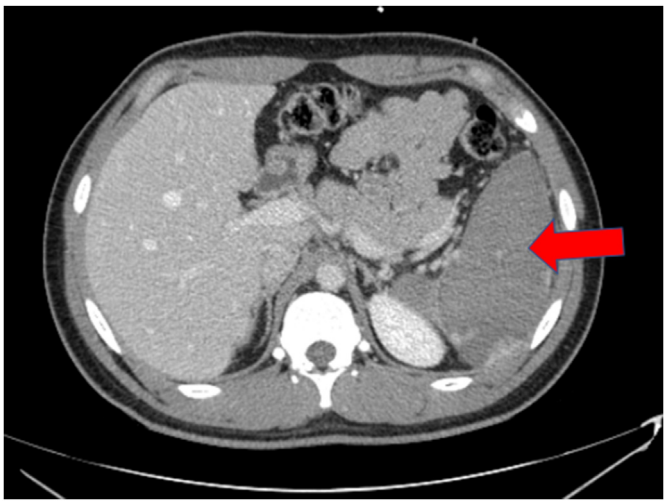

Fig. 1. Abdominal CT showing enlarged spleen with hypoperfusion, compatible with splenic infarction.

I 158 ng/L and procalcitonin 5.41 g/L. Previous laboratory results performed eight months earlier were unremarkable with hemoglobin 15.3 g/dL, platelets 151,000/μL and leukocytes 6100/μL. Levetiracetam levels on admission were below the therapeutic range. Ethanol was not detected, and the urine toxic analysis was negative. A chest and an abdomen X-ray were normal, and an abdominal ultrasound showed mild splenomegaly (14 cm). SARS-CoV-2 RT-PCR testing in nasopharyngeal swab was positive. The patient was admitted to the COVID-19 ward.

On the third day of hospitalization, the patient presented worsening pain in the left flank. A computerized tomography (CT) of the thorax and abdomen was performed, revealing a massive splenic infarction with secondary 15-cm splenomegaly and patency of both the splenic artery and vein and its accessible divisions in the hilum (Fig. 1). In addition, foci of bronchopneumonia in the right lower lobe were also observed. Anticoagulant therapy with enoxaparin 1 mg/kg/12 hours was initiated.

An extensive etiological study was performed. Cardioembolic origin was ruled out after performing a 24-h Holter monitoring that was normal and a bubble saline contrast echocardiogram that ruled out valvular disease or atrial septal defects and showed basal akinesia of the inferior wall that was attributed to myocardial damage due to SARS-CoV-2. Autoimmunity study, including antiphospholipid antibodies, lupus anticoagulant, direct and indirect Coombs tests was normal as well as the hereditary thrombophilia study (Factor V Leiden and prothrombin 20210 mutation). A hemoglobinopathy study was performed using high-efficiency liquid chromatography, which confirmed the presence of 39.7% HbS. Full anticoagulation was then switched to prophylactic doses until hospital discharge.

During hospital stay, the patient presented persistent fever and left flank pain. Laboratory tests showed progressive thrombocytosis (peak 1,007,000 platelets/μL) secondary to functional asplenia, elevated LDH (peak 859 U/l) and elevated acute phase reactants (peak C-reactive protein 10.5 mg/dL). Empirical antibiotic therapy with piperacillin-tazobactam for one week and conventional analgesia were administered. Abdominal pain improved progressively and fever disappeared after the thirteen days of hospital stay. SARS-CoV-2 pneumonia was mild, and the patient did not develop respiratory failure and therefore did not require corticosteroids. Upon discharge, vaccination against encapsulated bacteria was scheduled. Two months after hospital discharge, the

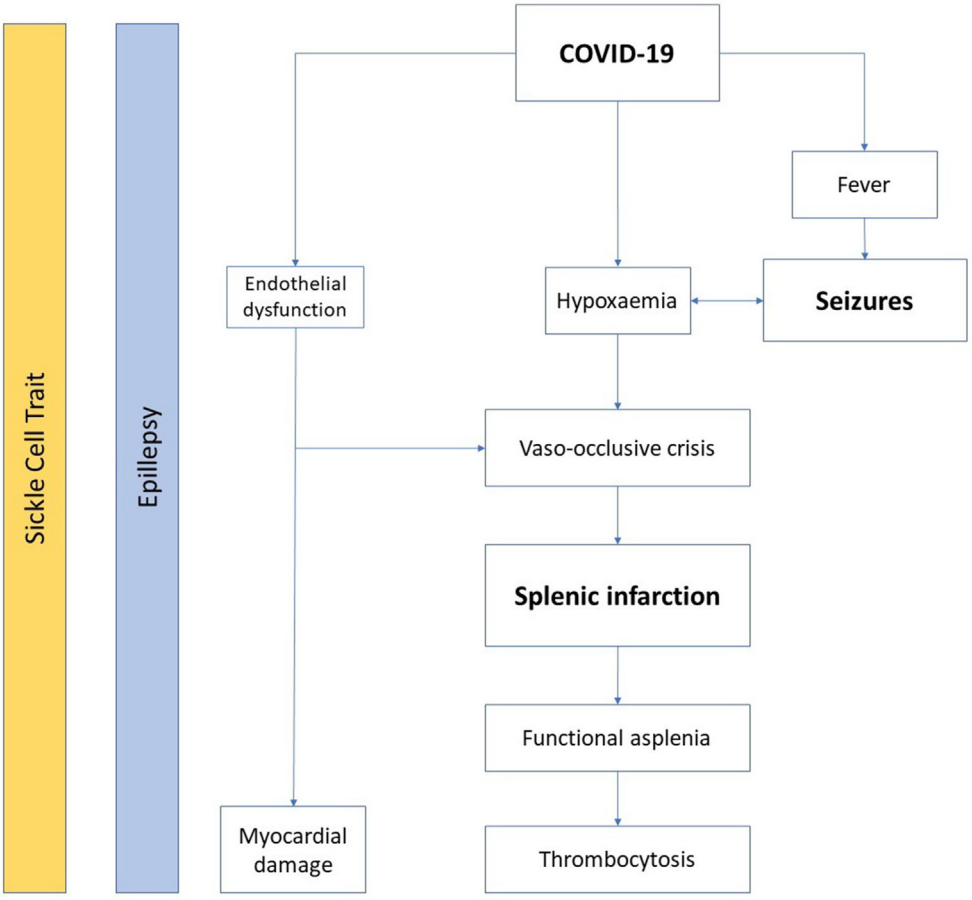

Fig. 2. Rationale for splenic infarction in our patient with COVID-19 and sickle cell trait.

patient presented an excellent clinical condition.

3. Discussion

Recently, the first case of SCD diagnosed in the setting of SARS-CoV-2 infection was described [3]. The patient was a 22-year-old female with fever and generalized bony aches, initially admitted with moderate COVID-19 pneumonia complicated with hemolytic anemia and thrombocytopenia. During hospitalization, a chest CT revealed osteonecrosis suggestive of sickle cell disease. To our knowledge, we report the first case of sickle cell trait diagnosed due to concomitant complication (splenic infarction) probably triggered by COVID-19 infection.

Splenic infarction can be caused by a variety of conditions. According to the largest case series published so far (163 patients), the most common conditions associated with splenic infarction are cardioembolic (25%), followed by cancer (20%) and sepsis (17%). SCD and its variants were the associated condition in 6% of cases, with SCT being present in 2 patients (1.2%) [2]. While the real incidence of splenic infarction in patients with SCT is unclear, it appears to be extremely rare, with less than 100 cases reported in the literature and most of them related with exposition to high altitude [4]. Our patient presented a massive splenic infarction due to a vaso-occlusive crisis (VOC) in the setting of COVID-19 and tonic-clonic seizures.

Known risk factors for VOC in SCD include hypoxia, infections and fever, among others. Deoxygenated sickle hemoglobin increases rigidity in red blood cells (RBCs) and gives them the characteristic “sickle” shape. VOC is initiated when this rigid RBCs obstruct the vasculature [5]. SARS-CoV-2 seems to cause endothelial dysfunction through complement activation and directly targeting pericytes that present high expression of angiotensin-converting enzyme 2 (ACE2) [6]. Recent evidence suggests that severe COVID-19 resembles the pathophysiology and phenotype of complement-mediated thrombotic microangiopathy [7]. On the other hand, there is *in vitro* evidence of activation of the alternative complement pathway in SCD during VOC. Sickle red blood cells seem more sensitive in binding C3 and C5b-9 or membrane attack complex [8]. We hypothesize that hypoxemia and endothelial dysfunction caused by SARS-CoV-2 infection could lead to complement activation and microangiopathy, triggering the VOC that led to splenic infarction. This would also explain the myocardial damage observed in our patient (Fig. 2).

COVID-19 is associated with an increased blood coagulability. COVID-19-associated coagulopathy (CAD) is a complication of SARS-CoV-2 infection characterized by increased D-dimer concentration, prolonged prothrombin time (PT) and increased fibrinogen degradation products, with no consumption of coagulation factors [9]. Inflammation-induced endothelial cell injury could lead to an activation of the fibrinolytic system which may explain the elevation of D-dimer levels. CAD is associated with a higher risk of arterial and venous thrombosis and also with an increased risk of clinical deterioration and death [9].

Our patient presented to the ER with splenic infarction symptoms (left flank pain and fever) and mild COVID-19 symptoms (fever). Similar to previous reports, the clinical course of his COVID-19 infection was rather mild considering the patients with SCD are immunocompromised. Some authors hypothesize that the background chronic inflammatory, hemolytic and anemic state in SCD might have a favourable influence in protecting this patient population from fatal COVID-19 infection [10]. Nonetheless, the consequences of a VOC in the context of COVID-19 are heterogeneous, from mild to potentially life-threatening complications.

In conclusion, the present case report outlines the importance of SCT, often regarded as merely a carrier state, as a condition with potential complications in COVID-19 patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] T.A. Kehinde, M.A. Osundiji, Sickle cell trait and the potential risk of severe coronavirus disease 2019—a mini-review, Eur. J. Haematol. 105 (5) (2020) 519–523.
[2] A.S. Brett, N. Azizzadeh, E.M. Miller, R.J. Collins, M.B. Seegars, M.A. Marcus, Assessment of clinical conditions associated with splenic infarction in adult patients, JAMA Intern Med 180 (8) (2020) 1125–1128.
[3] D. Sheha, M. El-Shayeb, Y. Eid, M. Amin, A. Saeed, D. Abdou, et al., Unfolding of sickle cell trait by coronavirus disease 2019 (COVID-19) infection, Br. J. Haematol. 191 (2) (2020) e38–e40.
[4] T.R. Kotila, Sickle cell trait: a benign state? Acta Haematol. 136 (3) (2016) 147–151.
[5] D.S. Darbari, V.A. Sheehan, S.K. Ballas, The vaso-occlusive pain crisis in sickle cell disease: definition, pathophysiology, and management, Eur J Hematol 105 (3) (2020) 237–246.
[6] E. Gavriilaki, P. Anyfanti, M. Gavriilaki, A. Lazaridis, S. Douma, E. Gkaliagkousi, Endothelial dysfunction in COVID-19: lessons learned from coronaviruses, Curr. Hypertens. Rep. 22 (9) (2020) 63.
[7] E. Gavriilaki, R.A. Brodsky, Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily, Br. J. Haematol. 189 (6) (2020) e227–e230.
[8] E. Gavriilaki, M. Mainou, I. Christodoulou, E.E. Koravou, A. Paleta, T. Touloumenidou, et al., In vitro evidence of complement activation in patients with sickle cell disease, Haematologica 102 (12) (2017) e481–e482.
[9] R.M. Martín-Rojas, G. Pérez Rus, V.E. Delgado-Pinos, A. Domingo-González, I. Regalado-Artamendi, N. Alba-Urdiales, et al., COVID-19 coagulopathy: an in-depth analysis of the coagulation system, Eur. J. Haematol. 105 (6) (2020) 741–750.
[10] F.A. Hussain, F.U. Njoku, S.L. Saraf, R.E. Molokie, V.R. Gordeuk, J. Han, COVID-19 infection in patients with sickle cell disease, Br. J. Haematol. 189 (5) (2020) 851–852.