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LETTER TO THE EDITOR

COVID-19 in a pediatric patient with Glanzmann thrombasthenia

To the Editor:

To date, management of coronavirus disease 2019 (COVID-19)-associated coagulopathy has been based on interim thromboprophylaxis guidance. Evidence still lacks, especially in constitutional bleeding disorders (CBD) given the additional bleeding tendency. We report here a case of COVID-19 in a young girl with type 1 Glanzmann thrombasthenia (GT).

On March 26, 2020 (day 1), this 16-year old girl presented influenza-like illness with myalgia, headache, dry cough, diarrhea, and 40°C fever, associated with loss of taste and smell. On day 3, azithromycin was initiated by her regular doctor. Epistaxis and menorrhagia appeared on day 6, with alteration of the patient's general condition requiring hospitalization in a conventional pediatric COVID-19 unit. At admission, oxygen saturation was 97%. Chest radiography revealed an interstitial syndrome. The blood cell count was normal. We noted a biological inflammatory syndrome (C-reactive protein: 184 mg/L, normal value (NV) < 4; fibrinogen: 7.03 g/L, NV 2-4). Hemostasis tests showed normal prothrombin time and activated partial thromboplastin time, increased D-dimers (2.80 µg/mL, NV < 0.5) and von Willebrand factor (vWF) antigen (238 IU/dL, NV 50-150), and strongly positive lupus anticoagulant (lupus anticoagulant [LA]; normalized dilute Russel viper venom time (dRVVT) screen/confirm ratio: 2.31, NV < 1.2).

Given the patient's hypercoagulable state, standard thromboprophylaxis with enoxaparin (4000 IU once per day) was introduced immediately (day 6), in association with azithromycin and amoxicillin. Regarding bleeding at admission, the epistaxis was handled with local measures. Menstrual blood loss was assessed with the pictorial Higham chart (PHC). The score returned to >100, in keeping with menorrhagia.[1] Both the bleeding and general condition improved after 96 h of hospitalization, without the transfusion of packed red cells and with continued enoxaparin.

Molecular diagnostic tests performed on days 6 and 7 by quantitative reverse-transcription polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were negative. A nasopharyngeal swab, while usually recommended, was impracticable given the high hemorrhagic risk inherent to GT. Instead, the tests were performed solely on expectorations and feces. An automated COVID-19 serology assay (immunoglobulin G [IgG]) was performed at the same time, although probably prematurely, and was negative.

On day 8, a chest computed tomography angiography performed to investigate the increase in D-dimers to 5.92 µg/mL excluded pulmonary embolism but showed areas of ground-glass opacity associated with enlarged hilar lymph nodes, evoking COVID-19 pneumonia. The biological parameters slowly improved, with a gradual decrease of the D-dimers and inflammatory syndrome (Table 1). The patient left the hospital after 9 days (on day 14) with further amoxicillin treatment for 1 month. Thromboprophylaxis with enoxaparin was continued as long as the D-dimers were above an empirical cutoff of 1.0 µg/mL.

TABLE 1 Patient's biological course during hospitalization

Day	Corresponding day of stay in hospital	C-reactive protein (mg/L)	Fibrinogen (g/dL)	D-dimers (µg/mL)
6	1	184	7.03	2.80
7	2	157	ND	3.80
8	3	101	6.90	5.92
9	4	72	6.24	5.66
10	5	52	6.44	5.39
11	6	ND	4.19	3.77
12	7	ND	5.31	3.09
13	8	ND	ND	2.41
14	9	10	4.73	1.50

Abbreviation: ND, no data.

In a follow-up consultation on day 21, the results showed normal D-dimers (0.47 µg/mL) and iron deficiency anemia (hemoglobin: 8.0 g/dL, NV 12-16; ferritin: 8 µg/L, NV 10-291) in connection with persistent menorrhagia (PHC score >100), leading us to discontinue enoxaparin. A new automated COVID-19 IgG assay was performed at this time and came back positive, finally confirming SARS-CoV-2 infection. No further complications were reported thereafter. Four months later, LA testing was repeated and finally came back negative.

Very little has been published to date on COVID-19 in patients with CBD. The few reported cases include one Italian patient with factor XIII deficiency[2] and one Chinese patient with hemophilia A.[3] GT is an autosomal recessive platelet aggregation disorder caused by quantitative or qualitative defects in integrin αIIbβ3, associated with early severe mucocutaneous bleeding.[4] We emphasize the difficulties to manage suspected COVID-19 in this condition. The high bleeding tendency contraindicated a nasopharyngeal swab for the SARS-CoV-2 molecular assay, limiting considerably its sensitivity. Performing the swab under replacement therapy (i.e., recombinant factor VIIa) was not considered, given the nonindispensable nature of the procedure

and the potential thrombotic risk of the therapy.[5] The COVID-19 diagnosis was thus delayed and was only possible later by a serologic assay. Interpretation of the initial acute serology results represented a further challenge. Delayed COVID-19 diagnosis could result in greater exposure for other people and potentially increase viral transmission. Consequently, we underscore the limits of current SARS-CoV-2 molecular assays, especially when a usual nasopharyngeal swab is unfeasible. Improved assay sensibility and specificity in alternative body fluids could be beneficial in this context.

Despite the bleeding status of our patient, markers of hypercoagulability (increased fibrinogen and D-dimers) and endothelial activation (increased vWF antigen) led us to decide on standard-dose thromboprophylaxis. COVID-19 coagulopathy and its management have been described in intensive care unit (ICU) and non-ICU patients. While little is known regarding ambulatory COVID-19 patients, recent guidance suggests standard thromboprophylaxis only in patients with morbid obesity or past thrombotic history.[6,7] Patients with CBD represent a specific condition, given the delicate balance between hemorrhaging and thrombosis. Thus far, unvalidated empirical recommendations have been proposed only for inpatients with hemophilia.[8]

LA can rise transiently in patients with critical illness and various infections and was initially strongly positive in our patient. Previous studies have shown that the incidence of LA is high in severe COVID-19 patients, although its role in the development of the coagulopathy requires further investigations.[9,10]

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Laurent Sattler and Dominique Desprez designed the study, analyzed the data, and wrote the paper. Laurent Sattler, Claire Hager, and Dominique Desprez contributed to acquisition and interpretation of the data. . All authors critically reviewed the manuscript and approved the final version.

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