Acquired Haemophilia associated with SARS-CoV2 infection

Hemofilia Adquirida asociada a infección por SARS-CoV2

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ABSTRACT

We present the case of a 73-year-old man, with a history of SARS-CoV2 infection (January 2021), who came to the emergency department three months post infection, with complaints of left hip and knee pain, that turned out to be a substantial thigh hematoma. Analysis showed a normocytic/ normochromic anaemia (9,0 g/dL), prolonged aPTT (63.2 seconds; normal range 24.7–39.0 sec.), with normal prothrombin time. We arrived at a diagnosis of Acquired Haemophilia A. Treatment was promptly started, with clinical and laboratory improvement. After the vaccination to SARS-CoV2, a relapse was observed.

Acquired Haemophilia A is a rare, autoimmune disease, distinguished by the presence of inhibitors against factor VIII. It's characterised by subcutaneous hematomas and muscle bleeding, with prolonged aPTT. SARS-CoV2 infection has already been mentioned as a possible cause.

Keywords: Acquired Haemophilia A, SARS-CoV2.

CASE REPORT

We reported the case of a 73-year-old man that was admitted to the emergency department (ED) in April 2021 with left knee and hip pain with one week of progression. No history of trauma was present. His past medical history included a stroke (1994), high blood pressure, chronic renal disease and SARS-CoV2 infection that didn't need hospitalisation (January 2021). Medicated with acetylsalicylic acid 150 mg once a day, enalapril 20 mg plus lercanidipine 10 mg once a day, sertraline 50 mg once a day, donepezil 5 mg once a day, nebivolol 2.5 mg once a day, olodaterol 2,5 mcg plus tiotropium bromide 2.5 mcg 2 puffs a day and pantoprazole 20 mg once a day. Upon Orthopaedics' examination, he had oedema from his left hip and knee, with pain in active and passive mobilisation. Laboratory analysis showed normocytic/ normochromic anaemia (9,0 g/dL), with leukocytosis (23.1 G/L), normal platelets count, prolonged activated partial thromboplastin time (63.2 seconds; normal range 24.7 – 39.0 sec.), with normal prothrombin time. An ultrasound performed on the left thigh, indicated possible quadriceps tendon rupture; this diagnosis was established, and the patient was admitted to the Orthopaedic ward. After 8 days with no improvement, he went into surgery so an evaluation could be made of his quadriceps tendon. They found a large thigh hematoma, without tendon rupture. In the recovery room he started to bleed from puncture sites. He remained under the Orthopaedics' department care for almost one month, in constant need of blood transfusions (14 red cell concentrates and 8 fresh frozen plasma in total). After this time, Internal Medicine was consulted, because the patient presented fever and cough. Analysis showed leukocytosis (23.07 g/L), normocytic/ normochromic anaemia (7.8 g/dL), thrombocytosis (639 G/L), an indomitable aPTT and an increase of C-reactive protein (17.08 mg/dL). The thorax x-ray showed multiple bilateral infiltrates. The diagnosis of nosocomial pneumonia was assumed, and the patient started piperacillin plus tazobactam. He was then transferred to the Internal Medicine department.

We started the study of his prolonged activated partial thromboplastin time. The mix test failed to correct aPTT (initial aPTT 140 seconds and after mix test 107 seconds), suggesting the presence of an inhibitor. The dosage of factor VIIIc was <1%, Lupus anticoagulant was negative, the dosing of specific inhibitors of factor VIII showed a residual activity of 29% and 719 Bethesda Units/ mL. IgG SARS-CoV2 antibody was positive. Thorax CT-scan suggested the presence of alveolar haemorrhage. The diagnosis of Acquired Haemophilia A (AHA) was subsequently made, due to the presentation of the thigh hematoma and alveolar haemorrhage. Treatment with activated factor VII, corticoid (prednisolone 1 mg/Kg/day) and rituximab (4 cycles) was performed. A clinical improvement and reduction of aPTT was documented. Causes of AHA such as haematological malignancies, solid malignancies and immunological disorders were excluded.

At discharge, in June 2021, he maintained previous medication and continued treatment with prednisolone 1 mg/kg/day. It was recommended that the patient should not be vaccinated against SARS-CoV2 because he had been treated with rituximab. Unfortunately, he was vaccinated two weeks after discharge, and one week later he was admitted to the ED with a new thigh hematoma and hemarthrosis. Blood tests revealed normocytic/ normochromic anaemia (9.4 g/dL) and prolonged aPTT (91.8 sec.). The patient passed away due to a complication from infection.

DISCUSSION AND CONCLUSION

Acquired haemophilia A is a rare disorder, characterised by the presence of inhibitors against factor VIII[1]. It frequently occurs in elderly patients[2]. Laboratory findings revealed an isolated, prolonged aPTT, reduced FVIII activity and presence of autoantibodies (Bethesda assay or enzyme-linked immunosorbent assay)[1]. Commonly, the patient presents large subcutaneous hematomas and muscle bleeding, but gastrointestinal, genitourinary and retroperitoneal bleeding can also occur[1,2]. In the case study we report, the patient presented a thigh hematoma, but also an alveolar haemorrhage. Until now, alveolar haemorrhage has not been described as a presentation of AHA.

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Cómo citar este artículo: Medeiros C, Brito D, Serras Jorge R
Hemofilia adquirida asociada a la infección por SARS-CoV2. Galicia Clin 2022; 83-3: 40-41
Recibido: 16/03/2022 ; Aceptado: 20/04/2022 // https://doi.org/10.22546/66/2809

In the majority of cases, no etiological factor is found[2], but AHA can be associated with cancer (haematological and solid), autoimmune diseases and infections[2].

The treatment strategy is to control the haemorrhage, eradicate the inhibitor, investigate and treat the cause[1,2]. To control haemorrhage, factor VIII bypassing agents should be used such as activated prothrombin complex concentrate or recombinant activated factor VII[1,2]. To eradicate the inhibitor, immunosuppressive therapy is mandatory[1]. The 2020 recommendations[1] state that immunosuppressive therapy is dependent on factor VIII activity. So if factor VIII is ≥1% and ≤20 BU/mL, proceed with a treatment of only steroids for 3 - 4 weeks, if factor VIII is <1% or >20 BU/mL, then double immunosuppressive therapy is necessary, with steroids plus cyclophosphamide or rituximab for 3 - 4 weeks[1]. These patients should be monitored frequently until they are in remission[7]. Complete remission can be achieved in 50% of patients with first-line immunosuppressive treatment[8]. With AHA mortality ranging between 30 and 40%[2].

Recently, SARS-CoV2 has been linked to AHA[3–5]. SARS-CoV2 infection has caused systemic alterations, and thromboembolic and coagulopathy has been reported[1]. *Franchini et al.*(2020) presented the case of a 66-year-old man who had a past history of AHA, that presented a relapse, after 9 years of normal blood tests, during the SARS-CoV2 infection[4]. *Hfzah* et al. (2021) references the case of a 73-year-old man who presented with AHA four months after having a SARS-CoV2 infection that did not need hospitalisation[5]. *Wang* et al. (2021) reported one case of a 65-year-old man, with a distant history of autoimmune thyroid disease, that was diagnosed with AHA, and was positive for SARS-CoV2 antibodies, probably the result of a previous asymptomatic infection[3].

This case shows the importance of being alerted to coagulation alteration in patients with SARS-CoV2 active infection or history of infection. After analysing the case study, we have concluded that the SARS-CoV2 infection, that occurred three months earlier, was the most likely trigger for this AHA case, and the relapse after receiving the SARS-CoV2 vaccine was one more point that supported the diagnosis. Until this paper was written, only three cases of AHA induced by SARS-CoV2 infection had been reported, and no relation with the SARS-CoV2 vaccination has been noted.

SARS-CoV2 is a multisystemic infection. Every day a new related manifestation, complication or association is being reported. The impact of the infection in the coagulation has been proven, and many thrombotic events have been reported. Autoimmunity appears to have an important role in many of the complications associated with the SARS-CoV2 infection. AHA is a rare autoimmune disease that requires a high index of suspicion to identify. Being recognized, diagnosed, and treated correctly has an impact on the prognosis. Our report describes one case of AHA, probably related to a SARS-CoV2 infection, that relapsed after the injection of the SARS-CoV2 vaccine, up until now the only reported.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

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