Title

An 89-Year-Old Man with COVID-19-Associated Coagulopathy Presenting with a Prolonged Partial Thromboplastin Time, Lupus Anticoagulant, and a High Titer of Factor VIII Inhibitor

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 89-year-old
Final Diagnosis: Acquired hemophilia A • COVID-19
Symptoms: Bleeding • hypoxia
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual clinical course

Background: Coagulation abnormalities are frequently encountered in patients with coronavirus disease 2019 (COVID-19), especially in those with more severe disease. These hematologic abnormalities are suspected to occur in the context of underlying immune dysregulation and endothelial dysfunction. Elevated D-dimer levels, COVID-19-associated coagulopathy (CAC), disseminated intravascular coagulation (DIC), and positive lupus anticoagulants are the most common findings to date. Current guidelines suggest that all patients with COVID-19 should receive pharmacologic thromboprophylaxis.

Case Report: An 89-year-old man with a medical history of hypertension, type 2 diabetes, and advanced prostate cancer in remission presented with generalized weakness. At our center, a reverse transcription-polymerase chain reaction test was positive for severe acute respiratory syndrome coronavirus 2, but the patient did not have symptoms of COVID-19. He was also found to have a prolonged activated partial thromboplastin time, secondary to both a high titer of factor VIII inhibitor and a lupus anticoagulant. He eventually developed respiratory compromise, during which his disease manifested as a bleeding rather than a prothrombotic state.

Conclusions: This report highlights the importance of a comprehensive evaluation of prolonged partial thromboplastin time, rather than making an assumption based on a positive lupus anticoagulant result. In the case presented, the concomitant factor VIII inhibitor caused the patient to have a greater bleeding tendency. It is imperative that physicians balance the risk of bleeding and clotting in patients with COVID-19 because patients seem to have varying presentations based on disease severity and level of immune dysregulation.

MeSH Keywords: COVID-19 • Factor VIII • Hemophilia A • Lupus Coagulation Inhibitor

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Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the global coronavirus disease 2019 (COVID-19) pandemic. Infection with the virus can lead to a hypercoagulable state known as COVID-19-associated coagulopathy (CAC), which is a distinct entity from disseminated intravascular coagulation (DIC) [1–4]. The important distinguishing features of CAC include lack of bleeding tendency, only mildly low platelets, elevated plasma fibrinogen levels, and identification of SARS-CoV-2 and complement components in regions of thrombotic microangiopathy (TMA) [5]. The tendency toward thrombosis is explained by Virchow's triad. Endothelial injury is caused by direct viral invasion of endothelial cells via binding to the angiotensin-converting enzyme 2 receptor [6]. The immobility associated with hospitalization for COVID-19 increases the risk of venous stasis. Finally, hypercoagulability has been attributed to a lupus anticoagulant associated with a prolonged activated partial thromboplastin time (aPTT). Interestingly, elevated factor VIII activity and von Willebrand antigen, presumed to be secondary to endothelial cell injury, are also observed [7]. One-third of critically ill patients with COVID-19 develop venous thromboembolisms, even while on prophylactic anticoagulation. In addition, arterial thrombosis, including strokes and acute limb ischemia, has also been reported [8–12]. Autopsy results from patients with COVID-19 have revealed macrovascular thrombosis consisting of erythrocytes, leukocytes, fibrin, and platelets, and microvascular thrombosis consisting of platelet-fibrin microthrombi in the venules, arterioles, and capillaries in all major organs. These findings of diffuse small-vessel occlusions suggest that an immune-triggered complement-mediated TMA exists in patients with COVID-19 [13,14].

The risk of thrombotic complications is higher in COVID-19 patients than in their noninfected counterparts, and once thrombosis has occurred, prognosis becomes fairly dismal [15]. Current guidelines suggest that all patients with COVID-19 be stratified for thrombotic risk and at minimum be maintained on prophylactic anticoagulation, if not a treatment dose, depending on their risk level. Once thrombosis has been confirmed, patients may need higher anticoagulation targets than normal [15]. Additional management options have been suggested addressing immune-mediated TMA complications with plasma exchange, intravenous immunoglobulin, and immunosuppression. Clinical trials are also widely available [5,13,14].

In addition to CAC, coagulopathy and antiphospholipid antibodies have been reported in patients with COVID-19. Zhang et al. [16] described 3 patients in the Intensive Care Unit (ICU), one of whom had clinically significant cerebral infarcts; all 3 had positive anticardiolipin IgA and anti-B2-glycoprotein IgA and IgG antibodies detected in the context of partial thromboplastin time (PTT) elevations [16]. Furthermore, in a series of 216 patients with SARS-CoV-2 infection, 44 (22%) had a prolonged PTT. After exclusions, 31 of 34 patients (91%) with COVID-19 and prolonged PTT were found to have positive lupus anticoagulant [17]. Harzallah et al. [18] found that 45% of 56 patients diagnosed with COVID-19 in France were positive for lupus anticoagulant with dilute Russel's viper venom time (DRVVT) tests, and only 10% had positive anticardiolipin and anti-B2-glycoprotein antibodies. Notably, none of these patients had deficiencies in factor VIII or factor IX that should be considered for prophylactic anticoagulation [17,18].

While most severe COVID-19 cases are associated with elevated factor VIII, CAC, DIC, or associated antiphospholipid antibodies, the current report involved a case of COVID-19-associated coagulopathy presenting with a prolonged PTT, lupus anticoagulant, and a high titer of factor VIII inhibitor in an 89-year-old man. To our knowledge, this is the first reported case of concurrent factor VIII inhibitors and lupus anticoagulants in the setting of COVID-19.

Case Report

An 89-year-old man with a medical history of hypertension, type 2 diabetes, and advanced prostate cancer in remission, presented with generalized weakness. At our center, a cobas® reverse transcription-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab was positive for SARS-CoV-2, although he did not have symptoms of COVID-19.

An isolated aPTT prolongation was noted on admission; aPTT values ranged from 100 to 130 s (normal aPTT range: 25–30). A complete blood cell count was within normal limits, other than a normocytic anemia (hemoglobin ranging from 7.0 to 8.0 g/dL) attributed to a history of Coombs-negative hemolytic anemia. He had a normal international normalized ratio, but elevated fibrinogen of >400 mg/dL and D-dimer ranging from 13 to 16 µg/mL (normal range 0 to 0.42 µg/mL). Renal function was normal. His total bilirubin declined from 4.9 mg/dL on admission and stabilized in the range of 1.0 to 2.0 mg/dL, suggesting that the hemolysis was resolving. He had a haptoglobin of 55 mg/dL, lactate dehydrogenase elevated above 600 U/L, and a negative direct antiglobulin test.

The patient was not taking any anticoagulation on admission and was noncompliant with his medications. The prolonged PTT was evaluated with a 50: 50 mixing study, which did not correct, confirming the presence of an immediate inhibitor. On initial screening, the β-2-glycoprotein IgA, IgG, and IgM; anticardiolipin IgG, IgA, and IgM; DRVVT; and lupus anticoagulant tests were within normal limits. Interestingly, factor VIII activity was less than 1% (normal range: 50–150%); a factor VIII

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enzyme-linked immunosorbent assay (ELISA) was positive indicating an IgG antibody to factor VIII, with an inhibitor potency of 2222 Bethesda Units. The patient's factor IX and factor XI activities were also less than 1%, while his factor X activity was within normal limits. Chromogenic factor VIII and IX assays also showed less than 1% activity.

Two weeks after the initial antiphospholipid studies, the tests were repeated. The anticardiolipin IgG was indeterminate, and the DRVVT screening remained negative so a DRVVT mixing study was not performed. However, the PTT-lupus anticoagulant screening, which uses phospholipid-dependent clotting tests, demonstrated prolongation of the PTT. The hexagonal phase phospholipid test confirmed the presence of a lupus anticoagulant. These results suggested that both a factor VIII inhibitor and a lupus anticoagulant were concurrently present in this patient.

One week after admission, the patient manifested respiratory symptoms of COVID-19. He received tocilizumab and convalescent plasma. Computed tomography angiogram did not show evidence for pulmonary embolism. Prophylactic anticoagulation was discontinued once the factor VIII and IX assays had normal results. He required transfer to the ICU for intubation and mechanical ventilation due to increased oxygen requirements. He had a repeat SARS-CoV-2 RT-PCR test performed on a bronchoscopy sample that was again positive. He remained stable in the ICU, but unfortunately developed acute DIC. The only hemorrhagic-related complication was moderate gross hematuria, which resolved after 2 doses of 2000 µg recombinant activated factor VII and bladder irrigation. He ultimately died in the ICU from acute cardiopulmonary failure.

Discussion

The patient described in this report appears to represent the first reported case of an isolated aPTT prolongation in a COVID-19 patient associated with both a factor VIII inhibitor and a lupus anticoagulant. Identifying both of these inhibitors can be a diagnostic challenge. In principle, the persistently prolonged aPTT could be due to either a factor inhibitor or an antiphospholipid antibody, such as a lupus anticoagulant, and the presence of either of these factors can result in spurious identification of the other. For example, lupus anticoagulants and other antiphospholipid antibodies can interfere with phospholipid-dependent aPTT assays, which include assays for factor VIII activity. In the current case, the ELISA-based measurement of the IgG antibody to factor VIII provided direct evidence of the presence of the factor VIII inhibitor. In addition, the high titer of the factor VIII inhibitor (2222 Bethesda Units) was not likely to be attributable to a lupus anticoagulant. Conversely, an extremely high factor VIII inhibitor, by prolonging the aPTT, may be misinterpreted as an antiphospholipid antibody. However, in our patient, the abnormal lupus anticoagulant test, which was run with and without excess phospholipid, provided direct evidence of an antiphospholipid antibody. Additionally, the PTT 50: 50 mixing study suggested an immediate inhibitor, which is more typical of lupus anticoagulant than time-dependent factor VIII inhibitors, further supporting the additional presence of a lupus anticoagulant.

Other coagulation factor abnormalities were noted, including reduced factor IX and XI activity levels. These activity assays are also aPTT-based assays, and the abnormalities in our patient were likely due to the high-titer factor VIII inhibitor, with potentially some contribution by the lupus anticoagulant. The lupus anticoagulant is known to interfere with the 1-stage clot-based assays that demonstrated the low factor IX and XI (as well as VIII) activities. However, the lupus anticoagulant would likely not account for the positive chromogenic assay for factor IX, which is a less phospholipid-dependent assay. In addition, neither the positive ELISA for the factor VIII inhibitor nor the high-titer Bethesda assay for factor VIII can be attributed to the positive lupus anticoagulant. Interestingly, the factor X assay, which is a non-phospholipid-dependent, prothrombin time-based assay, was within normal limits.

Acquired hemophilia A is caused by autoantibodies interfering with the activity of factor VIII and is the most common acquired coagulopathy [19]. Production of these antibodies is thought to be related to gene polymorphisms, such as HLA and CTLA4, as well as autoreactive $CD4^+$ T lymphocytes [20]. The most common underlying conditions for acquired hemophilia A include the postpartum state, malignancy, and autoimmune diseases, none of which were operative in this case [21]. Interestingly, acquired hemophilia A tends to cause spontaneous bleeds, and when a bleed does occur, it tends to be life threatening. Patients tend to have large hematomas, extensive ecchymosis, or severe mucosal bleeding [19]. The gross hematuria requiring multiple transfusions of recombinant factor VII was consistent with this presentation.

We concluded that this patient had a highly potent factor VIII inhibitor, confirmed by ELISA, which was affecting other factors within the intrinsic pathway, as well as an antiphospholipid antibody, as evidenced by the lupus anticoagulant. Antiphospholipid antibodies have recently been described in the context of COVID-19 [17]. Analogously, we speculate that the factor VIII inhibitor was produced in the setting of immune dysregulation from the underlying COVID-19 because the absence of significant bleeding history prior to hospitalization argues against the existence of a pre-existing factor VIII inhibitor. Although the patient eventually developed gross hematuria requiring activated factor VII and bladder irrigation, it is possible that the severity of bleeding was mitigated by the

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concurrent presence of the lupus anticoagulant and its tendency to cause a prothrombotic state.

Patients with the severe form of COVID-19 have a tendency to developing systemic coagulopathy and acquired thrombophilia, leading to presentations of venous, arterial, and microvascular thrombosis [14]. Both CAC and presence of a lupus anticoagulant have demonstrated an association with a thrombotic tendency rather than a bleeding tendency [14,17]. The current recommendations for management of this prothrombotic tendency is to initiate anticoagulation early, rather than awaiting further investigation of a prolonged aPTT, not uncommonly found in COVID-19 patients presenting to the hospital [17].

Despite the guidelines for management of high-risk COVID-19 patients with prophylactic anticoagulation, anticoagulation was withheld due to the potential bleeding risk associated with acquired hemophilia. Corticosteroids are being considered as a treatment for the acquired hemophilia A [21], but bleeding was stanched with supportive measures and the patient was managed expectantly. This case highlights an association between COVID-19, acquired hemophilia, and an antiphospholipid antibody, with the striking finding of 2 inhibitors to account for the aPTT prolongation.

Conclusions

Our case report demonstrates the importance of investigating alternative causes of aPTT prolongation in patients with high-risk COVID-19 presenting to the hospital. In the majority of cases, patients have a proclivity towards a prothrombotic state given described entities of CAC and associated antiphospholipid antibodies, but it is possible that immune dysregulation associated with COVID-19 may lead to other coagulation cascade factor inhibitors that would manifest toward a bleeding tendency. Management of this condition requires clinical acumen to balance the potential for bleeding and thrombotic complications associated with COVID-19.

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Conflict of interest

None.

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