High Risk of Venous Thrombosis Recurrence in Fully Anticoagulated Patient with Antithrombin Deficiency during COVID-19: A Case Report

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Abstract

Coagulation dysfunction is a serious issue in patients with Coronavirus disease-19 (COVID-19). With regard to recently published studies, a high number of patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 developed life-threatening thrombotic complications despite anticoagulation. We report a case of young woman with the type-II heparin-binding site (HBS) antithrombin (AT) deficiency (Budapest 3-homozygous), who developed acute deep vein thrombosis on two occasions due to COVID-19 infection in the course of stable anticoagulation with vitamin K antagonist. The first thrombotic event was observed during mild COVID-19 infection, while the second thrombotic event she developed 2 months after she was negative for severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2). Our case highlights the complexity of the treatment in this particular type of thrombophilia and the need for precaution even in mild forms of viral infection. In the treatment of acute thrombosis, AT-deficient patients may benefit from the use of AT concentrate along with low-molecular weight heparin (LMWH), while in cases of type II-HBS, AT supplementation is mandatory.

Keywords

- acute deep venous thrombosis
- recurrent thrombosis
- antithrombin deficiency
- type-II HBS
- COVID-19

Introduction

The clinical course of Coronavirus disease-19 (COVID-19) infection varies from asymptomatic, mild symptoms, severe illness and sepsis to death.[1,2] Coagulation dysfunction is a serious complication in patients with COVID-19, whereby fulminant thrombotic complications emerge as critical issues in those with severe COVID-19.[3] There are several changes in the prothrombotic direction, which can be explained by the profound inflammatory response as well as by hypoxia.[1,2] Significant activation of the coagulation system caused by this novel Coronavirus may result in vascular complications, mainly venous thromboembolism (VTE), which have significant implications on the clinical

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outcome for COVID-19 patients.[4] Thus, many patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 developed life-threatening thrombotic complications despite anticoagulation.[5] Additionally, inherited thrombophilia might contribute to the increased risk of VTE during COVID-19 infection. However, there is very little data on association of congenital thrombophilia and thrombotic events during COVID infection. A recently published study that included 13 patients with congenital thrombophilia showed that most patients with severe thrombophilia did not develop symptomatic thrombotic events during COVID-19, including those who had previous thromboses. They state that the possible explanation for the low incidence rate of thrombosis in thrombophilia patients may be related to the fact that these patients were already treated with anticoagulant drugs before the infection or at the very early stages of the disease.[6] Previous findings[3] also support that long-term anticoagulation at admission appears to protect COVID-19 patients from VTE.

Case Details

Here, we report the case of a young woman carrier of severe thrombophilia, type-II heparin-binding site (HBS) antithrombin (AT) deficiency (Budapest 3-homozygous), who developed acute deep vein thrombosis (DVT) in two occasions in the course of stable anticoagulation with vitamin K antagonist (VKA). The first thrombotic event was observed during mild COVID-19 infection, while the second thrombotic event developed 2 months after she was negative for severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2).

A young woman aged 32 was admitted in a COVID hospital due to development of respiratory symptoms, mild rhinitis and sore throat without fever. She was not a smoker, her body mass index (BMI) of 22.4 was in the normal range but with pronounced varicose veins in both legs. Previously, due to the development of spontaneous recurrent juvenile thrombosis (proximal DVT affecting both legs), she was diagnosed as an AT-deficient patient at the age of 14 years. She was subjected to long-term VKA. The use of VKA therapy was regularly monitored to maintain the therapeutic range of international normalized ratio (INR) between 2.5 and 3.5. During the last 6 months prior to COVID infection, she was on stable anticoagulation treatment, and the last control in early June showed an INR of 2.95.

In early July 2020, she contacted the anticoagulation service, asking for advice since her partner was found to be polymerase chain reaction (PCR)-positive for COVID-19. Given the severity of thrombophilia in her case and the effect of the COVID-19 infection on the development of thrombotic complications, she was advised to report to the COVID hospital immediately for testing and examination. Due to the development of respiratory symptoms and her thrombophilia status, she spent the next 7 days in the COVID hospital. Her nasopharyngeal swab SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test was positive on July 8, 2020, while a chest X-ray showed initial signs of bilateral pneumonia, and she was given standard therapy for COVID-19 treatment, including an antibiotic (azithromycin), vitamins and continuation of the VKA with the hematologist's recommendation that the INR level should be maintained around 3. She was afebrile at all times in a stable general condition with no need for any respiratory support. As someone with mild symptoms, she was discharged on July 15, 2020, in good condition with normal biochemical and hematological parameters (►**Table 1**) for home treatment, with advice to rest and continue the prescribed therapy.

A week after discharge from the hospital, she experienced a weird feeling in her right leg in an upright position but did not report any swelling. She was referred to the COVID hospital immediately for an examination due to suspected acute thrombosis. On admission to the hospital on July 23, 2020, an INR of 2.21 and D-dimer of 4.22 mg/L fibrinogen equivalent units (FEU) (0.5 mg/L cutoff value used for discrimination of VTE) were obtained. The ultrasound examination showed the presence of an acute thrombotic process with subocclusive thrombotic mass (5–7 cm long), affecting popliteal and tibial veins of the lower right leg. The vascular surgeon switched anticoagulant therapy from VKA to therapeutic doses of low molecular weight heparin (LMWH) and nadroparin 5700 IU subcutaneously (SC) twice daily. In consultation with the hematologist, AT concentrate was introduced. The first administered dose of AT III concentrate (Kybernin) was 3000 IU followed by 1500 IU in the next 5 days. An AT activity range of 80 to 100% was maintained with monitoring. After clinical improvement, VKA was reintroduced, overlapping LMWH until the therapeutic range of INR was reached. She was discharged on August 3, 2020, on stable anticoagulation, while her nasopharyngeal swab SARS-CoV-2 RT-PCR test was negative.

During next few weeks, stability of the anticoagulant therapy was confirmed by INR 3.0 and D-dimer 0.92 mg/L FEU, while AT activity at 12% (ref. range 83–113%) and factor VIII (FVIII) level of 2.5 IU/L (ref. range 0.50–1.50 IU/L) were obtained. The patient complained of fatigue and malaise. Two months after she become PCR negative for SARS-CoV-2, she reported pain in the right leg again. The ultrasound examination showed the presence of a new thrombotic event in the area of the gastrocnemius (solei veins). She was hospitalized again on September 3, 2020, with continued VKA therapy, maintenance of the INR level > 3, and inclusion of AT concentrate substitution at an initial dose of 3000 IU followed by 2000 IU daily. On September 9, 2020, she was discharged with stable anticoagulation (INR 3.8) and an AT level of 66%. For the next 6 months, the INR was monitored weekly with the aim of maintaining over 3. Factor VIII and AT activity were monitored monthly. In the following months, elevated levels of FVIII of 2.5 IU/L were observed, while AT activity of 45% was similar to the previously established AT level, which was obtained during the thrombophilia examination after her first DVT.

Discussion

As far as we know, this is the first case of recurrent acute DVT diagnosed during COVID-19 infection in a fully

Table 1 Biochemical, hematological and hemostatic parameters

	On discharge during the first hospitalization 15/07/2020		On discharge during the second hospitalization 03/08/2020	On discharge during the third hospitalization 09/09/2020
Biochemical parameters				
Glucose (mmol/L)	4.6		4.4	4.6
Urea (mmol/L)	3.6		2.9	4.3
Creatinine (umol/L)	65		52	56
Total bilirubin (umol/L)	7.1		4.7	7.3
Direct bilirubin (umol/L)	2		1.9	2.3
AST (U/L)	18		15	18
ALT (U/L)	15		13	13
LDH (U/L)	337		308	380
CK (U/L)	88		0.7	236
Total protein (g/L)	77		61	64
Albumin (g/L)	44		44	44
CRP (mg/L)	1.5		0.7	0.6
Ferritin (ug/L)	28		84	34
Hematological parameters				
WBC (10^9/L)	3.42		3.56	4.20
NEUT (%)	58.1		56.1	50.0
LYMPH (%)	31.6		33.6	41.0
MONO (%)	9.1		9.2	6.8
EO (%)	0.9		0.8	1.7
BASO (%)	0.3		0.3	0.5
RBC (10^{12}/L)	4.33		4.14	3.90
HGB (g/L)	131		123	119
HCT (L/L)	0.402		–	–
MCV (fl)	92.8		88.9	90
PLT (10^9/L)	225		215	214
Hemostatic parameters				
PT INR	3.30		2.71	3.60
APTT (s)	33.5		32.7	36.3
Fibrinogen (g/L)	3.0		2.5	2.8
D-dimer (mg/L FEU)	0.36		1.74	0.40
AT (%)	–		78.6	65.0
FVIII (IU/L)	–		–	2.42
Hemostatic test results between two hospitalizations				
	13/08/2020	**17/08/2020**	**21/08/2020**	**25/08/2020**
PT INR	5.40	2.50	4.50	3.00
APTT (s)	–	–	–	36.2
Fibrinogen (g/L)	–	–	–	3.6
D-dimer (mg/L FEU)	0.80	–	–	0.92
AT (%)	–	–	–	12.0
FVIII (IU/L)	–	–	–	2.50

Abbreviations: AT, antithrombin; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BASO, basophil; CK, creatine kinase; CRP, C-reactive protein; EO, eosinophil; FEU, fibrinogen equivalent unit; HCT, hematocrit; HGB, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; LYMPH, lymphocyte; MCV, mean corpuscular volume; MONO, monocyte; NEUT, neutrophil; PT, prothrombin time; PLT, platelet; RBC, red blood cell; WBC, white blood cell.
Innovance D-dimer (Siemens) normal range up to 0.55 mg/L FEU, AT Innovance AT (Siemens), normal range 83–118%.

anticoagulated patient taking VKA, who is a carrier of severe thrombophilia, type-II HBS AT deficiency (Budapest 3) in the homozygous variant. Since she was a patient with mild symptoms of COVID-19 and recovered very quickly without needing any respiratory support, no AT level was measured during the first hospitalization and she was discharged with advice to rest and continue the prescribed therapy. The symptoms of acute thrombosis appeared very soon, during the first week after discharge, while the second recurrent event developed in a period 2 months after she become PCR-negative for SARS-CoV-2. In both cases, she was fully anticoagulated but with the lowest ever measured AT activity of only 12% and a steadily elevated level of FVIII, whose values were maintained in the following months.

Presently, there is a consensus that all patients admitted to hospital with COVID-19 receive prophylactic anticoagulation.[7] According to existing guidelines, the use of LMWH is recommended in COVID-19-induced thrombosis. In those patients who are ready for discharge, direct oral anticoagulants (DOACs) or LMWH would be preferred to limit contact of patients with health care services required for INR monitoring for VKAs.[7,8] Due to the pointed severe thrombophilia and recurrent DVT, our patient was already on stable VKA with the INR level that was maintained in the range of approximately 3. However, considering the pathophysiological mechanism and effect of this particular type of AT deficiency in treatment for acute thrombosis, it was necessary to introduce substitution with AT concentrate together with therapeutic doses of LMWH.

Our case highlights the complexity of COVID-19 infection treatment in this particular type of thrombophilia. Although, in this case, AT levels were basically very low due to the homozygosity of the mentioned mutation, COVID-19 infection itself might cause a further decrease,[9,10] as was proved during the second recurrent event, with AT activity at only 12%. No less important is the finding that even 2 months after overcoming COVID-19 infection, a high concentration of FVIII was maintained. All of these can be considered as additional risk factors for recurrent events in this case.

Conclusion

AT-deficient patients are at high risk of VTE recurrence, even when the viral infection manifests with a mild clinical picture. The risk may be present for several months after COVID-19 infection, and we would like to raise awareness of this issue among physicians who are involved in the treatment of COVID-19. In the treatment of acute thrombosis, AT-deficient patients may benefit from the use of AT concentrate along with LMWH, while in cases of type II-HBS, AT supplementation is mandatory.

Conflict of Interest
None declared.

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