

# COVID-19 Presented with Deep Vein Thrombosis in a Patient with Paroxysmal Nocturnal Haemoglobinuria

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## Abstract

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired clonal haematological disease characterized by complement-mediated haemolysis, bone marrow failure and venous thrombosis. Anticomplement therapy eculizumab improves survival and reduces complications. Severe acute respiratory distress syndrome corona virus 2 (SARS-CoV-2) disease 2019 (COVID-19) is associated with high incidence of both venous and arterial thrombosis in hospitalized patients with pneumonia. Deep venous thrombosis (DVT) as the presenting symptom of COVID-19 is a rare event. We describe a well-controlled PNH patient on eculizumab for more than 5 years who presented with DVT, while on warfarin, as the first sign of COVID-19. To our knowledge, this is the first described case of DVT in a PNH patient with COVID-19.

## Keywords

- ▶ COVID-19
- ▶ thrombosis
- ▶ PNH
- ▶ eculizumab
- ▶ anticoagulation

## Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired clonal haematological disease caused by a somatic mutation of the pig-A gene (Xp22.1) in a clone of a bone marrow stem cell. The result is a defective synthesis of glycosylphosphatidylinositol (GPI)-anchored complement regulatory proteins expressed on erythrocytes. Consequently, PNH erythrocytes are highly susceptible to complement-mediated intravascular haemolysis. In addition to haemolysis, PNH is characterized by bone marrow failure and venous thrombosis; arterial thrombosis is far less frequent.<sup>1,2</sup> Thrombosis is the leading cause of death in PNH patients. Major risk factors for thrombosis in PNH seem to be PNH clone size and degree of intravascular haemolysis.<sup>3</sup> However, the basis for thrombosis in PNH is poorly understood. The development of eculizumab, a humanized monoclonal antibody directed against the terminal complement protein C5, resulted in a dramatic improvement of survival and a reduction in complications.

Optimal treatment and management of infection by severe acute respiratory distress syndrome corona virus 2 (SARS-CoV-2) disease 2019 (COVID-19) in patients affected by PNH may be challenging, given the rapid spread of the pandemic and limited literature so far. Specifically, COVID-19 is associated with relatively high incidence of both venous and arterial thrombotic events in patients hospitalized for pneumonia.<sup>4</sup> Median prevalence of venous thromboembolism (VTE) in those patients is approximately 30%<sup>5</sup> with deep venous thrombosis (DVT) prevalence of nearly 20% even on prophylactic doses of anticoagulation.<sup>5,6</sup> However, DVT as the first sign of COVID-19 is a rare event.<sup>7–11</sup>

We herein describe a case of a well-controlled PNH patient on eculizumab and warfarin for more than 5 years, who presented with DVT as the first sign of COVID-19.

## Case Description

Our patient is a non-smoker with no comorbidities. In the first quarter of 2009, he had experienced his first episode of

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Coombs-negative haemolytic anaemia with thrombosis of superior sagittal sinus, treated with anticoagulants for 2 years. At the end of 2013, six months before the presentation that led to diagnosis, he had noticed reddish urine. Midway through 2014, he presented with haemolysis and splenic vein thrombosis with spleen infarction and thrombosis in the superior and inferior mesenteric veins, with the size of the PNH clone at 82%, when the diagnosis of PNH was established. Anticoagulation was initiated at diagnosis, first with low-molecular-weight heparin (LMWH), and then with warfarin. Eculizumab, in standard dose regimen, was initiated for the first time early on in 2015 together with warfarin. With the earlier-described therapy, haemolysis was well controlled—haemoglobin ranged from 107 to 155 g/L with three compensated haemolytic crises during drug shortages with no subsequent thrombotic events (international normalized ratio [INR] was in the range of 2–3 more than 80% of the time; D-dimer was constant at <0.5 mg/L).

Now 33 years old, our patient presented in the second quarter of 2020 with swelling and pain in left leg and lower back pain followed by episode of subfebrility (37 °C) 10 days after the last dose of eculizumab. Co-amoxiclav and ciprofloxacin were started. Colour-duplex scan of lower limbs revealed proximal thrombosis of left popliteal vein. Nadroparin in full therapeutic dose was introduced (85.5 anti-Xa IU/kg SC BID). Laboratory tests showed decreased white blood cells ( $3.4 \times 10^9/L$ ; with absolute neutrophil count  $1.4 \times 10^9/L$  and absolute lymphocyte count  $1.4 \times 10^9/L$ ), mild thrombocytopenia ( $140 \times 10^9/L$ ), mild haemolytic anaemia with haemoglobin (113 g/L), absolute reticulocyte count ( $265.5 \times 10^9/L$ ; normal:  $50\text{--}100 \times 10^9/L$ ), lactate dehydrogenase (1,020 U/L; normal < 460), and absent haptoglobin. C-reactive protein was elevated at 36.4 mg/L (normal <10), as well as D-dimer at 4.3 mg/L (normal <0.5); active partial thromboplastin time was prolonged (43.7 seconds; normal range: 25.1–36.5), while fibrinogen was in normal range at 5.12 g/L (normal: 2.5–5.5). His INR value at the time of thrombosis occurrence was 2, while earlier values were in the range of 2 to 3. The next dose of eculizumab was given 5 days after thrombosis occurrence according to regular schedule. Nasopharyngeal swab RNA PCR showed SARS-CoV-2 positivity. The patient was afebrile and without respiratory symptoms throughout the period of thrombosis and follow-up. After 3 weeks, nadroparin was substituted with warfarin, with no recurrence of thrombosis in the subsequent 11 months.

## Discussion

We present a patient with well-controlled PNH on eculizumab who developed DVT, while on warfarin, as the initial presentation of COVID-19. Meta-analysis of 1,988 hospitalized COVID-19 patients showed that prevalence of DVT was 19.8% (95% confidence interval [CI]: 10.5–34%). However, while including only studies of patients on antithrombotic prophylaxis, DVT prevalence was 8% (95% CI: 2.3–2.4%).<sup>5</sup> While the majority of thrombotic cases were registered in hospitalized patients with COVID-19 pneumonia, up to this date only

few cases of VTE as the presenting symptom of COVID-19 in non-PNH patients were reported.<sup>7–11</sup> Putative risk factors for COVID-19 thrombosis are as follows: hyperinflammatory state, D-dimer greater than 1.5 mg/L, hypoxia, need for invasive mechanical ventilation, immobilisation, advanced age, increased body mass index, and male sex.<sup>12–16</sup> Besides male sex, in our patient, PNH as a prothrombotic state must be taken into account, with cumulative thrombotic incidence of 23 to 30% in pre-eculizumab era.<sup>17</sup> However, initiation of eculizumab reduced thrombotic events in PNH by 81.8%, with 0.62 events per 100 patient-years.<sup>17,18</sup> Although rare, complement-activating events such as viral infection can provoke haemolysis and thrombotic events in PNH patients despite eculizumab therapy.<sup>19</sup> Moreover, virus-induced complement activation and production of prothrombotic antibodies via a complement-dependent pathway<sup>20</sup> could be a potential mechanism by which SARS-CoV-2 leads to immunothrombosis in patients susceptible to complement activation, as in PNH patients. Occasional reports of PNH patients with COVID-19 show that patients on anticomplement therapy did not develop pneumonia, while others (treatment naive) did, suggesting protective properties of anticomplement drugs in COVID-19.<sup>19,21,22</sup> Also, none of the reported PNH patients developed VTE.<sup>19,21,22</sup> In light of this, several ongoing studies are evaluating eculizumab and other anticomplement therapies in severe COVID-19 patients with initial promising results.<sup>23–27</sup> Consistent with previous results, our patient did not develop pneumonia. Given that our patient had long period with stable PNH disease, without thrombosis on eculizumab, and that anticoagulation was mainly in therapeutic range, we propose that SARS-CoV-2 infection outweighed the protective effects of anticomplement and anticoagulant therapy. To the best of our knowledge, this is the first case describing DVT in a PNH COVID-19 patient. This reveals an open debate on several issues. In well-anticoagulated patients, should the development of VTE, during the COVID-19 epidemic, raise a red flag for SARS-CoV-2 testing? Also, considering hypercoagulable effect of SARS-CoV-2, in patients with VTE risk factors, is there a need for more intensified anticoagulation? Given the variability of INR in patients on warfarin, is it preferable to use LMWH or even direct-acting anticoagulants which are not registered in this setting?

## Conflict of Interest

The authors declare that they have no conflict of interest.

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## References

- 1 Risitano AM, Rotoli B. Paroxysmal nocturnal hemoglobinuria: pathophysiology, natural history and treatment options in the era of biological agents. *Biologics* 2008;2(02):205–222
- 2 Luzzatto L, Gianfaldoni G, Notaro R. Management of paroxysmal nocturnal haemoglobinuria: a personal view. *Br J Haematol* 2011; 153(06):709–720

- 3 Pu JJ, Brodsky RA. Paroxysmal nocturnal hemoglobinuria from bench to bedside. *Clin Transl Sci* 2011;4(03):219–224
- 4 Lodigiani C, Lapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020;191:9–14
- 5 Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost* 2020;46(07):763–771
- 6 Santoliquido A, Porfidia A, Nesci A, et al; Gemelli Against COVID-19 Group. Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. *J Thromb Haemost* 2020;18(09):2358–2363
- 7 Hughes C, Nichols T, Pike M, Subbe C, Elghenzai S. Cerebral venous sinus thrombosis as a presentation of COVID-19. *Eur J Case Rep Intern Med* 2020;7(05):001691
- 8 Hemasian H, Ansari B. First case of COVID-19 presented with cerebral venous thrombosis: a rare and dreaded case. *Rev Neurol (Paris)* 2020;176(06):521–523
- 9 Davoodi L, Jafarpour H, Taghavi M, Razavi A. COVID-19 presented with deep vein thrombosis: an unusual presenting. *J Investig Med High Impact Case Rep* 2020;8:2324709620931239
- 10 Mohammadi S, Abouzaripour M, Hesam Shariati N, Hesam Shariati MB. Ovarian vein thrombosis after coronavirus disease (COVID-19) infection in a pregnant woman: case report. *J Thromb Thrombolysis* 2020;50(03):604–607
- 11 Veyseh M, Pophali P, Jayarangaiah A, Kumar A. Left gonadal vein thrombosis in a patient with COVID-19-associated coagulopathy. *BMJ Case Rep* 2020;13(09):e236786
- 12 Rali P, O'Corragain O, Oresanya L, et al. Incidence of venous thromboembolism in coronavirus disease 2019: an experience from a single large academic center. *J Vasc Surg Venous Lymphat Disord* 2021;9(03):585–591.e2
- 13 Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020;18(06):1421–1424
- 14 Miesbach W, Makris M. COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. *Clin Appl Thromb Hemost* 2020;26:1076029620938149
- 15 Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M. Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines. *Swiss Med Wkly* 2020;150:w20301
- 16 Dobesh PP, Trujillo TC. Coagulopathy, venous thromboembolism, and anticoagulation in patients with COVID-19. *Pharmacotherapy* 2020;40(11):1130–1151
- 17 Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. *Ther Adv Hematol* 2017;8(03):119–126
- 18 Malato A, Saccullo G, Coco LL, et al. Thrombotic complications in paroxysmal nocturnal haemoglobinuria: a literature review. *Blood Transfus* 2012;10(04):428–435
- 19 Kulasekararaj AG, Lazana I, Large J, et al. Terminal complement inhibition dampens the inflammation during COVID-19. *Br J Haematol* 2020;190(03):e141–e143
- 20 Valerio L, Riva N. Head, neck, and abdominopelvic septic thrombophlebitis: current evidence and challenges in diagnosis and treatment. *Hamostaseologie* 2020;40(03):301–310
- 21 Shikdar S, Borogovac A, Mohamad E, Khawandanah M. COVID-19 infection in a patient undergoing treatment for paroxysmal nocturnal hemoglobinuria (PNH) with ravulizumab [preprint, version 1]. 2020. Accessed November 16, 2020 at: <https://doi.org/10.21203/rs.3.rs-84187/v1>
- 22 Schüller H, Klein F, Lübbert M, et al. Hemolytic crisis in a patient treated with eculizumab for paroxysmal nocturnal hemoglobinuria possibly triggered by SARS-CoV-2 (COVID-19): a case report. *Ann Hematol* 2020;100(03):841–842
- 23 Diurno F, Numis FG, Porta G, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci* 2020;24(07):4040–4047
- 24 Vlaar APJ, de Bruin S, Busch M, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. *Lancet Rheumatol* 2020;2(12):e764–e773
- 25 Clinicaltrials.Gov. CORIMUNO19-ECU: Trial Evaluating Efficacy and Safety of Eculizumab (Soliris) in Patients with COVID-19 Infection, Nested in the CORIMUNO-19 Cohort (CORIMUNO19-ECU). 2020. Accessed November 22, 2020 at: <https://clinicaltrials.gov/ct2/show/NCT04346797>
- 26 Mastellos DC, Pires da Silva BGP, Fonseca BAL, et al. Complement C3 vs C5 inhibition in severe COVID-19: early clinical findings reveal differential biological efficacy. *Clin Immunol* 2020;220:108598
- 27 Annane D, Heming N, Grimaldi-Bensouda L, et al; Garches COVID 19 Collaborative Group. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: a proof-of-concept study. *EClinicalMedicine* 2020;28:100590