



Acquired Factor XI Deficiency during SARS-CoV-2 Infection: Not Only Thrombosis

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An 80-year-old woman with a positive RT-PCR (reverse transcription polymerase chain reaction) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on nasopharyngeal swab was admitted to our COVID-19 department during the pandemic with fever, dyspnea, and need for oxygen therapy; two large hematomas were present bilaterally in the axillary zones. Her past medical history included Crohn's disease diagnosed 30 years ago after perforation of the ascending colon, hypertension, bilateral hip replacement, appendectomy, and tonsillectomy; no history of bleeding complications was reported during or after surgical interventions or in the postpartum, and no history of menorrhagia or easy-bruising. One month and a half before admission, she underwent right knee replacement surgery with no complications, no blood units, or plasma transfusions were required. At that time complete blood count and screening clotting test were within normal range.

Investigations on admission were as follows: white blood cell 11,380/mm³ (Neu 10,790; Ly 240); hemoglobin 8 g/dL; mean corpuscular volume 89 fL; platelets 251,000/mm³; PTr 1.16 (n.v. 0.80–1.21); PTr 1.49 (n.v. 0.80–1.18); D-dimer 2,161 µg/L (n.v. < 790); fibrinogen 455 mg/dL (n.v. 180–400); C-reactive protein 78.4 mg/L (n.v. < 5.0). A chest computed tomography scan outlined a picture of bilateral interstitial pneumonia with ground-glass areas and thickening of interstitium, consistent with a viral infection; moreover, the presence of hyperdense hematomas in the axillary zones was recorded (thickness 20–30 mm), no active bleeding was detected. Antiretroviral therapy with darunavir and ritonavir was started; hydroxychloroquine was not administered for prolonged QTc on electrocardiogram. Enoxaparin 4000 IU/day was introduced for prophylaxis and continued until hospital discharge.

The isolated prolonged PTr (silica) was confirmed in day +5 and +7 from admission (1.30 and 1.42, respectively), PTr (ellagic acid, reagent sensible to factors VIII, IX, XI deficiency) was prolonged too, so a PTT MIX test was required: the PTT MIX at time 0 was normal but PTr MIX at 2 hours at 37°C was above the normal range, consistent with the presence of an inhibitor (►Table 1); the fXI activity was 37% (n.v. 55–150) while fVIII, fIX, and fXII were in the normal range. Detection of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein I) resulted negative. The PTT MIX test and clotting factors activity was retested 3 days later and the presence of an acquired deficiency of fXI was confirmed. Patient was discharged in good clinical conditions more than 1 month after admission, no thrombotic or bleeding complications occurred during hospitalization.

Inhibitors against clotting factors generally occur in patients with severe congenital deficiencies who underwent periods of replacement therapy. Acquired factor inhibitors in the absence of congenital deficiency are rare events, among them the production of autoantibodies inhibiting fVIII is the most frequent acquired bleeding disorder. On the contrary, inhibitors against fXI have been reported only anecdotally in literature mostly associated to autoimmune disorders, that is, systemic lupus erythematosus,¹ rheumatoid arthritis,² Crohn's disease,³ membranoproliferative glomerulonephritis,⁴ or in association with malignancies, that is, chronic lymphocytic leukemia,⁵ gastrointestinal adenocarcinoma,³ and thymoma⁶; a case of transient acquired fXI deficiency after gynecological surgery has been reported.⁷ The risk of bleeding in conditions of fXI deficiency is relatively low and correlation between factor levels and symptoms is very poor; in these persons hemorrhage is usually provoked, exacerbated by trauma or surgical procedures.^{8,9}

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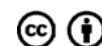


Table 1 Coagulatory and inflammatory parameters

	Unit	Ref.	March 17	March 21	March 23	March 26	April 7	April 12	April 18	April 21
Thrombin time	Ratio	[< 1.20]			1.08					
aPTTr (silica)	Ratio	[0.80–1.18]	1.49	1.30	1.42	1.55	1.40	1.30	1.30	1.24
aPTT MIX time 0	Ratio	[0.80–1.18]			1.17	1.24				
aPTT MIX 2 h 37°C	Ratio	[0.80–1.18]			1.20					
aPTTr (ellagic acid)	Ratio	[0.70–1.18]			1.36					
Factor VIII	%	[50–200]			120					
Factor IX	%	[65–140]			101					
Factor XI	%	[55–150]			37	38.5				
Factor XII	%	[55–180]			63					
D-dimer	µg/L	[< 790]	2,161		3,501		2,471	2,004	2,183	
Fibrinogen	mg/dL	[180–400]	455	541	505			541	568	
CRP	mg/L	[< 5.0]	78.4			55.6		12.7	34.7	

Abbreviations: aPTTr, activated partial thromboplastin time ratio; CRP, Creactive protein.

In the classical chart of the *intrinsic pathway* of coagulation waterfall the fXIIa activates the zymogen fXI which in turn activates fIX and so, through a series of enzymatic reactions, it conducts to thrombin formation. It is nowadays well documented that fXII has only a marginal role in the hemostasis *in vivo*, contributing more to inflammation and pathologic coagulation; in fact, fXI seems to be activated in a stronger way directly by thrombin, thus supporting and amplifying thrombin formation in loop.¹⁰ Moreover, it has also been shown how fXIa activates fXII after tissue factor-initiated coagulation (via *extrinsic pathway*).¹¹ Maybe coagulation is not a waterfall but a whirlpool!

But fXI is not only a component of the coagulation pathway, it also participates to the process of contact activation by mean of the bradykinin-generating kallikrein-kinin system (KKS) (including fXII, prekallikrein PK, high molecular weight-kininogen HK, and C1 esterase inhibitor C1INH) contributing in this way to several host-defenses and to the initial response to infection: in fact, the inflammatory response to viral infections is in part mediated by contact activation and it has already been demonstrated how hantavirus and herpes simplex virus 1 can lead to the activation of KKS pathway.¹² The fXI, together with fXII, seems to have a pivotal role in this context.¹³ In a sepsis setting of fXI deficient mice, Bane et al have shown how a reduced early cytokine response and KKS activation conduct to a survival benefit compared with wild-type mice.^{11,14}

Reconnecting to the case reported above, the reason for the occurrence of inhibitors production against fXI during SARS-CoV-2 infection is still not clear to us, but maybe we can speculate that the inhibition of fXI could be a means of the immune system to try to turn off a sustained inflammatory overresponse against an infective agent which can otherwise conduct to deleterious effects for the host. Why not to consider

this patient, with an autoimmune *milieu* (Crohn's disease), as evolutionary advantaged in this condition having the possibility to counterbalance the state of hypercoagulability and inflammation (the so-called, thromboinflammation¹⁵)? Why not to act directly against fXI, inhibiting it and on one side blocking the pathological coagulation loop with a mild risk of hemorrhage, as already demonstrated^{16,17} and on the other side disrupting the mechanism driving to the uncontrolled inflammatory overresponse by blunting KKS and complement activation?

By our, at this point, everyday experience and from the still scanty literature in this regard it seems to us that patients with severe pneumonias by SARS-CoV-2 can develop a hypercoagulable condition driving to a higher risk for (micro)vascular thrombosis, still to demonstrate^{18–21}; if true, considering the interface role of fXI in vascular thrombosis and inflammation, the development of therapies inhibiting this factor could be an intriguing leverage on which to act for trying to improve microvascular perfusion, reduce inflammation, and protect organ function during severe infections.

Conflict of Interest

None declared.

References

- 1 Wool GD, Trembl A, Miller JL. Acquired factor XI deficiency and therapeutic plasma exchange. *J Clin Apher* 2018;33(03):427–430
- 2 Reece EA, Clyne LP, Romero R, Hobbins JC. Spontaneous factor XI inhibitors. Seven additional cases and a review of the literature. *Arch Intern Med* 1984;144(03):525–529
- 3 Kyriakou DS, Alexandrakis MG, Passam FH, et al. Acquired inhibitors to coagulation factors in patients with gastrointestinal diseases. *Eur J Gastroenterol Hepatol* 2002;14(12):1383–1387
- 4 McManus MP, Frantz C, Gailani D. Acquired factor XI deficiency in a child with membranoproliferative glomerulonephritis. *Pediatr Blood Cancer* 2012;59(01):173–175

- 5 Goodrick MJ, Prentice AG, Copplestone JA, Pamphilon DH, Boon RJ. Acquired factor XI inhibitor in chronic lymphocytic leukaemia. *J Clin Pathol* 1992;45(04):352–353
- 6 Jethava Y, Alamelu J, Rangarajan S, Lang-Lazdunski L, van der Walt J, Fields P. Acquired agranulocytosis and factor XI deficiency in association with thymoma. *J Clin Oncol* 2011;29(20):e604–e606
- 7 Castaman G, Ruggeri M, Rodeghiero F. Acquired transitory factor XI inhibitor after gynaecological surgery. *Haemophilia* 2008;14(03):643–644
- 8 Wheeler AP, Gailani D. Why factor XI deficiency is a clinical concern. *Expert Rev Hematol* 2016;9(07):629–637
- 9 Peyvandi F, Palla R, Menegatti M, et al; European Network of Rare Bleeding Disorders Group. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. *J Thromb Haemost* 2012;10(04):615–621
- 10 Emsley J, McEwan PA, Gailani D. Structure and function of factor XI. *Blood* 2010;115(13):2569–2577
- 11 Bane CE Jr, Ivanov I, Matafonov A, et al. Factor XI deficiency alters the cytokine response and activation of contact proteases during polymicrobial sepsis in mice. *PLoS One* 2016;11(04):e0152968
- 12 Long AT, Kenne E, Jung R, Fuchs TA, Renné T. Contact system revisited: an interface between inflammation, coagulation, and innate immunity. *J Thromb Haemost* 2016;14(03):427–437
- 13 Shatzel JJ, DeLoughery EP, Lorentz CU, et al. The contact activation system as a potential therapeutic target in patients with COVID-19. *Res Pract Thromb Haemost* 2020;4(04):500–505
- 14 Tucker EI, Verbout NG, Leung PY, et al. Inhibition of factor XI activation attenuates inflammation and coagulopathy while improving the survival of mouse polymicrobial sepsis. *Blood* 2012;119(20):4762–4768
- 15 Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. *Blood* 2019;133(09):906–918
- 16 Chen W, Carvalho LP, Chan MY, Kini RM, Kang TS. Fasxiator, a novel factor XIa inhibitor from snake venom, and its site-specific mutagenesis to improve potency and selectivity. *J Thromb Haemost* 2015;13(02):248–261
- 17 Büller HR, Bethune C, Bhanot S, et al; FXI-ASO TKA Investigators. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* 2015;372(03):232–240
- 18 Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res* 2020;220:1–13
- 19 Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol* 2020;95(07):834–847
- 20 Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020
- 21 Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020. Doi: 10.1111/jth.14850