Case Report:
Deep Vein Thrombosis Associated With COVID-19

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ABSTRACT

The novel coronavirus disease 2019 (COVD-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The immunothrombosis could occur during infection with viruses. Deep vein thrombosis (DVT) is a devastating condition that usually involves the lower extremities. The typical course of DVT is associated with an episode of enormous limb swelling and pain. In this case report, we aimed to present one of the COVID-19 possible complications: DVT in a 38 years old man infected with SARS-CoV-2. A 38 years old man presented with leg pain. He had a dry cough and fatigue suspicious symptoms of COVID-19. For further evaluations, the lung Computed Tomography scan (CT-scan), labratorical assessments, and doppler sonography of the common femoral vein (CFV) of both legs were done. Also, for investigating the other underlying causes of DVT, abdominopelvic CT-scan and lumbosacral Magnetic Resonance Imaging (MRI) were done. The CT-scan showed Ground-Glass Opacity (GGO) view. Labratorical assessment proposed a thrombotic condition. The doppler sonography of the CFV of both legs revealed a massive thrombosis in the left CFV suggesting an acute DVT. Abdominopelvic CT-scan and lumbosacral MRI were negative for other underlying causes of DVT. COVID-19 is associated with the classical syndrome named disseminated intravascular coagulation and the subsequent consumption coagulopathy presented as DVT.

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1. Introduction

The novel Coronavirus Disease 2019 (COVD-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has created several challenges for healthcare providers. Since the first cases reported in Wuhan, Hubei Province (China) in December 2019, up to now, a broad spectrum of clinical manifestations has been described for COVID-19, included lower respiratory tract infection with fever, dry cough, diarrhea, and dyspnea. These symptoms sometimes combine with mild to severe pneumonia with dyspnea, tachypnea, and disturbed gas exchange. Approximately 5% of infected patients develop severe lung dysfunction, a need for ventilation, shock, or multiple (extrapulmonary) organ failure [1-3]. Nevertheless, some patients were presents with different manifestations and lacked typical clinical symptoms described before.

COVID-19 may also be associated with massive pro-inflammatory cytokine production, including interleukin (IL)-2, IL6, IL-7, IL-10, Granulocyte Colony-Stimulating factor (G-CSF), interferon γ-induced protein 10 (IP-10), Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage Inflammatory Protein-1α (MIP-1α), and Tumor Necrosis Factor- α (TNF-α). Previous studies demonstrated the close connection between thrombosis and inflammation [4, 5]. Deep Vein Thrombosis (DVT) is a long-term and devastating condition that usually involves the lower extremities. DVT mostly occurs as an acute condition, but its sequel could be very bothersome. The typical course of DVT is associated with an episode of enormous limb swelling and pain [6].

Herein we present a case where the primary symptom expressed by the patient infected by SARS-CoV-2 was the lower extremity swelling and pain without typical COVID-19 clinical symptoms.

2. Case Presentation

A 38-year-old man with a history of mild dry cough and fever from several days ago presented with swelling of lower extremities in emergency care services. He was a healthy man without any comorbidity or underlying disease. He was a construction worker and was fully ambulated until one week before admission. Physical examination and workup revealed a body temperature of 37°C, blood pressure of 120/70 mm Hg, a pulse of 110 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 91% while the patient was breathing ambient air. The lung Computed Tomography scan (CT-scan) showed the peripheral bilateral Ground-Glass Opacity (GGO) presentation (Figure 1), a typical lung view in COVID-19. During laboratory analyses, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and International Normalized Ratio (INR) were reported receptively 12.9 s, 51 s, and 1.1, which propose a thrombosis condition (Table 1). Doppler sonography of Common Femoral Vein (CFV) of both legs was performed and, a massive thrombosis was seen in the left CFV suggesting an acute DVT. After an abdominopelvic CT-scan and lumbosacral Magnetic Resonance Imaging (MRI) [7], no other factor was observed, such as a tumor that causes DVT. Thus, the secondary causes of DVT were rejected. Then the patient received enoxaparin (80 mg, BID), hydroxychloroquine (200 mg, BID), and lopinavir/ritonavir (400 mg/100 mg, BID). The treatment resulted in a stable condition. After confirmatory analysis, he was released from the hospital. After hospital discharge, the treatment with enoxaparin (80 mg, BID) and warfarin 5 mg/d was continued, and the swelling of the lower extremities showed a significant decrease. Enoxaparin was discontinued, and now our patient is under warfarin treatment 7.5 mg/d controlled by INR.

3. Discussion

Coagulation can act as an immunorespone to defense against several severe infections [8]. Several studies have reported that coagulation could occur in response to several diseases because they enhance the physiological response [9-11].

During activation of the coagulation cascade, a positive feedback loop induces platelet activation via generation of thrombin, promoting micro thrombosis in response to inflammation and infection. This process is called immunothrombosis [12]. As a result, excessive responses of the immune system during infection are often associated

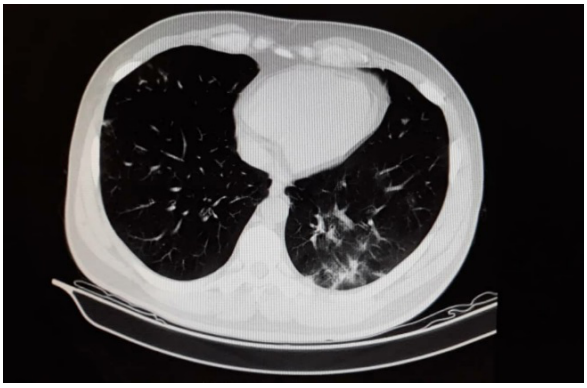

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Figure 1. Ground-Glass Opacity (GGO), view in Lung CT-scan

Table 1. Laboratory analysis upon patient's admission

Laboratory Test		Result	Normal Range
CBC	HMG, g/dL	12.8	11.7-16
	LYMPH, %	11.7	20-50
	PLT, $x^{10\times3}$	153	130-400
	RBC -	4.65	-
	WBC, $x^{10\times3}$	10.6	4.5-11
	Poly, %	73.3	37-72
	MIX, -	15	-
	HCT, %	38.4	35-47
	MCV, fL	82.6	80-99
	MCH, pg	27.5	27-35
	MCHC, g/dL	33	32-37
	RDW-CV, %	14.3	10.6-15.7
	PDW, fL	12.1	9-17
	P-LCR, %	25.4	13-43
Biochemistry	Magnesium, mg/dL	1.66	1.2-2.6
Coagulation	PT, s	12.	11-13
	PTT, s	51	24-35
	INR, -	1.1	-
Urine analyses	Urea, mg/dL	20	13-43
	Creatinine, mg/dL	0.9	Males: 0.6-1.4 Females: 0.6-1.3
Electrolyte analyses	Na, mEq/L	137	135-145
	K, mEq/L	3.7	3.5-5.5
Blood group-RH		O(+) POSITIVE	-
ESR		18	-
CRP, mg/dL		8.19	Up to 6 mg/dL

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with overstated and dysregulated activation of coagulation and thrombosis [13]. Further studies have revealed that IL-1β, IL-6, MCP-1, and tumor necrosis factor-β (TGF-β) have been upregulated during thrombogenesis [14], factors which were overexpressed during COVID-19 cytokine releasing.

Cytokine Releasing Syndrome (CRS) is a common complication of COVID-19, which could be caused by infection, characterized by a sharp increase in the level of many pro-inflammatory cytokines, including IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, Granulocyte-Macrophage Colony-Stimulating Factor (GMCSF), interferon-γ (IFN-γ), TNF-α, IP10, MCP1, MIP1α, and Macrophage Inflammatory Proteins-1β (MIP1β) [15, 16].

Some previous studies demonstrated a high correlation between some pro-inflammatory cytokine and DVT, which demonstrated a higher IL-6, C-Reactive Protein (CRP), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and lower IL-10 levels in patients with DVT [17]. Also, excess amounts of IL-6, CRP, lower IL-10, and overexpression of the NF-κB signaling pathway, which play an essential role in a cytokine storm, have recently been reported for COVID-19 [18].

The close connection between thrombosis and inflammation has been described in the previous studies. Two processes that reciprocally reinforce each other. It is acclaimed that coagulation factors (pro- and anti-coagulants) and platelets, besides their hemostasis effects, could play an important role in modulating the host immune response, exhibiting pro-inflammatory function [19, 20]. Altogether, it is assumed that COVID-19 is associated with the classical syndrome named disseminated intravascular coagulation and the subsequent consumption coagulopathy [21].

4. Conclusion

There is a tight interconnection between inflammation and hemostasis, which reciprocally reinforce each other. It is postulated that there is a dramatic link between some cytokine and DVT, which cytokine upregulation during SARS-CoV-2 sepsis increases the susceptibility to DVT. Besides, it is assumed that COVID-19 is associated with the classical syndrome named disseminated intravascular coagulation and the subsequent consumption coagulopathy.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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Authors' contributions

Conceptualization and supervision: Ehsan Zaboli and Roya Ghasemian; Methodology: Roya Ghasemian; Investigation, Writing – original draft, writing – review & editing: Mahdi Abounoori, Mohammad Zahedi, Ehsan Zaboli; Data collection: Seyyed Abbas Hashemi.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel Coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020; 25(3):2000045. [DOI:10.2807/1560-7917.ES.2020.25.3.2000045] [PMID] [PMCID]

[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13):1239-42. [DOI:10.1001/jama.2020.2648] [PMID]

[3] Rahaman ST. A Review on Effect of Covid-19 in Pregnant Women. Pharm Biomed Res. 2020; 6(Special Issue 1 on COVID-19):17-26. [DOI:10.18502/pbr.v6i(s1).4397]

[4] Jackson SP, Darbousset R, Schoenwaelder SM. Thrombo-inflammation: Challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019; 133(9):906-18. [DOI:10.1182/blood-2018-11-882993] [PMID]

[5] Iba T, Levy J. Inflammation and thrombosis: Roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost. 2018; 16(2):231-41. [DOI:10.1111/jth.13911] [PMID]

[6] Siddiqui NA, Moosa MA, Shaikh FA, Shahzad N, Nazir S, Sophie Z. Predictors of poor quality of life after primary lower limb deep venous thrombosis: A perspective from a developing nation. Ann Vasc Dis. 2020; 13(1):63-8. [DOI:10.3400/avd.oa.19-00126] [PMID] [PMCID]

[7] Maiti S, Banerjee A. Epigallocatechin gallate and theaflavin gallate interaction in SARS-CoV-2 spike-protein central channel with reference to the hydroxychloroquine interaction: Bioinformatics and molecular docking study. Drug Dev Res. 2020; 10.1002/ddr.21730. [DOI:10.1002/ddr.21730] [PMID] [PMCID]

[8] Loof TG, Mörgelin M, Johansson L, Oehmcke S, Olin AI, Dickneite G, et al. Coagulation, an ancestral serine protease cascade, exerts a novel function in early immune defense. Blood. 2011; 118(9):2589-98. [DOI:10.1182/blood-2011-02-337568] [PMID]

[9] Gershom E, Sutherland M, Lollar P, Pryzdial E. Involvement of the contact phase and intrinsic pathway in herpes simplex virus-initiated plasma coagulation. J Thromb Haemost. 2010; 8(5):1037-43. [DOI:10.1111/j.1538-7836.2010.03789.x] [PMID]

[10] Antoniak S, Mackman N. Multiple roles of the coagulation protease cascade during virus infection. Blood. 2014; 123(17):2605-13. [DOI:10.1182/blood-2013-09-526277] [PMID] [PMCID]

[11] Minasyan H, Flachsbart F. Blood coagulation: A powerful bactericidal mechanism of human innate immunity. Int Rev Immunol. 2019; 38(1):3-17. [DOI:10.1080/08830185.2018.1533009] [PMID]

[12] Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nature Rev Immunol. 2013; 13(1):34-45. [DOI:10.1038/nri3345] [PMID]

[13] Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med. 1999; 341(8):586-92. [DOI:10.1056/NEJM199908193410807] [PMID]

[14] Shebuski RJ, Kilgore KS. Role of inflammatory mediators in thrombogenesis. J Pharmacol Exp Ther. 2002; 300(3):729-35. [DOI:10.1124/jpet.300.3.729] [PMID]

[15] Teijaro JR. Cytokine storms in infectious diseases. Springer Semin Immunopathol. 2017; 39(5):501-3. [DOI:10.1007/s00281-017-0640-2] [PMID] [PMCID]

[16] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: Interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020; 55(5):105954. [DOI:10.1016/j.ijantimicag.2020.105954] [PMID] [PMCID]

[17] Du T, Tan Z. Relationship between deep venous thrombosis and inflammatory cytokines in postoperative patients with malignant abdominal tumors. Braz J Med Biol Res. 2014; 47(11):1003-7. [DOI:10.1590/1414-431X20143695] [PMID] [PMCID]

[18] Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020; 38(1):1-9. [DOI:10.12932/AP-200220-0772] [PMID]

[19] Assinger A, Schrottmaier WC, Salzmann M, Rayes J. Platelets in sepsis: An update on experimental models and clinical data. Front Immunol. 2019; 10:1687. [DOI:10.3389/fimmu.2019.01687] [PMID] [PMCID]

[20] Claushuis T, de Stoppelaar S, Stroo I, Roelofs J, Ottenhoff R, van der Poll T, et al. Thrombin contributes to protective immunity in pneumonia-derived sepsis via fibrin polymerization and platelet-neutrophil interactions. J Thromb Haemost. 2017; 15(4):744-57. [DOI:10.1111/jth.13625] [PMID]

[21] Marietta M, Ageno W, Artoni A, De Candia E, Gresele P, Marchetti M, et al. COVID-19 and haemostasis: A position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfusion. 2020; 18(3):167-9. [PMCID] [PMID]

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