The roles and potential therapeutic implications of C5a in the pathogenesis of COVID-19-associated coagulopathy

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ABSTRACT

Emerging evidence has documented that multisystem organ failure in coronavirus disease 2019 (COVID-19) patients is strongly associated with various coagulopathies. Treatments for COVID-19-associated coagulopathy are still a clinical challenge. An advancement in the knowledge of mechanisms of the excessive or inappropriate activation of the complement cascade involved in the genesis of COVID-19-associated coagulopathy might be a fundamental approach for developing novel classes of anticoagulant drugs. In this context, there is emerging evidence indicating that C5a, a component of the complement system, and its receptors (C5aRs) play a critical role in the genesis of the COVID-19-associated hypercoagulable state. Thus, this review describes the mechanisms by which C5a/C5aR signaling participates in the cascade of events involved in the pathophysiology of COVID-19-associated coagulopathy. Furthermore, it highlights the current possibilities for the development of a novel therapeutic approach for COVID-19 patients that targets C5a/C5aRs signaling.

1. Introduction

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] has afflicted more than 17 million individuals worldwide. As of today (October 5, 2020), SARS-CoV-2 has infected 35,027,546 people and killed over 1,034,837 worldwide (data from regularly released WHO reports) [2]. Clinically, patients with coronavirus disease 2019 (COVID-19) have labored breathing, progressive hypoxemia, elevated D-dimer levels and fibrin/fibrinogen degradation products [3]. The distinctive features of COVID-19 pulmonary autopsy specimens include diffuse intravascular coagulation and large vessel thrombosis [4], which are linked to multisystem organ failure, including acute respiratory distress syndrome (ARDS), heart failure and kidney failure. Although additional research is needed to elucidate the relationship of these findings with the clinical course of COVID-19, emerging evidence documents that multisystem organ failure in COVID-19 patients is strongly associated with various

coagulopathies. The latest data suggest that the incidence of thrombotic complications is between 16 % and 49 % in patients with COVID-19 admitted to intensive care units [5]. However, a central question that could inform the management of COVID-19-associated coagulopathy remains under debate: are the hemostatic changes a consequence of severe inflammation, or are they a specific effect mediated by the virus [5]?

The pathogenesis of COVID-19-associated coagulopathy has not been fully elucidated. However, recent studies have indicated that thrombogenic coagulopathy in COVID-19 patients is mediated through C5a and its receptors (C5aRs) [9]. In this article, we summarize recent developments in our understanding of the role of C5a in mediating COVID-19-associated coagulopathy.

2. Complement cascade activation

The complement system plays an important role in host defense

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Fig. 1. Complement cascade activation pathway. The classical pathway is activated by the C1q/r/s complex, and the lectin pathway is activated by MBL/MASPs attached to carbohydrates on the surface of microorganisms. Both pathways converge to release C3 convertase (C4bC2b). The alternative pathway is constitutively active at a low level due to the spontaneous breakdown of C3 into anaphylatoxin C3a and the active C3b fragment. C3b also serves to generate the next generation of C5 convertases. C5 convertases cleave the C5 molecule into the C5a anaphylatoxin and the C5b fragment, which initiates the terminal MAC and target cell lysis.

against microbial infection. However, the complement cascade can be excessively or inappropriately activated through three major pathways (namely, the classical, alternative and lectin pathways) in different courses of COVID-19 [6]. The classical pathway is activated by the C1q/r/s complex assembled on antigen-bound antibodies or in an antibody-independent manner, resulting in generation of the cofactor C4b, which accelerates enzymatic generation of C3a, C3b and the mild anaphylatoxin C4a [7]. The lectin pathway is initiated by mannose binding lectin (MBL)/MBL-associated serine proteases (MASPs) attached to carbohydrates on the surface of microorganisms. Both pathways converge to release the common C3 convertase (C4bC2b), which results in C3b/C3a production. The alternative pathway is constantly activated by spontaneous hydrolysis of the intramolecular thioester within C3, thus providing C3 convertase (C3(H2O)Bb/C3bBb), which cleaves C3 into anaphylactic and antimicrobial C3a and C3b, an opsonin that is deposited on nearby surfaces and serves to amplify activation signals. C3b also serves to generate the next generation C5 convertases. Notably, the common pathways converge on complement C5 [8]. Cleavage of C5a and C5b successively leads to the production of the C5b-9 membrane attack complex (MAC), which lyses target cells,

resulting in cell death [9]. A schematic representation of the complement cascade activation pathway is shown in Fig. 1. As a potent inflammatory mediator and chemoattractant, the complement anaphylatoxin C5a contributes to endothelial barrier loss and organ injury and potentially enhances the pathogenesis of COVID-19-associated coagulopathy [10].

3. Clinical presentations of COVID-19-associated coagulopathy

Coagulation disorders are emerging as an important issue in patients with COVID-19 [11]. COVID-19 is associated with thrombogenic coagulopathy with a range of presentations [12]. Preliminary reports on initial coagulopathy of COVID-19 have shown that infected patients may have elevated D-dimer (46.4 %) and commonly develop thrombocytopenia (36.2 %) [13], and these rates are even higher in patients with severe COVID-19 (59.6 % and 57.7 %, respectively) [13]. Emerging data support that prominent elevation of D-dimer and fibrin/fibrinogen degradation product levels and abnormalities in platelet counts, prothrombin time, and partial thromboplastin time are associated with poor prognosis in patients affected by the novel

coronavirus [3,11]. Additionally, as the distinctive feature of COVID-19-associated coagulopathy, thromboses can occur in all severities of COVID-19 and range from small to large vessel clots [14], among which recent studies have documented the presence of disseminated intravascular coagulation (DIC), microvascular thromboses, pulmonary emboli [4], aortoiliac and mesenteric thrombi [15], and large vessel strokes [16].

4. COVID-19-associated coagulopathy and disease severity

Findings from the SARS-CoV-2 pandemic indicate that the presence of coagulopathy is consistently associated with disease severity and mortality in patients with COVID-19. Coagulopathy has been reported in up to 50 % of patients with severe COVID-19 manifestations [17]. Autopsy studies of patients who died of COVID-19 identified small vessel occlusion and endotheliitis in the lungs, kidneys, liver, heart, and intestine [18]. Additionally, a recent study indicated that multiple processes may contribute to COVID-19-associated microvascular and macrovascular thrombosis. These processes include cytokine storm with activation of leukocytes, endothelium and platelets, resulting in upregulation of tissue factor, activation of coagulation, thrombin generation and fibrin formation; disrupted coagulation with imbalances in plasminogen activator inhibitor-1 (PAI-1) and tissue factor pathway inhibitor; activation of protein C, which promotes fibrin generation and limits fibrinolysis; and direct viral effects resulting in cell activation [17]. These findings highlight that dysregulation of coagulation and fibrinolysis pathways contributes to COVID-19 severity, possibly through altering the hemostatic balance with subsequent coagulation-induced ischemic injury.

The complete spectrum of presentations of COVID-19-associated coagulopathy has not been fully elucidated. Both D-dimer elevation and thrombocytopenia can be explained by the excessive activation of the coagulation cascade and platelets [[11]]. Multiple pathogenetic mediators are involved in the imbalance between procoagulant and anticoagulant homeostatic mechanisms in COVID-19, including endothelial

Dysfunction [19], neutrophil activation and neutrophil extracellular trap (NET) release [20,21], and complement system activation [22]. Emerging data suggest that C5a activation provides rapid protection from infectious challenge and can also transition to the 'dark side', becoming a driver or exacerbator of pathology in COVID-19-associated coagulopathy [10,23].

5. C5a and C5aRs in COVID-19

Human C5a is a 74-amino acid protein composed of four α-helices in an antiparallel configuration with bridging disulfide bonds. It is formed by cleavage of the amino terminus of C5 by the C5a convertase in the plasma. C5a exerts its functions via two distinct receptors, C5aR1 and C5aR2 [24], both of which harbor seven transmembrane (7 T M) helix architectures.

C5aR1, also referred to as CD88, is a prototypical G-protein-coupled receptor (GPCR) [24] that is expressed on all cells of myeloid origin (such as neutrophils, subpopulations of monocytes, and macrophages), some lymphocytes, and many nonmyeloid cells, including epithelial cells [25]. The C5a-C5aR1 interaction is generally acknowledged to have proinflammatory roles in promoting adhesion molecule expression, chemotaxis, degranulation, phagocytosis, and oxidative bursts. From a signaling perspective, C5a-C5aR1 activation alters cAMP/PKA, ERK1/2, p38 MAPK, calcium mobilization, and β-arrestin (βarrs)-mediated signaling responses to modulate cytokine production and secretion [26]. However, uncontrolled activation of the C5a-C5aR1 axis has been

associated with a myriad of acute and chronic inflammatory diseases [25].

Interestingly, Skendros and colleagues demonstrated that C5aR1

blockade attenuates platelet-mediated, NET-driven, COVID-19-associated thrombogenicity [27]. These data presented in a recent study support the role of the C5a-C5aR1 axis in inflammatory mechanisms underlying coagulopathy development in patients at early or late stages of SARS−COV-2 infection [28].

C5aR2, also referred to as C5L2 or GPR77, is abundantly expressed in human tissues, such as the bone marrow, spleen and lungs [25]. It displays predominant intracellular expression in most myeloid cells and selected T cell subsets, such as neutrophils, monocytes, monocyte-derived macrophages, and NK cells [29]. Although a detailed mechanism of C5aR2 signaling and its functional consequences remains to be elucidated, recent progress has shown that C5aR2 binds C5a and desarginated C5a (C5a-desArg) and internalizes them for intracellular degradation, thereby providing a negative regulatory mechanism to remove excess C5a from the circulation [25]. C5aR2 serves as a negative regulator and balancer of C5aR1 surface expression and helps to prevent overactivation of C5aR1 [23]. Additionally, C5aR2 induces robust high mobility group box 1 (HMGB1) production upon C5a stimulation associated with MEK1/2, JNK1/2, and PI3K/Akt activation [30]. C5aR2 also exerts significant immunomodulatory effects on other pattern recognition receptors and innate immune systems, such as NOD-like receptor protein 3 (NLRP3) inflammasomes [31].

Fatal COVID-19 has been associated with a systemic inflammatory response accompanied by a coagulopathy state and organ damage, particularly microvascular thrombi in the lungs and kidneys. As the strongest inflammatory peptide in the complement cascade that induces proinflammatory cytokine release [32], C5a and C5aRs involved in the pathogenesis of SARS-CoV-2 infection were examined in a recent study [33]. We review recent developments in the role of C5a in mediating COVID-19-associated coagulopathy through the prism of Virchow's triad.

6. C5a and vessel wall abnormalities in COVID-19

Emerging studies have shown that extensive endotheliitis in the lung, heart, kidneys, liver, and small bowel is associated with an accumulation of inflammatory cells in patients with severe COVID-19 [34]. Endothelial cell swelling with foam-like changes, subendothelial expansion, and endothelial proliferation were observed in COVID-19-associated endotheliitis [35]. Deposition of the complement-derived fragment C5 in lung autopsies [36] and elevated circulatory levels of C5a were observed in severe cases of COVID-19 [33].Together with evidence that treatment of COVID-19 patients with an anti-C5a antibody led to immediate clinical improvement, as measured by increased lung oxygenation and decreased systemic inflammation [33], we support the hypothesis that C5a, as a potent anaphylatoxin, plays a critical role in the pathogenesis of COVID-19-associated endotheliitis. The proposed central role of endothelial cells in contributing to the initiation and propagation of severe COVID-19 prompts the question of whether vascular normalization strategies could be useful in the management of COVID-19-associated coagulopathy escalation [37]. Three clinical trials have been registered for off-label compassionate use of eculizumab to verify the use of a complement C5 inhibitor for the treatment of patients with COVID-19 (ClinicalTrials.gov Identifiers: NCT04288713, NCT04346797, and NCT04355494) [34]. Normalization of the vascular wall through a C5a inhibitor could be considered a potential route of intervention in COVID-19-associated coagulopathy.

7. C5a and altered blood flow in COVID-19

The vascular endothelium is a dynamic endocrine, paracrine, and autocrine organ with a vital role in regulating vascular tone and homeostasis. Secretion by the endothelium includes fibrinolytic agents, antiplatelet agents and venodilators, which in turn are related to the rheological properties of the blood. Through control of the degree of vascular relaxation and constriction, the endothelium regulates regional
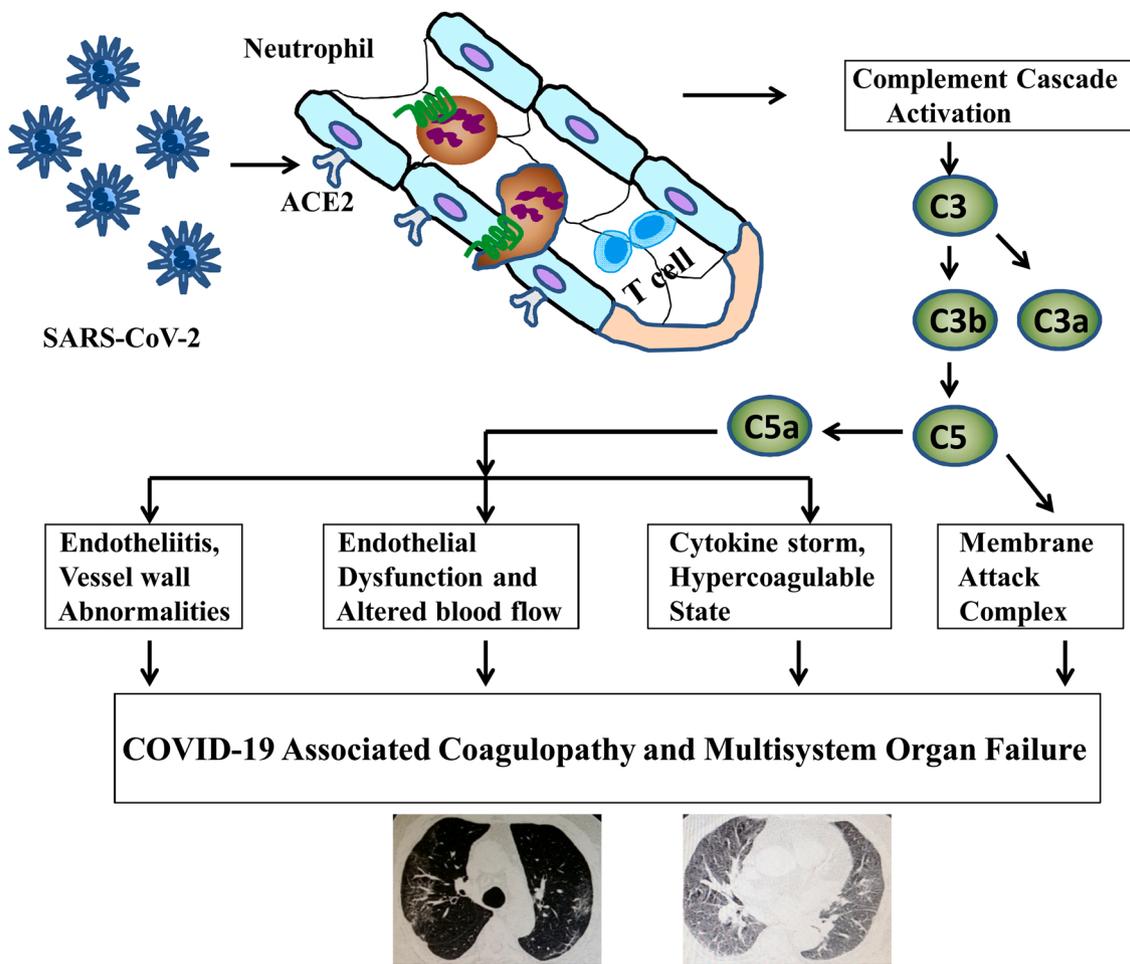
Fig. 2. Illustrative representation of the invasion of SARS-CoV-2 virus and the role of complement C5a in the pathogenesis of COVID-19-associated coagulopathy. The SARS-CoV-2 virus likely enters alveolar pneumocytes through respiratory epithelial cells and endothelial cells that supply the lungs and other organs and express the ACE2 receptor. This invasion triggers a rapid innate immune response by neutrophils, T cells, NK cells, and macrophages. Substantial damage to capillaries and persistence of the virus induce complement cascade activation and production of C5a and the MAC. The C5a anaphylatoxin induces more widespread and stronger cytokine storms, endotheliitis, endothelial dysfunction, vessel wall abnormalities, altered blood flow, and a hypercoagulable state [63], contributing to COVID-19-associated coagulopathy and multisystem organ failure.

blood flow [38]. Endothelial dysfunction leads to abnormalities in the anticoagulant and fibrinolytic mechanisms, abnormalities of blood coagulation factors (such as increases in plasma D-dimer, circulating thrombin and activated protein C) and detrimental shifts in the vascular equilibrium towards vasoconstriction, inflammation, and a procoagulant state resulting in thrombosis [39,40]. Recently, emerging studies have shown that thrombotic events in COVID-19-associated coagulopathy are

associated with endothelial cell dysfunction [19]. Moreover, Henry et al. proposed that complement activation and direct viral invasion of the endothelium could be responsible for endothelial dysfunction [41]. Several underlying mechanisms associated with COVID-19-associated coagulopathy have not been clearly defined, but the association of endothelial dysfunction with COVID-19 and enhancement of the activated complement components C5a and C3a has been verified in severe COVID-19 patients [42].

The glycocalyx is a thick coat of proteins and carbohydrates on the outer surface of the vascular endothelium [43]. It is formed by glycoproteins and proteoglycans (PG) and has a multilayer structure that reduces endothelial contact with cellular and macromolecular blood components. The glycocalyx plays an important role in vascular homeostasis, regulating vascular permeability and cell adhesion [44]. It can also act as a mechanotransducer, enabling the detection of mechanical stress through its intracellular protein domain [44]. The link

between the glycocalyx and vascular endothelial cell dysfunction in COVID-19 requires further research [45]; however, evidence increasingly suggests that COVID-19 induces multiple injuries, including damage to the endothelial glycocalyx and endothelial dysfunction, which has been attributed to endothelial activation and dysfunction [46]. Interestingly, Bongoni et al. demonstrated that complement protein C5a plays a key role in endothelial dysfunction through damage to the vasculoprotective endothelial glycocalyx [47]. The combination of endothelial dysfunction and complement C5a may contribute to the overall procoagulative state described in COVID-19.

8. C5a and hypercoagulability of blood in COVID-19

Recent prospective studies of autopsy findings from consecutive deaths from COVID-19 found that thromboembolic events were a common cause of mortality in patients infected with COVID-19 [48]. Initial cohort studies showed that the incidence of thromboembolic complications in patients with COVID-19 is 35–45 % [49]. As the pandemic is spreading and the complete details are yet unknown, these emerging studies provide important insight into the hypercoagulable state and thromboembolic events associated with COVID-19 [50].

The underlying pathophysiology contributing to the hypercoagulable state may be related to the cytokine storm, which is characterized by high concentrations of proinflammatory cytokines and chemokines

Table 1
Clinical trials of C5 inhibitors therapeutics in COVID-19.

Drug	Drug type	The hypothesis of the proposed intervention	Administration route	Company	ClinicalTrials.gov Identifier	Clinincal Phase
Ravulizumab	Antibody	Ameliorating COVID 19 induced thrombotic microangiopathy, acute kidney injury.	Intravenous injection	Alexion Pharma	NCT04570397	Phase 3
Ravulizumab	Antibody	Inhibiting acute lung injury and acute respiratory distress syndrome post COVID-19.	Intravenous injection	Alexion Pharma	NCT04369469	Phase 3
Zilucoplan	Peptide	Inhibiting acute lung injury post COVID-19, promoting lung repair mechanisms.	Subcutaneous injection	UCB Pharma	NCT04382755	Phase 2
Eculizumab	Antibody	Inhibiting acute lung injury and Respiratory failure post COVID-19.	Intravenous injection	Alexion Pharma	NCT04346797	Phase 2
Eculizumab	Antibody	Inhibiting acute lung injury and acute respiratory distress syndrome post COVID-19.	Intravenous injection	Alexion Pharma	NCT04355494	Expanded Access Status: Available
Eculizumab	Antibody	Modulating the activity of the distal complement preventing the formation of the membrane attack complex.	Intravenous injection	Alexion Pharma	NCT04288713	Expanded Access Status: Available

[51]. Cytokine storms promote the release of ultra-large von Willebrand factor (VWF) multimers and the production of tissue factor (activation of extrinsic coagulation pathways) and FVII/FVIIa (activation of intrinsic coagulation pathways) [41], leading to increased endothelial damage and thrombin generation and decreased levels of endogenous anticoagulants (such as tissue factor pathway inhibitors, antithrombin, and activated protein C) [52]. Increasing clinical data also suggest that cytokine storms are associated with COVID-19 severity and are a crucial cause of death from COVID-19 [53].

Cytokine storms consist of an excessive immune response to external stimuli. The pathogenesis of cytokine storms includes impairment of SARS-CoV-2 clearance [54], decreased levels of interferons (IFNs) [55], increased NETs [56] and pyroptosis, and miscellaneous other mechanisms that contribute to the loss of regulatory control of proinflammatory cytokine production [57,58]. Cellular entry of SARS-CoV-2 depends on the binding of S proteins covering the surface of the virion to the cellular angiotensin-converting enzyme 2 (ACE2) receptor [59]. After entering respiratory epithelial cells, SARS-CoV-2 provokes an immune response with inflammatory cytokine production accompanied by a weak IFN response [58]. Then, pathogenic Th1 cells and monocytes are activated, and macrophages and neutrophils infiltrate into the lung tissue, which results in a cytokine storm [60].

The involvement of the complement system in the pathogenesis of COVID-19-associated coagulopathy has been examined in several studies [[61] [62],]. The hyperactivation of complement C5a, which is the strongest inflammatory peptide in the complement cascade, induces the release of proinflammatory cytokines and contributes to the cytokine storm [[61]]. C5a and C5aRs involved in the pathogenesis of the hypercoagulable state in COVID-19 patients were examined in a recent study [33]. Recently, a combination of ruxolitinib (a JAK1/2 inhibitor) and eculizumab (an anti-C5a complement monoclonal antibody) was administered to patients with a hypercoagulable state and ARDS due to COVID-19, and very good clinical responses with a high level of safety were reported [63–65]. Fig. 2 illustrates the invasion of the SARS-CoV-2 virus and the role of complement C5a in the pathogenesis of COVID-19-associated coagulopathy.

9. Experimental and clinical therapeutic applications of C5a

Inhibitors of complement C5a have long been of interest as potential drugs for the treatment of diseases such as sepsis, ischemia-reperfusion injuries, atypical hemolytic-uremic syndrome (aHUS), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, rheumatoid arthritis, and inflammatory bowel disease [66–68]. More recently, a role of C5a inhibitors in viral infectious diseases, such as COVID-19, has been identified. In general, these small molecule C5a inhibitors can be divided into three types: anti-C5a antibodies (mAbs) [69], C5a antagonists [66], and chimeric C5a compounds (C-terminal- or N-terminal-modified C5a) [70].

BDB-001 is a mouse-human chimeric antibody against human C5a

[33]. Experimental results demonstrated that BDB-001 can significantly alleviate N protein-induced C5a activation and lung injury in vitro and in vivo [33]. Moreover, clinical outcomes in eculizumab (an anti-C5a complement mAb)-treated COVID-19 patients showed significant improvements in respiratory symptoms and radiographic pulmonary lesions and a decrease in circulating D-dimer levels [65]. Currently, clinical trial outcomes also suggest that C5a antagonists, as anticoagulants, could be employed to minimize lung damage and prevent systemic involvement in COVID-19 patients [71]. Zilucoplan is a small compound composed of a 15-amino acid macrocyclic peptide that binds to C5 with high affinity and specificity [72]. In the field of C5 complement therapeutics for COVID-19 (shown in Table 1), a recent registered clinical trial (EudraCT 2020−001736-95, registered April 28, 2020) has been undertaken to evaluate the safety and efficacy of zilucoplan in COVID-19 patients [12,73].

10. Conclusion

Collectively, the present review strongly indicates that activation of the complement anaphylatoxin C5a plays a significant role in the extensive endotheliitis, endothelial dysfunction, and hypercoagulable state in COVID-19 patients; contributes to the generation of endothelial barrier loss and organ injury and potentially enhances the pathogenesis of COVID-19-associated coagulopathy. Moreover, the increasing body of data demonstrates that targeting C5a and C5aR signaling will lead novel therapeutic options for the prevention or attenuation of the hypercoagulable state that is currently observed in patients with COVID-19.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.12.001.

References

[1] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (February (11)) (2020) 1061–1069.

[2] Coronavirus disease, (COVID-19) Pandemic, Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed: 5 October 2020, 08:00 GMT+8, 2019.

[3] J.M. Connors, J.H. Levy, COVID-19 and its implications for thrombosis and anticoagulation, Blood 135 (June (23)) (2020) 2033–2040.

[4] M. Ackermann, S.E. Verleden, M. Kuehnel, et al., Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19, N. Engl. J. Med. 383 (2020) 120–128.

[5] The Lancet Haematology, COVID-19 coagulopathy: an evolving story, Lancet Haematol. 7 (June (6)) (2020) e425.

[6] C.M. Campbell, R. Kahwash, Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? Circulation 141 (June (22)) (2020) 1739–1741.

[7] Conway EM, Pryzdial ELG, Is the COVID-19 thrombotic catastrophe complement-connected? J. Thromb. Haemost. 6 (August) (2020) https://doi.org/10.1111/jth.15050. Online ahead of print.

[8] G.M. Vercellotti, A.P. Dalmasso, T.R. Schaid Jr, et al., Critical role of C5a in sickle cell disease, Am. J. Hematol. 94 (March (3)) (2019) 327–337.

[9] C.B. Xie, D. Jane-Wit, J.S. Pober, Complement membrane attack complex: new roles, mechanisms of action, and therapeutic targets, Am. J. Pathol. 190 (June (6)) (2020) 1138–1150.

[10] A.M. Risitano, D.C. Mastellos, M.Y. Huber-Lang, et al., Complement as a target in COVID-19? Nat. Rev. Immunol. 20 (June (6)) (2020) 343–344.

[11] D. Giannis, I.A. Ziogas, P. Gianni, Coagulation disorders in coronavirus infected patients: COVID-19, SARSCoV-1, MERS-CoV and lessons from the past, J Clin Virol. 127 (June) (2020), 104362.

[12] M.W. Lo, C. Kemper, T.M. Woodruff, COVID-19: complement, coagulation, and collateral damage, J. Immunol. 22 (July) (2020) ji2000644.

[13] W.J. Guan, Z.Y. Ni, Y. Hu, et al., Clinical Characteristics of Coronavirus Disease 2019 in China, N. Engl. J. Med. 382 (April (18)) (2020) 1708–1720.

[14] D. McGonagle, J.S. O'Donnell, K. Sharif, P. Emery, C. Bridgewood, IMmune mechanisms of pulmonary intravascular coagulation in COVID-19 pneumonia, Lancet Rheumatol 2 (July (7)) (2020) e437–e445.

[15] P. Vulliamy, S. Jacob, Davenport RA.ACute aorto-iliac and mesenteric arterial thromboses as presenting features of COVID-19, Br. J. Haematol. 189 (June (6)) (2020) 1053–1054.

[16] T.J. Oxley, J. Mocco, S. Majidi, et al., Large-vessel stroke as a presenting feature of Covid-19 in the young, N. Engl. J. Med. 382 (May (20)) (2020) e60.

[17] W. Miesbach, M. Makris, COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation, Clin. Appl. Thromb. Hemost. 26 (January-December) (2020), 1076029620938149.

[18] Z. Varga, A.J. Flammer, P. Steiger, et al., Endothelial cell infection and endotheliitis in COVID-19, Lancet 395 (May (10234)) (2020) 1417–1418.

[19] S. Pons, S. Fodil, E. Azoulay, L. Zafrani, The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection, Crit. Care 24 (June (1)) (2020) 353.

[20] Y. Zuo, S. Yalavarthi, H. Shi, et al., Neutrophil extracellular traps and thrombosis in COVID-19, medRxiv 5 (May (2020)) (2020), 04.30. 20086736.

[21] Y. Zuo, S. Yalavarthi, H. Shi, et al., Neutrophil extracellular traps in COVID-19, JCI Insight 5 (June (11)) (2020), e138999.

[22] D.C. Mastellos, D. Ricklin, J.D. Lambris, Clinical promise of next-generation complement therapeutics, Nat. Rev. Drug Discov. 18 (September (9)) (2019) 707–729.

[23] S. Pandey, J. Maharana, X.X. Li, T.M. Woodruff, A.K. Shukla, Emerging insights into the structure and function of complement C5a receptors, Trends Biochem. Sci. 45 (August (8)) (2020) 693–705.

[24] S. Yu, D. Wang, L. Huang, et al., The complement receptor C5aR2 promotes protein kinase R expression and contributes to NLRP3 inflammasome activation and HMGB1 release from macrophages, J. Biol. Chem. 294 (May (21)) (2019) 8384–8394.

[25] X.X. Li, J.D. Lee, C. Kemper, T.M. Woodruff, The complement receptor C5aR2: a powerful modulator of innate and adaptive immunity, J. Immunol. 202 (June (12)) (2019) 3339–3348.

[26] H. Lee, P.L. Whitfeld, C.R. Mackay, Receptors for complement C5a. The importance of C5aR and the enigmatic role of C5L2, Immunol. Cell Biol. 86 (February (2)) (2008) 153–160.

[27] P. Skendros, A. Mitsios, A. Chrysanthopoulou, et al., Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis, J. Clin. Invest. 6 (August) (2020), 141374.

[28] J. Carvelli, O. Demaria, F. Vély, et al., Association of COVID-19 inflammation with activation of the C5a-C5aR1axis, Nature 29 (July) (2020), https://doi.org/10.1038/s41586-020-2600-6. Online ahead of print.

[29] P. Pundir, C.A. MacDonald, M. Kulka, The novel receptor c5ar2 is required for c5a-mediated human mast cell adhesion, migration, and proinflammatory mediator production, J. Immunol. 195 (September (6)) (2015) 2774–2787.

[30] D. Rittirsch, M.A. Flierl, B.A. Nadeau, et al., Functional roles for C5a receptors in sepsis, Nat. Med. 14 (May (5)) (2008) 551–557.

[31] M.D. Haggadone, J.J. Grailer, F. Fattahi, F.S. Zetoune, P.A. Ward, Bidirectional crosstalk between C5a receptors and the NLRP3 inflammasome in macrophages and monocytes, Mediators Inflamm. 2016 (2016), 1340156.

[32] Eivind O. Samstad, Nathalie Niyonzima, Stig Nymo, et al., Cholesterol crystals induce complement-dependent inflammasome activation and cytokine release, J. Immunol. 192 (March (6)) (2014) 2837–2845.

[33] T. Gao, M. Hu, X. Zhang, et al., Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation, medRxiv (2020), https://doi.org/10.1101/2020.03.29.20041962(2020).

[34] M. Noris, A. Benigni, G. Remuzzi, The case of complement activation in COVID-19 multiorgan impact, Kidney Int. 98 (August (2)) (2020) 314–322.

[35] H. Su, M. Yang, C. Wan, et al., Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China, Kidney Int. 98 (2020) 219–227.

[36] C. Magro, J.J. Mulvey, D. Berlin, et al., Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases, Transl. Res. 220 (June) (2020) 1–13.

[37] L.A. Teuwen, V. Geldhof, A. Pasut, P. Carmeliet, COVID-19: the vasculature unleashed, Nat. Rev. Immunol. 20 (July (7)) (2020) 389–391.

[38] A. Krüger-Genge, A. Blocki, R.P. Franke, F. Jung, Vascular endothelial cell biology: an update, Int. J. Mol. Sci. 20 (September (18)) (2019) 4411.

[39] W. Mosleh, K. Chen, S.E. Pfau, A. Vashist, Endotheliitis and endothelial dysfunction in patients with COVID-19: its role in thrombosis and adverse outcomes, J. Clin. Med. 9 (June (6)) (2020) 1862.

[40] J.A. Alvarado-Moreno, A. Majluf-Cruz, COVID-19 and dysfunctional endothelium: the mexican scenario, Arch. Med. Res. 51 (August (6)) (2020) 587–588.

[41] B.M. Henry, J. Vikse, S. Benoit, E.J. Favaloro, G. Lippi, Hyperinflammation and derangement of renin-angiotensin- aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis, Clin. Chim. Acta 507 (August) (2020) 167–173.

[42] B. Joob, V. Wiwanitkit, Hemorrhagic problem among the patients with COVID-19: clinical summary of 41 thai infected patients, Clin. Appl. Thromb. Hemost. 26 (January-December) (2020), 1076029620918308.

[43] J.G. Gandhi, D.L. Koch, M.J. Paszek, Equilibrium modeling of the mechanics and structure of the Cancer glycocalyx, Biophys. J. 116 (February (4)) (2019) 694–708.

[44] C. Aldecoa, J.V. Llau, X. Nuvials, A. Artigas, Role of albumin in the preservation of endothelial glycocalyx integrity and the microcirculation: a review, Ann. Intensive Care 10 (June (1)) (2020) 85.

[45] H. Okada, S. Yoshida, A. Hara, S. Ogura, H. Tomita, Vascular endothelial injury exacerbates coronavirus disease 2019: the role of endothelial glycocalyx protection, Microcirculation 13 (August) (2020) e12654.

[46] M.R. Hayden, Endothelial activation and dysfunction in metabolic syndrome, type 2 diabetes and coronavirus disease 2019, J. Int. Med. Res. 48 (July (7)) (2020), 300060520939746.

[47] A.K. Bongoni, B. Lu, J.L. McRae, et al., Complement -mediated damage to the glycocalyx plays a role in renal ischemia- reperfusion injury in mice, Transplant. Direct 5 (March (4)) (2019) e341.

[48] D. Wichmann, J.P. Sperhake, M. Lütgehetmann, et al., Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study, Ann. Intern. Med. 173 (August (4)) (2020) 268–277.

[49] F.A. Klok, M.J.H.A. Kruip, N.J.M. van der Meer, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (July) (2020) 145–147.

[50] J.M. Connors, J.H. Levy, Thromboinflammation and the hypercoagulability of COVID-19, J. Thromb. Haemost. 18 (July (7)) (2020) 1559–1561.

[51] P. Mehta, D.F. McAuley, M. Brown, et al., COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (March (10229)) (2020) 1033–1034.

[52] Y. Zhang, M. Xiao, S. Zhang, et al., Coagulopathy and antiphospholipid antibodies in patients with Covid-19, N. Engl. J. Med. 382 (April (17)) (2020) e38.

[53] B. Hu, S. Huang, L. Yin, The cytokine storm and COVID-19, J. Med. Virol. 27 (June) (2020), https://doi.org/10.1002/jmv.26232. Online ahead of print.

[54] Z. Xu, L. Shi, Y. Wang, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (April (4)) (2020) 420–422.

[55] M. Soy, G. Keser, P. Atagündüz, F. Tabak, I. Atagündüz, S. Kayhan, Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment, Clin. Rheumatol. 39 (July (7)) (2020) 2085–2094.

[56] B.J. Barnes, J.M. Adrover, A. Baxter-Stoltzfus, et al., Targeting potential drivers of COVID-19:neutrophil extracellular traps, J. Exp. Med. 217 (June (6)) (2020), e20200652.

[57] M. Soy, G. Keser, P. Atagündüz, F. Tabak, I. Atagündüz, S. Kayhan, Cytokine storm inCOVID-19:pathogenesis and overview of anti-inflammatory agents used in treatment, Clin. Rheumatol. 39 (July (7)) (2020) 2085–2094.

[58] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the `Cytokine Storm' in COVID-19, J. Infect. 80 (June (6)) (2020) 607–613.

[59] P. Zhou, X.L. Yang, X.G. Wang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.

[60] M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (April (2)) (2020) 271–280, e8.

[61] M. Mahmudpour, J. Roozbeh, M. Keshavarz, S. Farrokhi, I. Nabipour, COVID-19 cytokine storm: the anger of inflammation, Cytokine 133 (September) (2020), 155151.

[62] M. Panigada, N. Bottino, P. Tagliabue, et al., Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis, J. Thromb. Haemost. 18 (July (7)) (2020) 1738–1742.

[63] J. Laurence, J.J. Mulvey, M. Seshadri, et al., Anti-complement C5 therapy with eculizumab in three cases of criticalCOVID-19, Clin. Immunol. 6 (August 219) (2020), 108555.

[64] F. Diurno, F.G. Numis, G. Porta, et al., Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience, Eur. Rev. Med. Pharmacol. Sci. 24 (April (7)) (2020) 4040–4047.

[65] V. Giudice, P. Pagliano, A. Vatrella, et al., Combination of Ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-Related acute respiratory distress syndrome: a controlled study, Front. Pharmacol. 5 (June 11) (2020) 857.

[66] N. Robertson, M. Rappas, A.S. Doré, et al., Structure of the complement C5a receptor bound to the extra-helical antagonist NDT9513727, Nature 553 (January (7686)) (2018) 111–114.

[67] M. Noris, M. Galbusera, S. Gastoldi, et al., Dynamics of complement activation in aHUS and how to monitor eculizumab therapy, Blood 124 (September (11)) (2014) 1715–1726.

[68] D.R.W. Jayne, A.N. Bruchfeld, L. Harper, et al., Randomized trial of C5a receptor inhibitor avacopan in ANCA-Associated vasculitis, J. Am. Soc. Nephrol. 28 (September (9)) (2017) 2756–2767.

[69] S. Sun, Y. Jiang, R. Wang, et al., Treatment of paraquat-induced lung injury with an Anti-C5a antibody: potential clinical application, Crit. Care Med. 46 (May (5)) (2018) e419–e425.

[70] Y. Oda, K. Tokita, Y. Ota, et al., Agonistic and antagonistic effects of C5a-chimera bearing S19 ribosomal protein tail portion on the C5a receptor of monocytes and neutrophils, respectively, J. Biochem. 144 (September (3)) (2008) 371–381.

[71] H.S. Shin, Empirical treatment and prevention of COVID-19, Infect. Chemother. 52 (June (2)) (2020) 142–153.

[72] J.F. Howard Jr, R.J. Nowak, G.I. Wolfe, et al., Clinical Effects of the Self-administered Subcutaneous Complement Inhibitor Zilucoplan in Patients With Moderate to Severe Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial, JAMA Neurol. 77 (May (5)) (2020) 582–592.

[73] T. Wilkinson, R. Dixon, C. Page, et al., ACCORD: a multicentre, seamless, phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID-19 in hospitalised patients: a structured summary of a study protocol for a randomised controlled trial, Trials 21 (July (1)) (2020) 691.

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