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Hematological aspects of the COVID-19 syndrome

U.Y. MALKAN, I.C. HAZNEDAROGLU

Department of Hematology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Abstract. – OBJECTIVE: Viral infections could complicate hematopoiesis and, in some cases, they may worsen the clinical prognosis of blood disorders. SARS-CoV-2 and COVID-19, as a viral disease, can have serious impact on the disease course of hematological neoplastic diseases and can cause hematological complications. The aim of this paper is to review the hematologic aspects of COVID-19 syndrome and the potential management options for SARS-CoV-2 including the convalescent plasma, hemostatic agents and proper anticoagulant treatment.

MATERIALS AND METHODS: Up to February 2022, literature searches were performed using the internet search engines MEDLINE and EMBASE: (i) COVID-19; (ii) Hematology. PRISMA flow diagram described the COVID-19 and hematology search.

RESULTS: According to our COVID-19 and hematology research on research databases, we included 82 studies in the current paper. The issues of the impact of the COVID-19 pandemic on hematological diseases, the role of t-lymphocytes in donor lymphocyte infusion and viruses, hemato-immunologic research in COVID-19, local bone marrow renin-angiotensin system and viral infections, clinical management of COVID-19 infection *via* hemostatic agents, immune plasma treatment of COVID-19, anticoagulant treatment of COVID-19 associated thrombosis are comprehensively described in this paper.

CONCLUSIONS: The final episode of this pandemic will include the "chimerism-mediated immunotherapy" that will eventually lead to end of the COVID-19 process. The recent Omicron variant seems to have unique evasion effects on the interferon gene expression which will boost the chimerism-mediated immunotherapy without high mortality rates.

Key Words:
SARS-CoV-2, COVID-19, Hematology.

Introduction

Viral infections could complicate hematopoiesis, and, in some cases, they may worsen the clinical prognosis of the blood disorders. SARS-CoV-2 or COVID-19, as a viral disease, can have serious impact on the hematological neoplastic diseases' course and can cause hematological complications. Viruses can exert hematopoietic effects directly or with the cytokines. The role of T-lymphocytes is essential in viral effects, as well as several hematological treatments like donor lymphocyte infusion. Hematologic and immunologic research regarding the COVID-19 syndrome is important to understand the SARS-CoV-2 mechanism throughout the human body. The renin-angiotensin system (RAS) is both found locally in different organs and systemic circulating RAS throughout the body. Particularly, local bone marrow RAS is involved in several mechanisms in SARS-CoV-2 infection. Hematologic treatment options include the hemostatic agents which have therapeutic effects against SARS-CoV-2, immune plasma treatment and the proper anticoagulation for SARS-CoV-2 associated thrombosis. SARS-CoV-2 may also be related to other hematological conditions, such as leukemogenesis.

The aim of this paper is to review the hematologic aspects of COVID-19 syndrome and the potential management options for SARS-CoV-2 including the convalescent plasma, hemostatic agents and proper anticoagulant treatments.

Viral Infections in Hematological Disorders

Hematopoietic stem cell transplant patients are severely immunocompromised, which leads to life threatening infections. Herpes simplex virus (HSV) may cause infections in chronic myeloid leukemia patients with blastic transformation[1]. HSV infections may lead to tonsillar abscesses, which can be successfully treated with antiviral treatments. Herpetic infections in the differential diagnosis of oropharyngeal small sized lesions in the immunocompromised patient population with hematological disorders are very important[1]. Varicella zoster virus (VZV) infection can be seen in myeloproliferative hematological neoplasia in bone marrow transplanted patients[2]. Viral activation after pharmacological JAK-STAT inhibition may be seen. VZV infection generally manifests with cutaneous lesions. These cutaneous lesions may also occur in patients with myeloproliferative disorders who were given ruxolitinib[2]. More-

Corresponding Author: Umit Yavuz Malkan, MD; e-mail: umitmalkan@hotmail.com

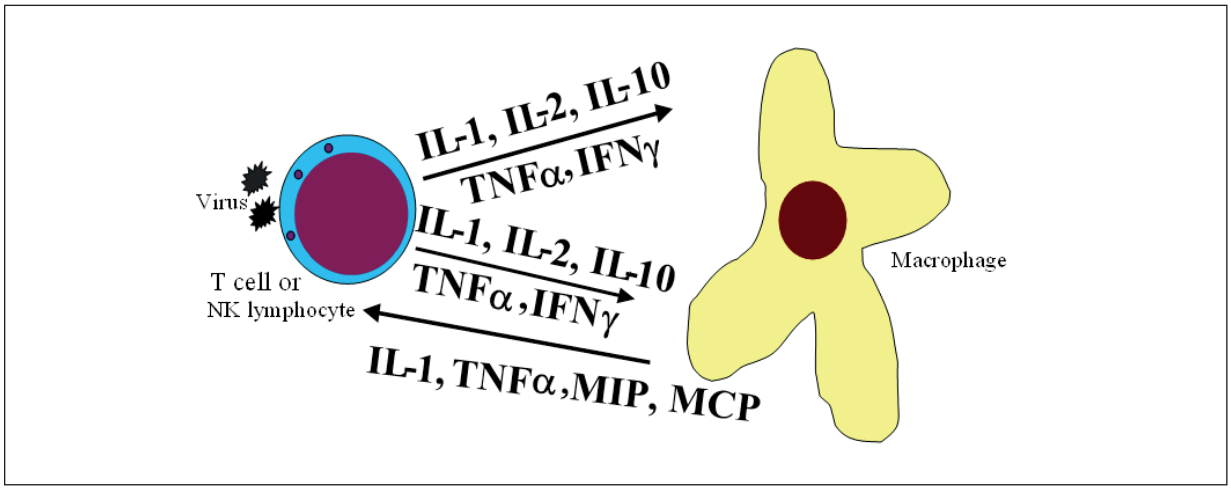

Figure 1. The mechanism of hemaphagocytosis due to viral infections. Abbreviations: IL: interleukin, TNF: Tumor necrosis factor, IFN: Interferon, MIP: Macrophage inflammatory protein, MCP: monocyte chemoattractant protein.

over, ruxolitinib can cause the pathological expression of the transcription factors significant in lymphoma development, reduction of repressor transcriptions protective for lymphoma genesis, inhibition of apoptosis, promotion of neoplastic proliferation, transcriptional stimulation, and increase of malignant neoplastic B cells[3]. Hepatitis B, hepatitis C, human immunodeficiency virus (HIV) could also be seen in hematologic patients with hereditary coagulation disorders[4].

Many other viral infections are related to, can be seen in and might be triggered by hematological disorders Acquired erythroblastopenia (AE) is characterized by the reduction of erythroid precursors in the bone marrow[5]. Drugs, Parvovirus B19 and other infectious reasons, lymphoid and myeloid neoplasia, autoimmune diseases, thymoma and pregnancy may cause AE[5]. The most common reasons of erythroblastopenia are myelodysplastic syndrome (17.7%) and idiopathic pure red cell aplasia (17.7%)[5]. Parvovirus infection was also found as an important factor for AE[5].

Viral Effects on Hematopoiesis

Viral attack on the bone marrow can affect all aspects of hematopoiesis. Bone marrow need appropriate molecular and anatomical microenvironment in order to function normally. Toxins like alcohol, quinine, antiviruses, IFN may impair bone marrow functions[6,7]. The mechanisms of viral attack on bone marrow is previously defined as direct infection, direct recognition of a pathogen, by pro-inflammatory cytokines released by other cells and by alterations in the bone marrow microenvironment[8]. Immune attack on bone marrow is a dominant mechanism in immune thrombocytopenic purpura, systemic lupus erythematosus, HIV[9]. Ultrastructure of the bone marrow in HIV infection has been defined, but HIV infection leads to dyshematopoiesis and stromal cell damage of the marrow[10]. The viruses like HIV can damage hematopoiesis and lead to pancytopenia.

Viral infections are also related to hemaphagocytosis. Hemophagocytic lymphohistiocytosis is a potentially mortal clinicopathologic syndrome in which an uncontrolled immune activation could lead to the state of hyper-inflammation. Although infections, malignancies, autoimmune diseases, and acquired immune deficiencies may stimulate hemaphagocytosis, the most consistent relation is with viral infections, especially Epstein-Barr virus (EBV)[11]. EBV leads to hemaphagocytosis *via* IL-18, TNFα, IFNγ and other cytokines (Figure 1)[12]. It can also cause lymphoma and both lymphoma and EBV may eventually lead to hemaphagocytosis, which can cause mortality because of multi-organ failure[13,14].

Materials and Methods

Up to February 2022, literature searches were performed using the internet search engines MEDLINE and EMBASE, using the words: (i) COVID-19; (ii) Hematology. Only articles written in English and research conducted on people were taken in the search. All abstracts were scanned. The studies that were found to be methodologically weak with limited applicability and/or poor presentation of the findings were excluded. Arti-

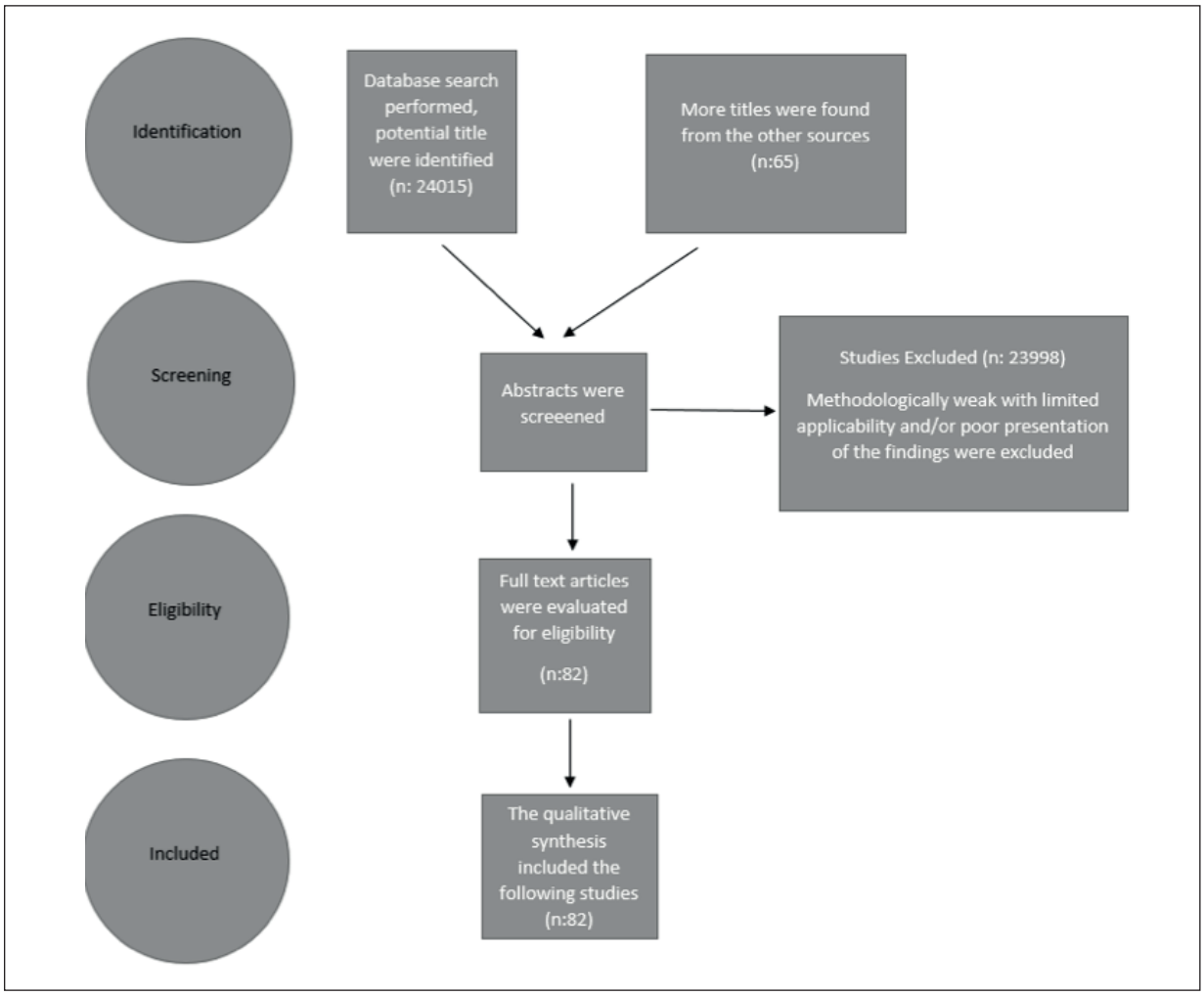

Figure 2. PRISMA flow diagram for the COVID-19 and hematology search.

cles in full text were evaluated for eligibility and quality. The qualitative synthesis included the studies reported in Figure 2.

Results

During the database search, 24,015 potential titles were identified. 65 titles were found from other sources. 23,998 methodologically weak studies were excluded. According to our COVID-19 and hematology research on the research databases, we included 82 studies in this review. The hematological impact of the COVID-19 pandemic, the role of t-lymphocytes, hemato-immunologic research in COVID-19, the relationship between local bone marrow renin-angiotensin system and viral infections, the role of hemostatic agents in the clinical management of COVID-19 infection, immune plasma treatment of COVID-19, anticoagulant treatment of COVID-19 related thrombosis are comprehensively described in this paper.

The Impact of COVID-19 Pandemic on Hematological Diseases

The outpatient hematology patients have been stratified during the pandemic. The severe patients like leukemia patients have been handled normally just like the pre-pandemic era; however, other patients are followed-up less frequently and handled in outpatient clinics rather than inpatient clinics as much as possible. The other issue is that the chemotherapeutic agents and other treatments, as well as the direct effect of hematological diseases, lead to the immunosuppression of hematology patients. These patients are at high risk for COVID-19 infection because of their immunosuppression. The use of steroids for COVID-19

treatment is more frequent in hematology patients, which indicates that the COVID-19 infection is more severe in hematology patients[15]. Moreover, admission to intensive care units and mechanical ventilator support is more frequent in hematology patients than in the normal population[15]. The mortality rate was found in 42.1% of cases with hematological diseases, while 9.7% of patients had other chronic diseases[15].

The Role of T-Lymphocytes in Donor Lymphocyte Infusion and Viruses

T-cell reactions to SARS-CoV-2 have been identified in treated patients. This fact can be important for immunity after infection and vaccination in addition to the genesis of an adoptive immunotherapy for immunosuppressed patients. SARS-CoV-2 targeted T-cell immunotherapy against structural proteins; most significantly membrane protein can be used for the inhibition or early treatment of SARS-CoV-2 infection in immunosuppressed cases with hematological diseases. Also, it can be used after stem cell transplantation to succeed antiviral control though modifying severe inflammation[16]. Therefore, if donor lymphocyte infusion is performed from a COVID-19 recovered donor, this lymphocyte infusion may be beneficial for both underlying hematological disease and COVID-19 infection in the host.

Hemato-Immunologic Research in COVID-19

Throughout this pandemic, healthcare professionals have benefited from each other's practices in fighting against the COVID-19 syndrome. COVID-19 associated studies[15,17] have been conducted by several research groups in Turkey and in the whole world. Several treatment agents including lopinavir/ritonavir, favipiravir, neuraminidase inhibitors, remdesivir, umifenovir, azithromycin, and chloroquine have been investigated in different studies[17]. Also, our research team conducted several studies[17,18] aiming at clarifying the hemato-immunologic relations of COVID-19. We have aimed at investigating the expression changes of the RAS and non-RAS genes, mostly immune response genes, in the lung epithelial cells following the infection with SARS-CoV. RAS genes play a role in the initiation of the coronavirus family members' infections and could have an association with the exchange of immune genes in due course after the infection[18]. Schurink et al[19] reported the multi-systemic COVID-19-related inflammatory alterations in the lungs, heart, kidneys, and brain. All of these tissues have a local autocrine tissue renin-angiotensin system which can be affected by the SARS-CoV-2 ACE2 relations and its immune and inflammatory consequences[20]. Likely, COVID-19 should be considered as an immune syndrome which eventually results in a multi-systemic disorder triggered by the SARS-CoV-2 infection. We defined the COVID-19 process and separated each clinical and genomic phase. The clinical phases of COVID-19 syndrome were presented as "asymptomatic/pre-symptomatic phase", "respiratory phase with mild/moderate/severe symptoms" and "multi-systemic clinical syndrome with impaired/disproportionate and/or defective immunity". The correlating genomic phases are: ACE2, ANPEP transcripts in the initial phase; EGFR and IGF2R transcripts in the propagating phase; the immune system related critical gene involvements of the complicating phase (Figure 3)[21]. The separation of these phases enabled us to focus on each unique phase. Our group proposed that ANPEP gene pathway could be targeted for the vaccine development. Considering the important role of renin-angiotensin system in association with COVID-19, the MAS agonists, TXA127, Angiotensin (1-7) and soluble ACE2 may have a role in the treatment of COVID-19 syndrome[21]. Furthermore, our research group had published the SARS-CoV-2 contagion transmission dynamics in community[22]. SARS-CoV-2 RNAs can be reverse-transcribed and integrated into the human genome. The ultimate aim of the SARS-CoV-2 is the incorporation into human genome, becoming an element of the intestinal virobiota[22]. The SARS-CoV-2 genomic incorporation into human virobiota mainly depends on three pathobiological stages that could be nominated as the "induction", "consolidation", and "maintenance" stages. The stage of 'recurrence' could complicate any stage depending on the viral load, exposure time, and more contagious strains and/or mutations. Following the incorporation of SARS-CoV-2 virus into the human genome *via* the induction, consolidation, and maintenance stages as a part of intestinal virobiota, the chimerism can be established[22].

Local Bone Marrow RAS and Viral Infections

The locally active ligand peptides, mediators, receptors and signaling pathways of the hematopoietic bone marrow autocrine/paracrine RAS play major role in hematopoiesis[23]. Hematopoiesis, erythropoiesis, myelopoiesis, formation of monocytic and lymphocytic lineages, thrombopoiesis and other stromal cellular elements are

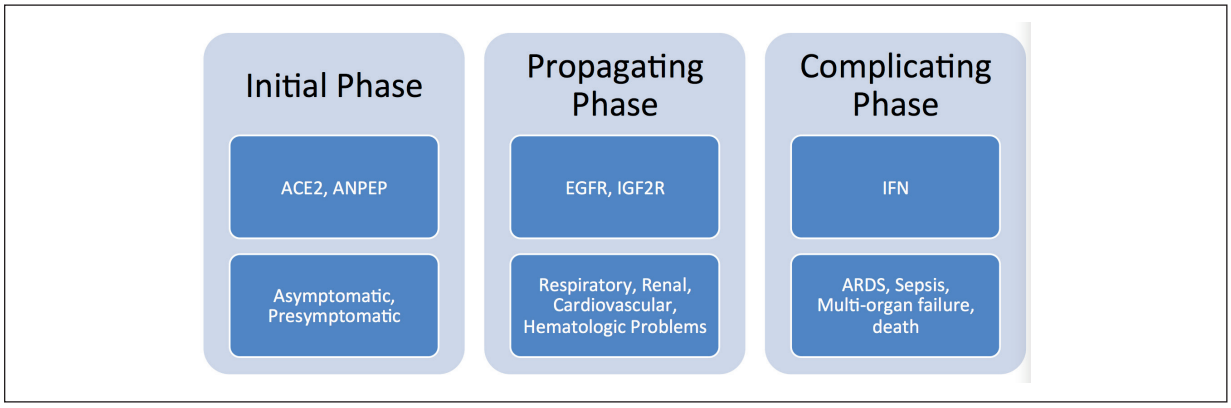

Figure 3. Clinical and genomic phases of the COVID-19 syndrome and corresponding clinical features.

controlled by the local bone marrow RAS. The local tissue RAS affects tumor development and metastases in an autocrine and paracrine way, meaning by modifying several carcinogenic mechanisms, such as angiogenesis, apoptosis, cellular proliferation, immune responses, cell signaling and extracellular matrix formation[23]. Most of the RAS molecules such as *ACE*, *ACE2*, *AGT*, *AGTR1*, *AGTR2*, *AKR1C4*, *AKR1D1*, *ANPEP*, *ATP6AP2*, *CMA1*, *CPA3*, *CTSA*, *CTSD*, *CTSG*, *CYP11A1*, *CYP11B1*, *CYP11B2*, *CYP17A1*, *CYP21A2*, *DPP3*, *EGFR*, *ENPEP*, *GPER*, *HSD11B1*, *HSD11B2*, *IGF2R*, *KLK1*, *LNPEP*, *MAS1*, *MME*, *NR3C1*, *NR3C2*, *PREP*, *REN*, *RNPEP*, and *THOP1* are existent in the bone marrow microenvironment[24]. Moreover, local hematopoietic bone marrow RAS plays an important role when associated to vascular biology and cellular events from embryogenesis to definitive hematopoiesis leading vascular atherosclerosis[20]. Local bone marrow RAS has played an important role on hematopoietic systems, predominantly on myeloid and erythroid cells[25]. The receptors of Ang 1-7 and MAS exist in the bone marrow stroma[26]. Bone marrow hematopoietic stem/progenitor cells (HSPCs) are in contact with the cells of secondary lymphoid organs, which modify HSPC differentiation and maturation[27,28]. COVID-19 clinical progress frequently goes together with hematological problems. Lymphopenia, as well as increased white blood cell (WBC) with granulocytosis, anemia, thrombocytopenia and thrombophilia, can be considered as the most frequent hematological problems occurring during in COVID-19[29]. Coagulation alterations in COVID-19 patients are called "COVID-19-associated coagulopathies (CACs)" and they represent prognostic predictors for a poor clinical outcome[30]. The etiology of CAC could be sepsis or critical illness, however also there are other causes. There are several thrombotic mechanisms of COVID-19, namely: endothelial injuries, severe inflammations, tissue hypoxia, immobilization, respiratory failures, mechanical ventilation and catheters use[30]. Inflammatory mediators and cytokines that are secreted in the acute phase of COVID-19 infection play a role in the additional stimulation of the pro-coagulant mechanism. Vascular endothelial injury takes part into the tissue factor expression, leading to augmented micro-vessel occlusions[30,31]. Vascular endothelium is the key target organ of SARS-CoV-2[32,33]. During the binding of SARS-CoV-2 to the ACE2 receptor, endothelial damage happens, leading to the hypercoagulable state[30]. Severe hypoxemia, caused by pulmonary inflammation and pulmonary vasoconstriction, may also play a role in the blood viscosity and thrombosis[30,34]. Focal pulmonary thrombosis, related to alveolar injuries, worsens the inflammatory response and microvascular thrombi[35]. Vascular microthrombosis is eventually concluded with the consumption coagulopathy and organ dysfunction[30,35]. If considered all together the consumption coagulopathy in COVID-19 is different from sepsis-related disseminated intravascular coagulopathy (SIC). SIC is that CAC is more likely to occur with thrombosis than bleeding[36]. Thrombocytopenia was detected in 36.2% COVID-19 patients[37,38]. A recent meta-analysis showed that thrombocytopenia rates in severe disease were between 4-57%. Thrombocytopenia at presentation was found to be related with an increased risk of

severe disease and death[39]. Reports regarding COVID-19 cases showed that only around 5% of patients have moderate and severe thrombocytopenia and 70–95% of cases have with mild thrombocytopenia[31]. SARS-CoV-2 infects human body via human angiotensin converting enzyme 2 (ACE2), leading to severe pneumonia and high mortality[40]. Circulating RAS and local paracrin-autocrin-intracrin tissue-related RAS plays role in several pathobiological events. Pro-inflammatory, pro-fibrotic, and pro-thrombotic clinical events related with local RAS stimulation have been observed at cellular and molecular level[40]. Regenerative progenitor cell treatment in reaction to RAS-controlling pharmacotherapy in the setting of endothelial cell damage and regeneration emerged as a supporting treatment to recover regeneration of the vascular endothelium[40].

Clinical Management of COVID-19 Infection via Hemostatic Agents

The high mobility group box-1 (HMGB1) molecule had been known as a pro-inflammatory cytokine that controls endotoxin lethality of mice. There are several articles regarding[41,42] targeting the HMGB1 within the contexts of infection, inflammation, and cancer. The pathogenic effect of HMGB1 to the severe acute respiratory syndrome (SARS) and treatment of the disorders with herbal formulations aiming this unique protein have already been suggested[41]. On the other hand, the reports of the several ineffective anti-viral therapies on the current viral infections cast reassessment of the potential associations about the HMGB1 and SARS-CoV-2. The potential role of external and/or inhalation preparation of antiviral/antibacterial herbal agents aiming HMGB1 for the treatment of patients with COVID-19 infection have been described[41]. As HMGB1 is inhibited by glycyrrhizin, this substance could be possibly useful as a treatment in COVID-19[42]. Beneficial effects of glycyrrhizin and licorice extracts in combating against COVID-19 have been reported[43]. ABS (Ankaferd hemostat) could inhibit HMGB1 gene pathway with its content of Glycyrrhiza glabra and ABS can be topically used for the cases that are in the initial phase of COVID-19 and have sore throat-oropharyngeal mucositis[21]. The novel herbal antiviral preparation comprising Zataria multiflora Boiss, Glycyrrhiza glabra, Cinnamomum Vermont, Allium sativuml, and Syzygium aromaticum significantly improved the survival rate and reduced mortality in critically ill patients with COVID-19[44]. Also, glycyrrhizic acid was shown to be the most efficient and nontoxic broad-spectrum anti-coronavirus molecule *in vitro*[45]. Highly biocompatible glycyrrhizic acid (GA) nanoparticles (GANPs) were produced based on GA[46]. GANPs block the proliferation of the murine Coronavirus' MHV-A59 and decrease pro-inflammatory cytokine secretion by MHV-A59 or the N protein of SARS-CoV-2. In an MHV-A59-stimulated surrogate mouse model of COVID-19, GANPs exactly targeted areas with severe inflammation, such as the lungs, that seemed to improve the accumulation of GANPs and enhanced the effectiveness of the treatment. GANPs has antiviral and anti-inflammatory effects, preventing organ damage and providing an important survival advantage to infected mice[46]. Glycyrrhiza glabra has anti-inflammatory roles for the immune system and positive effects of Glycyrrhiza glabra in support with several agents to fight against COVID-19[47]. GA found to poses antiviral activity by its effect on virus cell binding[48].

Furthermore, new treatment agent candidates for re-purposing comprise medications should aim COVID-19 pathobiology, including pharmaceutical formulations that inhibits proteinase-stimulated receptors (PARs), especially PAR-1[49]. Stimulation of the PAR-1, mediators and hormones effect on the hemostasis, endothelial activation, alveolar epithelial cells and mucosal inflammatory reactions seem to be important for the COVID-19 pathophysiology. Ankaferd hemostat, which is an already accepted hemostatic agent affecting vital erythroid aggregation and fibrinogen gamma, may be a possible topical medication for the mucosal treatment of COVID-19[49]. ABS is proven to be a harmless and effective topical hemostatic agent of plant origin that has a pleiotropic impact on endothelial cells, angiogenesis, cell proliferation and vascular dynamics. ABS had been allowed as a topically used hemostatic agent for the treatment of post-surgical/dental hemorrhages and healing of infected inflammatory mucosal wounds. The anti-inflammatory and proteinase-stimulated receptor axis features of ABS underline that ABS is about to clinical re-positioning for COVID-19-related mucositis rather than its well-known hemostatic features. Topical ABS as a biological reaction controller could reduce SARS-CoV-2 related microthrombosis, endothelial dysfunction, oropharyngeal inflammation and mucosal lung damage[49]. Furthermore, PAR-1 inhibition role of ABS could decrease the initial virus propagation and mucosal spread of COVID-19.

Immune Plasma Treatment of COVID-19

The distorted immune response of the host is one of the most significant reasons of the increase in the severity of the infection, therefore treatment strategies should aim to decrease aberrant immune stimulation to overcome COVID-19. Convalescent plasma (CP), which is obtained from recently recovered patients and has neutralizing antibodies and many other immunomodulatory molecules, is likely to be the most suitable way to reestablish normal immune function considering the fast-spreading nature of the ongoing pandemic[50]. Antibody-based treatments will constitute not only CP but also polyclonal antibodies such as hyper immune globulin from pooled plasma of donors to develop an unbranded standard antibody product[50]. CP therapy reported as an effective treatment for COVID-19 in severe and critically ill patients[51]. Hospitalized COVID-19 patients transfused with convalescent plasma exhibited a lower mortality rate compared to patients receiving standard treatments[52]. Moreover, there are several case reports on CP treatment in COVID-19. CP treatment in a myelodysplastic COVID-19 patient with disseminated tuberculosis has been shown to be effective[53]. The anti-inflammatory role of CP is independent from its neutralizing antibody content. Neutralizing antibodies, as well as decreases in circulating interleukin-6 and interferon-γ–inducible protein 10, contributed to marked rapid decreases in hypoxia in COVID-19 patients in response to CP[54]. For the best results, CP treatment should be given in phase 1 or the beginning of phase 2 of COVID-19 syndrome. In the late phase 2 and phase 3, CP treatment could only attenuate the systemic hyperinflamation[21].

Anticoagulant Treatment of COVID-19 Associated Thrombosis

Locally stimulated RAS have critical roles in the initiation and progression of coronary artery diseases[55]. AT1Rs expression on bone marrow-derived cells and vascular endothelium, with locally synthesized Ang II, control the pathogenesis of atherosclerosis by speeding up the infiltration of bone marrow-derived inflammatory cells into the vessel wall. Therefore, inhibiting RAS components in both the systemic circulation and also cardiac and bone marrow may be a leading strategy to avoid the progression and destabilization of the cardiovascular system[55]. SARS-CoV-2 has many interactions with the RAS system during the invasion of human body[18]. Complications, such as thrombosis in SARS-CoV-2 infected patients, can be attributed to the effects of SARS-CoV-2 on the local RAS systems.

The reason of COVID-19-associated coagulopathy is more than just sepsis or critical illness. The primary thrombotic mechanisms of COVID-19 include endothelial injury, severe inflammation, tissue hypoxia, immobilization, respiratory failure, mechanical ventilation and catheter use[30]. The inflammatory mediators and cytokines that are secreted in the acute phase of COVID-19 result in more stimulation of the pro-coagulant pathways. Vascular endothelial injury results in tissue factor expression leading to aggravated micro-vessel occlusions[30,31]. Vascular endothelium is the key target organ of SARS-CoV-2[32,33]. When the SARS-CoV-2 virus binds to the ACE2 receptor, endothelial damage occurs, leading to a hypercoagulable state[30]. Severe hypoxemia through pulmonary inflammation and pulmonary vasoconstriction may also result in blood viscosity and clinical thrombosis[30,34]. Focal pulmonary thrombosis related to alveolar injury worsens the inflammatory response and microvascular thrombi[35]. Vascular microthrombosis is terminated with the consumption coagulopathy and organ dysfunction[30,35]. The consumption coagulopathy in COVID-19 is different from sepsis-related disseminated intravascular coagulopathy (SIC). Recent studies have shown less prominent thrombocytopenia and consumption of coagulation proteins in CAC than SIC. One additional difference from SIC is that CAC is more likely to occur with thrombosis than hemorrhage[36]. Therefore, early and effective anticoagulation should be given beyond the standard thromboprophylaxis of severe medical conditions in COVID-19 cases. The use of prophylactic doses of low-molecular-weight heparin (LMWH) or fondaparinux is recommended by both the International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) for all hospitalized COVID-19 cases, except if they have active hemorrhage, hemorrhage risk or platelet count $< 25 \times 10^9/L$[56,57]. Critically ill COVID-19 cases have higher risk for thrombotic events; however the usage of therapeutic-intensity anticoagulation in the absence of confirmed or suspected venous thromboembolism (VTE) in these cases is not yet clarified. Several studies[58-60] with COVID-19 patients admitted to the intensive care unit (ICU) reported VTE in 69%, 25% and 9% of patients. In a previous study[61], the incidence of VTE in patients with severe COVID-19 admitted to ICU was 25% and the authors proposed that none of the patients would receive thromboprophylaxis. In another

multicenter study about thrombotic complications of 184 severe COVID-19 patients admitted to ICU, the incidence of confirmed VTE was 27% and the incidence of arterial thrombotic events was 3.7%. Pulmonary embolism (PE) was the most frequent thrombotic complication, and all cases were receiving thromboprophylaxis[62]. A study comparing the thrombotic complications of severe, non-severe COVID-19 patients showed that 47% of the patient in ICU developed VTE, whereas only 3.3% of patients in wards developed VTE. All ICU patients were receiving thromboprophylaxis at standard or double doses[63]. Another study in a cohort of 156 patients admitted in non-intensive care units with COVID-19 pneumonia confirmed the 14.7% incidence of asymptomatic deep venous thrombosis (DVT). All patients except 3 were receiving standard doses of thromboprophylaxis[64]. In another study[65] 388 patients from Italy (61 requiring ICU) showed that 16.7% of the ICU patients and only 6.4% of general ward patients developed at least one thromboembolic event despite receiving thromboprophylaxis with low-molecular-weight heparin. Thromboprophylaxis was used in 100% of ICU patients and 75% of those on the general ward. In another study[66] that included linked administrative data of 1,865,059 admissions, the hospital-associated VTE incidence rate was 9.7 per 1,000 admissions. In a major study[67] examining more than 600 million hospitalizations, incidences (number of diagnoses/100 hospitalizations) of DVT, PE, and venous thromboembolism were 0.4%, 0.93%, and 1.24%, respectively. Considering that the vast majority of hospitalized patients for COVID-19 have pneumonia, it would be more accurate to compare the risk of thromboembolism in patients with pneumonia of the responsible microorganism other than SARS-CoV-2. In a related study[68], the risk of PE + DVT in patients with pneumonia among hospitalized patients increased by 7.9 times. The Scientific Board of the Republic of Turkey's Ministry of Health located early and effective thromboprophylaxis recommendations[69]. According to its guidelines[69] on the management of COVID-19 patients, following diagnosis, coagulopathy should be evaluated and thromboprophylaxis should be applied to all hospitalized COVID-19 patients. For the patients with D-dimer < 1,000 ng/ml dose LMWH [Enoxaparin 40 mg/day if creatinine clearance (CrCl) ≥ 30 ml/min and unfractionated heparin 5,000 units (U) subcutaneous (sc) 2x1 or 3x1 If CrCl < 30 ml/min]. For the patients with D-dimer ≥ 1,000 ng/ml and CrCl ≥ 30 ml/min Enoxaparin 0.5 mg/kg, 2x1, CrCl < 30 ml/min, unfractionated heparin 5,000 U (sc) 2x1 or 3x1 is recommended. At discharge in low-risk patients with normalized inflammation markers and without additional thrombosis risk factors, it was recommended to stop thromboprophylaxis. But if inflammation markers did not normalize and there was an additional thrombosis risk factor, it was recommended to continue thromboprophylaxis for one month more after the inflammation markers had returned to normal values. In the high-risk patients who have elevated D-dimer level, lymphopenia, severe pneumonia and in elderly patients with/or comorbid diseases, if the inflammation markers are normalized and there is no thrombosis during hospitalization, it is recommended to continue Enoxparin 0.5 mg / kg 1x1 (sc) for 1 month or more after the inflammation markers and D-dimer level return to normal values. But if any thrombosis was defined during hospitalization and if inflammation markers and D-dimer levels did not return to normal values, it was recommended to continue Enoxaparin 1 mg/kg 2x1 (sc) for 3 months or more after the inflammation markers and D-dimer had returned to normal values. Then re-evaluation was recommended.

Discussion

SARS-CoV-2 and its variants affect hematopoiesis utilizing angiotensin peptides, in particular ACE2, within the concept of local bone marrow renin-angiotensin system[40]. Hematological aspects of the COVID-19 immuno-inflammatory pro-thrombotic syndrome represent the crossroads of type I interferon response in relation to the innate immunity. The end of COVID-19 pandemic could be related to immunological processes as well. The recent variant of Omicron seems to have unique features and boosts interferon responses alike "live attenuated virus". The Omicron variant has unique features which will boost the chimerism-mediated immunotherapy.

"Chimerism-Mediated Immunotherapy" Could Be the 'Main Exit' from the COVID-19 Process

Zhang et al[70], in the Journal, have recently pointed out that SARS-CoV-2 RNAs can be reverse transcribed and integrated into the DNA of human cells. Their findings are compatible with the hypotheses that the genetic bits of COVID-19 may be integrated into human chromosomes. Likewise, the insertions could explain

the common finding that people recovered from COVID-19 may still be SARS-CoV-2 PCR-positive for months. The authors detected target site duplications flanking the viral sequences and consensus LINE1 endonuclease recognition sequences at integration sites, supporting a LINE1 retro transposon-mediated, target-primed reverse transcription and retro-position mechanism. The "chimerism-mediated immunotolerance" among the SARS-CoV-2 virus and human immunity-related virobiota is the key for the termination of the yet ongoing pandemic[71]. The cellular immunity, predominantly of T cells, would have the most significant influence on the immune tolerance and formation of the host-virus chimerism since the importance of the protective mucosal T cells against SARS-CoV-2 may be involved in the chimerism-mediated immunity within the intestinal tract. Thus, chimerism would result upon following the SARS-CoV-2 virus introduced into the human genome through the induction, consolidation and maintenance phases of COVID-19 as an element of the intestinal virobiota. The virobiota of *Homo sapiens* is composed of a wide variety of distinct viruses, hosted by the human body[72]. The human virome is defined as huge and complex, comprising approximately 10^{13} particles per human individual. The diversity of viromes in different body regions, their associations with disease states, mechanisms of the human virome formation in early life and the viral community states may be associated with disease and health in a given population. The biological significance of intestinal virobiota had been indicated in distinct experimental settings. For instance, simian immunodeficiency virus (SIV) infection of rhesus monkeys is associated with the injury to the intestinal barrier (enteropathy), which increases AIDS progression since the SIV infection is associated with an overgrowth of intestinal virome, where the viral expansion leads to the enteropathy[73]. The critical role of the immune system for controlling the intestinal virome has also been outlined. The intestinal local renin-angiotensin system (RAS) might have an important role in the genomic incorporation of SARS-CoV-2 into the human intestinal virobiota[71]. Moreover, intestinal SARS-CoV-2 colonization associated with the interferon response is an important step of the incorporation into the virobiota, usually following the recovery from the clinically symptomatic viral infection. The recently approved SARS-CoV-2 vaccines trigger innate immunity to promote durable immunological memory as well[74]. For the overall global termination of the COVID-19 process, the vaccines are the key chimerism-mediated immunotherapy agents that promote chimerism-mediated immunity, which will eventually lead to chimerism-mediated immuno-tolerance between human virobiota and SARS-CoV-2.

SARS-CoV-2 and Leukemogenesis

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is highly contagious and leads to lymphocytopenia[75]. Considering the relatively rapid development of cytopenias after recovery from COVID-19, it could not be excluded that SARS-CoV-2 have a role in leukemogenesis. Based on previous *in vitro* studies[76], the renin-angiotensin system imbalance stimulated by SARS-CoV-2 may possibly promote *in vivo* leukemogenesis through several mechanisms. In a recent study, Erdogdu et al[77] suggested that SARS-CoV-2 affects hematopoiesis and cause cytopenias. They have also proposed that viral spike protein cytotoxicity inflicts damage on hematopoietic stem cells. On the other hand, the mRNA vaccines produce endogenous spike protein too. Therefore, it is possible that mRNA vaccines may mobilize clonal neoplastic cells from the bone marrow microenvironment into the peripheral blood.

Omicron Variant Features and Interferon

The investigators tried to understand what underlies critical COVID-19 pneumonia in the COVID-19 cases. They have suggested that, in some cases, insufficient type I IFN immunity in the respiratory tract during the first few days of infection may be responsible for the spread of the virus, leading to pulmonary and systemic inflammation[78]. Patients with lacking type I IFN in the respiratory epithelium cannot be able to avoid the dissemination of the virus to lungs, blood, and other organs during the first few days of infection. Inflammation may develop when stimulated leukocytes, including myeloid and lymphoid cells of an innate or adaptive nature infiltrate the site of infection and try to resolve the pulmonary and systemic infection that had already been established because of the lack of the control by type I IFN[79]. A late inflammatory stage, the therapeutic type I IFN, did not help hospitalized SARS-CoV-2 cases[80]. IFN response in the early phase of SARS-CoV-2 is beneficial and necessary for the prevention of virus dissemination, whereas late IFN response increases complications and mortality in SARS-CoV-2 patients.

Omicron variant is the recent variant of COVID-19 pandemic. Our research team has defined the phases of COVID-19 syndrome[21]. In the complicating phases of COVID-19, IFN and immune-related genes play the major roles. Hematopoietic stem cell proliferation pathway is found to be affected by the viral SARS-CoV infection in a previous study aiming to assess IFN-gene family alterations after the SARS-CoV infection in relation with the iron metabolism and lymphoid biology[81]. Omicron has acquired an increased capability to inhibit IFN-beta stimulation upon infection and to better withstand the antiviral state imposed by exogenously added IFN-alpha[82]. Therefore, it seems like Omicron variant do not progress into the complicating phase of COVID-19 syndrome because it evades the IFN response, thereby avoiding the clinical picture of multi-organ failure.

Conclusions

Future Perspectives

The hematologic aspects of COVID-19 syndrome include the viral infections and hematologic responses, the impact of pandemic on hematological disorders, the hematological and immunological mechanism of SARS-CoV-2, the role and effects of local bone marrow RAS system in the context of COVID-19 syndrome. The potential treatment options for SARS-CoV-2 including the ABS, CP and proper anticoagulant treatment are discussed in this paper. Clinicians should harmonize the evidence-based clinical medicine with each patient's unique characteristic features along with clinician's past clinical experiences. With this harmony, the compelling COVID-19 pandemic could be properly handled.

Conflict of Interest

The authors declare that they have no conflict of interest.

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