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THE EFFECT OF COVID-19 PANDEMIC ON HEMATOLOGY PRACTICE: A COMPREHENSIVE REVIEW

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Abstract:

The Severe Acute Respiratory Syndrome Coronavirus Disease-2 (SARS-CoV-2) is the causative agent of coronavirus disease-19 (COVID-19). This outbreak has been declared a pandemic by the World Health Organization, and it has become a public health emergency of international concern. Most of the population is experiencing signs and symptoms similar to the flu and common cold. Despite that, alveolar destruction resulting in progressive lung failure has also been underlined. Although SARS-CoV-2 has been noted principally to affect the lungs, other system involvement has been described too. Hematological involvement has also been emphasized in the literature, including lymphopenia, anemia, cytopenia, and thrombocytopenia. The coagulation abnormalities and disseminated intravascular coagulation were observed in severe COVID-19 cases. This COVID-19 pandemic has also affected the hospital services, injured blood product supply, disturbed chemotherapy treatment, and hematopoietic stem cell transplantation program. Hematological and immune abnormalities are often encountered in critical illness and have prognostic significance. Careful monitoring of hematological constraints at the outset and disease course is useful for identifying patients at high risk of severe disease. Moreover, patients with pre-existing hematological disorders are at increased risk of severe infection. Patients with hematological involvement usually experience a wide range of signs and symptoms such as shortness of breath, headache, nausea, drowsiness, vomiting, tachycardia, and tachypnea. The pandemic of SARS-CoV-2 has become an unprecedented challenge for the physicians and the hematologists. This review has summarized the data from published literature to describe the disease's hematological manifestations, and its implication on patients' management observed in COVID-19 cases.

Keywords: *SARS-CoV-2, COVID-19, hematology, anemia, thrombocytopenia, lypmphopenia.*

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INTRODUCTION:

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), the causative agent of COVID-19 (coronavirus disease-2019), originated from Wuhan during late December 2019. It began as an outbreak which led to an epidemic with 44,672 confirmed cases in China by February 14, 2020, with a reported mortality rate of 2.3%, which was comparatively lower than the previously known epidemics caused by human coronaviruses (Severe Acute Respiratory Syndrome Coronavirus [SARS-CoV] and the Middle East Respiratory Syndrome Coronavirus [MERS-CoV]) in 2003 and 2012 respectively [1, 2]. It spread outside of China to the whole world rapidly, mainly through human-to-human transmission by airborne droplets or possibly through the fecal-oral route. World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020 [3]. With the disease spread to 216 countries, over 27,769,074 reported confirmed cases worldwide, including over 19,851,252 deaths as of September 09, 2020 [4]. The infection presents most commonly as dry cough, fever, shortness of breath, and sore throat, with severe respiratory involvement in patients with advanced age (over age 80). The overall case fatality rate in this age group is about 14.3% [5]. This disease's severity is characterized by severe pneumonia, respiratory failure requiring mechanical support, sepsis, myocardial injury, multiorgan failure, and mortality increases in patients having underlying comorbidities such as cardiovascular disease, diabetes, chronic kidney disease, and chronic respiratory disease [6, 7]. However, some patients may act as asymptomatic carriers or may have very mild symptoms suggesting that the number of actual cases may be way higher than reported [2]. Given the rapid spread of the virus, researchers across multiple nations have dedicated themselves to understanding the virus, disease pathophysiology, and developing effective drugs and preventive vaccines.

Although COVID-19 has been reported principally to affect the respiratory system, hematological involvement has also been underlined in the published literature. The amount of literature on hematological involvement by COVID-19 is small. However, we believe that a structured summary of existing data would be requisite for the hematologist. Being well informed about the hematological presentations would support them with a high index of clinical doubts and take obligatory precautions. This paper has summarized the information from published literature, including case reports and open-source data sets, to describe the spectrum of hematological manifestations and complications observed in COVID-19 cases.

MATERIAL AND METHODS:

We reviewed the literature on COVID-19 and its relevance to our hematology practice. A comprehensive literature search was performed using a combination of keywords (MeSH terms and free text words), including 'COVID-19'/'SARS-CoV-2' and "hematology". PubMed, EMBASE, and Cochrane Library were searched up to September 30, 2020. A limit of after December 2019 was imposed since COVID-19 was first reported in late 2019. Additional articles were sought from the reference lists of the included articles. All articles identified from the literature search were identified and screened by two independent reviewers. We included studies on SARS-CoV-2 in adult patients. This review included case series, observational studies, non-randomized studies, and randomized trials published in English. Conferences abstracts, commentaries, letters to editors, and editorials were excluded. Studies related to obstetrics and gynecology were also excluded.

For eligible studies, study information including first authors, site of study, inclusion and exclusion criteria, sample size, age, and sex were recorded. A standardized form for data entry has been devised to focus on the following areas: (1) hematological manifestations of COVID-19; (2) special considerations in hematological conditions. Relevant data were analyzed and summarized.

Review:

Mechanism of COVID-19 and genomic analysis of hematological manifestations:

The genome of the SARS-CoV-2 comprises single-stranded positive-sense RNA encapsulated within a membrane envelope, which contains glycoprotein spikes giving SARS-CoV-2 crown-like appearance [7]. Of the four classes of coronaviruses (alpha, beta, gamma, and delta), SARS-CoV, MERS-CoV, and SARS-CoV-2, are included in the class beta. While SARS-CoV, MERS-CoV, and SARS-CoV-2, all attack the lung, especially the lower respiratory tract, SARS-CoV-2 also affects the heart, gastrointestinal system, and liver, kidney, and the central nervous system, eventually leading to multiorgan failure [8, 9]. Glycosylated spike (S) protein, one of the structural proteins programmed by the coronavirus genome, is a chief inducer of host immune response. This protein binds to a protein located on the host cell surface membrane, angiotensin-converting enzyme 2 (ACE2) receptor protein, and mediates the host cell invasion [9, 10]. ACE2 (entry receptor for SARS-CoV) was particularly confirmed in COVID-19 infection regardless of mutations at key receptor-

binding domains. Inhuman transmission and pathogenesis of COVID-19 are based on the interactions involving virus binding, receptor recognition, cleavage of protease, and membrane fusion.

Lung involvement is the primary target for SARS-CoV-2. However, hematological involvement may get involved in several ways. The invasion of SARS-CoV-2 is due to ACE2 receptors expressed in blood vessels, responsible for hematological manifestations.

High expression of ACE2 receptors on lymphocytes results in lymphopenia in around 80% of symptomatic patients and correlates with disease severity (11). Regulatory T-cells (T-regs) and CD4+ helper T cell functions are impaired by SARS-CoV2, resulting in initial hyperactivation followed by the rapid exhaustion of cytotoxic CD8+ T-cells (12), thus triggering a hyperinflammatory response leading to secondary hemophagocytic lymphohistiocytosis (sHLH) and cytokine release syndrome(CRS). It is characterized by markedly increased interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α promoting atrophy of lymphoid organs leading to lymphocyte apoptosis (13). Thrombocytopenia is frequently encountered in COVID-19 and attributable to immune-mediated destruction, cytokine storm, increased consumption due to lung injury, and direct toxic effect on bone marrow megakaryocytes (14). COVID-19 associated coagulopathy (CAC) can lead to widespread thrombosis or bleeding manifestations. Elevations of d-dimers and fibrinogen levels are the most common coagulopathy pattern and correlate with an increase in inflammation markers.

In contrast to classic DIC resulting from bacterial sepsis or trauma, aPTT elevation is often less than PT elevation, degree of thrombocytopenia is mild, and microangiopathy is absent in patients with CAC. Patients with hematological malignancies are more susceptible to severe COVID-19 and have coexisting lactic acidosis and more severe lymphopenia (15). Venous thromboembolism and arterial thrombosis are increasingly reported in COVID-19 patients. The possible mechanisms include endothelial cell damage and activation due to the virus binding to the ACE2 receptor and the release of inflammatory cytokines leading to a prothrombotic state. Moreover, immobilization, mechanical ventilation, central venous catheterization may predispose to a prothrombotic state.

Covid infection is well known to be associated with unusual hematological parameters. Autopsy of patients who died of viral infection showed significantly shrunken spleen with reduced lymphocyte, macrophage proliferation, and phagocytosis (16). Lymphocytes were also exhausted in lymph nodes, and all hematopoietic cell lineages were abridged in the bone marrow. The fight against COVID-19 is likely to be a longwinded, and the pandemic has a significant influence on health care systems in several countries (16). The Covid virus will continue to pretense a risk to people without immunity to it.

Hematological and biochemical abnormalities during COVID-19 infection:

Time from exposure to SARS-CoV2 and symptom onset varies between 2-14 days (median 5 days). Clinical presentation ranges from no symptoms to acute disease requiring mechanical ventilation. The most common symptoms include fever, dry cough, fatigue, and shortness of breath. Initially, COVID-19 pneumonia was considered to be the leading cause responsible for morbidity and mortality. Evidence across the globe suggests that severe COVID-19 is a multisystem disease involving neurological, pulmonary, cardiac, gastrointestinal, renal, and hematopoietic systems presenting as stroke, encephalopathy, and diarrhea disseminated thrombosis, arrhythmias, and myocardial infarction. Very little data is available on the outcome of patients with hematological disorders acquiring SARS-CoV2 infection. Malard *et al* (18) reported fever, cough, shortness of breath, and lymphopenia as the most common clinical presentations among patients with pre-existing hematological diseases having COVID-19. Among affected patients, 52% developed ARDS, and mortality at 1 month was 40%, which is significantly higher than other risk groups. Importantly less than half of patients were receiving active treatment, indicating immunocompromised status due to previously administered chemotherapy contributed towards poor survival outcomes (18). Hematological abnormalities are common in patients with COVID-19 presenting as leukocytosis, lymphocytopenia, monocytopenia, thrombocytopenia, and coagulation defects (19). Antiphospholipid antibodies and widespread thrombosis, causing ischemic stroke, myocardial infarction, venous thromboembolism, have been documented in COVID-19(22). Increased tissue penetration of SARS-CoV2 results in the release of inflammatory cytokines leading to sHLH and cytokine storm. Affected patients develop high-grade fever, cytopenias, visceromegaly, hyper-ferritinemia, hypofibrinogenemia, coagulopathy progressing to

multiorgan dysfunction syndrome, and poor prognosis (Figure 1).

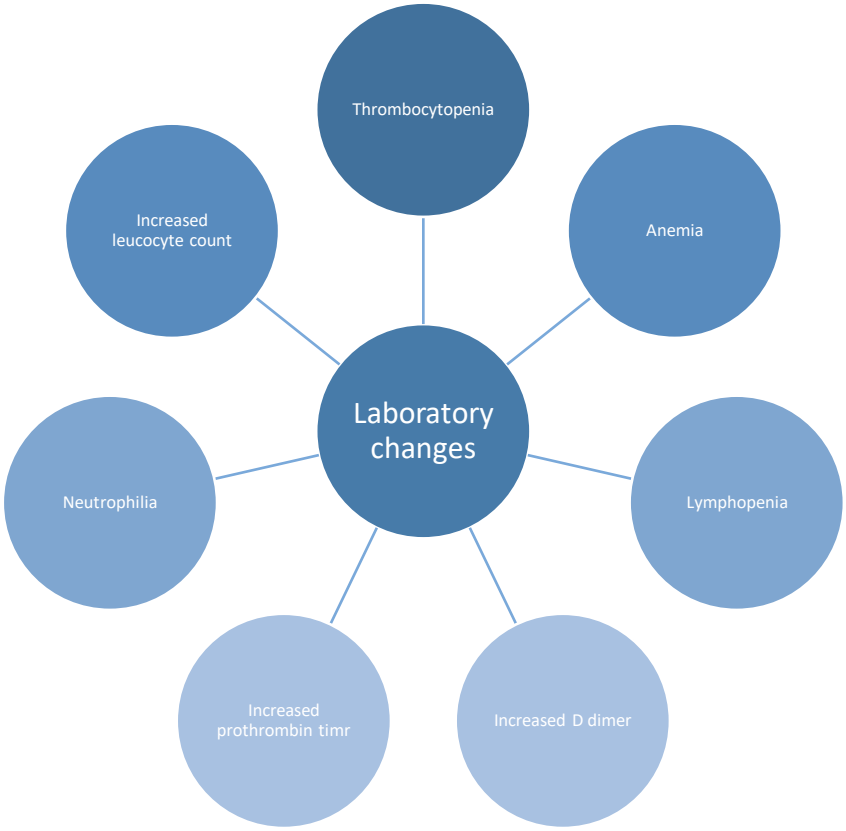

Figure 1: Hematological and biochemical abnormalities during COVID-19 infection

Management from a hematologist viewpoint:

Management of patients with COVID-19 involves a multidisciplinary team approach to risk stratifying patients as per the severity and provide optimal supportive care and timely intervention. Hematologist opinion is frequently sought for cytopenias, a rise in inflammatory markers, and coagulopathy. Moreover, the management of patients with pre-existing hematological disorders and HSCT recipients are at increased risk of severe COVID-19, and careful selection and monitoring are required for such cases. Based on the recently published data, we propose longitudinal monitoring of WBC, lymphocyte count, D-dimers, prothrombin time, ferritin, and platelet count in all patients who present with COVID-19 infection. This may help predict patients at risk of severe disease to plan early intervention and critical care support.

Coagulopathy and thrombosis:

1. All patients with COVID-19 should undergo platelet count, d-dimers, fibrinogen, prothrombin time testing at initial diagnosis, and serially. The ideal interval for serial monitoring is not defined (20).
2. All patients with COVID-19 should receive prophylactic anticoagulation unless contraindicated. Low molecular weight heparin (LMWH) is preferred (21).
3. Therapeutic anticoagulation should be considered for high-risk coagulopathy, including patients receiving Continuous Renal Replacement Therapies (CRRT) and Extracorporeal membrane oxygenation (ECMO), documented thromboembolism, and signs of microthrombi induced organ dysfunction (22).
4. Aspirin should be considered in patients with elevated troponin and cardiac dysfunction.
5. Thresh holds for transfusion of blood products are as follows.
    1. No active bleeding: Keep platelet count >25 x109/l
    2. Active bleeding: Keep platelet count >50 x109/l, plasma fibrinogen > 1.5 g/l, PT ratio <1.5.

CONCLUSION:

The pandemic of COVID-19 presents for a hematologist some unprecedented challenges. We perceive that SARS-CoV-2 may have various hematological manifestations, and in many cases, the hematological signs and symptoms may precede typical respiratory symptoms. Holistic knowledge of the spectrum of the hematological consequences of COVID-19 is crucial to get a hold of the spread of the virus. The most vital clinical information which we meet is that anemia and lymphopenia may be a presenting feature of COVID-19. Therefore, a high catalog of suspicion for such patients will be essential to prevent or, at least, minimum exposure to health care providers and other patients. With the gradual settling of the outbreak, it can be predicted that several post-infectious hematological complications will surface up. The proper caution must be practiced while treating and managing patients with hematological comorbidities, particularly those with blood disorders and leukemia. The above review of the hematological manifestations of COVID-19 will help the hematologist have a necessary preparation, which is of extreme importance to prevent infections.

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