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Letter to Editor

COVID-19, Aging, and Progress Toward Hematological Malignancies or Cardiovascular Diseases

Majid Teremmahi Ardestani*, Marzieh Norouzian

Department of Laboratory Sciences, Faculty of Para-Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

***Correspondence to:** Majid Teremmahi Ardestani, Tel:+989132612535, Email: majidardestani50@gmail.com

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Dear Editor,

Pneumonia infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan in December 2019. The World Health Organization (WHO) officially named it coronavirus disease 2019 (COVID-19). SARS-CoV-2 binds to host cells via the angiotensin receptor (ACE) 2 (ACE2R). The expression of ACE2R is particularly high in the lungs, heart, veins and arteries, and hematopoietic stem cells (1).

A range of clinical manifestations is accompanied with COVID-19, including fever, dry cough, pulmonary involvement, and coagulopathy. One of the most important clinical manifestations of COVID-19 disease is cytokine storm, which can lead to systemic inflammation and multiple organ failure. Accordingly, it is clear that the prognosis of the disease has been influenced by multiple organ dysfunctions. Older age and comorbidities such as cardiovascular disease (CVD) have been the most common risk factors for the severity and mortality of the COVID-19 infection (2).

According to the Centers for Disease Control and Prevention, the probability of hospitalization increases with age so that adults over 65 years old have a 3- to 15-fold increased chance of being hospitalized due to this infection. In addition, the chance of death in COVID-19 patients over 65 years old is 90-630 times higher (3). The effect of COVID-19 on the hematopoietic system can be deduced from hematologic manifestations such as lymphopenia and thrombocytopenia, which are highly common in hospitalized COVID-19 patients. It was shown that COVID-19 affects the hematopoietic system and inhibits hematopoiesis through the induction of apoptosis in hematopoietic stem cells or the activation of inflammatory signaling pathways (4, 5). In recent data, the COVID-19 infection has been reported to be involved in the damage of hematopoietic stem cells through activating nucleotide-binding domain leucine-rich repeat protein-3 inflammasome (5).

The hematopoietic system in the elderly is extremely vulnerable due to many genetic and epigenetic changes and damages during life. The clonal hematopoiesis of indeterminate potential (CHIP) refers to the existence of hematopoietic cell clones with driver mutations (DNMT3a, TET2, ASXL1, and the like) without the evidence of blood malignancies (6). The acquisition of these mutations has an age-related pattern and is prevalent in the elderly so that the incidence of CHIP in people over 80 years is approximately 30% (7). The increasing body of evidence has confirmed the role of CH-driver mutations in the polarization of immune cells toward a pro-inflammatory phenotype that is involved in CH-associated disease development and poor outcomes (8). Inflammation is considered an important risk factor in the progression of CH to blood malignancies or non-blood diseases such as CVD (9). CH-related genes such as DNMT3A, TET2, ASXL1, and JAK2 have been strongly linked to CVD (10). Jaiswal et al and Fuster et al first described the contribution of CHIP-related mutations to CVD. In their studies, an increase in the atherosclerotic plaque size was found following the bone marrow transplantation of *Tet2*-deficient cells in mouse models (11, 12). Further analysis revealed that the increase in the plaque size was associated with enhanced expression of inflammatory cytokine by *Tet2*-deficient cells within the plaque (11). Recently, Abplanalp et al have reported a highly inflamed transcriptome of T-cells and the monocytes of patients with heart failure harboring CHIP-mutated hematopoietic stem cells, leading to the aggravation of chronic heart failure (13).

Moreover, inflammation provides a competitive advantage for the proliferation of CHIP-associated hematopoietic stem cells. Therefore, the formation of cytokine storm and hyperinflammation in the COVID-19 disease and the resulting adverse effect on the hematopoietic system in the elderly is the critical issue that should be taken into consideration. Studies

on COVID-19 patients demonstrated direct correlations between age-related CH and disease severity and mortality (14, 15). However, some unanswered questions need to be taken into account in future experiments, including whether clonal hematopoiesis is a cause or consequence of disease outcomes in COVID-19 patients and whether CH or associated mutant clones can have an impact on the COVID-19 infection to promote mortality diseases such as heart diseases and malignancies.

Generally, screening for mutations associated with CH in elderly patients with COVID-19 may be necessary for monitoring their progress toward malignant blood diseases or cardiovascular disorders and designing a targeted or individualized therapy.

Authors' Contribution

Conceptualization and design: MTA and MN.

Conflict of Interest Disclosures

The authors declare that there is no conflict of interests.

Ethical Statement

Not applicable.

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