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COVID-19 type III hypersensitivity reaction

To the editor,

The outbreak of the novel COVID-19 (coronavirus disease 2019) centered in Hubei Province of the People's Republic of China and spread to many other countries in the world and on thirty of January 2020, the WHO declared a global health emergency in the world [1]. Tyrell and Bynoe in 1966 were first described and cultivated coronaviruses as enveloped, positive single-stranded large RNA viruses that infect humans and animals [2]. The median incubation period after infection is three days ranged from 0 to 24 days [3]. The clinical manifestation of the disease consisting of fever, dry cough, nasal congestion, fatigue, headache and the disease progress to dyspnoea and pneumonia [4]. Some reports describe gastrointestinal, fulminant myocarditis [5]. COVID-19 infects lung alveolar epithelial cells using receptor-mediated endocytosis through coronavirus S (spike) protein contains a ligand binding domain with the angiotensin-converting enzyme II (ACE2) [6]. After virus entery; the first line of defence mechanism (Innate) is recognition of invaded virus by pathogen associated molecular patterns (PAMPs) via endosomal RNA receptors, TLR3, TLR7 and the cytosolic RNA sensor, RIG-I/MDA5. This recognition leads to activation of the downstream signaling cascade NF-κB and IRF3 that induce expression of type I IFN and other pro-inflammatory cytokines that activates the JAK-STAT pathway that initiate the transcription of IFN type 1 [7]. There is also increased in number of neutrophils and decrease in number of lymphocytes (lymphopenia) which is the second line of defense mechanism (Adaptive) and elevated of inflammatory markers like C-reactive protein and proinflammatory cytokines like IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα which is correlate with disease severity and death [8]. The virus then directly infects macrophages and T cells [9]. The macrophages will present viral antigenic peptide to T cells that differentiate into follicular helper cells (T_{FH} cells), activated T cells CD4, CD8 + T cells and antibody secreting cells (ASC) (CD3–CD19 + CD27hiCD38hi ASC and CD4 + CXCR5 + ICOS + PD-1 + cTFH cell). This will recruitment of different immune cell populations ASCs, TFH cells and activated CD4 + and CD8 + T cells with IgM and IgG SARS-CoV-2-binding antibodies in the patient's blood [10]. The COVID-19 viral antigens lead to stimulate antibodies formation of IgM in acute phase and IgG type in chronic phase which is facilitate viral entry and fusion with infected cell through uptake of the virus-IgG complex via the Fc family of receptors and later viral fusion with antigen presenting cells like macrophages, B cells, monocytes via FcR family, and vascular endothelium through the neonatal Fc receptor (nFcR) instead of antibodies induced viral agglutination and this is known as antibody dependent enhancement (ADE) [11–13]. This Ag-Ab (IgG1 and IgG3) immune complex that deposit in the lung will also end in complement activation by classical pathway of the complement (membrane attack complex MAC) end in formation C3a, C5a and C5b67 that leads to vasoactive amines release from mast cell and basophile and platelets aggregation leads to microthrombus formation which block coronary blood vessels of the heart and also leads to neutophiles infiltration and aggregation at site of infection in alveoli leading to sever tissue damage which is the main cell in type III hypersensitivity reaction and the patient showed increased in neutrophils number which is the same immune mechanism in rheumatoid arthritis [14]. Thus function of complement activation instead of viral clearance and antigen presentation, phagocytosis now act as other route for viral infection [15]. In addition to that; the immune complex Anti-S protein:CoV immune complexes leads to increased cytokine release like MCP-1 and IL-8 in lung macrophages which is known as cytokine storm syndrome while in the rheumatoid arthritis known as cytokine soup [16]. Some trails used the same monoclonal antibodies that used in treatment of rheumatoid arthritis like Tocilizumab which is monoclonal antibodies against IL-6R [17].

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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