



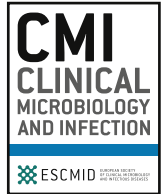
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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the editor

Re: 'the unique COVID-19 presentation of patients with B cell depletion' by Belkin et al.

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ARTICLE INFO

Article history:

Received 16 October 2022

Accepted 17 October 2022

Available online xxx

Editor: M. Paul

To the Editor,

We read with great interest the article by Belkin et al. entitled 'The unique COVID-19 presentation of patients with B cell depletion—definition of the persistent inflammatory seronegative COVID' [1]. We agree with our colleagues on the need for defining the disease that is characterized by a recurrent or relapsing coronavirus disease 2019 (COVID-19) in patients with primary or acquired humoral immunodeficiency. Patients with B cell-depleting diseases or treatments can present with a very specific clinical course after SARS-CoV-2 infection. Cases of this condition have been described in patients with congenital or acquired hypogammaglobulinemia or in treatment with anti-CD20 antibodies [2,3].

We studied all the patients who had received treatment with anti-CD20 antibodies in the first year of the pandemic in our hospital and found that 17.3% of them presented with a recurrent or relapsing episode that was characterized by symptoms compatible with acute COVID-19, including persistent or new onset interstitial lung infiltrates, with no alternative aetiologic diagnosis. Viral persistence was demonstrated in all the patients, either in the

upper or lower respiratory tract samples, whereas many of them lacked the hyperinflammatory response [4].

Therefore, we do not agree with the authors that inflammation is a defining feature of this entity. Instead, we propose that, in these patients, persistent and/or recurrent active viral replication is the main pathogenic finding. It has been described that CD8+ T-cell response is responsible for the course of acute infection, whereas humoral B-lymphocyte response together with a robust CD4+ T-cell response are necessary to achieve long-lasting viral clearance. Therefore, patients with B cell depletion are associated with prolonged viral replication [5]. The prolonged presence of the virus in respiratory cells and its sustained replication may cause a local and systemic inflammatory response, which results in recurrent and relapsing symptoms in these patients, which can sometimes progress to more severe forms of COVID-19 because of an exaggerated release of cytokines, which occurs in the general population or other immunocompromised patients. However, we do not believe that it can be defined as a hyperinflammation response, but of an inflammatory response secondary to the viral presence.

We believe that it is important not to emphasize the inflammatory response in the definition of this entity, because this idea can lead to its treatment with immunomodulatory drugs (such as steroids) that can worsen viral clearance and therefore prolong the condition or aggravate it. We believe that the mainstay of treatment for this entity should target viral replication, and therefore should focus on antiviral drugs. In our experience, when these patients are treated with immunomodulatory drugs, they initially improve but frequently present later with a new relapse [4]. In addition, we believe that the combination of antiviral drugs with effective monoclonal antibodies or hyperimmune plasma is important; therapies that compensate the impair of these patients to mount an adequate humoral responses are necessary to achieve viral clearance [5]. Therefore, we propose the name 'persistent seronegative COVID-19', which we believe is more appropriate for this condition.

Furthermore, we agree that its definition should include host, clinical, and virological criteria. This virological criterion is essential for the diagnosis of this disease. We would emphasize that it should

DOI of original article: <https://doi.org/10.1016/j.cmi.2022.10.007>.

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consist of demonstrating the negativity for coronavirus 2 (SARS-CoV2) antibodies PLUS the presence of the virus by SARS-CoV-RT-PCR test. The former could be either in the nasopharynx, lower respiratory tract samples, blood or lung biopsy specimens, as many of these patients do not present positive test in upper respiratory tract, and it is necessary to obtain samples from the lower respiratory tract or even tissue for diagnosis [4]. We could propose to add other test to the virology criterion, such as demonstrating SARS-CoV2 presence on lung biopsy results by using immunohistochemical techniques. We also propose that, to classify the relapses/flares, the presence of SARS-CoV2 should be demonstrated during the episode, and it should not be sufficient to have a positive RT-PCR during the previous 90 days.

The definition of this disease entity must lead to its study, collecting multicentric clinical data, to better define its incidence and the most appropriate treatments. This disease entity should be included in the different guidelines of clinical practice with its differential characteristics compared with other forms of COVID.

Author contributions

Elena Múñez-Rubio and Jorge Calderón-Parra conceptualized the paper and wrote the original draft and supervised the project. Elena Múñez-Rubio, Jorge Calderón-Parra, Ana Fernández-Cruz, Víctor Moreno-Torres, Silvia Blanco-Alonso, and Antonio Ramos-Martínez edited the manuscript.

Transparency declaration

Elena Múñez-Rubio has received consulting fees or payment for lectures, presentations, and speakers from Glaxo SmithKline, Roche, Gilead, and Merck Sharp and Dohme. Jorge Calderón-Parra, Ana Fernández-Cruz, Víctor Moreno-Torres, Silvia Blanco-Alonso, and Antonio Ramos-Martínez report no conflicts of interest. The study received no external funding.

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