Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

The unique presentation of SARS-CoV-2 Infection in patients with B-cell depletion: definition of 'persistent inflammatory sero-negative COVID'

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Patients with genetic and acquired humoral immunodeficiencies present with an atypical course of coronavirus disease 2019 (COVID-19). Persistent viral shedding with multiple viral relapses continues in these patients for weeks [1]. Lymphopenia, recent anti-cluster of differentiation (CD)20 therapy, chimeric antigen receptor T-cell therapy, hypogammaglobulinaemia and haematopoietic stem cell transplantation are associated with virological persistence [2]. These patients have low sero-conversion rates following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination and are predisposed to SARS-CoV-2 infection and severe disease [3].

Clinical cases of protracted illness with intermittent flares or relapses of clinical COVID-19 which require hospital readmissions have also been described [1,2]. The protracted course reported in patients with B-cell depletion includes prolonged or intermittent systemic and/or respiratory symptoms, along with persistent respiratory viral shedding, and the absence of sero-conversion [4,5]. Waxing and waning of symptoms occurs over several weeks from diagnosis, with one study reporting a median duration of symptoms of 62 days, with a maximum of 300 days. The persistence of PCR positivity and infection during the first 12 months following anti-CD20 therapy has been reported to be associated with mortality [1].

In addition to several case reports, the two largest series up to date reported overall 28 patients with a protracted or relapsing COVID-19 course, mostly after anti-CD20 therapy [1,2]. The included patients had considerable rates of severe-to-critical illness and mortality [6]. Parra et al. [5] reported nine patients out of 52 (17%) who had recurrence or relapse following anti-CD20 therapy. The authors used a definition of recurrence or relapse previously suggested for the general population (i.e. clinical recurrence of symptoms compatible with COVID-19 accompanied by a positive or persisting PCR result within 90 days of the primary infection); however, the time frame of possible relapse was extended to over 90 days [7]. Recurrence or relapse was reported at a median of 51 days (range, 36–105) after an acute infection, with four patients having more than one relapse. All patients with relapse received anti-CD20 therapy during the 6 months prior to COVID-19, and most presented with fever, dyspnoea and cough [1]. Lee et al. [2] reported 19 patients with readmissions because of COVID-19-related clinical symptoms, most of them within a year of receiving anti-CD20 therapy. The median duration of PCR positivity among these patients was 59 days (range, 26–344 days), and five patients died during follow-up. Sequencing of viral isolates supported on-going infection over re-infection [2].

Not all SARS-CoV-2 infections in patients with B-cell depletion lead to a protracted clinical course, likely because of an effective T-cell response. Hence, persistent viral shedding and sero-negativity are insufficient to explain this condition [4,7]. There is growing evidence that these patients have an abnormal or dysregulated T-cell response [8,9]. This abnormal T-cell function leads to a hyper-inflammatory response, which does not lead to eradication of the virus. This response leads to fever, severe prostration, pneumonitis and elevated levels of inflammatory markers [2]. The inflammatory

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Table 1
Diagnostic criteria of persistent inflammatory sero-negative COVID[a]

A patient is defined as having persistent inflammatory sero-negative COVID if they fulfil the following criteria and no alternative diagnosis:	
1. Host criterion	B-cell depleting disease or therapy, including the following: • Primary immunodeficiency causing hypogammaglobinaemia (X-linked agammaglobulinaemia, common variable immunodeficiency, other primary hypogammaglobinaemia). • Secondary immunodeficiency - anti-CD20 treatment in the past year; chronic lymphoblastic leukaemia, non-Hodgkin lymphoma, multiple myeloma accompanied by hypogammaglobinaemia or receiving immunotherapy directed against B cells (bi-specific antibodies or antibody-drug conjugates against CD19, CD20 or BCMA); chimeric antigen receptor T-cell therapy or allogeneic or autologous haematopoietic stem cell transplantation within 1 y.
2. Clinical criterion	Prolonged or remitting fever (total >7 d) with elevated CRP levels plus either one of the following: prostration, non-resolving cough and dyspnea (total >14 d), abnormal chest imaging showing pneumonitis (bilateral ground glass opacities).
3. Virological criterion, defined as either of the following	• Persistent or intermittent positive SARS-CoV-2 RT-PCR result over >21 d.[b] • Positive SARS-CoV-2 RT-PCR result in the last 90 d + sero-negativity for SARS-CoV-2 14 d after the initial infection in monoclonal antibody-naïve patients.[c]

B-cell maturation antigen (BCMA), CD, cluster of differentiation; COVID, coronavirus disease; CRP, C-reactive protein; Real-time PCR (RT-PCR); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Being sero-negative before and at the time of the onset of acute infection (regardless and despite vaccination) is a characteristic of this entity. It was not comprehensively included in the criteria for diagnosis because of practical reasons; the diagnosis can be made without a specialized blood test.

[b] A positive SARS-CoV-2 result from either a nasopharyngeal swab or lower-respiratory specimen demonstrating the same variant using sequencing supports the diagnosis but is not mandatory.

[c] Undetectable levels or low titres according to a local serology platform; patients who were treated with monoclonal antibodies for prevention may have higher titres.

component may be responsive to corticosteroids, which some of these patients received [6].

The diagnosis of this entity may be easily missed. A time lag between the initial, often mild, SARS-CoV-2 infection and the inflammatory phase; the non-ubiquitous nature of nasopharyngeal shedding; and the uncommon feature of hyper-inflammatory responses in immunocompromised patients all contribute to misdiagnosis.

There are no specific recommendations for the treatment of these patients. The Ninth European Conference on Infections in Leukemia provided recommendations for the treatment of COVID-19 in patients with haematologic diseases in general [10]. In practice, patients with B-cell depletion and COVID-19 are often treated with anti-viral drugs, steroids and antibody preparations, with no clear recommendations on type, timing and dose [9]. In the absence of a clear definition of the condition, currently, there is wide variability in the treatment regimens of the acute event and, even more so, of relapse episodes. The lack of definition and awareness of this entity may lead to delayed diagnosis and unnecessary use of antibiotics. In addition, these patients are often managed as cases of severe COVID-19 according to clinical trials that usually did not include this type of patients and lacked external validity.

Yahav et al. [9] previously suggested definitions of COVID-19 re-infection, relapse and PCR re-positivity. We propose revised definitions specifically for patients with B-cell depletion. We propose a disease entity termed as 'persistent inflammatory sero-negative COVID', which is probably caused by some combination between persistence of the virus, even in low quantities, and an abnormal hyperactive inflammatory response. We suggest diagnostic criteria that combine the following: type of baseline immunodeficiency; clinical signs, virological persistence and sero-negativity. A comprehensive definition in provided in Table 1.

The clinical presentation can mimic 'standard' but prolonged and, sometimes, severe COVID-19 infection or any other bilateral lung infection or can present as prolonged fever with prostration weeks and months after mild SARS-CoV-2 infection. The spectrum of this syndrome may range from mostly inflammatory, with low viral loads, and indolent progression to high viral loads, with obvious pulmonary involvement and a progressive clinical course. The use of a single terminology will enable the collection of multicentre clinical data, assessment of incidence and planning of prevention and treatment strategies for this specific condition. Additional data are needed to further characterize this disease entity. Variable cycle thresholds were reported in a series addressing these patients; however, no specific cut-off for diagnosis can be yet determined; in addition, radiological features should be further characterized and differentiated from organizing pneumonia following severe COVID-19.

Studies are needed to evaluate the effectiveness of monoclonal antibodies as prophylaxis in this specific population, to define optimal therapy for mild disease to prevent progression to persistent inflammatory sero-negative COVID, and for the persistent inflammatory phase. Properly reporting cases will also assist in defining chemotherapy or biological regimens which are associated with this condition. Because the syndrome affects the immunosuppressed population, reasonable exclusion of other infections should be performed.

Author contributions

AB and DY conceptualized the paper, wrote the original draft and supervised the project. AB, DY, AL and LS reviewed and edited the manuscript.

Transparency declaration

The authors declare that they have no conflicts of interest. The study received no external funding.

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