B cells and COVID-19: Lessons from agammaglobulinemia patients and the study of functional B cell polymorphisms

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The SARS-CoV-2 pandemic (corona virus disease 2019, COVID-19) is one of the greatest challenges in modern medicine. It is noteworthy that not all individuals affected by SARS-CoV-2 display a specific pattern of infection; approximately 40% of infected individuals are completely asymptomatic, 40% display mild flu-like disease and the remaining 20% present a more severe clinical phenotype, with one quarter of these individuals developing severe respiratory disease, characterized by the development of pneumonia and/or severe acute respiratory distress syndrome (SARS) [1]. Older age (over 65 years), obesity, hypertension and chronic inflammatory diseases represent the most important risk factors, which are related to the development of serious sequelae of the disease and a poor outcome [1]. Studies trying to explain the unfavorable prognosis of COVID-19, focus mainly on the role of immunosenesence or of chronic inflammatory status [2], also addressing the respective therapeutic approaches [3]. However, the specific mechanisms implicated in the disease prognosis remain unclear.

B cells represent a significant arm of immunity against pathogens. This is particularly relevant for COVID-19, where the production of neutralizing antibodies has been considered as a major defense mechanism eradicating the virions and providing immunity to the host [4]. However, Quinti et al. have recently described two patients with agammaglobulinemia who displayed remarkably mild disease of short duration and no requirement of any treatment, suggesting that inflammatory functions of B cells may contribute to the deterioration of COVID-19 disease and their control could block cytokine production, thus improving disease outcome [5].

Key words: B cells, BTK, X-linked agammaglobulinemia, BAFFR, COVID-19.

Palabras clave: Células B, BTK, agammaglobulinemia ligada a X, BAFFR, COVID-19.
In this context, we further describe the clinical presentation of three Greek patients with X-linked agammaglobulinemia (XLA) infected by COVID-19. Furthermore, we analyzed by molecular assays as described [6] the potential contribution of the most common functional polymorphisms of B cells, namely BAFFR-P21R (rs77874543) and BAFFR-H159Y (rs61756766), to the clinical phenotype of 240 COVID-19 patients (male/female: 165/75, mean age ± SD: 40.6 ± 2.2 years). Patients were divided into five groups according to the severity of their disease: (a) asymptomatic, (b) mild without requiring hospitalization, (c) moderate requiring hospitalization, (d) severe with pneumonia, and (e) severe with SARS (requiring ICU care) (Supplementary Table 1). Written informed consent was obtained from all participants. The study was approved by the ethical committee of the Faculty of Medicine, University of Thessaly (No. 2115) and was carried out in accordance with the principles of the Helsinki Declaration.

Our XLA patients presented at our outpatient clinics after molecular confirmation for the presence of viral SARS-CoV-2 RNA, following nasopharyngeal swab tests. They displayed a remarkable absence of disease to mild clinical disease without requiring hospitalization, they did not receive any treatment (except of a patient receiving paracetamol once for fever) and they recovered quickly following SARS-CoV-2 infection (Table 1); interestingly, their relatives exhibited a more severe COVID-19 course, although none needed hospitalization. Finally, XLA patients were found negative for SARS-CoV-2 on the twelfth, the fifteenth and the fifteenth day, respectively, after their initial diagnosis.

Considering BAFFR functional polymorphisms, the BAFFR-P21R disturbs BAFFR-dependent survival and activation of B cells, also predisposing P21R-carriers to primary antibody deficiencies [7], while BAFFR-H159Y counteracts the function of P21R, resulting in sustained overactivated BAFF signaling [8,9]. In our cohort of 240 COVID-19 patients, 27 (11.7%) carried the P21R polymorphism all in heterozygous state, and 3 of P21R-carrying patients (1.2% out of the total) also had in heterozygosity the H159Y polymorphism. As presented in Supplementary Table 1, we
did not observe any significant genotype and allele frequency differences between the subgroup of patients according to their clinical phenotype.

Therefore, we demonstrated an absence of severe clinical phenotype in our XLA patients with COVID-19, as well as no association of BAFFR polymorphisms in disease prognosis. XLA is caused by mutations in the BTK gene, and patients present with low to absent B cells in the periphery and agammaglobulinemia, suffering from severe and recurrent infections from infancy [5,10]. As mentioned, Quinti et al. also described two agammaglobulinemia patients with extremely mild COVID-19 disease [5]. However, Ho et al. reported three XLA patients displaying more severe disease, requiring hospitalization and supportive treatment, but even these patients exhibited reduced inflammatory responses and better outcomes compared to patients with other types of primary immunodeficiencies [10]. Finally, Soresina et al. reported two adult XLA patients with COVID-19 who developed interstitial pneumonia but had never required oxygen ventilation or management in ICU [11].

While we do not currently have a clear explanation, we are excluding the possibility that replacement immunoglobulin treatment had an impact on COVID-19 prognosis, since patients with other antibody deficiencies under replacement treatment displayed a more severe clinical phenotype [5,10]. Therefore, we suggest that BTK signaling may primarily contribute to COVID-19 prognosis, since BTK is also expressed by monocytes and dendritic cells, and the impairment of BTK signaling also results in severe consequences of innate immune responses [12,13]. Thus, BTK-dependent NF-kappaB and NLRP3 activation result in the production of proinflammatory cytokines such as IL-1β and IL-6 (which also contribute to COVID-19 pathogenesis [14,15]), while BTK inhibition dampened the inflammatory response [12,13]. This notion is also supported by recent studies describing the outcomes of patients with B cell malignancies and COVID-19, who were receiving BTK-inhibitors (BTKi) displaying a favorable outcome (reviewed by Stack et al. [13]). As a result, there are currently active clinical trials investigating BTKi in COVID-19 patients (ClinicalTrials.gov Identifier:
NCT04528667, NCT04440007, NCT04439006), which will further elucidate their possible therapeutic effects. However, considering that other studies reported that BTK deficiency or inhibition lead rather to enhanced inflammation [13], it is obvious that the exact role of BTK-signaling in innate immune responses needs to be further explored.

Therefore, we could speculate that the “inability” of B cells, monocytes and dendritic cells to produce proinflammatory cytokines in both XLA patients and patients receiving BTKi may cause the mild COVID-19 phenotype. Our data support the notion that BTK signaling contributes to the inflammatory process of COVID-19, suggesting that its damper may represent a possible therapeutic target, improving the disease outcome.

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Conflicts of Interest

The authors declare no competing conflicts of interest.

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References


Table 1. Demographic, genetic, and clinical data of XLA patients of the study.

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Genetic defect</th>
<th>XLA treatment and co-morbidities</th>
<th>Clinical symptoms of COVID-19</th>
<th>Duration of COVID-19 symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>28</td>
<td>Male</td>
<td>c.1174_insA (frameshift defect)</td>
<td>fSCIG 30gr/4w, tension headache for the last 2 years</td>
<td>Fatigue, no fever</td>
<td>1 day</td>
</tr>
<tr>
<td>#2</td>
<td>15</td>
<td>Male</td>
<td>c.1700C&gt;T, p.A567V (missense mutation)</td>
<td>fSCIG 25gr/3w, no co-morbidities</td>
<td>Headache, fever (over 37.6 °C)</td>
<td>1 day</td>
</tr>
<tr>
<td>#3</td>
<td>18</td>
<td>Male</td>
<td>c.519_insCTGCATTGAGA (frameshift defect)</td>
<td>fSCIG 30gr/3w, no co-morbidities</td>
<td>Headache, runny nose, fever (over 37.8 °C)</td>
<td>2 days</td>
</tr>
</tbody>
</table>

Abbreviations: fSCIG, facilitated subcutaneous immunoglobulin; XLA, X-linked agammaglobulinemia