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Mild to moderate clinical course of COVID-19 infection in patients with common variable immune deficiency

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Abstract

The association of immunocompromised patients and severity of COVID-19 infection is not well established. According to the Centers for Disease Control and Prevention (CDC), primary immune deficiencies (PIDs) are among the conditions that can predispose to a more severe course of COVID-19. We report the clinical course and immunological evaluation of five patients with common variable immune deficiency (CVID) who have experienced SARS-CoV-2 virus. Here we assess the severity of the infection, the immunophenotypic profile of the major lymphocyte subgroups, the nonspecific T-cell functional capacity and the SARS-CoV-2 specific effector T-cell immune response. Our results showed that the course of COVID-19 infection in CVID patients was mild to moderate and none of them developed a critical form of the disease. All patients developed a specific SARS-CoV-2 T cell immune response. Lymphopenia as well as impaired T-cell response prior to COVID-19 appeared to be related to a more severe course of the infection. Data on a good specific T cell response against SARS-CoV-2 in CVID patients will help to make the right vaccination decision and establish its efficacy. Clinical outcome even in these individual cases was in agreement with the therapeutic recommendations underlining that regular maintenance with subcutaneous immunoglobulins can be beneficial against immune system overreaction and a severe disease course and convalescent plasma is a treatment option in patients with CVID and COVID-19.

Key words: *COVID-19 infection, common variable immune deficiency, T cell immune response.*

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SARS-CoV-2 disease has a broad spectrum of clinical phenotypes [1]. Many studies have shown the heterogeneity in the clinical course of COVID-19 in terms of demographics, comorbidity, and both B and T cell adaptive immune responses. Host genetic risk factors have also emerged as a potential explanation for clinical heterogeneity and, in addition, offer the potential for personalized therapy [2]. According to the Centers for Disease Control and Prevention (CDC), primary immune deficiencies (PIDs) are among the conditions that can predispose to a more severe course of COVID-19. A number of authors however suggest low morbidity and severity of COVID-19 infection in individuals with PID, thus classifying them at a standard risk for severe disease [3, 4].

We present our experience regarding the course of COVID-19 infection in five patients with common variable immunodeficiency (CVID). COVID-19 infection was confirmed either with positive RT-PCR or with a rapid antigen test. The patients are part of the Bulgarian National PID Registry and were diagnosed, monitored and treated in our clinic. They signed an informed consent form before undergoing immunological tests. We discuss the immunophenotypic profile of the main lymphocyte subgroups, the non-specific functional capacity of T cells and the specific SARS-CoV-2 effector T cell immune response. These data are of interest and will help to make the right decision about vaccines and evaluate the efficacy after vaccination. Summarized demographic, clinical and immunological data of CVID patients are presented in Table 1. All patients were adults between 40 and 63 years old, of Bulgarian ethnicity; three of them were female and two were male. None of the patients were overweight. The body mass index (BMI) was in the range from 17.8 to 22.3. CVID manifestations in-

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Table 1. Demographic, clinical and immunological data of presented patients

Patient	CVID comorbidities	COVID-19 symptoms (length of illness in days)	Treatment targeting SARS-CoV-2	T Ly (mm^3)	T Ly (%)	NLR	Non-specific T cell activation capacity at the time of CVID diagnosis in % PHA/CD3 and CD28 Dynabeads*	Specific anti-SARS-CoV-2 T-cell response to spike antigen**	Specific anti-SARS-CoV-2 T-cell response to NC antigen**
#1 Age: 40 Sex: F BMI: 17.8	Pulmonary emphysema, chronic sinusitis and systemic sarcoidosis	Temperature up to 37.5°C, mild runny nose and headache within 7 days	Not applied	At CVID diagnosis (1232) Day 21 (1496)	At CVID diagnosis (88) Day 21 (88)	At CVID diagnosis (1.3) Day 21 (1.1)	70/85	Day 21 (16) Month 6 (8)	Day 21 (15) Month 6 (5)
#2 Age: 50 Sex: M BMI: 20.8	Chronic obstructive bronchitis, bronchiectasis and hepatic steatosis	Fever up to 39°C, sweating, asthenia and adynamia, dry cough and mild shortness of breath within 14 days	Not applied	At CVID diagnosis (1888) Day 21 (693)	At CVID diagnosis (77) Day 21 (77)	At CVID diagnosis (2.0) Day 21 (5.0)	46/25	Day 21 (324) Month 6 (164)	Day 21 (184) Month 6 (77)
#3 Age: 43 Sex: F BMI: 22.3	Recurrent sinopulmonary infections	Recurrent fever up to 40°C, pneumonia, pericardial effusion, severe asthenia and adynamia, peripheral neuropathy of the lower extremities with periods of exacerbation up to 180 days	Remdesivir, convalescent plasma	At CVID diagnosis (1335) Day 21 (368)	At CVID diagnosis (89) Day 21 (92)	At CVID diagnosis (1.1) Day 21 (7.5)	61/30	Day 21 (64) Month 6 (61)	Day 21 (41) Month 6 (128)
#4 Age: 63 Sex: M BMI: 18.3	Bronchiectasis pulmonary fibrosis	Fever up to 38°C, asthenia and adynamia, dry cough, shortness of breath, loss of taste and smell within 10 days	Not applied	At CVID diagnosis (1816) Day 21 (nt)	At CVID diagnosis (65) Day 21 (nt)	At CVID diagnosis (2.2) Day 21 (nt)	61/44	Day 21 (57)	Day 21 (67)
#5 Age: 56 Sex: F BMI: 18.0	Chronic sinusitis, bronchiectasis and IBD	Subfebrile fever, anosmia and muscle pain within 7 days	Not applied	At CVID diagnosis (2325) Day 21 (nt)	At CVID diagnosis (93) Day 21 (nt)	At CVID diagnosis (2.3) Day 21 (nt)	65/72	Day 21 (137)	Day 21 (85)

F – female, M – male, BMI – body mass index, T Ly – T lymphocytes, NLR – neutrophil/lymphocyte ratio, PHA – phytohemagglutinin, NC – nucleocapsid

** A cut-off of 40% activated T cells was set as a reference range for the CD3 and CD28 Dynabeads test.*

*** Number of detected spots to spike antigen and nucleocapsid antigen. More than 8 spots in panels A (S) and B (NC) were considered positive.*

cluded mainly recurrent lower and upper respiratory tract infections. All of them had well-identified comorbidities predisposing to severe COVID-19 disease including bronchiectasis, sarcoidosis and inflammatory bowel disease (IBD). In none of the patients was a mutation found in genes responsible for the development of CVID. They were provided with regular immunoglobulin therapy in the last 8 years with subcutaneous gamma globulin and maintained serum IgG levels above 7 g/l. Two of the patients with bronchiectasis received intermittent prophylaxis with azithromycin. The patients were not vaccinated against COVID-19 prior to infection (except patient 5, in whom the first dose of vaccine coincided with infection onset). Three of five CVID patients with COVID-19 remained at home with mild symptoms; one of them was treated with immunosuppressive drugs (azathioprine 2 mg/kg and methylprednisolone 10 mg/per day) due to sarcoidosis and the second patient was on biological therapy with anti-TNF monoclonal antibodies (adalimumab 20 mg twice per month) due to Crohn's disease. The other two patients had a moderate course of disease and required hospitalization because of COVID-19-related pneumonia but without mechanical ventilation. Subjective assessment of lung severity score (LSS) was 2 (25% to 50% of the lungs were affected). One of the patients with a moderate form of infection had a prolonged course up to 6 months with three temperature peaks and impaired respiratory function with consistent subfebrility between exacerbations. Patients with a mild form of the disease had no change in laboratory parameters. None of the patients had baseline lymphopenia, with total counts less than 1200 cells/mm^3. Laboratory data of patients with a moderate course of the disease showed normal white blood cell counts, reduced total lymphocyte count, increased inflammatory markers, i.e. erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin and elevated values of neutrophil-lymphocyte ratio (NLR) during infection. In the patient with a moderate (protracted) course of COVID-19 infection, the inflammatory markers (CRP, ESR) remained high during the infection, then low-grade inflammatory activity was maintained for nearly 3 months. She had normal leukocyte count, but constantly rising values of NLR which showed accurate predictive capacity for an unfavorable course of the infection. The same patient was the only one to undergo specific therapy against COVID-19 with remdesivir. Due to persistence of symptoms she was transfused with 4 packages of 200 ml of convalescent plasma after the third temperature peak with a very good therapeutic response and involution of pulmonary changes. In the remaining patients the treatment was symptomatic.

The main lymphocyte populations in peripheral blood and the ability of T lymphocytes to be activated at the time of CVID diagnosis and during COVID-19 infection were evaluated in order to identify unfavorable profiles before infection onset and/or during the disease. Conventional flowcytometry was used to estimate the absolute count and percentage of T-, B- and NK cells as well as CD4/CD8 ratio. T cell activation capacity was assessed by two technologies: non-specific stimulation with phytohaemagglutinin (PHA) and anti-CD3/CD28 Dynabeads (Dynabeads Human T-Activator CD3/CD28, Thermo Fisher Scientific). Except for a decrease in the absolute lymphocyte count of the studied cell populations and a decrease in the percentage of total lymphocytes during COVID-19 infection, we found no change between pre- and peri-infectious immunological cell profiles. CVID patients with mild COVID-19 had preserved capacity for a T cell non-specific response, while the patients with a moderate form of COVID-19 demonstrated decreased T cell activation via the CD3/CD28 activation pathway.

The specific anti-SARS-CoV-2 T-cell response was assessed by ELISPOT analysis (T-SPOT.COVID assay, Oxford Immunotec). The number of cytokine-secreting T cells in response to stimulation with two SARS-CoV-2 antigens, spike protein (S) and nucleocapsid protein (NC), was determined. Patients with CVID were tested on the 21st day after the onset of infection and 3 of them were followed up at the 6th month. Patients with CVID developed a specific anti-SARS-CoV-2 T-cell response. In general, the T-cell response to S antigen was more pronounced than that to NC (except for one patient with a mild course). The intensity of the cellular immune response to SARS-CoV-2 antigens decreased over time (nearly 50% reduction after 180 days) in followed up patients. In the patient with a moderate (prolonged) course, an inverse correlation was noted: an enhanced T-cell response to NC after 6 months.

In the current study we present five CVID patients with a mild to moderate course of COVID-19 infection. We did not find any correlation of COVID-19 course with age, gender, CVID-related comorbidity or serum levels of IgG prior to infection. We did not establish any relationship between the percentage distribution of the patient's main lymphocyte populations and the severity of the infection, either before or during the disease. In cases with a moderate course of infection, relative and absolute lymphopenia during COVID-19 was established. Similar results have been obtained by other authors and lymphopenia was considered as an independent risk factor for moderate and severe forms [5]. During COVID-19 infection elevated NLR ratio indicating higher inflammatory activity was also observed in patients with an unfavorable course, compared to mild forms. Our result confirmed that NLR could be used as a reliable indicator to determine disease severity in CVID patients with COVID-19 as well [6].

We found a correlation between the severity of clinical course of the infection and the T-lymphocyte functional capacity. In CVID patients with mild COVID-19, preserved capacity for a T-cell non-specific response was observed. Patients with a moderate form of COVID-19

demonstrated reduced T-cell activation via the CD3/CD28 pathway. Thus, we can postulate that lymphopenia and dysfunctional T-cell immune response were among factors that predispose to more severe infection. These findings, together with studies that have demonstrated a dominant role of T cells in mitigating disease severity in COVID-19, suggest that cell-mediated immunity may be an important aspect of the immune response to SARS-CoV-2 [7, 8].

A positive correlation was observed between early detection of SARS-CoV-2 specific T cells and early control of infection, resulting in milder disease outcomes in three of our patients. In patients with moderate SARS-CoV-2 and lymphopenia, SARS-CoV-2-specific T cells were detected and retained for 6 months after infection. This indicates that despite lymphopenia, SARS-CoV-2-specific T cells are generated during the early response to infection. This is in agreement with another study, which also showed that early onset of SARS-CoV-2-specific T cells was associated with better disease outcome [9]. These observations raised critical questions about the efficacy of vaccination against COVID-19 in patients with CVID. It could be assumed that investigation of non-specific and specific T cell responses to COVID-19 in patients with antibody deficiencies might be used to stratify the risk of severe infection course and vaccine efficacy. A validated diagnostic assay for T-cell response to SARS-CoV-2 may be an essential part of individual management. It is likely that CVID patients will have variable responses to different COVID-19 vaccines compared to individuals with preserved immune function. Patients with poor T-cell responses may require several doses or combinations of vaccines for optimal protection. Obviously vaccination against COVID-19 will require an individualized approach in patients with CVID and other immunodeficiency disorders [10].

Participants in the current study received long-term immunoglobulin infusions before the infection and were supplemented at the time of infection as well. One might speculate that immunoglobulin pools are likely to contain antibodies that could cross-react with SARS-CoV-2 proteins by exerting a priming effect on the host immune response. Alternatively, immunoglobulins could provide an immunomodulatory action on monocytes and tissue resident macrophages that are involved in the "cytokine storm" [11]. Administration of convalescent plasma to one of the patients with a protracted course resulted in infection recovery, thus supporting the observation that modulation of the immune response by administration of convalescent plasma in antibody deficient patients appears effective, and *ex vivo* studies have confirmed virus neutralization [12]. Several other reports suggesting that convalescent COVID-19 donor plasma may be a valuable therapeutic approach to treat CVID patients with severe COVID-19 are also available [13, 14]. Furthermore, it was recently shown that antibody-based treatments, administration of dexamethasone and remdesivir, as monotherapy or in combination, improved survival in this cohort [15].

Conclusions

The CVID patients presented here showed a mild to moderate form of COVID-19 infection without the need for intensive care. The clinical outcome even in these individual cases was in agreement with the therapeutic recommendations emphasizing that regular maintenance with subcutaneous immunoglobulins can be beneficial against immune system overreaction and a severe disease course and convalescent plasma is a treatment option in patients with CVID and COVID-19. Further studies are needed to correlate the variability in a particular T-cell response with clinical manifestations of infection. Of note, our patients were able to generate a significant effector-specific T-lymphocyte response against SARS-CoV-2, which suggests that vaccination of CVID patients is an optimal therapeutic approach. Sharing data on the clinical course and changes in the adaptive T cell response to SARS-CoV-2 will contribute to better elucidation of immune mechanisms and development of therapeutic strategies in patients with rare diseases such as PIDs.

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The authors declare no conflict of interest.

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