LETTER TO EDITOR

Severe COVID-19 in Patients with B Cell Alymphocytosis and Response to Convalescent Plasma Therapy

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To the Editor,

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. In most cases, COVID-19 is a self-limited infection but some patients will present with severe respiratory distress requiring intensive care unit admission and mechanical ventilation. The main risk factors for severe forms are older age, cardiovascular, and chronic pulmonary diseases [1]. The role of primary or acquired immune deficiencies (ID) in the onset of severe COVID-19 is still controversial. This could be explained by the great heterogeneity of ID, with variable risks depending on the ID subtype. The risk of developing a severe form of COVID-19 in patients with primary ID such as common variable immunodeficiency (CVID) or agammaglobulinemia is not known [2], Herein, we describe two patients with hypogammaglobulinemia and B cell alymphocytosis who presented with severe COVID-19 including a patient with a chronic viremic form that persisted after acute respiratory distress syndrome (ARDS) recovery and successfully treated with convalescent plasma.

Case 1

A 41-year-old woman was admitted to the hospital at the mid of the COVID-19 pandemic because of dyspnea, fever, headache, diarrhea, abdominal pain, ageusia, and anosmia that had been ongoing for 17 days. She had a medical history of breast implants and an anal horseshoe abscess and fistula treated surgically 6 months before with non-caseating granuloma found on histological examination. No other infections were reported. Her respiratory rate was 40/min and SpO2 was 89%. She received oxygen supplementation. Hydroxychloroquine (600 mg/day) was started and maintained for 10 days with ceftriaxone and spiramycin as local standard of care. Her nasopharyngeal swab tested positive for SARS-CoV-2. Laboratory tests showed lymphopenia (660/mm^3) and elevated C-reactive protein (CRP) at 134 mg/L. Chest CT scan showed extensive infiltrates (50 to 75% of lungs involved) consistent with severe COVID-19 and a 10-cm right lower mediastinal mass. Two days later, her clinical condition worsened and Boussignac continuous positive airway pressure (CPAP) was started. Control chest CT scan found progression of pulmonary infiltrates without pulmonary embolism. Her

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condition partially improved, and she was discharged 16 days after admission while maintaining oxygen supplementation of 1 L/min. At day 41 after first COVID-19 symptoms, she had persistent dyspnea, coughing, and fever (> 39 °C) without any evidence of infection besides COVID-19. SpO2 was normal but fell at 88% after walking just a few steps. Control chest CT scan found partial improvement of pulmonary infiltrates with incipient pulmonary fibrosis, and prednisone was started at 1 mg/kg (60 mg/day). Her clinical condition momentarily improved, but fever started again after 1 week, with persistent dyspnea. Prednisone was stopped. A bronchoscopy with bronchoalveolar lavage (BAL) was performed without evidence of opportunistic infection but with a positive SARS-CoV-2 PCR. SARS-CoV-2 RNA was still positive in nasopharyngeal swab and was found positive in blood sample. Serologic test for SARS-Cov-2 antibodies was negative. Severe hypogammaglobulinemia was found and confirmed on a frozen serum sample (from day 19 after first symptoms), with absence of B cells (Table 1). Thymoma was confirmed on the biopsy of the mediastinal mass, and a diagnosis of Good syndrome with persistent SARS-Cov-2 infection was made. Because she had persistent fever, an SpO2 of 96%, and a respiratory rate of 32/min with oxygen supplementation of 1 L/min and elevated CRP (73 mg/L), a treatment with plasma from COVID-19 convalescent patients was decided. The patient received at day 71 and at day 72 after first symptoms two daily infusions of 200 mL of plasma from COVID-19 convalescent patients obtained from the "Etablissement Français du Sang." Two plasma units had an anti-SARS-CoV-2 antibody titer of 1/160 and the two others of 1/40. Fever and exertion dyspnea resolved and CRP normalized within 4 days. Nasopharyngeal and plasma SARS-CoV-2 PCR were negative. She was discharged and scheduled for thymectomy and for starting intravenous immunoglobulin replacement therapy.

Case 2

The patient was a 65-year-old male with a diagnosis of CVID established at age 33 after presenting with repeated ENT and upper respiratory tract infections and a *Campylobacter jejuni* infection with concomitant hypogammaglobulinemia and near absence of B cells (Table 1). No infection related to an associated T cell defect was reported. *BTK* was sequenced and failed to identify any variant in the exons and its flanking regions. No mutations were found for *BAFFR*, *BLNK*, *CD19*, *CD79A*, *CD79B*, *ICOS*, *IGHM*, *TACI*, and *IGLL1*. He also has a significant intellectual disability and a clinical history of surgery for pulmonary artery stenosis in 1964. Secondary causes of hypogammaglobulinemia were excluded. He received monthly immunoglobulin replacement.

In the mid of the COVID-19 pandemic, he presented with asthenia and fever, followed with coughing and dyspnea. Nasopharyngeal SARS-CoV-2 PCR swab was positive. He was hospitalized at day 21 since first symptoms because of a desaturation at 88%. Chest CT was suggestive of COVID-19 pneumonia. He had persistent fever and CRP was 126 mg/L. Eleven days after admission (day 32 since first symptoms), the patient was transferred to ICU because of respiratory distress. A considerable progression of pulmonary involvement was found on chest CT without evidence of pulmonary embolism. Endotracheal intubation was performed and prone ventilation started. The BAL showed persistent SARS-CoV-2 infection with concomitant *Haemophilus influenzae*. Treatment with lopinavir/ritonavir was started with broad-spectrum antibiotics. The patient died 19 days after admission (day 40 after first COVID-19 symptoms) of ARDS.

Discussion

We describe two cases of severe COVID-19 with ARDS in patients with hypogammaglobulinemia and B cell alymphocytosis. One patient died despite mechanical ventilation and one required CPAP. Patient 1 had a concomitant diagnosis of Good syndrome, an acquired immunodeficiency associated with thymoma, whereas patient 2 had a diagnosis of primary hypogammaglobulinemia many years before. To our knowledge, this is the first case of Good syndrome revealed by COVID-19.

Whether primary or acquired ID play a role in the onset of severe COVID-19 is not known. ID might increase the risk of severe disease in case of SARS-CoV-2 infection. COVID-19 occurring in patients with CVID has been reported in 5 patients and seems to confer an increased risk of severe COVID-19 [2, 3]. However, previous reports argue that absence of B cells in patients with hypogammaglobulinemia is associated with a mild course of COVID-19 (5/9 patients) which could suggest a role of B cells in the SARS-CoV-2–induced inflammation (Table 2) [2, 4]. Our data provides new evidence suggesting that besides the severity of hypogammaglobulinemia, prolonged B cell depletion could favor chronic severe COVID-19 infection. This is consistent with the key role of B cells in controlling some viral infections as demonstrated by the chronic enterovirus infections seen in patients with X-linked agammaglobulinemia (XLA) [5]. As BTK is also expressed in monocytes, dendritic cells, and phagocytic cells [6], additional defects resulting in a more global immune deficiency could be involved in the pathogenesis of chronic enteroviral infections in Bruton's disease. This example raises the possibility of additional defects besides B cell alymphocytosis that might be involved in severe COVID-19 and the clinical course of the disease in patient 2.

Table 1 Characteristics of immunodeficiency at diagnosis and of COVID-19 viral shedding

	Patient 1	Patient 2
Characteristics of ID at diagnosis		
Serum immunoglobulin		
IgG, g/L	3.79	1.86
IgA, g/L	0.27	< 0.1
IgM, g/L	0.18	< 0.1
Lymphocyte phenotyping (date)	Day 71	04/2016
Lymphocyte, /mm^3	1625	2400
T cell CD3+, /mm^3 (%)	1571 (97)	1700 (70)
CD4 T cell CD3 + CD4+, /mm^3 (%)	700 (43)	1200 (50)
Naive	54%	49%
Central memory	28%	19%
Transitional CD45-CCR7-CD27+/CD3 + CD4+	6%	NA
Effector	11%	32%
TEMRA	1%	NA
CD8 T cell CD3 + CD8+, /mm^3 (%)	720 (44)	400 (17)
Naive	27%	46%
Central memory	3%	5%
Transitional	20%	NA
Effector	17%	50%
TEMRA	20%	30%
CD56+CD16+, /mm^3 (%)	50 (3)	504 (21)
CD19+, /mm^3 (%)	0 (0)	5 (0.2)
CD20+, /mm^3 (%)	0 (0)	5 (0.2)
Mitogen-stimulated T cell proliferation		
Response to PHA stimulation	Normal	NA
SARS-CoV-2-specific T cell response evaluated by ELISPOT		
S1, SFC/million CD3+	893	NA
S2, SFC/million CD3+	383	NA
M, SFC/million CD3+	1733	NA
N, SFC/million CD3+	1883	NA
Positive controls		
CEFX Ultra SuperStim pool (JPT), SFC/million CD3+	TNTC	NA
PHA, SFC/million CD3+	TNTC	NA
Characteristics of COVID-19 viral shedding		
Elapsed time (in days) since first COVID-19 symptoms and		
First positive SARS-CoV2 PCR in nasopharyngeal swab	17 (Ct = 31)	5 (Ct = 25)
First positive serum SARS-CoV2 PCR	64 (Ct = 38)	NA
Last positive SARS-CoV2 PCR in nasopharyngeal swab	61 (Ct = 39)	NA
Positive SARS-CoV2 PCR in BAL	64 (Ct = 35)	32 (Ct = 23)
First negative SARS-CoV2 PCR in nasopharyngeal swab	78	Last PCR still positive
First negative serum SARS-CoV2 PCR	78	NA

ID, immunodeficiency; *BAL*, bronchoalveolar lavage; *Ct*, cycle threshold; *NA*, not available; *ELISPOT*, enzyme linked immunoSpot; *S1*, spike protein peptide pool 1; *S2*, spike protein peptide pool 2; *M*, membrane protein; *N*, nucleoprotein; *PHA*, phytohaemagglutinine; *TNTC*, too numerous to count

T cell defects have been described in Good syndrome and in CVID patients, clinically or biologically [7, 8], and T cell phenotype of previously reported patients with B cell alymphocytosis and COVID-19 has not been fully addressed (Table 2). Therefore, additional immunological defects could account for COVID-19 presentations described here but they most likely had a marginal role in our patients due to the following reasons. First, lack of B cells may prevent

Table 2 Characteristics of immunodeficiency at diagnosis and of COVID-19 viral shedding

Study	London et al.		Quinti et al.							Fill et al.	Soresina et al.	
Patient number	1	2	1	2	3	4	5	6	7	1	1	2
Age	41	65	56	34	59	32	57	52	41	53	34	26
Sex	F	M	M	M	F	F	M	M	M	F	M	M
Comorbidities	None	None	CRD	CRD	CRD	None	CRD, HT, OB	CRD	CRD	CRD, cancer, Sjögren	None	None
Lymphocyte phenotyping (date)	Day 71	04/2016	01/2020	11/2019	01/2020	01/2020	10/2019	12/2019	09/2019	NA	03/2020	03/2020
Lymphocyte, /mm³	1625	2400	1300	1700	1600	2050	3400	890	1800	normal	NA	NA
CD3+CD4+, /mm³ (%)	700 (43)	1200 (50)	460	900	672	950	2767	274	800	NA	495 (42)	849 (45)
CD3+CD8+, /mm³ (%)	720 (44)	400 (17)	739	700	338	850	1658	258	700	NA	509 (43)	578 (31)
CD56+CD16+, /mm³ (%)	50 (3)	504 (21)	25	28	46	30	21	85	15	NA	NA (11)	NA (5.3)
CD19+	0 (0)	5 (0.2)	0	0	400	200	96	55	278	NA	0	0
Immunodeficiency	Good	CVID	ARA	XLA	CVID	CVID	CVID	CVID	CVID	CVID	XLA	XLA
Genetic background	NA	Neg for BTK, BAFFR, BLNK, CD19, CD79A, CD79B, ICOS, IGHM, TACI, IGLL1	Neg for BTK, IGHM	BTK mutation	NA	NA	NA	NA	NA	NA	BTK mutation	BTK mutation
COVID-19 clinical symptoms	F, H, Dy, Di, AP, Ag, An	F, C, As	None	F	F, Dy	F, Dy, C	F, Dy	F, Dy	F, Dy, C, My	F, My, H, C, CP, Dy, As	F, C	Ag, Vo, As, F
Maximum O₂ requirement	15 L/min	MV	0	0	MV	4 L/min	MV	0	MV	MV	0	0
Device for O₂ delivery	CPAP	MV	None	None	MV	Mask	MV	None	MV	MV	NA	NA
ICU	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes	No	No
COVID-19 WHO clinical progression scale (0–10)	6	10	1	4	10	5	7–9*	4	7–9*	7–9*	4	4
COVID-19 specific treatment	HCQ, CS, ATB, CCPT	Lo/Ri, ATB	HCQ, AZM, Da/Co	HCQ, ATB, Lo/Ri	HCQ, AZM, TCZ	HCQ, Da/Ri, TCZ	HCQ, Lo/Ri, Rem, CS	HCQ, AZM, Lo/Ri	HCQ, ATB, Lo/Ri, TCZ, Rem	HCQ, ATB, Lo/Ri	Lo/Ri, HCQ,	HCQ, AZM, ATB
Duration of symptoms until recovery or death, days	75	40	0	14	20	16	25	21	19	21	22	NA
Maximum CRP, mg/L	307	126	1	26	NA	7.5	120	NA	315	17	78	4
Outcome	Recov	Death	Recov	Recov	Death	Recov	Recov	Recov	Recov	Recov	Recov	Recov

ARA autosomal recessive agammaglobulinemia, OB obesity, HT hypertension, CRD chronic respiratory disease, My myalgia, CVID common variable immunodeficiency, XLA X-linked agammaglobulinemia, F fever, Dy dyspnea, Di diarrhea, H headache, AP abdominal pain, Ag ageusia, An anosmia, C cough, CPAP continuous positive airway pressure, HCQ hydroxychloroquine, ATB antibiotics, CCPT convalescent plasma treatment, Lo/Ri lopinavir/ritonavir, AZM azithromycin, Da/Ri darunavir/ritonavir, TCZ tocilizumab, Da/Co darunavir/cobicistat, RemNA not available, Neg negative, MV mechanical ventilation, Recov recovery

* Score between 7 and 9

seroconversion and viral clearance as illustrated by the clinical course of patient 1, whose disease amended with plasma therapy. Moreover, Lacombe et al. reported similar clinical presentations in patients who received B cell depletion therapy using rituximab [9], underlining the role of B cells in seroconversion and viral clearance. Second, chronic enteroviral infections encountered in Bruton's disease can be controlled by intravenous immunoglobulin therapy. Finally, no previous infections related to T cell defects occurred for either patient, and for patient 1, the only phenotypic abnormalities found on T cells were an increase in activated T cells and an increase in terminally differentiated effector CD8 T cells as often seen in viral infections (Table 1). In addition, for patient 2, mitogen-stimulated T cell proliferation was normal and SARS-CoV-2-specific T cell response evaluated by enzyme-linked immunoSpot (ELISPOT) was positive (Table 1) and similar to what is usually seen in non-ID patients with COVID-19 (data not shown). Altogether, this suggests that B cell defects can play an important role in the development of severe and chronic forms of COVID-19.

Anti-type 1 interferon antibodies could have contributed to severe COVID-19 in patient 1 since patients with Good syndrome are known to develop anti-cytokine antibodies [10] and since anti-type 1 interferon antibodies have recently been described in 10% of severe COVID-19 patients [11]. Unfortunately, anti-cytokine antibodies were not tested for this patient. The convalescent plasma therapy could have lowered anti-cytokine antibodies in patient 1 as plasma may act by lowering autoantibody levels. Nevertheless, as patient 1 failed to seroconvert, a role in antibody replacement is also highly probable. Moreover, patients receiving repeated administrations of rituximab, a treatment that has been shown to be effective in anti-cytokine disease [12], are prone to develop severe COVID-19 [9]. This supports the role of neutralizing antibodies in convalescent plasma therapy efficacy.

The present observations suggest that patients with persistent B cell alymphocytosis could represent a high-risk population for severe COVID-19 and that this might be due to altered plasma cell generation and ineffective humoral response, as suggested by negative seroconversion. This also shows that treatment with convalescent plasma might be an effective treatment of uncontrolled or prolonged infection with SARS-CoV-2 in patients with persistent B cell alymphocytosis. Further studies are required to confirm efficacy of convalescent plasma in COVID-19 in other settings.

We describe the first two cases of severe COVID-19 in patients with hypogammaglobulinemia and absence of B lymphocytes and of efficacy of convalescent plasma in one patient with prolonged SARS-CoV-2 infection. Further studies are needed to accurately determine if the absence of B lymphocytes contribute to severe COVID-19 onset.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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