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Case Report

COVID-19 in a patient with Good's syndrome and in 13 patients with common variable immunodeficiency

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ABSTRACT

Antibody deficiencies constitute the majority of primary immunodeficiencies in adults. These patients have a well-established increased risk of bacterial infections but there is a lack of knowledge regarding the relative risks upon contracting COVID-19. In this monocentric study the disease course of COVID-19 in 1 patient with Good's syndrome and in 13 patients with common variable immunodeficiency (CVID) is described. The severity of disease ranged from very mild to severe. Several patients required hospitalization and immunomodulatory treatment but all survived. Although viral infections are not a typical feature of humoral immunodeficiencies we recommend that vigilance is increased in the management of patients with Good's syndrome and CVID during the COVID-19 pandemic.

Introduction

Good's syndrome is a rare adult onset immunodeficiency of unknown etiology distinguished by the association of thymoma, lack of B cells, hypogammaglobulinemia, and an increased susceptibility to infections [1]. In contrast, common variable immunodeficiency (CVID) is more common with a worldwide incidence of approximately 3 per 100 000, but is similarly characterized by hypogammaglobulinemia and weak antibody responses to new antigens [2]. Since the outbreak of the COVID-19 pandemic in early 2020 a lack of knowledge regarding susceptibility to the infection as well as risk of severe disease course for this patient group has complicated clinical management. Here we summarize the disease course of all 13 CVID-patients that have had confirmed COVID-19 at our center before vaccination was introduced. We also describe in detail the COVID-19 disease course of a patient with Good's syndrome.

Case presentations

Severe COVID-19 in a 67-year-old woman with Good's syndrome

The patient had a history of frequent bacterial respiratory tract infections and had developed bronchiectasis. At the age of 55, a thymoma was discovered and excised and Good's syndrome was diagnosed. At the time, she had undetectable B cells, low CD4 T cells, and low antibody levels with a total IgG of (result [normal range]) 4.5 g/L [6.7–14.5]. IgG levels against *Streptococcus pneumoniae* and *Haemophilus influenzae* were in the low end of the normal range (25 mg/L [10–191] and 0.11 [0.09–19.5], respectively). Immunoglobulin replacement therapy (IGRT) was initiated. She continued to have an increased frequency of bacterial respiratory and urinary tract infections as well as recurring herpes simplex infections. She had osteoporosis and an uncharacterized functional thrombocyte defect but no other chronic diseases. In recent years she contracted recurrent urinary tract infections (UTI) with *Escherichia coli* and was colonized with *H. influenzae* in the respiratory tract. Her precursor B cell development in the bone marrow has been previously reported ("patient 6") [3].

At the beginning of the second wave of COVID-19 in Sweden, the patient had a gradual onset of mild fever, dysuria, malaise, but no respiratory symptoms (Fig. 1 and Table 1). On day 9 she tested positive for SARS-CoV-2 by PCR. *E coli* was detected in her urine and she was started on nitrofurantoin for a UTI. She became increasingly affected by fatigue, fever, and dyspnea. On day 17 she sought medical care and was admitted to the hospital. At admission she had a respiratory rate of 30/min, temperature of 38.4, and required 2 l/min of O_2 to maintain a saturation above 95%. She still had urinary tract symptoms and a chest X-ray revealed diffuse peribronchial infiltrates that suggested a secondary bacterial infection in the lower respiratory tract. Treatment with cefotaxime was started. Routine COVID-19 thrombosis prophylaxis was administered throughout her hospital stay. A computed tomography (CT) scan showed pulmonary ground-glass opacities consistent with COVID-19 and SARS-CoV-2 PCR was positive in serum. The next few

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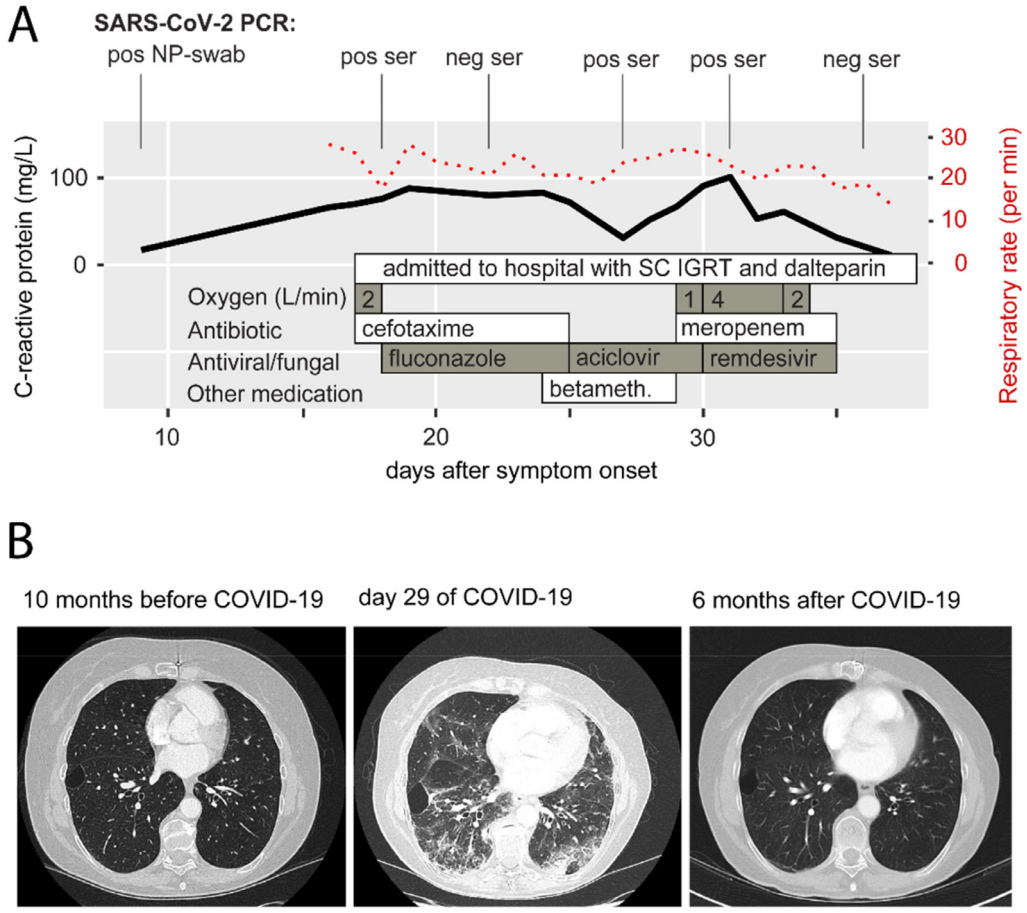

Fig. 1. Disease course of COVID-19 in a patient with Good's syndrome. **A** Timeline representing C-reactive protein (solid black line) and respiratory rate (dotted red line) in relation to SARS-CoV-2 PCR results in nasopharyngeal (NP) swab and serum (ser) as well as significant treatments during hospitalization. IGRT, 6 g/wk; dalteparin, 5000 IU/d; cefotaxime, 1 g x 3/d; meropenem, 1 g x 3/d, fluconazole, 100 mg/d; aciclovir 200 mg x 5/d; remdesivir 200 mg day 1 then 100 mg/d; betamethasone, 2 mg/d. **B** Computed tomography of the lungs at peak of disease (center panel) showing ground-glass opacities in all lobes and bilateral basal confluent infiltrates, compared to time points several months before and after COVID-19. Pos, positive; neg, negative; SC, subcutaneous; IGRT, immunoglobulin replacement therapy; betameth., betamethasone.

days her clinical condition improved. A 5-day course of betamethasone was started to dampen inflammation but after its cessation her fever increased and breathing difficulties worsened. A CT-scan showed progression of pulmonary ground-glass opacities but no embolism (Fig. 1B). She deteriorated further during the night before day 29 and meropenem was started but cultures did not show any bacterial growth in blood, sputum, or urine. This coincided with the highest neutrophil counts and ferritin levels during the disease course (Fig. 2). The next day she was put on remdesivir for 5 consecutive days followed by a marked improvement regarding clinical and laboratory parameters. She was also treated for herpes simplex reactivation and oral candidiasis. During the hospital stay a borderline positive reaction in a SARS-CoV-2 specific T cell proliferation assay [4] was observed but a repeated assessment 8 months after disease onset showed a clearly positive SARS-CoV-2 specific T cell reaction. SARS-CoV-2 serology returned negative repeatedly. On follow-up 6 weeks after discharge, a degree of fatigue remained but she had no breathing difficulties and could perform all her daily activities.

COVID-19 in 13 patients with CVID

The 90 CVID patients that are followed at the Immunodeficiency Unit at Karolinska University Hospital were systematically assessed for past infection with SARS-CoV-2 and 13 cases were identified. All were diagnosed according to the CVID ICON 2015-criteria [5], were on IGRT, and had serum IgG levels in the normal range at the time (Tables 1 and 2). Two were on immunosuppressive treatment due to Granulomatous-lymphocytic interstitial lung disease (GLILD) and one had maintenance treatment with prednisolone and sulfasalazine for Crohn's disease. Approximately half of the patients had subnormal to non-detectable B cells and 6 had subnormal CD4 T cells, with the lowest being 260 × 10^6/L (ref 490–1340 × 10^6/L), at the latest routine follow-up before COVID-19 (Table 3). These 13 patients had a mean age of 51 and two had a BMI that classified them as obese. The majority had at least one other chronic disease, although none was severely affected by comorbidity. None of the patients herein reported were vaccinated against COVID-19 by the time of their infection

Six of the CVID patients had positive serology after recovering but 2 of these could be explained by treatment with convalescent plasma or bamlanivimab. Five out of 6 tested patients had some level of T cell reactivity towards SARS-CoV-2 during or after COVID-19. Only 5 patients cleared the infection without hospitalization, 2 required treatment in the intensive care unit (ICU) but all survived.

Discussion

The COVID-19 disease course has previously been described for 2 patients with Good's syndrome, one that had a fatal outcome [6] and one that had severe disease and survived [7]. The patient that died was a 49-year-old male whose clinical history was comparable with the pa-

Table 1
Demographic data and COVID-19 disease characteristics in 1 patient with Good's syndrome and in 13 patients with CVID.

#	Age	Sex	BMI	Other diseases	Treatment*	Severity	Disease course	COVID-19 treatment	PCR	Serology	T Cell
Good's Syndrome											
1	67	F	22	bronchiectasis, thymoma (at age 55)	IGRT	Hospital	Mild RTI symptoms and dysuria, slow deterioration, admitted, needed 4 liter/min O_2 at most.	Oxygen	pos	neg	yes
CVID											
2	43	F	24	-	IGRT	ICU	RTI symptoms, later developed dyspnea, ICU and needed HFNC	Oxygen, betamethasone, doxycycline, aztreonam, meropenem, remdesivir, convalescent plasma	pos	pos†	weak
3	47	M	44	CD, asthma, Hodgkins lymphoma (at age 45) PE (at age 36)	IGRT, prednisolone (15mg/d), Sulfasalazine (2g/d)	ICU	Mild RTI, progressively worse, ICU and intubated.	Oxygen, betamethasone, cefotaxime, remdesivir, bamlanivimab, convalescent plasma	pos	NA	NA
4	38	M	21	GLILD, bronchiectasis	IGRT, azathioprine (50mg/d), rituximab (2g 3 months before COVID-19)	Hospital	Biphasic, mild RTI symptoms that resolved, after 10 days worse and developed dyspnea, admitted for observation and received convalescent plasma	Convalescent plasma	pos	NA	NA
5	39	M	24	Psoriasis-arthritis	IGRT	Hospital	Flu-like symptoms, admitted for observation only	-	pos	pos	yes
6	54	F	27	psoriasis, DM type II, asthma, breast cancer (at age 52)	IGRT	Hospital	Flu-like symptoms, admitted for observation only	-	pos	neg	NA
7	65	F	22	asthma, bronchietasis, ITP, liver fibrosis	IGRT	Hospital	Flu-like symptoms, admitted for observation only	Amoxicillin/cavulanic acid, bamlanivimab	pos	pos†	NA
8	74	M	30	asthma, angina pectoris	IGRT, prednisolone (5mg/d)	Hospital	RTI with dyspnea, admitted, 8 liter/min O_2 at most	Oxygen, betamethasone, remdesivir	NA‡	pos	NA
9	83	M	25	hypertension, atrial fibrillation, liver fibrosis	IGRT	Hospital	Moderate RTI, developed dyspnea and was admitted day 7, 1 liter/min O_2 briefly	Oxygen, betamethasone, cefotaxime, remdesivir	pos	pos	NA
10	32	F	24	psoriasis, asthma	IGRT	Mild	Mild RTI symptoms	-	NA	pos	no
11	39	F	21	psoriasis	IGRT	Mild	Mild RTI symptoms	-	NA	pos	NA
12	42	M	21	GLILD	IGRT, ibrutinib (420mg/d)	Mild	Flu-like symptoms	-	pos	neg	yes
13	48	F	28	asthma	IGRT	Mild	Flu-like symptoms	-	pos	NA	NA
14	55	F	23	CD	IGRT	Mild	Mild RTI symptoms	-	pos	NA	yes

CVID, common variable immunodeficiency; BMI, body mass index; PCR, polymerase chain reaction; T cell, SARS-CoV-2 specific T cell proliferation assay; IGRT, immunoglobulin replacement therapy; GLILD, granulomatous–lymphocytic interstitial lung disease; CD, Crohn's disease; PE, pulmonary embolism; DM, diabetes mellitus; ITP, Immune thrombocytopenic purpura; RTI, respiratory tract infection; NA, not available; ICU, intensive care unit; HFNC, high-flow nasal canula.

* Immunodeficiency-related treatment

† likely positive due to having received treatment with polyclonal or monoclonal SARS-CoV-2 specific immunoglobulins.

‡ SARS-CoV-2 antigen test positive

tient reported by us. After hospitalization he improved initially with normalized temperature and C-reactive protein. On day 6 his condition worsened, and he was taken to the ICU. Remdesivir was not administered according to local guidelines. Intubation was not attempted due to an underlying oncological disease not specified in the report. The other reported patient was a 79-year-old female, apparently with no history of susceptibility to infections or co-morbid conditions. Despite oxygen support and dexamethasone, the patient developed acute respiratory distress syndrome. She received treatment with tocilizumab and was admitted to the ICU. After 22 days of hospitalization, she was discharged and eventually recovered fully. Good's syndrome is phenotypically heterogeneous, which may explain the difference in outcome in the 3 reported patients, including ours, but the presence of other well-established COVID-19 risk factors such as male sex and co-morbidities may be more important.

Few reports of COVID-19 in CVID patients exist and the relative risk for this patient group is uncertain. Comparable CVID patients with COVID-19 have been described in recent reports with 10-30% mortality, which is distinctly higher than in the general population [8,9]. On the other hand, 10 CVID patients with an average age of 39 have been described, all of which had mild disease and only one needing hospitalization [10]. In relation to these reports, we observed intermediate severity of COVID-19 with 2 of the 13 CVID patients described herein needing treatment in the ICU.

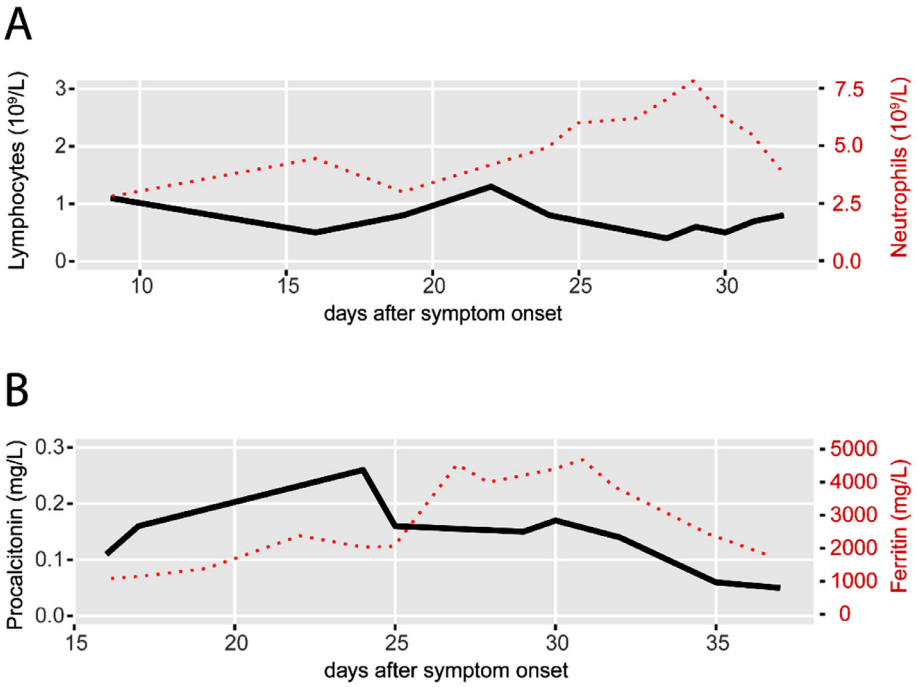

Fig. 2. Timeline representing laboratory results throughout the disease course of COVID-19 in a patient with Good's syndrome. **A** Total lymphocyte counts (solid black line) in relation to neutrophil counts (dotted red line). **B** Procalcitonin (solid black line) in relation to ferritin (dotted red line).

Table 2
Summary of disease characteristics of 1 patient with Good's syndrome and 13 patients with CVID.

#	Diagnosed	TLC	CD4	CD8	NK	CD19	IgG	IgA	IgM	Genetics	BG
Good's syndrome											
1	2008	4500	600	1330	120	ND	11.3	0.27	ND	NA	A
CVID											
2	2009	4600	310	120	40	50	6.41	ND	ND	ND	B
3	2001	4400	510	310	180	310	8.11	0.38	ND	ND	B
4	2005	5200	1140	310	210	550	12.2	ND	ND	*NFKB1*[*]	B
5	2007	5500	740	135	250	10	14.9	ND	0.18	NA	B
6	2015	2800	280	140	80	50	10.7	ND	ND	NA	A
7	1978	4100	370	440	160	110	10.7	ND	ND	NA	0
8	2020	6200	1030	170	520	ND	10.1	0.43	0.31	NA	A
9	2004	2400	260	240	210	20	9.77	0.07	ND	NA	B
10	2013	6700	750	660	130	300	6.22	ND	0.49	NA	0
11	2008	4700	430	240	150	210	8.48	ND	0.23	NA	0
12	2007	3300	370	350	40	80	7.23	ND	ND	NA	A
13	<1993	3700	530	440	80	480	10.8	ND	ND	NA	0
14	<1999	5000	690	500	100	160	8.49	ND	ND	NA	NA

White blood cells (cells/μL) and Immunoglobulins (g/L). All values are from the latest routine follow-up before COVID-19. All patients were on Immunoglobulin replacement therapy at the time of sampling. CVID, common variable immunodeficiency; Diagnosed, year Good's syndrome or CVID was diagnosed; TLC, total lymphocyte count; CD4, CD4 T cells; CD8, CD8 T cells; NK, natural killer cells; CD19, $CD19^+$ B cells; Ig, immunoglobulin; Genetics, genetic analysis results; BG, blood group; ND, not detected; NA, not available.

[*] heterozygous frameshift mutation leading to termination after 11 amino acids.

A limitation in our report, as well as in the other reports cited here, is that asymptomatic infection was not systematically assessed. Furthermore, the viral strains were not evaluated for this study. In light of recent reports of autoantibodies to type I interferon being associated with severe COVID-19 [11] it is of interest to note the reports of cytokine autoantibodies in patients with thymoma and subsequent increased susceptibility to infection [12,13] However, autoantibodies to cytokines were not assessed for our patients.

Severe viral infections are not a typical feature of patients with defects in humoral immunity. Thus, other arms of the immune system possibly play more important roles in protection against COVID-19. Notably, It has been shown that CVID patients and controls develop comparable frequencies of antigen specific T cells after influenza vaccination [14] as well as after COVID-19 [15]. On the other hand, some benefit of administering convalescent plasma to selected patients with COVID-19 has been shown implying that specific antibody responses are not redundant [16,17]. Humoral immunity is per definition dysfunctional in all the presented cases. However, with available treatment, all presented patients cleared SARS-CoV-2 resulting in a positive outcome in all cases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Table 3
B and T cell subpopulations (%) of 1 patient with Good's syndrome and 13 patients with CVID*.

#	Switched memory B cells	Activated B cells	Transitional B cells	Naïve T helper cells	Regulatory T cells
Good's Syndrome					
1	< 0.5	3	2	5	33
CVID					
2	1	12	1	6	52
3	< 0.5	31	7.8	7.1	13
4	1.4	6.4	3.5	8.7	35
5	1	14	2	4	31
6	0.8	9.6	15	7	43
7	6	8	1	7	13
8	0.8	1.6	3.1	7.8	68
9	< 0.5	20	< 0.5	2	10
10	< 0.5	< 0.5	< 0.5	4	31
11	< 0.5	13	< 0.5	5.8	8
12	2	59	< 0.5	2	10
13	< 0.5	< 0.5	< 0.5	7	31
14	< 0.5	< 0.5	< 0.5	3.2	47
Ref	8–9	0–4	0–1	5.3–10.5	22–62

All values are from the latest routine follow-up before COVID-19. IgM^- IgD^- $CD27^+$ switched memory B cells (% of $CD19^+$ cells); $CD21^{low}$ $CD38^{low}$ activated B cells (% of $CD19^+$ cells); $CD38^{high}$ IgM^{high} transitional B cells (% of $CD19^+$ cells); $CD4^+$ $CD45RA^+$ naïve T helper cells (% of $CD3^+$ cells); $CD25^+$ $CD127^-$ regulatory T cells (% of $CD3^+$ $CD4^+$ cells). Ref, reference range based on healthy blood donors aged 18-65. Values below reference range are highlighted in bold for T cells and switched memory B cells. Values above reference range are highlighted for $CD21^{low}$ activated and transitional B cells.

* The total number of $CD19^+$ cells, $CD3^+$ cells, and $CD3^+$ $CD4^+$ cells are presented in Table 2.

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The authors have no conflicts of interest to declare.

Declarations

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Informed Consent Informed consent to participate and to publish was obtained from all patients included in the report.

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