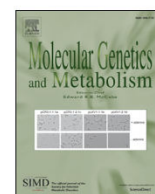




Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Review article

The clinical spectrum of SARS-CoV-2 infection in Gaucher disease: Effect of both a pandemic and a rare disease that disrupts the immune system

Praveena Narayanan^a, Shiny Nair^a, Manisha Balwani^b, Maricar Malinis^c, Pramod Mistry^{a,*}^a Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, United States of America^b Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America^c Section of Infectious Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, United States of America

ARTICLE INFO

Article history:

Received 13 July 2021

Received in revised form 3 August 2021

Accepted 7 August 2021

Available online xxxx

Keywords:

Gaucher disease

SARS-CoV-2

ABSTRACT

Introduction: The impact of SARS-CoV-2 in rare disease populations has been underreported. Gaucher disease (GD) is a prototype rare disease that shares with SARS-CoV-2 a disruption of the lysosomal pathway.

Materials-methods: Retrospective analysis of 11 patients with Type 1 GD who developed COVID-19 between March 2020 and March 2021.

Results: Seven male and 4 female patients with Type 1 GD developed COVID-19. One was a pediatric patient (8 years old) while the remainder were adults, median age of 44 years old (range 21 to 64 years old). Two patients required hospitalization though none required intensive care or intubation. All 11 patients recovered from COVID-19 and there were no reported deaths.

Conclusions: Our case series suggests that GD patients acquired COVID-19 at a similar frequency as the general population, though experienced a milder overall course despite harboring underlying immune system dysfunction and other known co-morbidities that confer high risk of adverse outcomes from SARS-CoV-2 infection.

© 2021 Elsevier Inc. All rights reserved.

Contents

1.	Introduction	0
1.1.	Gaucher disease	0
1.2.	GD and SARS-CoV-2	0
2.	Methods	0
3.	Results	0
3.1.	Case 1	0
3.2.	Case 2	0
3.3.	Case 3	0
3.4.	Case 4	0
3.5.	Case 5	0
3.6.	Case 6	0
4.	Discussion	0
4.1.	Role of cytokines	0
4.2.	Impact of GD severity and GD therapy with COVID-19	0
4.3.	COVID-19 management within our cohort	0
4.4.	Impact of other co-morbidities in GD patients and COVID-19	0
4.5.	Pediatric GD and COVID-19	0
5.	Conclusions	0
	Disclosures	0
	References	0

Abbreviations: GD, Gaucher disease; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; ERT, enzyme replacement therapy; SRT, substrate reduction therapy.

* Corresponding author at: Department of Medicine, Yale School of Medicine, PO Box 208019, New Haven, CT 06520-8019, United States of America.

E-mail addresses: praveena.narayanan@yale.edu (P. Narayanan), manisha.balwani@mssm.edu (M. Balwani), maricar.malinis@yale.edu (M. Malinis), pramod.mistry@yale.edu (P. Mistry).

<https://doi.org/10.1016/j.ymgme.2021.08.004>

1096-7192/© 2021 Elsevier Inc. All rights reserved.

Please cite this article as: P. Narayanan, S. Nair, M. Balwani, et al., The clinical spectrum of SARS-CoV-2 infection in Gaucher disease: Effect of both a pandemic and a rare disease that disrupts the immune system, *Molecular Genetics and Metabolism*, <https://doi.org/10.1016/j.ymgme.2021.08.004>

1. Introduction

The emergence of the SARS-CoV-2 virus pandemic from the winter of 2019 into 2021 has led to a devastating impact on human health, especially among patients with chronic disorders. SARS-CoV-2 infection is associated with higher morbidity and mortality compared to seasonal influenza [1]. While certain demographics such as older adults and those with chronic co-morbidities appear to be more susceptible to complications, COVID-19 has overall been a heterogeneous disease process ranging from a lack of symptoms to development of severe acute respiratory distress syndrome and multi-organ failure. Risk factors associated with poor outcomes of SARS-CoV-2 include male sex, obesity, diabetes mellitus, cardiovascular disease, hypertension, chronic kidney disease, chronic lung disease, and immunodeficiency [2]. Particularly, the association between the aforementioned conditions and impairment of the innate and adaptive immune systems has been thought to lead to an inadequate host response to the pathogen.

Rare genetic diseases affect millions of Americans and the impact of SARS-CoV-2 infection in these underserved patient populations is not known. Many genetic disorders involve immune dysregulation [3] and may increase the risk of severe COVID-19 infection especially when co-existing with other comorbid conditions. It is also possible that some genetic disorders may involve mutations that allow the host immune system to evade SARS-CoV-2. For example, one small case series assessing patients with primary antibody deficiencies found that 3 of the 5 patients with combined variable immunodeficiency (CVID) experienced severe manifestations of COVID-19 requiring ICU admission and resulting in one death, while two patients with agammaglobulinemia both had milder courses with full recovery [4]. Albeit limited in extrapolation by the sample size, it is possible that lacking B lymphocytes in agammaglobulinemia is protective against severe COVID-19 compared to harboring dysfunctional B lymphocytes as seen in CVID [5].

1.1. Gaucher disease

Gaucher disease (GD) is a prototype of a rare genetic disorder whose underlying physiology, like the novel coronavirus, involves the lysosomal system. Both also share the central role of proinflammatory myeloid cells to the causal insult [6–8]. GD exemplifies many of the issues affecting the larger umbrella of inherited lysosomal diseases [9] for which the potential associations with SARS-CoV-2 remain undefined.

GD is caused by biallelic pathogenic variants in *GBA1*, the gene encoding lysosomal glucocerebrosidase (GCase, acid β -glucosidase, EC 3.2.1.45). These variants lead to variable degrees of defective glucocerebrosidase function along with the lysosomal accumulation of excess glucosylceramide (glucocerebroside, Gb1, GL1) and its downstream immune-active metabolite glucosylsphingosine (lyso-Gb1, Lyso-GL1). Diverse co-morbidities of GD, such as metabolic syndrome, malignancies, neurodegenerative disease, splenectomy and pulmonary involvement raised immediate concern early in the pandemic for an adverse outcome from SARS-CoV-2 infection [10]. The lipids accumulating in GD are proinflammatory and underlie impaired macrophage function and immune dysregulation involving multiple myeloid cell lineages that result in chronic metabolic inflammation [11,12]. Interestingly, the latter involves B cell proliferation mediated via type 2 Natural Killer Type (NKT) cells with T_{HH} phenotype and provide B cell help [11]. There are two main available therapies for GD with the goals of improving visceral and hematological symptoms as well as preventing irreversible complications. Enzyme replacement therapy (ERT) involves the administration of recombinant glucocerebrosidase targeted to macrophages via the macrophage mannose receptor and substrate reduction therapy (SRT) works upstream to inhibit glucosylceramide synthase to decrease the excessive production of glucosylceramide [13].

1.2. GD and SARS-CoV-2

Recently, we reported that GD does not appear to confer a heightened risk for severe effects of SARS-CoV-2 infection [14]. There still remains limited characterization, however, of SARS-CoV-2 infection in GD. Herein, we aimed to define the clinical spectrum of SARS-CoV-2 infection in our cohort of GD patients, report outcomes, and assess the potential risk factors for moderate or severe infection. We describe 11 patients with Type 1 GD and polymerase chain reaction (PCR) positive SARS-CoV-2 diagnosed from March 2020 to March 2021. These observations may be useful to guide monitoring and stratification to optimize management for SARS-CoV-2 in patients with GD and likely, other rare lysosomal diseases.

2. Methods

We conducted a retrospective, observational study involving chart review from March 2020 to March 2021. The cases described were derived from those followed at Yale National Gaucher Disease Treatment Center ($n = 11$). Our center follows one of the world's largest cohorts of Type 1 GD patients comprising 167 total patients. Patients were assessed by frequent calls or by video visit and individualized testing was performed when possible. All patients in this case series had confirmed nasopharyngeal SARS-CoV-2 PCR positive test. A detailed COVID-19 symptomology history was obtained. Available data was extracted from the electronic medical record including demographic, comorbidities, pertinent medications, and calculated body mass index. If available, laboratory data was collected including complete blood count (CBC), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), D-dimer, ferritin, and liver enzymes. Due to pandemic restrictions for phlebotomy and imaging, it was not feasible to collect comprehensive, uniform data sets for all patients.

3. Results

Table 1 lists the characteristics of the 11 patients which included 6 adult males, 4 adult females and 1 pediatric male patient. The patient discussed in Case 1 was hospitalized at Yale-New Haven Hospital which allowed for access to continuous data points, medication dosing, and information otherwise not available in the other cases. Cases 1–6 are described below with Tables 1 and 2 summarizing pertinent information across all 11 patients.

3.1. Case 1

A 45-year-old male with Type 1 GD on enzyme replacement therapy (ERT), chronic myeloid leukemia (CML) in remission on nilotinib, history of osteonecrosis, hypertension and diabetes developed symptoms in April 2020 of fever, dyspnea, cough, fatigue, diarrhea, loss of taste and smell. He had no known sick contacts. Due to worsening dyspnea, he was hospitalized 9 days after symptom onset with positive RT-PCR testing confirming positive SARS-CoV-2. His chest x-ray imaging revealed bilateral infiltrates (Fig. 1). On admission, nilotinib was stopped and broad-spectrum antibiotics vancomycin and piperacillin-tazobactam were started though discontinued after 48 h. He was treated with a 5-day course of hydroxychloroquine (400 mg twice daily loading dose followed by 200 mg twice daily) and a 1 dose of tocilizumab (8 mg/kg). He required supplemental oxygen (3 l/min) that was successfully weaned off. He was able to receive his ERT while inpatient and was discharged on hospital day 6. He was evaluated by telemedicine visit within one week of his discharge and he reported resolution of symptoms. At 4 weeks from symptom onset, there was a sustained normalization in C-reactive protein (CRP), ferritin and D-dimer which were all elevated during the active stage of infection (Fig. 2). Serum cytokines on admission, which includes interleukin 1 beta (IL-1 β), interleukin 2 (IL-2), interleukin 2 (IL-2), interleukin 17 (IL-17) and interferon

Table 1
Clinical characteristics.*

Patient	Age	Sex	Ethnicity	BMI (kg/m ²)	GBA1 genotype	DS3	SSI	Treatment	Splenectomy	Co-morbidities
1	45	M	White/Caucasian	24.5	N370S/84GG	1.74	3	ERT	No	Hypertension, Diabetes, CML
2	55	M	White/Caucasian	27.8	N370S/N370S	2	10	ERT	No	Hypertension, OSA
3	59	M	White/Caucasian	32	N370S/N370S	0.4	2	SRT	No	Recurrent pericarditis
4	32	F	White/Caucasian	20	N370S/N370S	3	6	ERT	No	
5	44	F	White/Caucasian	24.4	N370S/N370S	0	2	SRT	No	PCOS,FMF
6	38	M	White/Caucasian	27	N370S/L444P	1.34	5	SRT	No	MGUS
7	44	F	White/Caucasian	39	N370S/R47X	0	8	ERT	No	Hypertension, Diabetes, OSA, NAFLD
8	52	F	White/Caucasian	35.96	N370S/L444P	8	4	ERT	Yes	Pulmonary hypertension
9	64	M	White/Caucasian	27.17	N370S/N370S	3	7	SRT	No	
10	21	M	White/Caucasian	20	N370S/N370S	5.67	3	SRT	No	
11	8	M	White/Caucasian	N/A	L444P/K118N	3	7	ERT	No	Hydrocele

* BMI = Body mass index; The Zimran Severity Score Index (SSI) and Disease Severity Scoring System (DS3) are two validated measures for staging severity of Gaucher Disease Type 1 namely in adult patients with higher numbers indicating increased severity; CML = chronic myeloid leukemia, OSA = obstructive sleep apnea, PCOS = polycystic ovary syndrome; FMF = Familial Mediterranean Fever, MGUS: monoclonal gammopathy of undetermined significance, NAFLD = non-alcoholic fatty liver disease.

gamma (IFN- γ), were elevated (Fig. 3). The increased cytokine levels were consistent with elevation of inflammatory markers, including C-reactive protein (CRP), ferritin and D-dimer. Longitudinal analysis of these cytokines showed stable or decreased levels of IL-1 β , IL-2R, IL-2, IL-17 and IFN- γ levels after 4 days of admission concurrent to decreases in surrogate inflammatory markers, such as CRP, ferritin and D-dimer. IL-6 on admission was less than 5 pg/mL but transiently increased to 126 pg/mL following receipt of tocilizumab. This observation is consistent with previously reported findings attributed to impaired clearance after drug saturation of the IL-6 receptor [15]. Similarly, he had initial mild elevations in alkaline phosphatase (normal lab range 39–117 IU/L), alanine aminotransferase (ALT, normal lab range 12–78 U/L) and aspartate aminotransferase (AST, normal lab range 5–37 U/L) that also normalized within one month (Fig. 4). Available data 1 year prior to SARS-CoV-2 infection was notable for a ferritin level, aminotransferases and alkaline phosphatase that were within normal range. (See Fig. 4.)

3.2. Case 2

A 55 year-old male with Type 1 GD on ERT and hypertension developed symptoms in late March 2020 of high fevers, fatigue, diarrhea,

**Fig. 1.** Chest x-ray imaging with bilateral pulmonary infiltrates in Case 1.**Table 2**
SARS-CoV-2 infection related parameters.*

Patient	Lympho-penia	Thrombo-cytopenia	Liver test abnormalities	Ferritin elevation	CRP elevation	D-dimer elevation	Symptoms	COVID-19 specific therapy	Hospitalization	Oxygen Requirement
1	Yes	Yes	Yes	Yes	Yes	Yes	fever, dyspnea, cough, fatigue, diarrhea, anosmia, ageusia	Hydroxychloroquine Tocilizumab	Yes	Yes
2	Yes	Yes	N/A	Yes	Yes	Yes	fever, fatigue, diarrhea, profound weight loss	Hydroxychloroquine, Azithromycin	Yes	No
3	No	Yes	N/A	N/A	No	N/A	fever, cough, delirium, lethargy	None	No	No
4	Yes	Yes	N/A	Yes	Yes	No	fever, chills, fatigue, diarrhea, headaches, myalgias	None	No	No
5	Yes	Yes	N/A	Yes	No		fever, chills, diarrhea, headaches	None	No	No
6	No	No	N/A	Yes	Yes	No	cough, headache, chest tightness, anosmia, ageusia	None	No	No
7	No	No	N/A	N/A	N/A	N/A	Asymptomatic	None	No	No
8	No	No	N/A	N/A	N/A	N/A	Asymptomatic	None	No	No
9	No	No	N/A	N/A	N/A	N/A	Asymptomatic	None	No	No
10	No	No	N/A	N/A	N/A	N/A	fever, fatigue, headache, myalgia	None	No	No
11	No	No	N/A	N/A	N/A	N/A	Asymptomatic	None	No	No

* Laboratory values represent those on initial presentation. Lymphopenia defined by absolute lymphocyte count $<1.0 \times 1000/\mu\text{L}$. Thrombocytopenia defined as Platelet count <150 and reduced from patient's baseline. Liver test abnormalities defined by having any of the following: Total bilirubin >1.2 mg/dL, Alkaline phosphatase >122 U/L, Alanine transferase (ALT) >34 U/L, or Aspartate transferase (AST) >33 U/L. Ferritin elevation defined as >400 ng/mL. CRP elevation defined as high sensitivity CRP >0.4 mg/L. D-dimer elevation >0.50 mg/L with age adjustment as necessary.

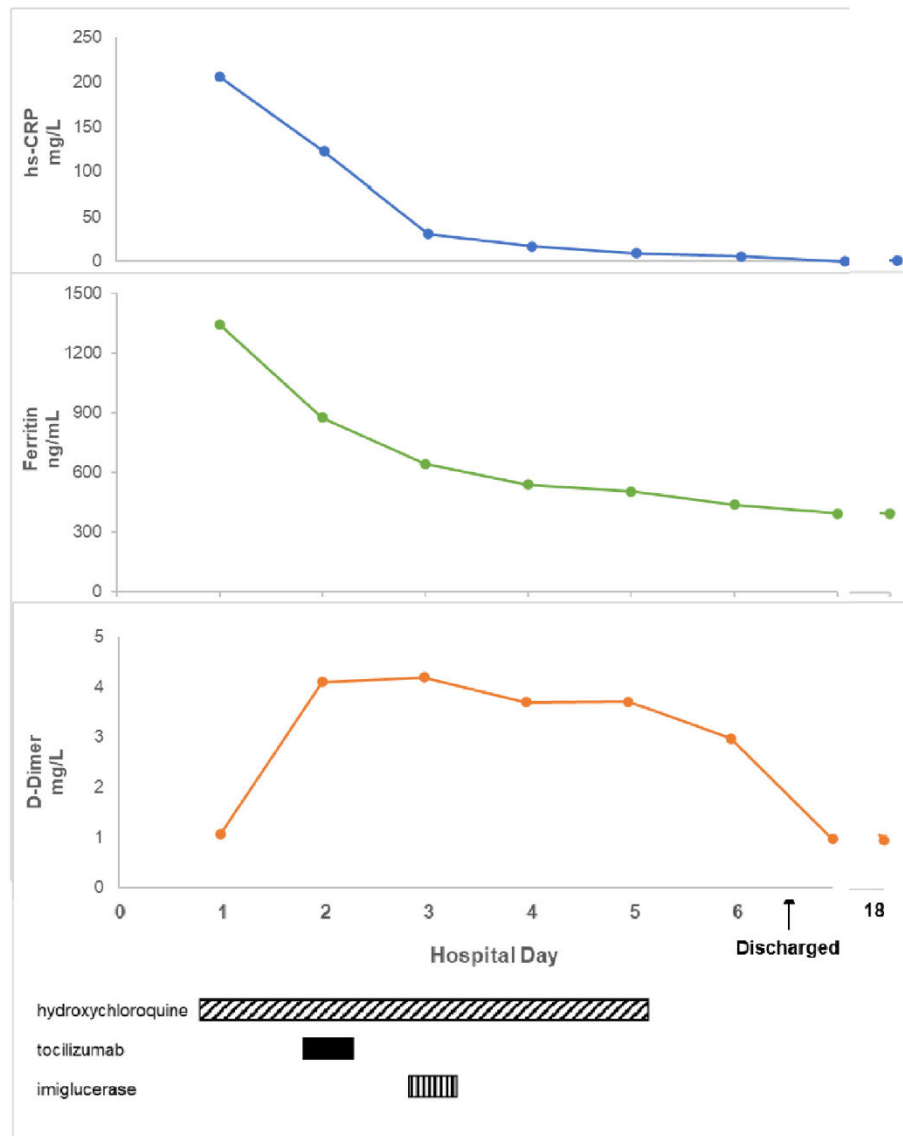


Fig. 2. Laboratory marker trends in Case 1.

weakness, and weight loss, 10 days after exposure to an infected co-worker. His SARS-CoV-2 infection was confirmed by PCR testing on day 3 from symptom onset with a notably normal chest x-ray performed on day 5. He was admitted to the hospital on day 6 for closer monitoring though he did not have any oxygen requirements. Computerized tomography (CT) chest imaging revealed peripheral ground glass opacities. He received a course of azithromycin and hydroxychloroquine. He was discharged on day 11 from symptom onset. Although he reported recovery of fevers and other symptoms by day 14, he did experience a 20-pound weight loss.

3.3. Case 3

A 59 year-old male with Type 1 GD with rare complication of recurrent pericarditis, on eliglustat substrate reduction therapy (SRT) that had led to resolution of pericarditis. He developed symptomatic SARS-CoV-2 infection with high fevers, cough, delirium, and extreme lethargy. Interestingly, objective testing, including chest x-ray, electrocardiogram, serum ferritin, D-dimer, C-reactive protein, complete blood counts and liver enzymes were completely within

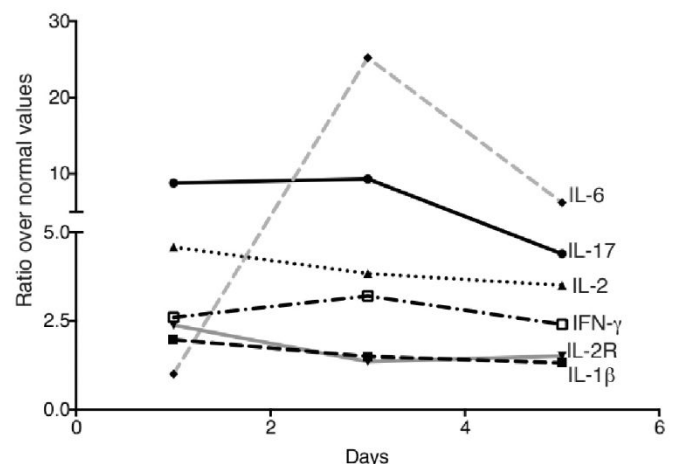


Fig. 3. Cytokine trend by hospital day in Case 1. Elevations recorded as a ratio of each cytokine's laboratory value relative to the upper limit of normal.

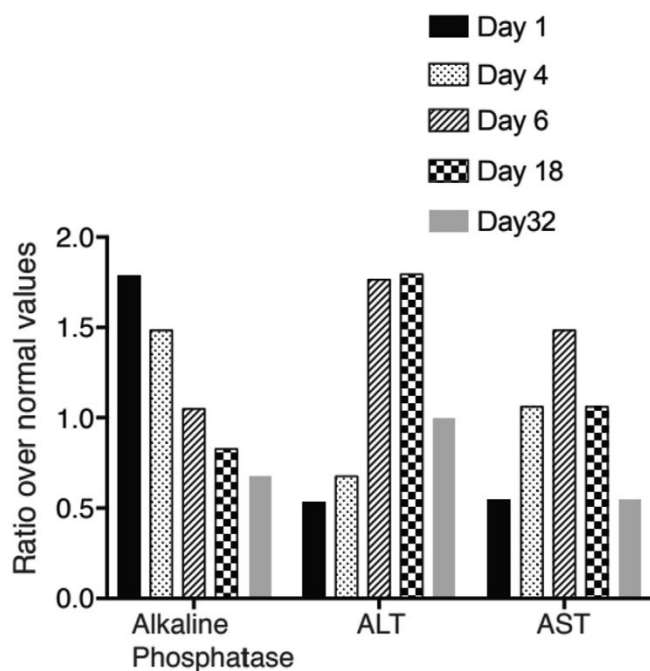


Fig. 4. Liver enzymes by hospital day in Case 1.

the normal range at presentation and throughout the course of his illness. He made a complete recovery at home over the following one month.

3.4. Case 4

A 32 year-old female with Type 1 GD on ERT without other comorbidities was on strict isolation measures aside from receiving her ERT when she developed fevers, chills, myalgias, fatigue, headaches and diarrhea. She was sent for SARS-CoV-2 testing 2 days after symptom onset which initially reported negative though there was concern whether she had provided an adequate sample. Other diagnostics revealed findings consistent with COVID-19 infection as follows: lymphopenia, thrombocytopenia (Platelet count 100,000/ μ L from prior baseline 180,000/ μ L), elevated ferritin 261 ng/mL (reference range upper limit 252 ng/mL), elevated CRP 20 mg/L (normal <1 mg/L) and D-dimer 0.2 mg/L within normal age adjusted limits. A repeat SARS-CoV-2 PCR test was positive at day 4 after symptom onset. Her symptoms resolved in less than one week, however she did have evidence of bruising particularly over her upper extremities (Fig. 5).



Fig. 5. Right forearm and right upper arm bruising associated with thrombocytopenia in Case 4.



Fig. 6. Petechial rash across patient's forearm associated with new onset thrombocytopenia in Case 5.

3.5. Case 5

A 44 year-old female with Type 1 GD on SRT, Polycystic Ovarian Syndrome (PCOS) and Familial Mediterranean Fever (FMF) developed fevers, chills, headaches, ear pain and diarrhea. Her teenage son had been treated empirically with hydroxychloroquine weeks prior after reporting loss of taste and smell. Her lab findings were notable for SARS-CoV-2 PCR positive, lymphopenia, thrombocytopenia (platelet count 114,000/ μ L from baseline 140,000/ μ L) and CRP 2.4 mg/L. She improved with supportive measures. She did note a petechial rash on her forearm (Fig. 6). Her cytopenia and rash resolved without specific treatment.

3.6. Case 6

A 38 year-old male with Type 1 GD on SRT and IgM Kappa Smoldering Myeloma was found to be SARS-CoV-2 positive after learning that his partner tested positive. He developed symptoms 6 days after positive testing with headaches, chest tightness and loss of taste and smell. His cytokine panel showed elevated IL-6, IL-8, IL-10 and tumor necrosis factor alpha (TNF- α). He made a complete recovery without needing specific therapy.

4. Discussion

The patients in our case series presented with a diversity of symptom profiles, incubation timelines, and associated complications. In comparison to large scale population data that has emerged in New York City, our cohort was younger (average 42 years versus 62 years old), but shared a predominance of male gender. [16]. Of the confirmed cases in our GD cohort, there were no deaths, none required intensive care and all recovered within 2 weeks of symptom onset. Indeed, by current definition, all of the GD patients featured in this case series had mild or moderate disease [17] with most recovering without progression to severe hyperinflammatory phase of SARS-CoV-2 infection [18]. While we acknowledge the limited objective data available for many of the patients in our case series, an overall pattern of disease and disease severity was able to be discerned. Our results remain instructive in illustrating the clinical spectrum of COVID-19 in GD. Further large, multicenter studies are needed to confirm our observation that patients with GD experience a less severe course with SARS-CoV-2 infection.

At the onset of the COVID-19 pandemic, there was concern that patients with immune system compromising conditions would be most vulnerable. Early data from other cohorts such as kidney transplant recipients supports this assumption that chronic immunosuppression may lead to higher incidence of severe disease, higher morbidity and

mortality with COVID-19 [19]. We initially suspected patient's with GD would be especially susceptible to macrophage activation syndrome given the central role of macrophages in disease pathophysiology, their chronic hypercytokinemia and underlying dysfunction of the lysosomal system [20]. Other cohort and survey studies on the impact of COVID-19 in the GD population early in the pandemic revealed few patients developed severe disease [21,22]. A Spanish cohort study was the first and only thus far to publish a death related to SARS-CoV-2 in a GD patient, a 79 year-old man with Alzheimer's dementia and prior renal malignancy [23]. This patient was significantly older in comparison to those in our case series.

4.1. Role of cytokines

In Cases 1 and 6, cytokine profiles at the time of COVID-19 infection were available. Elevations in IL-6 were shared in both cases and elevation IL-2R in Case 1 are consistent with findings in the general population with COVID-19 [24]. Numerous studies have suggested that, in addition to direct viral damage, exuberant inflammation contributes to disease severity in COVID-19 [25] [26]. Clinical evidence indicates that in SARS-CoV-2 infection, hyperproduction of cytokines, also known as a cytokine storm due to an unbalanced immune response, can be very damaging to the patients. On the other hand, local and systemic cytokine responses play an important role in host's initial anti-viral response. In particular, higher concentrations of pro-inflammatory cytokines (IFN- γ , IL-1 β , IL-6, IL-12, TGF- β , MCP-1, and IL-18) was observed in severe cases of COVID-19 patients relative to patients with mild-moderate symptoms. Notably in our study, we find minimal increase in proinflammatory cytokines, even in the symptomatic phase, with the levels gradually returning to baseline during convalescent phase; suggesting a mild COVID-19 infection. Hyperferritinemia and elevated TNF-alpha are common in GD1 and serve as biomarkers of effective response to therapy [27]. Indeed, both GD and COVID-19 have associated inflammation and coagulopathy. As such, there is overlap in the markers being used to correlate disease severity in both conditions—D dimer, ferritin, platelet count, CRP. While this makes the diagnosis and grading of severity in patients with GD who develop COVID-19 challenging by bloodwork alone, our case series shows that clinically, our patients presented with mild, and rarely moderate disease activity.

4.2. Impact of GD severity and GD therapy with COVID-19

There has been documented associations between certain viral infections such as Epstein-Barr virus (EBV), and acute worsening of GD [28]. In GD patients who have undergone splenectomy, bacterial infection by encapsulated organisms also poses a hazard and can be lethal [29]. Yet, there is no report of seasonal influenza resulting in worse outcomes in GD patients. In our case series, it also appears that COVID-19 infection did not precipitate complications of GD. Unfortunately, it was not possible to test the patients for Gaucher disease biomarkers, however by clinic reports, there were no bone crises. The patients in cases 4 and 5 developed mild thrombocytopenia associated with rash. Cutaneous manifestations like those seen in our patient cases are common in COVID-19, often transient, and typically do not require specific treatment [30]. Therefore, it is not possible to conclude whether thrombocytopenia represented worsening of GD.

While many of our patients had their GD under adequate control on either ERT or SRT, Case 9 involved an older patient with active, residual disease despite being on ERT. Even in the setting of active inflammation from GD, this patient was spared severe complications of SARS-CoV-2. All patients were encouraged to continue their GD therapy. There was no apparent difference in treatment modality and SARS-CoV-2 infection with 6 patients in this series on ERT and 5 on SRT. Two of the 6 patients on ERT were hospitalized while none among the 5 on SRT were hospitalized. Because the patients in our cohort were all actively on ERT or

SRT, we are unable to comment on the effect of SARS-CoV-2 in GD patients with delayed or missed therapy.

4.3. COVID-19 management within our cohort

The heterogeneity within our GD cohort, of not only COVID-19 presentation, but also timing in the pandemic and rapidly evolving therapies could affect the assessment of its impact. Most of our cases presented in the first half of the pandemic when the outcomes in persons with multiple comorbidities was poor. Case 1 illustrates a patient with GD who developed a classic presentation of COVID-19 pneumonia supported by laboratory findings and chest x-ray imaging. Both Cases 1 and 2 occurred early in the pandemic prior to the introduction of more studied and effective therapies for COVID-19 such as remdesivir and dexamethasone [31,32]. Despite receiving treatments such as hydroxychloroquine that have since been confirmed ineffective for COVID-19 [32], both these patients recovered with short hospitalization and without need to be transferred to the intensive care unit.

4.4. Impact of other co-morbidities in GD patients and COVID-19

Case 3 demonstrates that particularly within our GD cohort, we cannot reliably associate severity of symptoms with degree of laboratory abnormalities. The patient had worrisome rare complication of pericarditis and was debilitated from SARS-CoV-2 infection, yet all his laboratory tests remained persistently normal throughout the illness. Case 7 is a woman with Class II obesity and multiple active obesity related co-morbidities (hypertension, diabetes, obstructive sleep apnea, non-alcoholic fatty liver disease) who recovered from COVID-19 infection without complications. In Case 8, a woman with Class II obesity, asplenia and severe pulmonary arterial hypertension, also recovered from COVID-19 infection without progression to severe disease. For these patients, having a significant risk factor did not correlate with poor outcomes.

4.5. Pediatric GD and COVID-19

Our cohort also includes a child with GD who remained asymptomatic with COVID-19 infection. In general, it is not surprising that our young patient (Case 11) had a favorable course given the pediatric population generally experience less complications and deaths from COVID-19 than adults. However, there have been cases of multisystem inflammatory syndrome in children (MIS-C) and increased deaths in infants <1 year of age and those with underlying metabolic, neurologic and developmental conditions [33]. Of note, there is a case report in the literature of a pediatric patient with GD (2 years and 8 months in age) developing COVID-19 who was found to have a cavitary lung lesion [34].

5. Conclusions

Overall, our case series suggest that COVID-19 infection in GD is not as severe as initially feared. Our GD patients are used to taking precautions as a relatively immunocompromised group, but they did not appear to be any less susceptible to the high infectivity and transmission rates of SARS-CoV-2. Perhaps, then it is the lysosomal involvement and interaction of myeloid cell inflammatory pathways that determines the outcomes of COVID-19 in lysosomal diseases. There has also been increasing evidence that SARS-CoV-2 requires an intact lysosomal function to carry out its life cycle [35]. Further investigation is needed to understand possible mechanisms or therapy related features that may be involved in the correlation between GD and more mild disease from COVID-19.

Disclosures

PKM receives research grant and travel support from Sanofi Genzyme

MB has received honoraria for participation in advisory boards from Sanofi Genzyme and Takeda.

References

- [1] M.A. Lake, What we know so far: COVID-19 current clinical knowledge and research, *Clin. Med. (Lond.)* 20 (2) (2020) 124–127.
- [2] N. Chow, K. Fleming-Dutra, R. Gierke, A. Hall, M. Hughes, T. Pilishvili, Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 – United States, February 12–March 28, 2020, *MMWR Morb. Mortal. Wkly Rep.* 69 (13) (2020) 382–386.
- [3] T.N. Tarasenko, P.J. McGuire, The liver is a metabolic and immunologic organ: a reconsideration of metabolic decompensation due to infection in inborn errors of metabolism (IEM), *Mol. Genet. Metab.* 121 (4) (2017) 283–288.
- [4] 211 3 e4. I. Quinti, V. Lougaris, C. Milito, F. Cinetto, A. Pecoraro, I. Mezzaroma, et al., A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia, *J. Allergy Clin. Immunol.* 146 (1) (2020).
- [5] F. Babaha, N. Rezaei, Primary immunodeficiency diseases in COVID-19 pandemic: a predisposing or protective factor? *Am. J. Med. Sci.* 360 (6) (2020) 740–741.
- [6] C. Lucas, P. Wong, J. Klein, T.B.R. Castro, J. Silva, M. Sundaram, et al., Longitudinal analyses reveal immunological misfiring in severe COVID-19, *Nature* 584 (7821) (2020) 463–469.
- [7] G.A. Grabowski, A.H.M. Antommarchia, E.H. Kolodny, P.K. Mistry, Gaucher disease: basic and translational science needs for more complete therapy and management, *Mol. Genet. Metab.* 132 (2) (2021) 59–75.
- [8] N. Yang, H.M. Shen, Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19, *Int. J. Biol. Sci.* 16 (10) (2020) 1724–1731.
- [9] C. Lampe, C. Dionisi-Vici, C.M. Bellettato, L. Paneghetti, C. van Lingen, S. Bond, et al., The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetabERN surveys, *Orphanet J. Rare Dis.* 15 (1) (2020) 341.
- [10] P. Mistry, M. Balwani, D. Barbouth, T.A. Burrow, E.I. Ginns, O. Goker-Alpan, et al., Gaucher disease and SARS-CoV-2 infection: emerging management challenges, *Mol. Genet. Metab.* 130 (3) (2020) 164–169.
- [11] S. Nair, C.S. Boddupalli, R. Verma, J. Liu, R. Yang, G.M. Pastores, et al., Type II NKT-TFH cells against gaucher lipids regulate B-cell immunity and inflammation, *Blood* 125 (8) (2015) 1256–1271.
- [12] M.K. Pandey, T.A. Burrow, R. Rani, L.J. Martin, D. Witte, K.D. Setchell, et al., Complement drives glucosylceramide accumulation and tissue inflammation in gaucher disease, *Nature* 543 (7643) (2017) 108–112.
- [13] A. Van Rossum, M. Holsopple, Enzyme replacement or substrate reduction? A review of Gaucher disease treatment options, *Hosp. Pharm.* 51 (7) (2016) 553–563.
- [14] L. Fierro, N. Nesheiwat, H. Naik, P. Narayanan, P.K. Mistry, M. Balwani, Gaucher disease and SARS-CoV-2 infection: experience from 181 patients in New York, *Mol. Genet. Metab.* 132 (2020) 44–48.
- [15] N. Nishimoto, K. Terao, T. Mima, H. Nakahara, N. Takagi, T. Kakehi, Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and castleman disease, *Blood* 112 (10) (2008) 3959–3964.
- [16] P. Goyal, J.J. Choi, L.C. Pinheiro, E.J. Schenck, R. Chen, A. Jabri, et al., Clinical characteristics of Covid-19 in New York City, *N. Engl. J. Med.* 382 (2020) 2372–2374.
- [17] R.T. Gandhi, J.B. Lynch, C. del Rio, Mild or moderate Covid-19, *N. Engl. J. Med.* 383 (2020) 1757–1766.
- [18] H.K. Siddiqi, M.R. Mehra, COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal, *J. Heart Lung Transplant.* 39 (5) (2020) 405–407.
- [19] E. Akalin, Y. Azzi, R. Bartash, H. Seethamraju, M. Parides, V. Hemmige, et al., Covid-19 and kidney transplantation, *N. Engl. J. Med.* 382 (2020) 2475–2477.
- [20] P. Mistry, M. Balwani, D. Barbouth, et al., Gaucher disease and SARS-CoV-2 infection: emerging management challenges, *Mol. Genet. Metab.* 130 (2020) 164–168.
- [21] A. Sechi, D. Macor, S. Valent, R.M. Da Rioli, M. Zanatta, A. Spinelli, et al., Impact of COVID-19 related healthcare crisis on treatments for patients with lysosomal storage disorders, the first italian experience, *Mol. Genet. Metab.* 130 (3) (2020) 170–171.
- [22] A. Zimran, J. Szer, S. Revel-Vilk, Impact of gaucher disease on COVID-19, *Intern. Med.* 150 (7) (2020) 894–895.
- [23] M. Andrade-Campos, B. Escuder-Azuara, L.L. de Frutos, I. Serrano-Gonzalo, P. Giraldo, Geedl, et al., Direct and indirect effects of the SARS-CoV-2 pandemic on gaucher disease patients in Spain: time to reconsider home-based therapies? *Blood Cells Mol. Dis.* 85 (2020) 102478.
- [24] F. Lorenz, E. Pawlowicz, M. Klimkowska, S. Beshara, A. Bulanda Brustad, A.B. Skotnicki, et al., Ferritinemia and serum inflammatory cytokines in swedish adults with Gaucher disease type 1, *Blood Cells Mol. Dis.* 68 (2018) 35–42.
- [25] M. Merad, J.C. Martin, Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages, *Nat. Rev. Immunol.* 20 (6) (2020) 355–362.
- [26] D.M. Del Valle, S. Kim-Schulze, H.H. Huang, N.D. Beckmann, S. Nirenberg, B. Wang, et al., An inflammatory cytokine signature predicts COVID-19 severity and survival, *Nat. Med.* 26 (10) (2020) 1636–1643.
- [27] V. Azmy, K. Kaman, D. Tang, H. Zhao, C. Dela Cruz, J.E. Topal, et al., Cytokine profiles before and after immune modulation in hospitalized patients with COVID-19, *J. Clin. Immunol.* 41 (4) (2021) 738–747.
- [28] G. Pines, A. Morag, D. Elstein, A. Abrahamov, A. Zimran, Viral infections and phenotypic heterogeneity in Gaucher disease, *Blood Cells Mol. Dis.* 27 (2) (2001) 358–361.
- [29] Y. Zhang, Y.F. Mao, J.M. Du, Case report serious pulmonary infection in a splenectomized patient with adult type 1 Gaucher disease, *Genet. Mol. Res.* 14 (2) (2015) 3338–3344.
- [30] G. Genovese, C. Moltrasio, E. Berti, A.V. Marzano, Skin manifestations associated with COVID-19: current knowledge and future perspectives, *Dermatology* 237 (1) (2021) 1–12.
- [31] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, et al., Remdesivir for the treatment of Covid-19 – final report, *N. Engl. J. Med.* 383 (19) (2020) 1813–1826.
- [32] Group RC, P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, et al., Dexamethasone in hospitalized patients with Covid-19, *N. Engl. J. Med.* 384 (8) (2021) 693–704.
- [33] D. Bixler, A.D. Miller, C.P. Mattison, B. Taylor, K. Komatsu, X. Peterson Pompa, et al., SARS-CoV-2-associated deaths among persons aged <21 years – United States, February 12–July 31, 2020, *MMWR Morb. Mortal. Wkly Rep.* 69 (37) (2020) 1324–1329.
- [34] M. Khalili, M. Gholamzadeh Baei, H. Saneifard, R.M. Ghanaie, B.S. Shamsian, Pediatric with Gaucher disease and Covid-19: Case report of uncommon manifestation of Covid-19 in chest Ct, *Vis. J. Emerg. Med.* 22 (2021), 100966.
- [35] R. Pande, E. Teeple, W. Huang, K.W. Klinger, D. Rajpal, D. Kumar, Lysosomal-immune axis is associated with COVID 19 disease severity: insights from patient single cell data, *bioRxiv* (2021) <https://doi.org/10.1101/2021.01.27.428394>.