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BRIEF REPORT

Coronavirus Disease 2019 in a Patient With a Systemic Autoinflammatory Syndrome due to an NLRC4 Inflammasomopathy

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The effect of autoinflammatory diseases on severe acute respiratory syndrome coronavirus 2 infection remains unknown. We report a case of coronavirus disease 2019 (COVID-19) in a patient with autoinflammation with infantile enterocolitis with inflammatory flares due to a mutation in the inflammasome component NLRC4. This case highlights the role of immunosuppression in patients with autoinflammation with COVID-19.

Keywords. COVID-19; SARS-CoV-2; autoinflammatory; inflammasome; NLRC4.

Inflammasomes are hubs of immune activation that relay signals of infection and stress from individual cells to the systemic immune system to mount protective responses against pathogens by regulating the secretion of proinflammatory cytokines. Inflammasomes comprise a sensor that detects pathogens (a Nod-like receptor protein, NLR), an adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and a protease that cleaves the cytokines pro–interleukin (IL) 1 and pro–IL-18 into their active forms, which are then released from cells. Cells with active inflammasomes undergo a form of cell death called pyroptosis that results in the expulsion of pathogens from the cell and inhibits their intracellular replication. Mutations in the inflammasome sensor NLRC4 cause spontaneous activation of the inflammasome and result in autoinflammation with infantile enterocolitis (AIFEC). Patients with AIFEC experience episodic enterocolitis, fevers, arthralgias, and severe episodes of autoinflammation including hemophagocytic lymphohistiocytosis (HLH) [1, 2].

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), causes a varied clinical presentation ranging from asymptomatic infection to fatal hypoxemic respiratory failure with multiorgan dysfunction. SARS-CoV-2 infection induces an inflammatory response that both is critical to providing protection against severe disease and contributes to morbidity and mortality. Notably, as compared to patients with mild and moderate COVID-19 disease, patients with severe disease exhibit increased levels of the inflammasome-regulated proinflammatory cytokines IL-1β, IL-18, and tumor necrosis factor (TNF) [3], and recent observational studies have begun to assess the efficacy of blockade of these cytokines in disease outcomes [4]. Immunosuppressive therapies such as dexamethasone and the anti–IL-6 receptor antibody tocilizumab provide mortality benefits to patients with severe COVID-19 infection [5, 6]. Nevertheless, individuals who lack critical immune components may fail to clear the virus or become reinfected [7, 8], demonstrating the balance of immune forces at play during infection. How chronic activation of signaling networks that regulate the secretion of IL-1 and IL-18, or their suppression in the setting of autoinflammatory diseases, contributes to COVID-19 remains an outstanding question.

CASE REPORT

A 52-year-old man with a history of a systemic autoinflammatory disease had been previously found to have a gain of function mutation in NLRC4 (V341A) causing AIFEC. At 2 weeks of age, he developed failure to thrive; fever; nonbilious, nonbloody vomiting; and diarrhea, requiring a prolonged hospital course. He has experienced lifelong polyarthritis and episodic fevers that were initially attributed to seronegative psoriatic arthritis and was treated with prednisone and sulfasalazine.

Nine years prior to this admission, this patient's first son died at 23 days of age after developing HLH, prompting exome sequencing. Neither of the patient's parents were carriers of the mutation and had not experienced any inflammatory diseases.

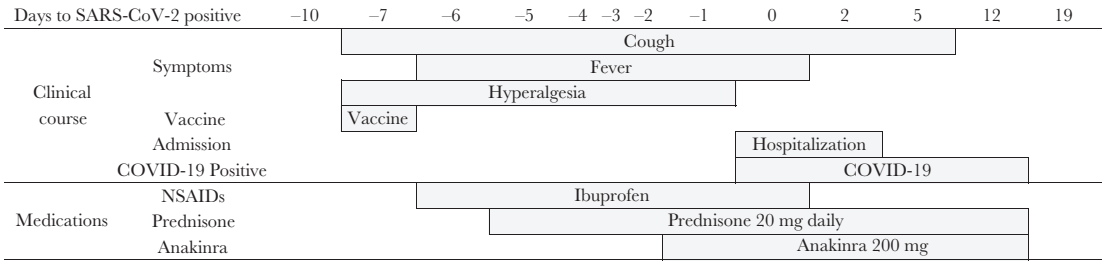
Approximately one week after his son's death, the patient developed a fever 40.6°C) and cough with progression to hypoxemic respiratory failure necessitating hospitalization. He developed pancytopenia, splenomegaly, and acute respiratory distress syndrome, requiring mechanical ventilation and vasopressor therapy. His ferritin was elevated to >29 000 ng/mL and a bone marrow biopsy showed evidence of hemophagocytosis. He was diagnosed with HLH and was treated with intravenous immunoglobulin, cyclosporine, and methylprednisolone with remission of his HLH. He remained off immunosuppressive therapy until 3 years later when he was started on the anti–IL-1rα monoclonal antibody

anakinra, which blocks IL-1 and IL-18 signaling, to prevent inflammatory episodes. Despite this, he experiences an average of 1 flare yearly that manifests as abdominal hyperalgesia, fevers, and cough. His flares are managed with prednisone.

COVID-19 DISEASE COURSE

Ten days prior to admission, the patient had a regular visit with his rheumatologist where he had unremarkable laboratory results and felt well (see Figure 1 for complete clinical course and laboratory values). Seven days prior to admission, he received a messenger RNA–based SARS-CoV-2 vaccine and the next day developed a fever to 38.3°C, chills, fatigue, a dry cough, and hyperalgesia of the skin overlying his anterior thorax. Initial clinical suspicion was for an adverse vaccine reaction for which he was advised to take ibuprofen.

The next day his fever worsened to 39.3°C; the possibility of an AIFEC flare was raised with concern for possible HLH, and he was started on 40 mg prednisone daily. Over the next several days, his fever, chills, and hyperalgesia improved although his cough persisted. On the day prior to admission, he became febrile to 38.8°C with worsening cough. His anakinra was increased from 100 mg to 200 mg daily. His C-reactive protein (CRP) level was elevated to 93.4 ng/mL, his erythrocyte sedimentation rate (ESR) was elevated to 66 mm/hour, and his ferritin level was 588 ng/mL. He had new-onset thrombocytopenia (91×10^3 platelets/μL) and lymphopenia (0.5×10^3 cells/μL). A chest radiograph showed bibasilar, ground-glass opacities concerning for a new-onset multifocal inflammatory process, which raised concerns for an acute infectious process. The next day, he was sent to the hospital out of concern for possible HLH. On presentation he was found to be SARS-CoV-2



Laboratory values											Reference range
Inflammatory markers	Temperature	37.4	38.3	39.3	38.8	38.4	36.4				36.5-37.5° Celsius
	CRP	6.9			93.4	103.4	33.6	5.7	0.7	5.2	<l mg/L
	ESR	15			66	55	48	41	10	24	0–20 mm/h
	Fibrinogen				576	515		318	250	325	194–488 mg/dL
	Ferritin	94			588	643	533	173	73	63	173–400 ng/mL
	Triglycerides					68	53	110		227	<150 mg/dL
	IL-lβ					<1.0					0–l pg/mL
	IL-6					7.9					0–7 pg/mL
	IL-8					15.9					0–14 pg/mL
	IFN-γ					5.4					0–4 pg/mL
	TNF					11.7					0–13 pg/mL
	sCD25					2314					435–2347 pg/mL
Hematologic markers	Hemoglobin	12.9			12.4	12.5	12.4	13.1	12.2	13.3	12.0–18.0 g/dL
	WBC	3.7			3	3.4	3.9	9	7.1	6.5	4–10 ($\times 10^3$/μL)
	ALC	0.8			0.5	0.7	1.1	0.9	1.2	0.5	1–4 ($\times 10^3$/μL)
	ANC	2.2			2.1	2.4	2.3	7.1	5.2	5.8	1–11 ($\times 10^3$/μL)
	Platelets	142			93	109	153	241	226	168	140–440 ($\times 10^3$/μL)
	PTT						26.2				23.9–26.9 seconds
	D-Dimer						0.93				≤0.52 mg/L
Hepatic markers	ALT	25			22	27	23	38	19	22	9–59 U/L
	AST	38			33	32	29	42	20	26	10–35 U/L
	ALP	98			69	63	61	72	79	93	9–122 mg/dL
	Albumin	4.5			3.8	3.9	3.2	4	3.8	4.2	3.6–4.9 g/mL
Renal markers	Creatinine	0.97			0.68	0.67	0.78	0.71	0.78	0.81	0.40–1.30 mg/dL
	BUN	12			16	15	19	14	14	15	6–20 mg/dL

Figure 1. Clinical course and laboratory data. Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; PTT, partial thromboplastin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sCD25, soluble CD25; TNF, tumor necrosis factor; WBC, white blood cell count.

polymerase chain reaction positive and was admitted for further management. Upon further discussion, the patient noted that in the 2 weeks prior to admission, he had been to several indoor dining establishments. Furthermore, the patient's roommate was not working from home and could have been a route of possible exposure to SARS-CoV-2.

Upon admission, he was afebrile, and well appearing. He complained of only a persistent cough but denied headache, nausea, vomiting, diarrhea, anosmia, and ageusia. His blood oxygen saturation was 98% on room air and he was not tachypneic. His examination was only notable for bilateral crackles. A cytokine panel showed an IL-1β level of <1.0 ng/dL, a soluble CD25 level of 2314 ng/dL, an IL-6 level of 7.9 ng/dL, and a TNF level of 11.7 ng/dL. His triglycerides were 68 mg/dL. He was continued on prednisone and the increased anakinra for the duration of his COVID-19 infection.

His clinical status remained stable throughout the next 2 days and his inflammatory markers improved, with his CRP decreasing to 33.6 ng/mL and his ESR to 48 mm/hour. His thrombocytopenia improved to 153×10^3 platelets/μL and his lymphopenia improved to 1.1×10^3 cells/μL. Given his resolving inflammatory markers and stable condition, he was discharged home to complete the remainder of his clinical course.

Three days after discharge, his cough and fatigue resolved, his inflammatory markers had returned to baseline and his cytopenias improved. Nineteen days after COVID-19 diagnosis, repeat laboratory tests showed stable hematologic markers, and this patient had returned to his usual physical activities.

DISCUSSION

SARS-CoV-2 infection induces a complex immune response necessary for viral clearance. Concurrently, an immunologic misfiring can result in collateral tissue damage resulting in hypoxemic respiratory failure with multiorgan failure [3]. An understanding of the contribution of discrete immune pathways to each disease state will be critical to guiding future therapy in patients with COVID-19, irrespective of underlying immune status. Here, we highlight a patient with a well-defined inflammasomopathy to highlight that immunologic suppression with high-dose anakinra and prednisone in this patient with AIFEC is not associated with worsened outcome of COVID-19 or an inability to resolve clinical symptoms.

The current understanding of COVID-19 divides the course into 2 nondiscrete phases—an early virologic disease, and a later immunologic process associated with viral clearance and worsening inflammatory markers. In this patient, long-term suppression of the IL-1 signaling axis by anakinra was not associated with worsening of clinical disease or an inability to resolve symptomatic infection due to SARS-CoV-2. IL-1β and inflammasome activation have been implicated as predictors of severe disease, and early evidence suggests that IL-1 inhibition may provide benefit to patients with moderate to severe COVID-19 [3, 4, 9, 10]. Indeed, this patient's disease course may have been improved by anakinra and prednisone and could explain his relatively mild infection. Further probing for possible exposures at the time of the initial fever, initially thought to be due to the vaccine, may have increased the suspicion of active SARS-CoV-2 infection and prompted earlier testing and treatment (eg, monoclonal antibody therapy).

Similar to patients with COVID-19, severe influenza infection is associated with elevated levels of proinflammatory cytokines that increase expression of inflammasome components, suggesting that these proinflammatory signaling circuits may contribute to poor outcomes in viral infections more broadly [11].

Intriguingly, some patients with moderate to severe COVID-19 elaborate autoantibodies against IL-1β and IL-18 that would inhibit these signaling pathways [12]. While anti–IL-1β and Anti-IL-18 antibodies increase mortality in mice, how these autoantibodies impact human infection remains unknown.

Given that inhibition of IL-1 would not ameliorate the effects of this mutation on cell death induced by inflammasomes, it remains an outstanding question whether this patient's inflammasomopathy provided benefit by restricting viral infection. It also remains unknown whether this patient will develop a protective immune response against SARS-CoV-2 in the setting of IL-1 and IL-18 inhibition and chronic inflammasome activation. The role of inflammasomes in adaptive immune responses remains controversial [13]. Ongoing reporting of SARS-CoV-2 infection in patients with defined immunoregulatory diseases is encouraged as it will contribute to the overall understanding of this complex host–pathogen interaction.

Notes

Patient consent statement. The patient's written consent was obtained, and information was anonymized wherever possible. This work does not include information or elements that requires approval of the Institutional Review Board.

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