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A male infant with COVID-19 in the context of ARPC1B deficiency

To the Editor,

The current pandemic of the novel SARS-CoV-2 infection has affected over 10 million humans around the planet. The clinical manifestations of coronavirus disease 2019 (COVID-19) are diverse, ranging from asymptomatic or mild flu-like symptoms to atypical pneumonia, severe respiratory distress syndrome, systemic inflammation, immune dysregulation, and coagulopathy.

Inborn errors of immunity (IEI) are a heterogeneous group of more than 430 rare congenital disorders with increased susceptibility to infection, autoimmunity, atopy, hyperinflammation, and cancer. Autosomal recessive ARPC1B deficiency is an actinopathy, as are DOCK8 deficiency and the Wiskott-Aldrich syndrome. Defective actin polymerization affects hematopoietic cells, impairing their migration and immunological synapse[1], which results in a combined immune deficiency characterized by leukocytosis, eosinophilia, platelet abnormalities, and hypergammaglobulinemia, and clinically, by eczema and food allergy; infections caused by bacteria, fungi, and viruses; vasculitis; and bleeding diathesis[2]. Here, we describe a male infant patient with known ARPC1B deficiency, who was hospitalized for COVID-19 pneumonia and improved without requiring intensive care or mechanical ventilation. Informed consent through protocols approved by the institutional review boards of the National Institute of Pediatrics was obtained from the patient's family.

An 8-month-old male infant was brought to the emergency department with high-grade fever. His family history is remarkable for one brother who died as a newborn from intracranial bleeding and an 11-year-old sister with the same genetic defect and decreased proliferative response to mitogens, who underwent hematopoietic stem cell transplantation twice without success, and is currently on antimycobacterial treatment, antimicrobial prophylaxis, and regular subcutaneous immunoglobulin. The patient was first seen at age 1 month for eczema and rectal bleeding attributed to cow milk protein allergy. At age 4 months, he developed bronchiolitis caused by respiratory syncytial virus (RSV) and oral candidiasis. Laboratory workup revealed leukocytosis (17 500-33 600/mm^3), eosinophilia (5600-20 100/mm^3), and a marginally high platelet count (467 000) with normal platelet volume, as well as high serum IgG (737 mg/dL) and IgA (165 mg/dL), with normal IgM (37.7 mg/dL). Lymphocyte subsets showed slightly low CD3+ (2.315 cells), normal CD4+ (23%, 1974), and low CD8+ (3%, 257 cells). B cells and NK cells were elevated at 48% (4116 cells) and 15% (1286 cells), respectively. Whole exome sequencing identified a homozygous 46-base pair deletion in exon 8 of *ARPC1B* (chr7: 99,392,784 hg38; p.Glu300fs).

Upon his arrival to the emergency department, he was febrile with tachycardia and signs of septic shock, requiring rapid fluid resuscitation. He showed no respiratory or gastrointestinal signs, although he also had a post-traumatic ulcerated lesion under the tongue with dark discoloration, which raised a concern for fungal infection. Intravenous antibiotics (ciprofloxacin) with antifungal coverage were started within the first hour and a dose of intravenous immunoglobulin (IVIG) at 1 g/kg. Blood counts revealed leukocytosis, neutrophilia, and mild eosinophilia without lymphopenia, while platelets were initially found within normal limits. A day later, blood culture had grown *Pseudomonas aeruginosa*.

During his second day of hospitalization, the patient persisted febrile, tachycardic, and tachypneic, with oxygen desaturation into the low 80s. Chest X-ray showed non-specific bilateral interstitial opacities in the perihilar regions (Figure 1). Real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2, an oral swab taken upon admission, came back positive, and he was then transferred to a COVID-19 isolation area. There was no known contact with another positive COVID-19 case.

The potassium hydroxide (KOH) test for oral thrush was negative for yeast cells, after which amphotericin was switched to fluconazole. Supplemental oxygen was discontinued on day 6 of hospitalization, when mild thrombocytopenia and a prolonged thromboplastin time (aPTT) (but normal fibrinogen and ferritin serum levels) were reported (see Table 1). After completing 14 days of antimicrobial treatment, the patient was discharged without ever requiring intensive care unit admission or mechanical ventilation. Specific serum antibodies to SARS-CoV-2 were assessed 8 weeks after the positive RT-PCR test and came back negative.

The behavior of COVID-19 in patients with IEI might help dissect the immune response to SARS-CoV-2. A few cases of adults with COVID-19 and predominantly antibody deficiencies have been reported[3,4]; some of them developed acute respiratory distress syndrome (ARDS), while some had a milder course of illness. Based on what we know, innate immune defects in genes involved in type 1 interferon response (such as IRF7, IRF9, TLR3) are the most likely candidates to result in severe disease and death in patients with flu-like virus infection[5]. In a few cases of fatal influenza A (H1N1), variants in genes associated with familial hemophagocytic lymphohistiocytosis (FHL) and a decreased cytolytic function of NK cells were also reported[6].

Our patient was on monthly supplemental IVIG treatment, and he received an additional dose during his hospital stay. This, and his young age, might have ameliorated the clinical course[7]. He had a favorable evolution, despite the known susceptibility to viral infection and immune dysregulation in ARPC1B-deficient patients[1]. There were no signs of severe infection, ARDS, and hyperinflammation or of "cytokine storm" unleashed by SARS-CoV-2. Despite him having

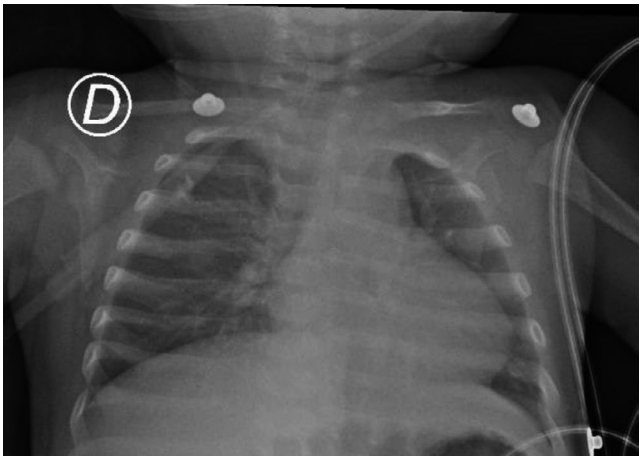

FIGURE 1 Bilateral interstitial infiltrates with perihilar predominance

TABLE 1 Blood counts and acute-phase reactants on admission and on day 5

	Hospital admission (day 0)	Day 5 of hospital admission
Hb	10.4 mg/dL	12.9 mg/dL
Leukocytes	40 300 cells/μL	9800 cells/μL
Neutrophils	30 100 cells/μL	3800 cells/μL
Lymphocytes	5400 cells/μL	2400 cells/μL
Eosinophils	600 cells/μL	2000 cells/μL
Platelets	165 000	109 000
C-reactive protein	Not available	Not available
D-dimer	Not available	Not available
Fibrinogen	Not available	265 mg/dL
Triglycerides	Not available	219 mg/dL
Ferritin	Not available	268 ng/mL

a combined immune deficiency, our patient fully recovered without the need of additional supportive measures other than IVIG, supplemental oxygen, and antibiotic treatment directed against the documented bacteremia.

Although pediatric cases of COVID-19 are fewer compared to adults, some severe presentations and deaths among children have been reported. The presence of a restricted repertoire of IgG (since infants have no previous exposure to coronaviruses) might play a role in the better outcome seen in pediatric patients. Antibody-dependent enhancement has been implicated in the development of severe COVID-19 in the elderly[8]. Additionally, lung cells from children and women show a lower expression of membrane-bound ACE-2, which may also be protective against severe pneumonia.

Conceivably, some immune defects could protect patients with certain IEIs from mounting a full uncontrolled inflammatory response against SARS-CoV-2[9]. The cytoskeleton is a regulator of gene transcription, coupling cell mechanics with the activity of NF-κB. RNA betacoronaviruses are thought to alter the cytoskeleton architecture to facilitate viral replication and output[10]. Thus, ARPC1B deficiency and other actinopathies might limit SARS-CoV-2 replication. Furthermore, Th2 cytokines modulate ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 expression in airway epithelial cells[11], and children with allergies (asthma and/or allergic rhinitis) have a lower expression of ACE2[12]. Patients with ARPC1B deficiency often have allergic diseases; their Th2-biased response could help explain the milder presentation seen in our patient. Insights from protective mechanisms in children, with and without certain immune defects, could facilitate the identification of therapeutic targets.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Lina Maria Castano-Jaramillo: Data curation (equal); investigation (equal); writing-original draft (lead); writing-review and editing (equal). **Marco Antonio Yamazaki-Nakashimada:** Investigation (equal); supervision (equal); writing-review and editing (equal). **Selma Cecilia Scheffler Mendoza:** Data curation (equal); supervision (equal); writing-review and editing (equal). **Juan Carlos Bustamante-Ogando:** Writing-review and editing (equal). **Sara Elva Espinosa-Padilla:** Supervision (supporting); validation (supporting); visualization (supporting); writing-review and editing (supporting). **Saul O. Lugo Reyes:** Conceptualization (lead); supervision (lead); writing-original draft (lead); writing-review and editing (equal).

ETHICAL APPROVAL

The patient and his family gave written informed consent for the diagnostic procedures and for publication of the case report.

PEER REVIEW

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Lina Maria Castano-Jaramillo[1]
Marco Antonio Yamazaki-Nakashimada[1]
Selma Cecilia Scheffler Mendoza[1]
Juan Carlos Bustamante-Ogando[2]
Sara Elva Espinosa-Padilla[2]
Saul O. Lugo Reyes[2]

[1]*Clinical Immunology Service, Mexico City, Mexico*
[2]*Immunodeficiencies Research Unit, National Institute of Pediatrics, Mexico City, Mexico*

Correspondence
Marco Antonio Yamazaki-Nakashimada, Immunodeficiency Clinic, Clinical Immunology Service at the National Institute of Pediatrics, Av Insurgentes Cuicuilco 3700-C, Col. Insurgentes Cuicuilco, Coyoacan 04530, Mexico City, Mexico.

Email: yzki71@yahoo.com.mx

Editor: Philippe Eigenmann

Marco Antonio Yamazaki-Nakashimada and Saul O. Lugo Reyes authors contributed equally.

ORCID

Marco Antonio Yamazaki-Nakashimada https://orcid.org/0000-0002-7609-3923
Saul O. Lugo Reyes https://orcid.org/0000-0002-3730-4150

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Natural history and predictors of recovery in children with chronic spontaneous urticaria

CORTELLAZZO WIEL ET AL.To the Editor,

Chronic urticaria (CU) is a relatively frequent disease with an estimated point prevalence of 0.7% around the world, subject to regional differences.[1] Children seem to display a slightly higher frequency of the disease compared to adults, but to date, limited epidemiological data are available regarding the pediatric age, with only a few studies specifically examining the Caucasian population.[1-4]

Although it is considered a self-limited disease, CU often lasts for years. However, data on the natural history of CU are lacking, particularly in children, and frequently are not specific to the different CU subtypes. Finally, management recommendations are mostly extrapolated from evidence in adults.

We aimed to describe the natural history of chronic spontaneous urticaria (CSU), the most frequent CU subtype, in a cohort of Caucasian children and to identify possible prognostic factors that could predict remission.

We performed an observational study at the Department of Paediatric Allergy and Immunology of the University Teaching Tertiary Hospital, Institute for Maternal and Child Health IRCCS "Burlo Garofolo" of Trieste. The Internal Review Board approved the study. Patients aged 0-18 years with CSU diagnosed from January 2006 to July 2016 were included. Inducible urticaria, disease onset more than 2 years before the first examination, or coexisting underlying conditions such as cardiovascular, hepatobiliary, and renal diseases were considered as exclusion criteria. Medical records were evaluated retrospectively, and the patients were eventually contacted by telephone to investigate their current CSU status. Remission was defined as an urticaria-free period of at least 3 months without treatment, while reappearance of symptoms after remission was considered as a relapse. Patients were divided into three groups to evaluate the effect of the treatment regimen on the remission rate. They were assigned to the first group if they used a single dose of antihistamine drug, to the second group if they needed more than one daily dose (two, three, or four doses per day), and to the third group if they used an adjunctive therapy, such as cyclosporin A or

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