

# Persistent COVID-19 lung infection in a child with a primary immunodeficiency

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## SUMMARY

SARS-CoV-2 infection in children with primary immunodeficiency disease (PID) and its complications have not yet been well described, the course of COVID-19 can range from mild illness to death. We aim to report the case of a child with a PID who developed a severe and persistent pulmonary COVID-19 infection. We present chronologically his clinical course, tests, interventions and radiological findings showing his irregular evolution and poor response to infection. This case highlights the need to accurately monitor the immune response in these cases to try to stop the progression of the damage.

## BACKGROUND

We are currently facing the COVID-19 pandemic that has generated devastating morbidity and mortality rates and where patients with comorbidities are the most susceptible to developing severe forms due to impaired respiratory function or due to systemic inflammatory response syndrome.<sup>1</sup>

Immunosuppressed individuals are highly susceptible to dying from bacterial pathogens and to their quality of life changing through progressive chronic diseases that affect multiple systems and are frequently associated with autoimmune and malignant disorders. As a group, they are highly susceptible to the current pandemic.<sup>2</sup>

As we learn more about the disease course of SARS-CoV-2 in patients with different primary immunodeficiencies (PID), it is likely that we will gain valuable information about the immune system response to COVID-19.<sup>3</sup>

We report on a child with PID who developed a persistent COVID-19 lung infection. We present chronologically its clinical evolution, tests, interventions and radiological findings showing its irregular development and poor response to infection.

## CASE PRESENTATION

This is a 12-year-old mestizo schoolboy from the province of Huancavelica-Peru, who from the first year of life has a diagnosis of PID due to a mutation in the LRBA gene (exon 5 and 36), an older sister with agammaglobulinaemia, and a history of multiple hospital admissions for recurrent pneumonia with mild pulmonary sequelae (bronchiectasis) and medicated with human intravenous immunoglobulin once a month at a dose of 800 mg per kg from the age of 10 years.

He was admitted to our emergency room in Lima-Peru, with a 10-day history of persistent cough and

fever and had had a previous exposure with his mother who tested positive for SARS-CoV-2 25 days before this admission. On arrival, his oxygen saturation (SpO<sub>2</sub>) was 92% in room air and he was positive for SARS-CoV-2 by Reverse transcription polymerase chain reaction (RT-PCR) with a negative antibody test (quantitative IgG and IgM ELISA for the S1 subunit of the SARS-CoV-2 spike protein and also a quantitative electrochemiluminescence immunoassay for total antibody to nucleocapsid (N) antigen). He was admitted for COVID-19 pneumonia, and started on antibiotics and received an early intravenous immunoglobulin dose (800 mg per kg) with slow clinical improvement and was discharged on day 18. Two days later, he was readmitted to the emergency department, for severe respiratory distress (SpO<sub>2</sub> of 74% on room air), with signs of circulatory collapse and a persistently positive RT-PCR for SARS-CoV-2 and a persistently negative antibody test. The images showed new bilateral infiltrates and ground glass appearance with bronchiectasis compatible with COVID-19 pneumonia (figure 1) and also had increased levels of inflammation markers, but did not meet the criteria for multisystem inflammatory syndrome (table 1). Due to his clinical deterioration, he required mechanical ventilation and vasoactive support and was transferred to the paediatric intensive care unit where he received broad-spectrum antibacterial and antifungal coverage as well as dexamethasone at 0.15 mg per kg per day for 1 week. The bronchoalveolar lavage (BAL) culture showed growth of *Stenotrophomonas maltophilia* and *Candida albicans*, for which the therapy was adjusted to intravenous trimethoprim-sulfamethoxazole and fluconazole for 15 days with a new control BAL culture without growth. Smear and culture of acid-fast bacilli, *Pneumocystis jiroveci* stain and galactomannan test were all negative. During his hospital stay, RT-PCR SARS-CoV-2 remained persistently positive and received another dose of intravenous immunoglobulin on day 20 of illness (800 mg per kg). After several days, a partial clinical improvement was observed and we were able to wean him initially to a high-flow nasal cannula (HFNC) and then to low flow oxygen. He was transferred to the general ward, but again developed respiratory distress and had to be put back on HFNC with slow weaning. He received another dose of intravenous immunoglobulin, and after we were able to support him with low flow oxygen.

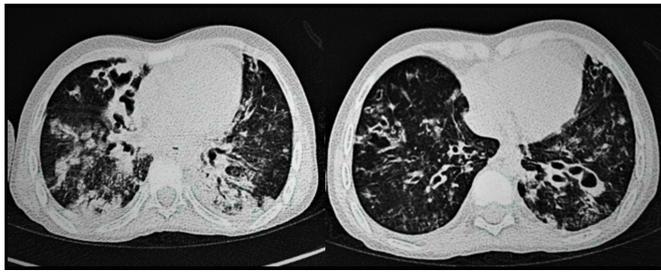
## OUTCOME AND FOLLOW-UP

After 6 weeks, the RT-PCR SARS-CoV-2 was finally negative but with no changes in antibodies, persisted



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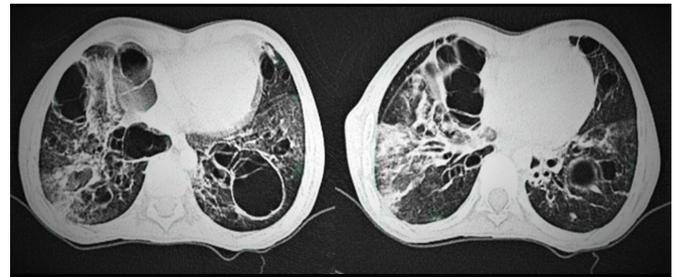
**Figure 1** Admission thoracic tomography. On admission to the hospital (10th day of illness), pulmonary CT showed alveolar radiopacities with interstitial and ground glass pattern in both lung fields, diffuse distribution, bilateral cystic radiolucent images of right predominance in relation to COVID-19 pneumopathy.

with mild respiratory distress, wheezing rales in both lung fields and required oxygen therapy with a reservoir mask at 5 L/min. On neurological examination, he showed signs of muscle atrophy and decreased strength predominantly in the lower limbs with a one-fifth on the left and two-fifths on the right. The last tomographic images showed severe pulmonary sequelae (figure 2). He was eventually discharged with home support and may require a lung and bone marrow transplant in the future. Figure 3 summarises the timeline during his care.

## DISCUSSION

An effective immune response against SARS-CoV-2 is decisive for its control.<sup>4</sup> Within the immunopathogenesis of SARS-CoV-2, it has been reported that macrophages, after being infected, present antigens to T cells that lead to their activation, differentiation and production of cytokines associated with the different subsets of T cells. B lymphocytes are instructed to produce high-affinity antibodies against SARS-CoV-2 epitopes.<sup>4,5</sup>

Some authors have postulated that in PID cases, the intrinsic lack of B cells would prevent the development of the entire inflammatory cascade by SARS-CoV-2, which would make them less likely to develop or experience a serious infection due to a defect in their immune system.<sup>6</sup> However, the evidence is still extremely limited



**Figure 2** Last thoracic tomography. Chest tomography on the 58th day of illness: a mosaic pattern in the upper lobes to rule out small airway disease, interstitial diseases, cystic bronchiectasis of bibasal location predominantly right. Parenchymal consolidations in right upper and lower lobe corresponding to parenchymal inflammatory process. It is configured as severe pulmonary sequelae that may require a definitive intervention such as a lung transplant.

and does not allow us to conclude whether an immunodeficiency is a protective or aggravating factor for COVID-19.<sup>2,6</sup>

The largest report comes from Delavari *et al.* Using the registry database hosted at the Children's Medical Center (Tehran, Iran) that among the 4717 registered patients, 19 reported a positive RT-PCR SARS-CoV-2 test showing an infection rate similar to that of the region, but with a 10-fold increase in deaths in PID cases (8 deaths, 42%).<sup>7</sup>

In general, reports are scarce and the clinical pictures varied, we highlight some. A report of two patients with X-linked agammaglobulinaemia showed that they developed SARS-CoV-2 interstitial pneumonia with fever, cough and anorexia and had elevated CRP and ferritin levels, but never required mechanical ventilation with or intensive care.<sup>8</sup>

Other examples are reported in cases of common variable immunodeficiency, which is the most symptomatic PID presenting with hypogammaglobulinaemia, recurrent infections and poor response to vaccines. Aljaberi and Wishah present an adult patient who developed a severe form of COVID-19 pneumonia and required treatment with mechanical ventilation. He also received antibiotics, hydroxychloroquine and high doses of immunoglobulin, with a favourable resolution with a brief hospitalisation.<sup>9</sup> Another case also presented an adult with a fatal outcome due to severe COVID-19 pneumonia, but this case did not receive regular immunoglobulin infusions at the time of infection.<sup>10</sup>

Intravenous immunoglobulin has been proposed as an immunomodulatory and anti-inflammatory treatment, especially if given in higher doses, and for patients with PID, it would also work to compensate for the lack of adequate antibody production with better evidence if instituted early.<sup>6</sup> In our case, we only observed mild lymphopenia after administration without additional adverse effects such as fever or seizures. Although we noticed a clinical improvement when applied, it is possible that this also decreased the natural response of the host and perpetuates susceptibility to the virus.

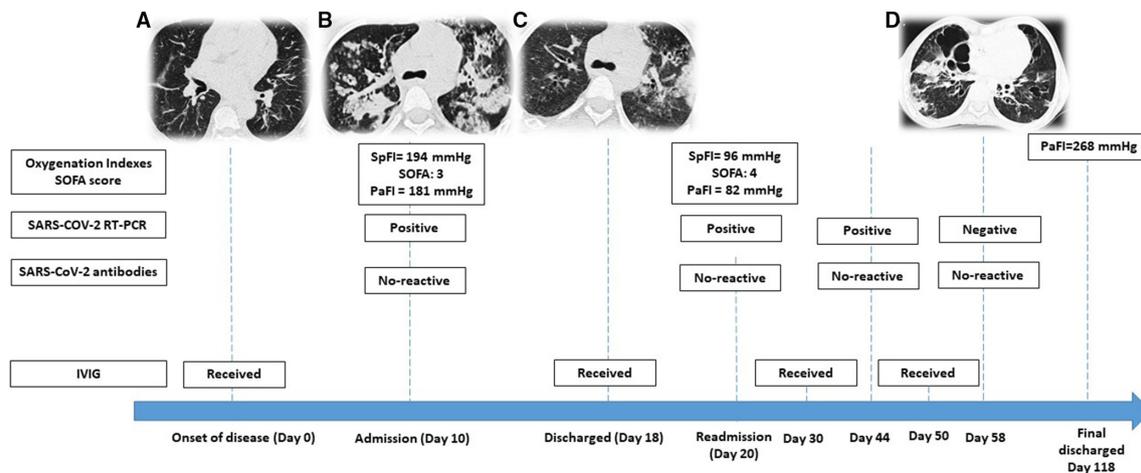
We considered all this in our patient as part of the established hospital treatment, and its limitation was the lack of positive antibody response to SARS-CoV-2, which can be a false-negative result. We also believe that in this case the infection persisted, as evidenced by the positive detection by SARS-CoV-2 viral RNA by RT-PCR and its clinical and imaging behaviour consistent with severe COVID-19 pneumonia.

In cases of COVID-19, the severity of the disease can be increased due to impaired cellular immunity, poor viral control and in the case of immune regulation, uncontrolled inflammatory

**Table 1** Laboratory test during second hospital stay

	DOI 20	DOI 21	DOI 31	DOI 44	DOI 58
BUN (mg/dL)	21.4	17.1	12.8	21.4	32.1
Creatinine (mg/dL)	0.5	0.32	0.41	0.61	0.85
AST (IU/L)	36	25	26	61	44
ALT (IU/L)	43	19	16	105	51
LDH (IU/L)		323			359
CRP (mg/L)	9.9	4.9	3.4	0.8	2.8
Leucocytes (10 <sup>3</sup> /μL)	11.79	5.8	5.2		8.92
Neutrophils (10 <sup>9</sup> /L)	6.51	3.3	2.65		4.58
Lymphocytes (10 <sup>9</sup> /L)	2.59	1.5	1.44		2.13
Monocytes (10 <sup>9</sup> /L)	2.03	0.7	0.64		1.56
Platelets (10 <sup>9</sup> /L)	336	239	245		369
D-dimer (mcg/mL)		1.7			
CPK-MB (pg/mL)		0.49			
NT-proBNP (pg/mL)		81.1			
Fibrinogen (mg/dL)		375			

ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CPK-MB, creatine phosphokinase-MB; CRP, C reactive protein; DOI, day of illness; LDH, lactate dehydrogenase; NT-pro-BNP, N-terminal pro B-type natriuretic peptide.



**Figure 3** Timeline of the persistent COVID-19 lung infection in a child with a primary immunodeficiency. Pulmonary tomography sequences: mild pulmonary bronchiectasis (baseline findings). Multiple images in the form of tarnished glass patches, bronchiectasis. Residual ground glass lung lesion, bronchiectasis. Inflammatory lung parenchyma in consolidation, multiple cystic bronchiectasis. IVIG, intravenous immunoglobulin; PaFi, arterial oxygen pressure/oxygen fraction; SOFA, Sequential Organ Failure Assessment score; SpFi, oxygen saturation/oxygen fraction.

responses may also make patients more susceptible to COVID-19.<sup>11</sup> While the new evidence indicates that RT-PCR positivity may persist for several weeks after recovery and that this does not necessarily imply the presence of viable or transmissible virus.<sup>12</sup>

Our patient presented clinical deterioration and two hospital admissions as a consequence of the prolonged course of the disease associated with the persistence of positive SARS-CoV-2 RT-PCR and negative antibodies test for 6 weeks even with treatment with exogenous human immunoglobulins. Currently, we do not have tocilizumab and there is no availability of convalescent plasma in children with COVID-19.

These data have some limitations as it is not part of a research protocol, but real-life information that is not collected in a systematic way, which limits the search for potentially confusing cofactors and limits the interpretation of the case. For example, the RT-PCRs were performed by the National Institute of Health of Peru and are reported only as positive or negative only, the cycle threshold was not available to correlate those viral loads with disease state.

## CONCLUSION

Given the limited evidence to date, the behaviour of SARS-CoV-2 infection and the persistence of SARS-CoV-2 RT-PCR in patients with PID is unclear, and current as studies have shown variable results in these patients so far, we need more information on how to approach these cases.

## Learning points

- ▶ Children with a primary immunodeficiency may be at increased risk of developing severe and persistent COVID-19.
- ▶ RT-PCR SARS-CoV-2 in these patients should be frequently monitored for a decision on isolation and may represent persistent infectivity.
- ▶ SARS-CoV-2 antibodies may not be useful for follow-up in case where intravenous immunoglobulin is used.

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