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LETTER TO EDITOR

Diagnosis of APS-1 in Two Siblings Following Life-Threatening COVID-19 Pneumonia

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To the Editor,

Inborn errors of immunity (IEIs) often increase susceptibility to severe and/or recurrent infection, but also autoimmunity, autoinflammation, allergy, and cancer. At the beginning of the COVID-19 pandemic, patients with IEIs were considered to be at risk for severe COVID-19. Recent studies however report that most patients with IEIs had silent infection with SARS-CoV-2 or mild COVID-19, as seen in the general population [1, 2]. However, the COVID-19-related mortality rates among IEI patients in global and Brazilian studies were higher than those of the general population [1, 2]. In this context, patients with autoimmune polyglandular syndrome type 1 (APS-1), which results from pathogenic variants in the *AIRE* gene, produce autoantibodies (autoAbs) against type I interferons (IFNs) from early childhood onwards, which predispose them to life-threatening COVID-19 pneumonia [3, 4]. We report two Brazilian brothers, 13 y.o. (P1) and 7 y.o. (P2), born to third-degree consanguineous parents of Italian and Polish descent. The boys presented with life-threatening COVID-19 pneumonia, which led to their diagnosis of APS-1.

P1 first exhibited fever and wheezing after contact with his father who had tested positive for SARS-CoV-2 and developed mild COVID-19 (Fig. 1A). With a history of asthma, P1 was prescribed azithromycin, prednisone, antipyretics, and a bronchodilator. Two days later, P1 presented to a metropolitan field hospital, near to the capital of Parana State in Brazil, with worsening respiratory pattern, cough, pulmonary hemorrhage, and oxygen desaturation (SpO_2 80%). He was sedated, intubated, and transferred to our hospital where he was admitted to the intensive care unit (ICU). RT-qPCR test indicated COVID-19 infection, chest X-ray showed diffuse nodular infiltrates, and chest computed tomography (CT) showed ground-glass opacities associated with intervening reticulations, and peribronchovascular and subpleural peripheral consolidations. Chest CT findings indicated probable COVID-19 pneumonia (CO-RADS 5) and possible alveolar hemorrhage in absorption (Fig. 1B). P1 developed peripheral lymphopenia (785/uL, normal range: 1200/uL to 6500/uL), increased C-reactive protein (CRP 318 mg/dL, normal range: < 10 mg/L), and elevated D-dimer levels (6277 ng/mL, normal range: < 500 ng/mL) and aspartate aminotransferase levels (81 IU/L, normal range: 15 to 40 IU/L). He was treated with oseltamivir, azithromycin, milrinone, heparin, noradrenaline, prophylactic enoxaparin, lorazepam, haloperidol, and dexamethasone, as well as COVID-19 convalescent plasma. P1 was extubated on day 14, transferred from ICU to a general COVID-19 ward on day 17, and discharged 16 days later (total of 33 days hospitalization with no long-term sequelae).

P2 first exhibited fever and cough two days after P1's initial symptoms. Two days later, he was admitted to the same ICU as P1 with respiratory distress (SpO_2 90%) requiring high-flow oxygen therapy (10 L/min) (Fig. 1A). Two hours later, P2 was intubated and experienced an episode of pulmonary hemorrhage. Chest CT showed extensive consolidation in the right upper lobe, lateral middle lobe, and bilateral lower lobes. Small peribronchovascular and subpleural consolidations and lobular ground-glass opacities were observed in both lungs (Fig. 1C). P2 was maintained on mechanical ventilation for 19 days. During that time, he had new episodes of pulmonary hemorrhage and one episode of subcutaneous emphysema in the cervical region. He was treated with cefuroxime, azithromycin, midazolam, morphine, rocuronium, ketamine, dexamethasone, prophylactic enoxaparin, and pipetazo, as well as

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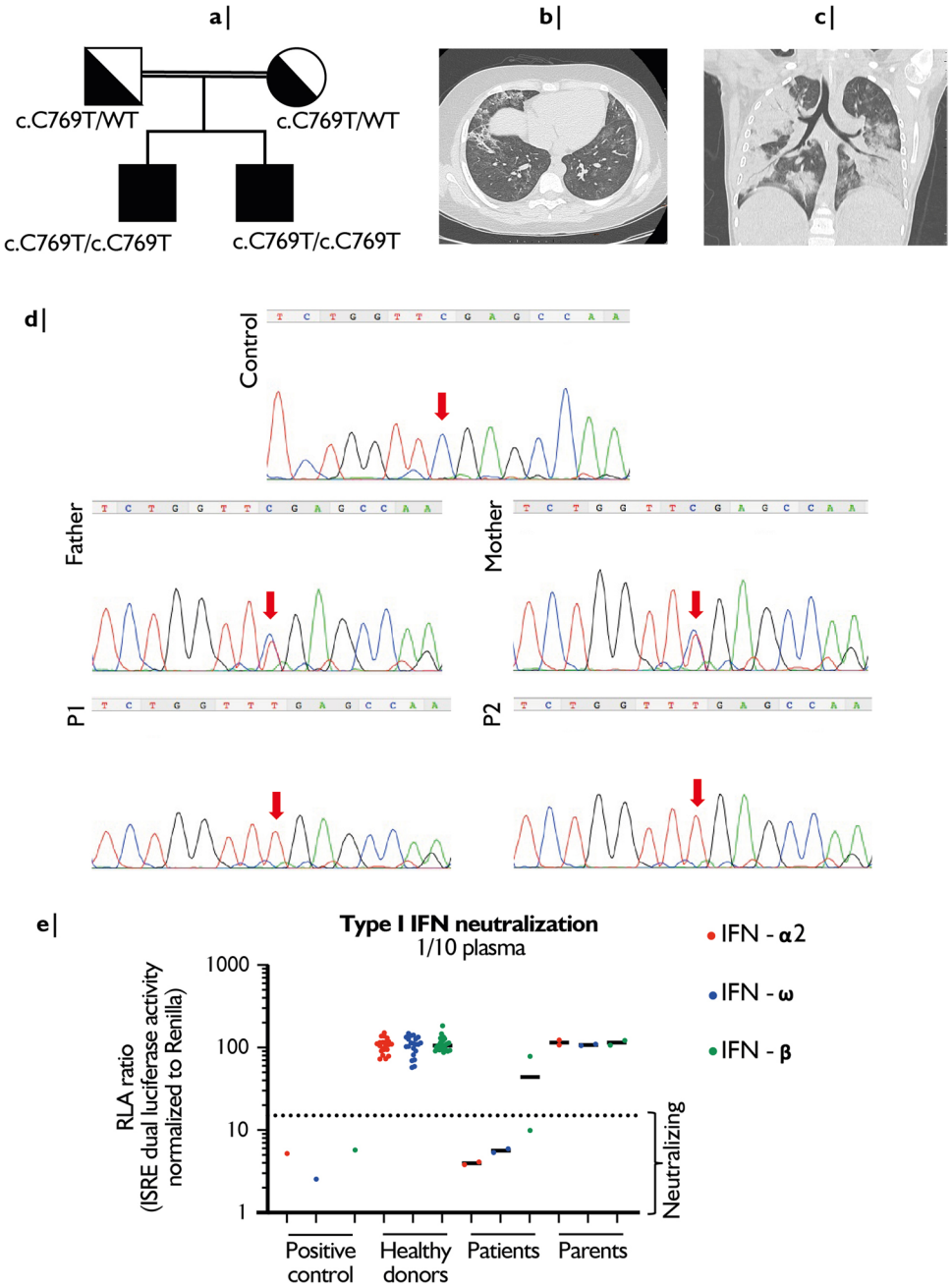

Fig. 1 APS-1 deficiency in two siblings with life-threatening COVID-19 pneumonia. **A** Pedigree of P1 and P2. **B** P1 chest computed tomography. **C** P2 chest computed tomography. **D** Sanger sequencing confirming the presence of the *AIRE* p.R257* variant. **E** Neutralization of 100 pg/mL of IFN-α2, IFN-ω, and IFN-β in the presence of plasma diluted 1/10 from P1, P2, and their parents, or positive (samples from other APS-1 patients with previously confirmed auto-Abs neutralizing type I IFNs) and healthy controls from the general population. The luciferase activity, measured after stimulation with type I IFNs, is shown, after normalization against *Renilla* (used as internal control). Luciferase activity is induced by the stimulation of ISRE (interferon-stimulated response element) by type I IFNs. RLA, relative luciferase activity

COVID-19 convalescent plasma. His blood exams had significant abnormalities similar to those of his brother: lymphopenia (523/uL, normal range: 1200/uL to 6500/uL), increased CRP (280 mg/dL, normal range: < 10 mg/L), D-dimer (7792 ng/mL, normal range: < 500 ng/mL), and aspartate aminotransferase levels (55 IU/L, normal range: 15 to 40 IU/L). Following extubation, P2 experienced fine tremors on movement, ataxia with gait disturbance, and urinary and fecal incontinence. He was transferred to a COVID-19 general ward on day 25, where his symptoms gradually improved until the patient was discharged home on day 34. During P1 and P2's hospitalization, their mother was diagnosed with asymptomatic COVID-19.

Prior to SARS-CoV-2 infection, P1 had been diagnosed with asthma and hypothyroidism since 8 y.o., and was being treated with formoterol, budesonide, and levothyroxine with adequate control of both conditions. P2 was being treated for uveitis, alopecia areata, and onychomycosis. P2 also had a clinical history of urticaria and chronic diarrhea associated with persistent recurrent aphthous lesions (from 1 y.o. to present). Neither had been tested for auto-Abs to endocrine tissues or cytokines, or for mutations in *AIRE*. A diagnosis of APS-1 had not been considered because

neither displayed more than one of the three classical clinical features of the APS-1 triad (adrenal insufficiency, hypoparathyroidism, mucocutaneous candidiasis) [3].

Due to the severity of COVID-19 and the potential relevance of their medical histories, the Immunology Team started testing the siblings for IEI, particularly APS-1. Whole exome sequencing revealed a homozygous mutation (c.C796T- p.R257*) in the *AIRE* gene, which was confirmed by Sanger sequencing (Fig. 1D) for P1 and P2. Both parents shared the same mutation at the heterozygous state (Fig. 1D). Subsequent investigation for neutralizing auto-Abs against type I IFNs revealed that P1 had neutralizing auto-Abs to IFN-α2 and IFN-ω but not against IFN-β, while P2 to IFN-α2, IFN-ω, and IFN-β (Fig. 1E). Auto-Abs were not present in serum samples from either parent (Fig. 1E), for whom COVID-19 was respectively mild and asymptomatic. Considering the severity of pulmonary manifestation and APS-1 diagnosis, thanks to Prof Michail Lionakis' laboratory, lung-specific autoantibodies to KCNRG or BPIFB1 were tested and resulted to be negative for both patients.

Studies that identified mutations in genes in the type I IFN pathway [5] and the presence of neutralizing auto-Abs against type I IFN [4] indicate that type I IFN has a crucial role in the COVID-19 immune response. Specifically, it is important to note that SARS-CoV-2 has a high mortality (about 20%) among unvaccinated patients with neutralizing auto-Abs against type I IFN [4]. Although an international cohort of 22 APS-1 patients demonstrates clinical heterogeneity, from asymptomatic to lethal infection [3], the condition has direct implication for the clinical management of COVID-19 symptoms, including the use of plasma exchange or intramuscular administration of IFN-β1a for APS-1 patients who do not produce auto-Abs to IFN-β [3]. However, none of these approaches was considered for the treatment of COVID-19 infection in P1 and P2 because their APS-1 diagnosis had not yet been made. On the contrary, convalescent plasma was used in P1 and P2. Fortuitously, probably the convalescent plasma used in this case was not collected from individuals with neutralizing auto-Abs to type I IFN, which could have further worsened the patient's clinical condition. Nevertheless, the presence of antibodies to SARS-CoV-2 in convalescent plasma may have contributed to the recovery of P1 and P2.

To our knowledge, this is the first published case report of APS-1 diagnosed following life-threatening COVID-19 pneumonia, including pulmonary hemorrhage. IEIs are a group of underdiagnosed diseases worldwide. Considering the high prevalence of COVID-19, it is important to raise awareness about the significant risk to patients with IEIs, like APS-1, posed by COVID-19 itself. The diagnosis of underlying APS-1 will contribute to an individualized approach to treating COVID-19 by either preventing its evolution to a critical clinical course, or when dealing with an established life-threatening condition.

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Author Contribution LS, API, and CP made genetic diagnosis. NC, LS, API, and CP collected clinical data. PB performed autoantibodies analysis. COVID-SUD and CP designed the study. CP supervised the study. All authors edited the manuscript.

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Data Availability All data and materials can be obtained by contacting the corresponding author.

Declarations

Ethical Approval This study was approved by the Ethics Committee of the Hospital Pequeno Príncipe (approval number 4.572.430/2020). The Pequeno Príncipe Ethics Committee maintains an Office for Human Research Protections (OHRP)-approved Federalwide Assurance Committee (FWA00022927) with expiration date March 2, 2026 (http://ohrp.cit.nih.gov/search/search.aspx).

Consent to Participate Patients and their parents provided informed consent to participate to this study.

Conflict of Interest The authors declare no competing interests.

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