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A COVID-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy, Italy: Letter to the Editor

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Running head: **COVID-19 in APS-1**

We thank the European Society of Endocrinology (ESE) for providing the global endocrinology community with the statement on coronavirus disease (COVID-19) and endocrine disorders [1].

Regarding Addison's disease, the ESE statement affirms that there is no evidence that patients with adrenal insufficiency are at increased risk of contracting COVID-19, and there are no reported data on the outcomes of COVID-19 infection in adrenal-insufficient individuals.

Herein, we present the case of a 32-year-old woman with autoimmune polyglandular syndrome type 1 who developed COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); she lived closed to the first Lombardy cluster spreading from Codogno, Italy. Her clinical, immunological, and genetic patterns have been previously described (as patient no. 4) in a case series of autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED), also known as autoimmune polyendocrine syndrome type 1 (APS-1) [2]. In summary, she carries a homozygous R203X mutation in exon 5 of the autoimmune regulator (*AIRE*) gene, resulting in primary adrenal insufficiency (PAI), hypoparathyroidism, hypogonadism, ectodermal dystrophy, candidiasis, pernicious anemia, and gastrointestinal dysfunction.

Because her chronic hypoparathyroidism was inadequately controlled by standard treatment alone, the patient had been on hormonal replacement therapy with recombinant human parathyroid hormone (rhPTH) (1-84) since January 2018. After starting rhPTH (1-84) 50 µg once daily as a subcutaneous injection, she stopped calcitriol and calcium supplementation, having achieved optimal and stable serum calcium levels. Her treatment was specifically approved by the Italian Medicines Agency (AIFA) before the marketing authorization in Italy, and the patient underwent regular follow-up at the University of Turin (Piedmont, Italy).

On February 19, the patient presented to the emergency department of the Cremona Hospital (Lombardy, Italy) with fever, cough, and dyspnea. High-resolution computed tomography

showed multiple and bilateral ground-glass opacities of the lungs. Bronchoalveolar lavage fluid was positive for SARS-CoV-2. After an unsuccessful trial of non-invasive ventilation, her progressive respiratory failure required endotracheal intubation and mechanical ventilation. Therefore, she was transferred to the Intensive Care Unit (ICU) of San Matteo Hospital in Pavia (Lombardy, Italy) on February 22. Pharmacological treatment included empirical antiviral regimens with lopinavir/ritonavir and ribavirin, and prophylaxis with hydroxychloroquine, azithromycin, piperacillin/tazobactam and trimethoprim-sulfamethoxazole. Hemodynamic support required norepinephrine and dobutamine infusion; intravenous hydrocortisone was subsequently introduced at a dose of 300 mg divided in bolus injections over 24 h. After 6 days, the patient was extubated and started helmet continuous positive airway pressure.

During hospitalization, the intravenous glucocorticoid dose was gradually tapered and eventually switched back to the pre-admission oral regimen.

Unfortunately, the patient's rhPTH treatment was interrupted after admission. Although the summary of product characteristics (SmPC) does not include diseases requiring intensive care among reasons for discontinuation, rhPTH has not been studied in this specific clinical setting. Therefore, calcitriol and calcium supplementation were needed again, leading to suboptimal serum calcium concentrations. A few days before discharge, the patient resumed treatment with rhPTH (1-84), with sufficient 25-hydroxy vitamin D stores. Following the instructions in the SmPC, oral calcium supplementation was progressively reduced, and calcitriol supplementation was stopped within 4 days, as the patient achieved adequate serum calcium concentrations.

The patient was discharged on March 27, after 37 days of hospitalization, with complete resolution of symptoms and two negative tests for SARS-CoV-2 at an interval of 24 hours. Her last chest X-ray showed bronchiolitis obliterans organizing pneumonia-like features that will need radiological and clinical follow-up.

As of March 27, among 86,498 confirmed COVID-19 patients in Italy, 4.3% required intensive care (data from the Italian Civil Protection Department website http://www.protezionecivile.it – English version available; last access on May 20). Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs in Lombardy have been recently published; median length of stay in ICU was 9 days, and almost all the patients required respiratory support, mainly invasive mechanical ventilation (88%) [3]. As soon as information is also available on the characteristics of non-ICU hospitalized COVID-19 patients in Italy, it would be interesting to explore whether PAI may worsen COVID-19 outcomes, such as length of hospital stay, incidence of acute respiratory distress syndrome, and the need for CPAP therapy and mechanical ventilation.

The ESE statement notes the occurrence of impaired natural immunity function in PAI, with defective action of neutrophils and natural killer cells, independent of the underlying etiology [4], suggesting that exogenous glucocorticoids play a role in modulating the immune system.

Our case might not be considered a paradigmatic example of PAI; at variance with other forms of autoimmune Addison disease, patients with APS-1 have primary immunodeficiency, which explains the T-cell deficiency-related chronic mucocutaneous candidiasis. This feature has relevant clinical consequences; in fact, a recent prospective study showed that the Finnish APS-1 cohort had an increased mortality from infections (standardized mortality ratio 36; 95% CI 6.4–110) in comparison to the general population [5].

Similarly, an increased risk of infections has been observed also in other forms of Addison's disease, with autoimmune or genetic basis. However, in these forms, there is no clear demonstration of primary immunodeficiency, and the infection risk in Addison's disease could be linked to the types or doses of glucocorticoid replacement.

A population-based, retrospective, open cohort study in the United Kingdom from 1995 to 2018 showed that the Addison's disease cohort, compared with matched controls, had a higher

risk of infections of the lower respiratory (adjusted incidence rate ratio [aIRR] 2.11; 95% CI 1.64–2.69), urinary (aIRR 1.51; 95% CI 1.29–1.77), and gastrointestinal (aIRR 3.80; 95% CI 2.99–4.84) tracts, leading to increased use of antimicrobial agents in the primary care setting [6]. Interestingly, the same study showed no increased risk of infection in patients with untreated congenital adrenal hyperplasia (CAH) but an increased infection risk in patients treated for CAH, suggesting that non-physiological delivery of glucocorticoid replacement may represent a risk factor for the development of infections [6].

All of these findings are in line with the increased infection-related mortality described in the literature. A population-based, retrospective study on the Swedish population from 1987 to 2001 found that the mortality rate resulting from infections in Addison's disease was five times higher than expected (risk ratio 5.57; 95% CI 2.04–12.14 in women; risk ratio 6.57; 95% CI 2.56–15.17 in men) [7]. Another Swedish population-based, retrospective study from 1964 to 2004 reported increased mortality from infections in patients with autoimmune PAI (standardized mortality ratio 5.9; 95% CI 4.0–8.4) [8]. In Norway, a population-based, retrospective study from 1943 to 2005 reported an increase in mortality from infections associated with Addison's disease (10% among causes of death [95% CI 5.1–14.9] vs. 6.0% in the general population) [9].

The first prospective study investigating causes of death in PAI and secondary adrenal insufficiency (SAI) was based on real-world data from 2,034 patients (801 PAI, 1,233 SAI) in the European Adrenal Insufficiency Registry (EU-AIR; ClinicalTrials.gov identifier NCT01661387). The primary objective of EU-AIR is to monitor the safety of long-term treatment with once-daily, modified-release hydrocortisone and other glucocorticoid replacement therapies in adrenal insufficiency. Of the 26 deaths registered from 2012 to 2017, only 8% occurred to subjects with Addison's disease. Infections accounted for 15% of the deaths. With the limitations of a small percentage of autoimmune PAI among infection-related

deaths and the EU-AIR inclusion of European adrenal insufficiency patients treated in highly specialized centers, the results of this observational, open-ended study appear to be consistent with the previous evidence from retrospective studies [10].

In conclusion, it is not clear whether the disease per se or the hormonal replacement without physiological glucocorticoid rhythm plays a pre-eminent role in the impaired immune function of PAI. Our case report, along with the aforementioned studies, calls attention to the increased risk of infections in Addison's disease, with or without associated primary immunodeficiency. Further research worldwide is required to conclude that a predisposition to COVID-19 exists and to assess its adverse short- and long-term outcomes.

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