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COVID-19 y coma mixedematoso: reporte de dos casos y revisión de literatura

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SUMMARY

Myxedema coma (MC) is a rare condition associated with high mortality in patients with hypothyroidism. We report two cases treated at a tertiary care hospital in Lima, Peru, between 2020 and 2021. Both patients achieved a diagnostic score greater than or equal to 60 on the Popoveniuc et al. scale. The cases met severity criteria for COVID-19. They presented with hypothermia and bradycardia following intubation and the administration of sedation and analgesia. It remains unknown how SARS-CoV-2 triggers MC. Evidence suggests a biochemical and immunological relationship between this virus and thyroid function. Thyroid disease and hypothyroidism are associated with a poor prognosis in COVID-19. The objective of this report was to describe the increased incidence of MC associated with SARS-CoV-2 infection during the COVID-19 pandemic.

KEYWORDS: hypothyroidism; COVID-19; mortality.

RESUMEN

El coma mixedematoso (CM) es una condición rara de alta mortalidad en pacientes con hipotiroidismo. Se reportan dos casos tratados en un hospital de tercer nivel en Lima, Perú, durante el periodo de 2020 a 2021. Ambas pacientes obtuvieron una puntuación diagnóstica en el *score* de Popoveniuc et al. mayor o igual a 60. Los casos cumplieron criterios de severidad para COVID-19. Presentaron hipotermia y bradicardia tras la intubación y administración de sedación y analgesia. Aún se desconoce cómo el SARS-CoV-2 desencadenaría el CM. Existe evidencia que sugiere una relación bioquímica e inmunológica entre este virus y la función tiroidea. La enfermedad tiroidea y el hipotiroidismo se asocian a mal pronóstico en la COVID-19. El objetivo del reporte fue describir la mayor incidencia de CM asociada a la infección por SARS-Cov-2 durante la pandemia de COVID-19.

PALABRAS CLAVE: hipotiroidismo; COVID-19; mortalidad.

INTRODUCTION

Myxedema coma (MC) is the most severe manifestation of untreated hypothyroidism with multiple organ abnormalities associated with altered sensorium and constitutes a medical emergency. The estimated incidence was 0.22 per million people per year in Western countries. The main manifestations are altered sensorium and thermoregulatory dysfunction due to a precipitating event ⁽¹⁾. Diagnosis is established by clinical parameters and confirmed with thyroid function tests ⁽²⁾. The mortality rate has been reported to be 60-80% but is currently estimated at around 20-25%. ⁽¹⁾

Since the SARS-CoV-2 pandemic, it has been shown that the virus can affect any organ in the body ⁽³⁾. Multiple endocrinological alterations have been reported, including thyroid dysfunction during and after SARS-CoV-2 infection, such as subclinical and atypical thyroiditis ^(4,5). Few cases and only one single-centre case series of MC probably precipitated by SARS-CoV-2 pneumonia have been reported in the literature to date. ^(6,7)

We present two cases of MC in a tertiary hospital in Lima-Perú. The objective of this report was to describe the increased incidence of MC that occurred in relation to SARS-CoV-2 infection during the COVID-19 pandemic because it is a life-threatening condition.

PRESENTATION OF CASES

Patient 1

A 40-year-old female with asthma, prediabetes, and morbid obesity presented to the emergency department with an 8-day history of cough with expectoration, dyspnea, and a temperature of 39 °C. There was no preexisting condition of hypothyroidism, and the physical exam showed no evidence of goiter, prior surgical incision in the neck, or generalized edema. The COVID-19 molecular test was positive. She presented

ventilatory deterioration, so she was admitted to the ICU and entered IMV. After sedation, she presented hypothermia <35 °C and a heart rate of 30 beats per minute (Table 1). Pulmonary CT scan showed cardiomegaly and bilateral opacities compatible with acute respiratory distress syndrome (ARDS). Thyroid studies showed a thyrotropin (TSH) of 6.51 µU/ml (0.3–4.7 µU/ml), free thyroxine (FT4) of 0.59 ng/dl (0.8–1.7 ng/dl) (Table 2). MC was confirmed, and treatment with 100 mg IV hydrocortisone followed by LT4 400 µg oral loading dose was started. LT4 200 µg was given for two days and then a maintenance dose of 150 µg. The body temperature and heart rate increased within 24 hours in response to LT4. After improving clinical parameters, she was transferred to the internal medicine floor and was discharged after 33 days of hospital stay.

Patient 2

A 56-year-old female with rheumatoid arthritis and a preexisting condition of hypothyroidism on irregular treatment presented to the emergency room with a 6-day history of cough, headache and dyspnea. An antigenic test for COVID-19 was positive. Physical examination revealed crackles in both hemithorax, gastric outlet obstruction, circulatory and ventilatory deterioration, so she was admitted to the ICU. As soon as sedation started, she presented hypothermia <35 °C and bradycardia (Table 1).

Pulmonary CT scan showed involvement in 60% of the lungs. Thyroid studies showed a thyrotropin (TSH) of 8.25 µU/ml (0.3–4.7 µU/ml), free thyroxine (FT4) of 0.69 ng/dl (0.8–1.7 ng/dl) (Table 2), and MC was confirmed. Hydrocortisone in continuous infusion followed by 300 µg of rectal LT4 was administered. Even though a second rectal loading dose of 500 µg of LT4 was given due to no clinical improvement, she presented with multiorgan failure and died on day 11 of hospitalization.

Table 1. Clinical characteristics of patients with COVID-19 and myxedema coma on ICU admission.

Clinical characteristic	Case	
	1	2
Years	40	56
Sex	Female	Female
Previous diagnosis of hypothyroidism	No	Yes
Comorbidities	Prediabetes, morbid obesity, asthma	RA
MAP (mm Hg)	70	90
HR (beats per minute)	30	56
Rectal temperature (°C)	<35	<35
SatO ₂ % at admission	93	68
BMI (kg/m ²)	44	36,4
GCS	15	15
Popoveniuc Score	65*	60**
SOFA	6	8
APACHE II	8	22
Outcome	Alive	Death

DM2: type 2 diabetes mellitus; HTN: arterial hypertension; ESRD: end-stage renal disease; RRT: renal replacement therapy; RA: rheumatoid arthritis; MAP: mean arterial pressure; HR: heart rate; GCS: Glasgow Coma Scale; SOFA: Sequential Organ Failure Assessment score; APACHE II: Acute Physiology and Chronic Health disease Classification System II.

* Hypothermia (20 points), bradycardia (30 points), precipitating factor (10 points), anorexia (5 points).

** Hypothermia (20 points), bradycardia (30 points), precipitating factor (10 points).

Table 2. Laboratory tests of patients with COVID-19 and myxedema coma.

Laboratory test	Case	
	1	2
Hemoglobin (g/dl)	11.0	13.8
White blood cells (103/ μ L–109/L)	8,350	9,310
Platelets (103/ μ L–109/L)	163,000	249,000
Glucose (mg/dl)	99	84
Creatinine (mg/dl)	0.6	0.5
Glomerular filtration rate (CKD-EPI) (ml/min/1.73 m ²)	116	110
Sodium (mEq/L)	140	140
Total bilirubin (mg/dl)	0.2	0.3
CPR	32	96
LDH (U/L)	562	NST
INR	0.94	1.0
Procalcitonin	NST	NST
D-dimer (ug/ml)	0.9	0.5
Ferritin (ng/ml)	NST	417
pH	7.425	7.48
PCO ₂ (mm Hg)	30.2	28.2
PaFiO ₂ (mm Hg)	1310	85.9

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CPR: C-Reactive Protein; LDH: Lactate dehydrogenase; INR: International Normalized Ratio; NST: No sample taken.

DISCUSSION

We report two cases of MC in a tertiary hospital that managed patients with COVID-19 in Lima-Perú during the pandemic. The main characteristics of the patients were female sex and being overweight or obese. Besides, the diagnostic scoring system for MC established by Popoveniuc et al. ⁽²⁾ was used to define the cases; both patients had a diagnostic score of 60 or higher, and all the cases met the severity criteria for COVID-19 ⁽⁸⁾. Hypothermia and bradycardia occurred after intubation and administration of sedation and analgesia in the ICU in all patients. It is difficult to determine whether these symptoms overlap because of sedatives or autonomic dysfunction induced by SARS-CoV-2. ⁽⁹⁾

Since the COVID-19 pandemic, pathophysiological mechanisms have been investigated. Angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) are involved in the internalization of SARS-CoV-2. The highest levels of ACE2 expression and activity were found in the lungs, small intestine, kidney, salivary glands, testis, as well as in thyroid follicular cells ⁽¹⁰⁾. A meta-analysis concluded that thyroid dysfunction was associated with a higher risk of a composite adverse outcome (severity, admission to ICU, hospitalization, and mortality), significantly influenced by increasing age in the setting of COVID-19. ⁽¹¹⁾

Thyroid hormones modulate the innate and adaptive immune response under genomic and non-genomic mechanisms ⁽¹²⁾, so it is hypothesized that they could affect the response to the virus.

Patients with uncontrolled hypothyroidism have higher levels of systemic inflammation, as well as oxidative stress ⁽¹³⁾, suggesting that SARS-CoV-2 infection indirectly affects the thyroid gland through hyperactivity of the Th1/Th17 immune response and cytokine storm ⁽¹⁴⁾. SARS genome sequences have been detected in the cytoplasm of hypothalamic neurons, which also suggests involvement of the hypothalamic-pituitary-thyroid axis ⁽¹⁵⁾. Elevated levels of IL-6, present in severe forms of COVID-19 pneumonia, seem to suppress the production of free thyroxine (FT4) and free triiodothyronine (FT3).

Non-thyroid illness syndrome (NTIS) should be seen as an adaptive mechanism in response to critical illnesses. This syndrome is characterized by decreased plasma T3 and increased plasma reverse T3. Despite being low T3 and T4, TSH is typically

maintained within its normal range or is slightly decreased ⁽⁸⁾. Underlying mechanisms during inflammation decrease TSH pulses ⁽¹⁶⁾, changes in the concentrations of thyroid hormone binding proteins and transporters, upregulation of D2 deiodinases in hypothalamic tanycytes due to the activation of NFκB ⁽¹⁷⁾, and downregulation of D1 expression in the liver upon interleukin 1β stimulation. ⁽¹⁸⁾

In patients with a combination of NTIS and hypothyroidism, those who have hypothyroidism have high serum TSH concentration, but it might decrease during the acute phase of illness, especially if dopamine or high doses of glucocorticoids are given ⁽⁸⁾, which can explain why TSH levels in both patients were slightly increased.

Our report included two patients with MC who developed respiratory failure secondary to SARS-CoV-2 infection, requiring IMV. The mortality rate was 50%, consistent with the literature.

Factors associated with mortality due to MC were lower GCS scores, higher scores on the Acute Physiology and Chronic Health Assessment II (APACHE II) and Sequential Organ Failure Assessment (SOFA), persistent hypothermia, the use of sedatives, and the requirement for mechanical ventilation at admission. ⁽¹⁹⁾

The use of corticosteroids (dexamethasone 6 mg/day) interferes with the metabolism of thyroid hormones at multiple levels; it blocks peripheral conversion of T4 to T3, lowers T3 values and alters TSH secretion in a dose-dependent manner ⁽²⁰⁾. In addition, as part of the management of severe forms of SARS-CoV-2 pneumonia, the protocol included thromboprophylaxis with fractionated and unfractionated heparin, which displaces thyroid hormone from its binding protein and affects directly the measurement of FT4 and FT3. ⁽²¹⁾

To sum up, although a direct cause between SARS-CoV-2 infection and the development of MC cannot be explained, this report constitutes the first series of cases in Latin America. More studies are required to elucidate the direct effects of the virus on the thyroid and the risk factors for MC in patients with COVID-19.

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