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Malignant hyperthermia in severe COVID-19: 2 case reports

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Abstract

Malignant hyperthermia is a rare but potentially fatal condition. We present 2 cases of young patients with coronavirus disease 2019 (COVID-19) requiring intubation for hypoxic respiratory failure who both developed significant hyperthermia post intubation and were suspected to have malignant hyperthermia. However, the 2 patients had different responses to conservative management and dantrolene. These cases highlight the increased challenge imposed by intubation complications when managing patients with COVID-19.

Keywords: Case report, COVID-19, Malignant hyperthermia

Introduction

Patients with severe coronavirus disease 2019 (COVID-19) develop hypoxemia and acute respiratory distress syndrome requiring invasive mechanical ventilator support within a week of disease onset.[1] Such patients may also develop high grade fever (>39 °C or 102 °F) and genetic variations could account for differences.[2] In addition, these patients are more likely to be exposed to anesthetic agents and neuromuscular blockers such as succinylcholine for sedation and rapid-sequence intubation. Taking this into consideration, these patients are at high risk for developing malignant hyperthermia (MH) – a rare but potentially fatal condition. We herein, present 2 COVID-19 patients who developed severe hyperthermia after endotracheal intubation, which raised concern for MH.

Report

Patient 1

A 29-year-old woman with a body mass index (BMI) of 59.71 kg/m^2, type 2 diabetes mellitus (DM), and Hashimoto thyroiditis presented with progressive cough and dyspnea with known COVID-19 exposure in March 2020. Upon presentation, she was hypoxic (blood oxygen saturation [SpO_2] – 61% on room air) which improved to 75% with a nonrebreather (NRB) mask. SARS-CoV-2 was detected by rapid PCR. Persistent hypoxemia led to emergent intubation utilizing rocuronium. She received tocilizumab and was started on hydroxychloroquine. On hospital day (HD) 3, she was started on remdesivir and methylprednisolone. Due to clinical improvement, normalization of inflammatory markers (Fig. 1A) and a successful spontaneous breathing trial, she was extubated to high flow nasal cannula (HFNC) on HD8. However, the patient required reintubation for progressive hypoxia 3 hours later using succinylcholine. On HD11, after clinical optimization she was extubated to Bilevel Positive Airway Pressure support. Steroids were started for possible upper airway edema. Subsequently, she became anxious and was started on infusions of lorazepam and dexmedetomidine; she also received 1 dose of olanzapine. Nevertheless, on HD12, she became hypoxic with increased work of breathing, requiring a second reintubation using etomidate, succinylcholine, and rocuronium.

Although her SpO_2 improved to 92% on volume control ventilation mode, she remained tachypneic with a respiratory rate of 54, tachycardic and hypotensive, requiring 3 vasopressors. Her arterial blood gas showed pH 7.24, pO_2 93 mmHg, pCO_2 of 52 mmHg. Four hours post intubation, she became hyperthermic (maximum 108.2 °F), which was unresponsive to supportive management. Laboratory results demonstrated lactic acid 17 mmol/L, creatinine kinase (CK) 49,792 U/L, serum myoglobin 4720 mcg/L, ferritin 68,250 ng/mL, aspartate aminotransferase 5251 U/L, and alanine transaminase 2724 U/L. Given the temporal correlation of rise in the temperature and exposure to succinylcholine alongside the above-mentioned laboratory findings, an empiric diagnosis of MH was entertained. The patient received 3 loading doses of dantrolene (2.5 mg/kg), followed by maintenance doses. Moreover, although she had only received 1 dose of olanzapine, bromocriptine was started for possible

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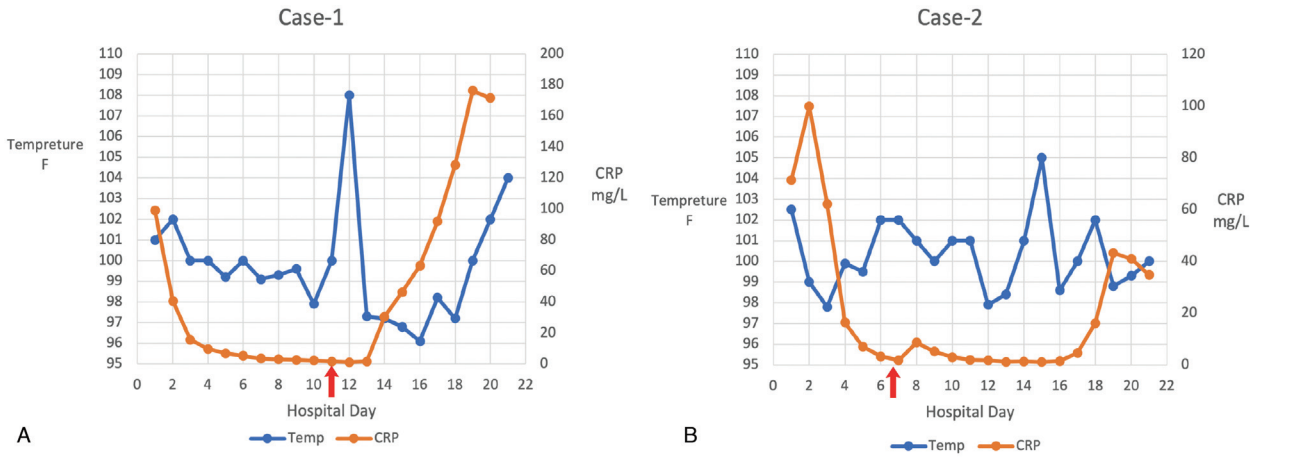

Figure 1. Hospital course. Red arrow indicates the time of third intubation for Case 1 and initial intubation for Case 2. CRP, C-reactive protein.

neuroleptic malignant syndrome (NMS). Six hours after the initiation of dantrolene, 12 hours postintubation, her temperature started down trending.

On HD13, she developed acute anuric renal failure requiring continuous veno-venous hemofiltration. She was empirically started on ceftazidime, metronidazole, vancomycin, and fluconazole; however, the infectious workup was negative. On HD15, she developed a coagulopathy manifesting as persistent bleeding from her endotracheal tube and central line catheter site; the platelet count dropped to 21 per microliter, raising concern for disseminated intravascular coagulation (DIC). On HD16, dantrolene was stopped given the worsening of transaminitis. She was started on steroids to address a possible late inflammatory response to COVID-19, even though her inflammatory markers prior to reintubation had normalized. On HD17, she again became febrile and repeat blood culture grew Candida Glabrata; her fluconazole was switched to anidulafungin. She remained minimally responsive off sedatives. Due to multi-organ failure and poor prognosis for meaningful neurological recovery, and per patient's family decision, she was transitioned to "Comfort Measures Only" and died on HD21.

Patient 2

A 31-year-old woman with a BMI of 45 kg/m^2 and type 2 DM presented in April 2020 with 10 days of subjective fever, cough, myalgia, and progressive dyspnea. She was hypoxic with SpO_2 of 50% on room air. SARS-CoV-2 infection was diagnosed by rapid PCR. She was started on a NRB mask and subsequently HFNC. She received 1 dose of tocilizumab and was started on hydroxychloroquine. During the next 4 days, she became afebrile with improvement in her inflammatory markers (Fig. 1B). However, her respiratory status remained precarious with SpO_2 of 90% despite maximum HFNC and prone positioning. On HD5, she was started on empiric broad-spectrum antibiotics and therapeutic anticoagulation for possible pulmonary embolism. On HD6, given worsening of her respiratory status, she underwent intubation, using succinylcholine, propofol, and rocuronium.

Seven hours after intubation, her temperature rose to 102 °F, which was unresponsive to acetaminophen and cooling with ice packs. She also developed hypercarbia (pCO_2 57 mmHg) and hypotension requiring pressor support. During this time, she had been tachypneic with a minute ventilation of 12 L. She was kept on broad-spectrum antibiotics, despite an unrevealing extensive infectious workup. Her temperature remained elevated with a maximum of 103.8 °F, 19 hours postintubation. Her physical exam revealed no rigidity; however, the serum CK rose to 1355 U/L and the myoglobulin to 953 ng/mL. Myoglobin was also detected in the urine. On HD7, an empiric trial of dantrolene was initiated for suspected MH post exposure to succinylcholine. She remained hypercapnic ($pCO_2 > 60$ mmHg), tachycardic, and febrile (102 °F) despite 4 bolus doses of IV dantrolene (2.5 mg/kg) every hour. Given the lack of response to dantrolene and persistent hypotension, dantrolene was discontinued. She completed two 8-day courses of broad-spectrum antibiotics with multiple negative infectious workups in 18 days. The patient was evaluated for possible drug related fever with a change in sedatives, including a trial off dexmedetomidine and change in her antibiotics; however, she remained persistently febrile. On HD16, her temperature rose to 105 °F despite intermittent use of supportive measures including Arctic sun. On HD22, she was started on stress dose hydrocortisone because of concern for adrenal insufficiency, given her persistent hypotension. On HD23, her oxygenation improved and she was extubated. Postextubation, she remained on phenylephrine and had low-grade fevers. On HD24, 2 days into the steroid course her fever started to resolve. On HD 26, phenylephrine was discontinued and she was transferred to the floor with improved oxygenation and resolution of fever. On HD35, she was discharged from the hospital without any neurologic sequela of high fevers.

Discussion

Malignant hyperthermia is a condition which is usually associated with inhaled anesthetic agents or depolarizing neuromuscular blockers such as succinylcholine in

genetically predisposed individuals.[3] It is rare, with an incidence ranging from 1 in 200 to 1 in 100,000 administered anesthetics.[4] The increased need for intubation and treatment with neuromuscular blockers in patients with severe COVID-19, as well as possible genetic susceptibility, can place patients with COVID-19 at increased risk for this rare, but potentially fatal complication.

Our COVID-19 patients developed hyperthermia post-intubation with succinylcholine, accompanied by hypercarbia, tachypnea, and elevations of the CK and myoglobin, all of which suggested MH.[3] However, muscle rigidity, another hallmark of MH, was absent in our patients. Using an MH clinical grading scale,[5] the first patient had an MH rank of 6 (almost certain). Even though she had previous exposure to succinylcholine without any complications, 50% of patients who develop MH might have prior uneventful exposures to the triggering agent.[6] The second patient, although she became hyperthermic after intubation, never developed multi-organ dysfunction or DIC and had no significant response to dantrolene; thus, she had an MH rank of 4 (somewhat greater than likely). However, as the diagnosis of MH is based on clinical suspicion, both of our patients appropriately received dantrolene as delayed initiation of treatment could result in complications and fatality.[3]

The presentation of these 2 patients, although similar in some ways, seems to reflect different courses and etiologies. The first patient most likely had MH given her positive response to dantrolene. In contrast, the second patient appeared to have persistently high fever due to COVID-19 infection exaggerated by hypocortisolemia, which is supported by the lack of response to dantrolene.

Whether COVID-19 infection played an independent role in our patients is unclear. Hyperpyrexia can be a late complication of COVID-19 due to brain involvement, inflammatory response, or adrenal insufficiency. Similar to other critical conditions, severe COVID infection can affect the hypothalamic–pituitary–adrenal axis, causing adrenal insufficiency.[7,8] Thus, in the second patient, COVID-19 infection could have caused adrenal insufficiency by promoting fever, which subsided after the initiation of steroids.

Aside from MH, a diagnosis of drug related fever was entertained and excluded. Even though the first patient received 1 dose of olanzapine, the incidence of NMS with atypical antipsychotics is rare.[9] Both of our patients were on therapeutic dose of anticoagulation which made venous thromboembolism an unlikely cause, even though it is common in patients with COVID-19.[10] Neither patient was found to have other infections causing hyperthermia. In case 1, initial hyperthermia post intubation subsided for 4 days before she spiked another fever and the repeat blood culture at that time revealed candidemia.

Although MH is rare, the COVID-19 pandemic has led to increased rates of intubation and the concomitant use of neuromuscular blockers such as succinylcholine, which could lead to more cases of MH. However, other possible etiologies of hyperpyrexia in these patients including severe inflammatory response or adrenal insufficiency can make it challenging to make a diagnosis of MH. Unresponsiveness to dantrolene treatment should prompt consideration for other diagnoses, such as adrenal insufficiency and drug related fever.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author contributions

SEA, RN, PR, AC, and MDS formulated the current study idea. SEA, RN, and PR extracted the cases data and wrote the first draft of the manuscript. AC and MDS critically commented on the manuscript, revised, and approved the final version.

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Ethical approval of studies and informed consent

Written informed consent was obtained from the patients/surrogates. This manuscript has the consent of the patients/surrogates for the use of data and for the publication of the data that appear in the article. Ethics Committee of Yale New Haven Hospital states that the publication of case reports is exempt from ethics approval. All authors have read the manuscript and approved its submission to the journal.

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Availability of data and materials

Available upon request.

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