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CASE REPORT

The Importance of Early Recognition and Management in Patients with Suspect of Malignant Hyperthermia: Case Report

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Abstract

Background: Malignant hyperthermia (MH) is a rare pharmacogenetic syndrome characterized by a severe hypermetabolic reaction after the administration of several halogenated inhalational anesthetics or depolarizing muscle relaxants such as succinylcholine, or both. MH is related to the exacerbated release of calcium in the myoplasm causing rhabdomyolysis. This case describes a rapid onset MH (15 minutes) after induction and intubation of general anesthesia.

Case Report: Male, 30 years old, 85 kg, 76 cm tall and 119 kg, admitted with pancreatitis, to undergo endoscopic retrograde cholangiopancreatography and passage of a biliary prosthesis. Anesthetic induction with 200 µg of fentanyl, 80 mg of lidocaine without vasoconstrictor, 200 mg of propofol, 100 mg of succinylcholine and sevoflurane. Fifteen minutes tachycardia, hypoxemia, increased $EtCO_2$, muscle stiffness. MH diagnostic hypothesis, arterial blood was collected, the entire respiratory system was changed, dantrolene and an ice pack were started. Gradual improvement, he was sent to the ICU where he remained for three days, being extubated on the 2nd day, discharged to the 4th to the ICU, and hospital discharge on the 5th day.

Conclusion: This case showed the MH with rapid diagnosis and despite being a potentially fatal disease, the rapid administration of dantrolene, together with maintenance doses, clinical control of symptoms, allowed a favorable outcome, with hospital discharge on 5th postoperative day. The patient refused to undergo genetic testing and that of family members.

Keywords: Inhalational Anesthetics, Malignant Hyperthermia, Dantrolene, Anesthetic Complications.

Key Points

What is already known?

- Malignant hyperthermia is defined as a progressive life-threatening hyperthermic reaction occurring during general anesthesia.
- Malignant hyperthermia has an underlying genetic basis.
- There are no specific clinical characteristics of the disease, and it can be fatal unless it is recognized and treated immediately.

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What This Case Report Adds

- The diagnosis was made quickly, and life support measures were started simultaneously with the drug.
- MH may occur at any time during anesthesia as well as in the early postoperative period, in this case it occurred 15 minutes after induction and intubation.
- The diagnosis was made immediately, which resulted in a favorable outcome, with hospital discharge on the 5th day.
- The patient refused to undergo genetic testing and that of family members.

1. Introduction

The history of malignant hyperthermia (MH) in April 1960 in Australia, when a 21-year-old student was hit by a car and suffered open fractures in the right tibia and fibula and published as a Case Report in 1962 [1]. In a recent review MH was defined as is a pharmacogenetic disorder that manifests as a hypermetabolic response to potent inhalation agents (such as halothane, isoflurane, sevoflurane, desflurane), the depolarizing muscle relaxant, succinylcholine, and rarely in humans, to stressors such as vigorous exercise and heat [2].

The incidence of MH during the anesthetic procedure varies between 1:10,000 and 1:250,000 anesthesia's performed [3], occurring more in men than in women (2:1) with children under 15 years of age accounting for around 52.1% of all reactions [2]. The associated mortality rate was around 60% before the advent of dantrolene, standard therapy for malignant hyperthermia, but is now 1.4% if diagnosed early and immediate treatment is instituted [4].

Early diagnosis of MH and immediate introduction of treatment can prevent patient death. The objective of this case report is to describe the appearance of MH in a young, previously healthy patient who underwent endoscopic retrograde cholangiopancreatography. Early suspicion of the disease and rapid institution of specific treatment were essential for a positive outcome for the patient.

2. Case Report

This case report was registered on Plataforma Brazil (CAAE: 66686322.5.0000.0082) and approved by the Ethics and Research Committee (Number: 6.081.459). The patient signed the Informed Consent Form for the procedure and publication. Male patient, 30 years old, 176 cm tall and 119 kg (BMI 38.4 kg/m^2), ASA lll, hospitalized 11 days ago due to severe acute pancreatitis of biliary etiology, admitted to the surgical center for surgery endoscopic retrograde cholangiopancreatography (ERCP) with prosthesis placement to resolve persistent jaundice. Exams from the day before the surgical procedure showed an increase in alkaline phosphatase, c-reactive protein, pyrurive and oxalaacetic transaminase (Table I).

Table 1. *Assessment of exams before surgery*

Hemoglobin	10.1 g/dL
Hematocrit	29%
Platelets	238,000/mm^3
Sodium	130 mEq/L
Potassium	3.0 mEq/L
Urea	11 mg/dL
Creatinine	0.4 mg/dL
Pyruvic transaminase	81 U/L
Oxaloacetic transaminase	64 U/L
Alkaline phosphatase	233 U/L
C-reactive protein	177.01 mg/L

During the pre-anesthetic visit, the patient denied drug allergies, comorbidities, smoking, alcohol consumption and drug addiction and did not use any ongoing medication. He also reported never having undergone any surgical procedure previously and there were no reports of anesthetic complications among first-degree relatives. Routine monitoring electrocardiogram (CM5), heart rate (100 bpm), noninvasive pressure measurement (140x80 mmHg), pulse oximetry (89%) in horizontal supine position in room air, afebrile, dehydrated (1+/4+), jaundiced (3+/4+), with previous central venous access in the right internal jugular vein.

Pre-oxygenation was started followed by induction, using the following medications: 200 µg of fentanyl, 80 mg of lidocaine without vasoconstrictor, 200 mg of propofol and 100 mg of succinylcholine. After fasciculation presented by the patient, orotracheal intubation was performed with a #7.5 wired endotracheal tube, capnography curve and vesicular murmurs were observed bilaterally without adventitious sounds on lung auscultation, with subsequent administration of sevoflurane to maintain general anesthesia.

Fifteen minutes after induction and intubation, the surgical procedure began with unsatisfactory oxygen saturation ranging between 86 - 92%, increasing heart rate, reaching values of 130 bpm, without changes in the electrocardiographic tracing and high initial capnography values (60 mmHg to 75 mmHg), which also progressed increasingly throughout the surgery. Initially, the diagnostic hypothesis of pulmonary atelectasis was raised, with no reason for obesity, but high capnography values were maintained despite alveolar recruitment maneuvers or changes in ventilatory parameters. There was no evidence of air leakage through the tracheal tube, with the cuff adequately inflated.

The diagnostic hypothesis of MH was suggested, and appropriate therapeutic management of the disease was promptly instituted. Arterial blood gases were collected and administration of dantrolene was started, with a loading dose of 2.5mg/kg, totaling 15 vials of dantrolene (20mg per vial). All breathing systems impregnated with sevoflurane were changed (anesthesia machine tracheas, filters, capnograph and mechanical ventilator), maintaining the anesthetic plan with propofol in a continuous infusion pump (3µg/ml), with a body temperature of 38°C.

Body cooling measures were initiated with ice packs distributed across the chest, abdomen and cervical region, large peripheral venous access was obtained (#16G), followed by vigorous hydration with a total of 2,000 mL of crystalloid (0.9% saline) in the first hour from the beginning of measurements, 250 mL of 20% Mannitol and 80 mg of IV furosemide. After 30 minutes of implementing the measures, the patient demonstrated a progressive improvement in hemodynamic patterns ($SatO_2$, MAP, HR) in addition to a progressive decrease in capnography values.

The blood gas analysis results showed respiratory acidosis with pH of 7.28, PO_2 of 80.1 mmHg, PCO_2 of 75.4 mmHg, Base Excess of 6.1 mEq/L and $SatO_2$ of 92%, Hb 10.9 g/dL, Ht 38.7%, Na 131mEq/L, K 3.2 mEq/L, Cl 92.8 mEq/L, Ionic Ca 1.053 mEq/L. The patient was then kept intubated, without the use of vasoactive drugs, maintained with sedoanalgesia with propofol and dantrolene in a maintenance dose (1mg/kg every 6 hours for 48 hours), being transferred to an ICU bed where he remained for 3 days. The results of blood gas analysis and tests performed at the time of diagnosis, on the 1st and 2nd day in the ICU and after discharge to the room on the 1st and 2nd day (Table II, Table III).

Within 24 hours in the ICU, the patient was extubated without complications, remaining afebrile, jaundiced 2+/4+, eupneic, hemodynamically stable, SaO_2 at 99% with an oxygen catheter at 2L/min, started on a light diet (water, tea, and gelatin), maintaining choluria, without compromising renal function (Urea:16 mg/dL and Creatinine:0.7 mg/dL) and positive fluid balance of +1,503 mL. Other laboratory tests remained within normal limits, such as potassium (K) and creatinephosphokinase (CPK), which did not show significant changes after the incident. Potassium of 3.2 mEq/L went to 3.5 mEq/L and CPK of 30 U/L, with no previous CPK values for comparison.

Table 2. *Evaluation of gasometry intraoperative and postoperative*

Gasometry	Intraoperative	Room 1st	Room 2nd
Collect	Arterial	Venous	Arterial
pH	7.28	7.35	7.49
pCO_2 (mmHg)	75.4	49.0	35.1
pO_2 (mmHg)	80.1	53.4	84.1
HCO_3 (mmol/L)	34.8	27	26.3
Basic excess	- 6.1	0.6	3
Oxygen saturation (%)	92	82.5	97.3

Table 3. *Evaluation of exams during hospitalization*

Exams	ICU 1st	ICU 2nd	Room 1st	Room 2nd
Hemoglobin (g/dL)	10.2	9.2	9.1	8.7
Hematocrit (%)	29.6	28.7	29	27.9
Platelets (n/mm^3)	271,000	287,000	355,000	404,000
INR	1.32	1.28	1.36	1.52
Prothrombin time (s)	14.1	13.7	14.5	16.2
Activated partial thromboplastin time (s)	26.1	28.3	28.6	35.3
Magnesium (mg/dL)	2.2	- - -	- - -	- - -
Sodium (mEq/L)	131	132	132	132
Potassium (mEq/L)	3.9	3.5	3.6	3.4
Urea (mg/dL)	20	15	16	17
Creatinine (mg/dL)	0.7	0.7	0.7	0.7
Pyruvic transaminase (U/L)	62	41	66.4	32
Oxaloacetic transaminase (U/L)	59	41	50.9	33
Alkaline phosphatase (U/L)	233	- - -	233	- - -
Total bilirubin (mg/dL)	8.6	4.6	3.5	3.0
Direct bilirubin (mg/dL)	8.5	4.3	3.4	2.9
Indirect bilirubin (mg/dL)	0.1	0.3	0.1	0.1
C-reactive protein (mg/L)	218.12	- - -	- - -	132.11
Ionic calcium (mmol/L)	5.2	- - -	- - -	1.024
Creatinephosphokinase (U/L)	32	- - -	- - -	32

Due to the intense involuntary contracture presented by the patient, it was observed intense difficulty in carrying out the procedure by the surgeon through the endoscope. Despite the surgical difficulties, the procedure lasted 35 minutes. Patient transferred to the ward and antibiotic therapy ended and was hospital discharge on the 5th day and referred for an in vitro muscle contracture test six months after the incident. The patient and family members received written explanations regarding the probable condition presented, its genetic nature and the need for investigation among first-degree relatives.

After being discharged from hospital every month for a year, we contacted the patient to perform a muscle biopsy, however the post-biopsy guidelines are quite restrictive, he would have to rest for at least five days. Therefore, to date the biopsy has not been performed.

3. Discussion

We are reporting on the case of a young male who had a MH during ERCP where the diagnosis was made almost immediately and with presented a positive outcome without leaving any sequelae. The present case began 15 minutes after induction and intubation of anesthesia with hypoxemia and increased $EtCO_2$, heart rate, and muscle contraction. He responded well to the administration of dantrolene, and measures to reduce hyperthermia with ice, increase $EtCO_2$ by changing the entire anesthesia device and removing sevoflurane and reducing muscle contracture.

Since 1991, there has been a telephone hotline service for MH in Brazil, available 24 hours per day, showed that the number of calls per year is still low [5]. In Brazil, despite the hotline service created a long time ago, there is no current data on the incidence of MH. However, under evaluation in the year in 2009 [5], approximately 1:50,000 episodes occurred in patients undergoing general anesthesia, which is how much would be expected 77 cases reported in this period [6]. The real prevalence of susceptibility to MH is always underestimated due to the various forms of this disease.

MH is a pharmacogenetic disorder that manifests as a hypermetabolic response to exposure to triggering agents: halogenated inhalational anesthetics (halothane, enflurane, isoflurane, sevoflurane, desflurane) and succinylcholine, a depolarizing neuromuscular blocker [2]. MH reactions may present with mild, nonspecific symptoms that may go unnoticed by medical staff [3]. Furthermore, individuals susceptible to MH may undergo several uneventful anesthetic procedures (on average three) before developing a fulminant MH reaction [3]. An important feature of

MH is calcium disturbance by defects in genes and proteins involved in excitation-contraction coupling dihydropyridine-ryanodine receptor complex, which acts as the main calcium release channel in muscles [7]. Malfunction of this complex causes constant activity of the channel function. This consequent overload of calcium in the sarcolemma induces maintained muscle contraction leading to sudden and potentially lethal rhabdomyolysis.

The laboratory changes that occurred were respiratory and metabolic acidosis, hyperkalemia, because of the accelerated muscle injury process, increased alkaline phosphatase, c-reactive protein, without increased creatine phosphokinase. In this patient there was also no appearance of disseminated intravascular coagulation. Probably rapid diagnosis and therapy with dantrolene and measures to reduce hyperthermia contributed to the favorable outcome of this patient.

Guidelines published in 2021 on MH, suggest that there are no specific clinical features of MH, and the condition may prove fatal unless it is recognized in its early stages and treatment is promptly and aggressively implemented [8]. Succinylcholine, a depolarizing muscle relaxant, can produce an explosive episode of malignant hyperthermia within 5 minutes of exposure [8]. The initial dose of dantrolene is 2-3 mg/kg with a further 1 mg/kg every 5 min until treatment goals are reached. The dose of dantrolene used was 2.5mg/kg, therefore within the 2021 guideline [8]. Associated with dantrolene, ice packs were placed, with a gradual decrease in temperature. Dantrolene was suspended once there was hemodynamic stability for 24 hours, core temperature lower 38ºC, decreased alkaline phosphatase, absence of myoglobinuria and disappearance of muscle rigidity.

The insidious onset of MH in a patient admitted for a hepatic tri-segmentectomy to treat a Klatskin's tumor, that progressed with greater severity than reported in other cases, culminating in the patient's death on the 7th postoperative day [9]. In this case report, 15 minutes after administration of succinylcholine and sevoflurane, increased heart rate, hypoxemia, increased $EtCO_2$ and muscle contracture, with immediate treatment resulted in a favorable outcome, hospital discharge on the 5th day.

4. Conclusion

MH may occur at any time during anesthesia as well as in the early postoperative period. In the patient, it started almost immediately after induction and intubation. Exposure to triggering agents in these patients may lead to unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space, resulting in an acute MH crisis. According to new guidelines, management of an MH crisis should immediately focus on stopping all trigger agents, hyperventilating with 100% oxygen at high flow, changing to a non-trigger anesthesia, asking the surgeon for termination or postponement of surgery, and disconnecting the vaporizer. Temperature control is essential, which was helped by dantrolene and the use of ice packs, at key points to reduce the temperature, which was done in this patient. Regarding the responsibility of the medical team, although rare, MH is a predictable pathology, but the predictability of the disease must be assessed on a case-by-case basis, and the conduct taken in this patient was responsible for the favorable outcome. A negative fact is that even during a year with monthly contact, the patient and family members did not want to take the test for family diagnosis.

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