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Diagnostic Challenges in Malignant Hyperthermia and Anesthesia-Induced Rhabdomyolysis: A Case Study

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Patient: Female, 42-year-old

Final Diagnosis: Malignant hyperthermia

Symptoms: Hypercarbia • rhabdomyolysis • masseter spasm

Clinical Procedure: —

Specialty: Anesthesiology • Critical Care Medicine

Objective: Rare disease

Background: Malignant hyperthermia (MH) and anesthesia-induced rhabdomyolysis (AIR) are rare, yet life-threatening complications that need prompt therapeutic actions and logistic preparedness for treatment success. Both conditions are triggered by general anesthetics, particularly volatiles and depolarizing muscle relaxants. In comparison with MH, which is an inherited pharmacogenomic disease of calcium channel receptor subpopulation and arises only after trigger exposure, AIR has been described mostly in patients with muscular dystrophies. In perioperative settings, rhabdomyolysis is also observed during propofol infusion syndrome, neuroleptic malignant syndrome, and cocaine, heroin, and alcohol intoxication. Despite their diverse etiology, the main clinical manifestations of MH and AIR overlap: a hypermetabolic state, hyperpyrexia, hypercarbia, acute renal failure, and hyperkalemia progressing to cardiac arrest, making the therapeutic approach to the patient extremely difficult.

Case Report: We present an unenviable and challenging clinical scenario of an obligatory general anesthesia with endotracheal intubation in a patient with difficult airways for breast conserving onco-surgery with simultaneous targeted intraoperative 20 Gy irradiation. The case was complicated even further by coincident suspicious clinical presentation of a mild and self-limited hypercarbia, together with a protracted rhabdomyolysis, without hyperpyrexia. Given the atypical and scarce clinical presentation leading to diagnosis uncertainty of MH or AIR, which was proved only after receiving the genetic results, dantrolene was not administered, and the patient underwent successful supportive treatment.

Conclusions: The study points to the diagnostic dilemma – crisis event MH or AIR – and raises issues about possible preoperative preventive measures and treatment options in patients with an uncertain diagnosis.

Keywords: Dantrolene • Hyperthermia • Rhabdomyolysis • Succinylcholine

Abbreviations: **MH** – malignant hyperthermia; **AIR** – anesthesia-related rhabdomyolysis; **ETI** – endotracheal intubation; **RYR1** – Ryanodine receptor-1; **CACNA1S** – calcium voltage-gated channel subunit alpha 1 S; **STAC3** – SH3 and cysteine-rich domain 3; **CK** – creatine kinase; **TARGIT-IORT** – targeted intraoperative radiotherapy

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2939 2 — 30

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Introduction

Malignant hyperthermia (MH) is a rare life-threatening hereditary disorder, which represents a hypermetabolic reaction to currently used halogenated volatile anesthetics and to succinylcholine [1-3]. It is an autosomal dominant disease with main mutations in *RYR1*, *CACNA1S*, and *STAC3* genes [3-5] encoding for abnormal ryanodine receptor (RYR) and dysregulated excitation-contraction coupling in skeletal muscles. Typically, trigger exposure leads to an unregulated massive passage of calcium ions from the sarcoplasmic reticulum into the intracellular space, combined with a transient receptor potential-mediated transsarcolemmal canonical Ca^{2+} influx. Given the excessive amount of intracellular calcium, an exaggerated muscle contraction throughout the body musculature (generalized muscle rigidity) leads to a marked hypermetabolic state with depletion of energy stores, hyperthermia, hyperkalemia, rhabdomyolysis, acute renal failure, and profound acidosis [2,6]. In comparison, anesthesia-induced rhabdomyolysis (AIR) is also a rare anesthetic complication and represents a rapid breakdown of skeletal muscles, with massive release of sarcoplasmic content into the bloodstream: electrolytes and proteins, notably creatine kinase (CK), lactate dehydrogenase, and potassium [6-9]. Succinylcholine and volatiles are the main AIR triggers in patients with muscular dystrophies. In perioperative settings, rhabdomyolysis also arises during propofol infusion syndrome in otherwise healthy patients after prolonged propofol administration, despite a potential risk in patients with mitochondrial myopathy [10]. Non-pharmacological rhabdomyolysis could be triggered by physical (trauma, crush-syndrome, burns, electrocution, seizures, compression, and compartment syndrome), chemical (toxins, alcohol, carbon monoxide or cyanide poisonings, heroin, and cocaine), and biological factors (hypoxia, infections, polymyositis, dermatomyositis, and thyroid disorders) [11]. AIR is presented by a diverse clinical picture, ranging from life-threatening hyperkalemia, with cardiac arrest, acute renal failure, and compartment syndrome, to asymptomatically increased CK, electrolyte, and enzyme imbalances [7,8,12].

Breast cancer is the most common heterogenous oncological disease in women worldwide, accounting for more than 2.3 million new cases in 2020, according to the Global Cancer Observatory database [13]. Targeted intraoperative radiation therapy (TARGIT-IORT) or delivering a high dose of radiation therapy to the fresh tumor bed immediately after lumpectomy by a multidisciplinary team of surgeons, anesthesiologists, radiation oncologists, and physicists during breast-conserving surgery is a safe and effective technique for early breast cancer, which is designed to serve as a replacement for whole breast external beam radiotherapy in low-risk patients [14,15]. This approach allows for precise irradiation of tissue where the possibility of remaining vital tumor cells is highest while sparing nearby vital organs, such as the heart and lungs. Unfortunately, due to the sophisticated procedure, there are long waiting lists in most centers worldwide. Giving new insights on a multifaceted MH picture, treatment options without dantrolene, and uneventfully performed temperature-sensitive procedure, the presented case is valuable and unique for the medical literature.

Case Report

A 42-year-old patient with short neck and obesity (thyromental distance 6 cm; Mallampati III; body weight of 98 kg; body mass index of 38.2 kg/m^2) received a diagnosis of a 20-mm tumor mass in the upper outer quadrant of the right breast, which was defined as low-differentiated invasive ductal cancer G3, (estrogenic receptor, negative; progesterone receptor, negative; human epidermal growth factor receptors 2, 3+/positive; inhibition constant 67, 80%) by core-needle biopsy. The patient was a known current heavy smoker, reporting more than 20 pack-years. The medical record showed that the patient underwent short general anesthesia in the past for a hysteroscopy, with no clear mention of administered anesthetics or specific events during the procedure. All laboratory test results were unremarkable, and the patient denied any knowledge of anesthesia-related accidents in relatives in ascending and descending lines. There were no signs of axillary nodal involvement, and the patient was referred for a breast-conserving surgery with simultaneous TARGIT-IORT with a 20-Gy cumulative dose.

After routine premedication (10 mg metoclopramide, 40 mg esomeprazole, and 12 mg dexamethasone) and pre-oxygenation, general anesthesia was induced intravenously (1.5 µg/kg fentanyl, 2 mg/kg propofol, and 1 mg/kg succinylcholine). Given the Cormac Lehane Class III-IV grade found during laryngoscopy, and an unsuccessful attempt for endotracheal intubation (ETI), the anesthesiologist (fellow with 2 years clinical experience) called for help and woke the patient up. The consultant anesthesiologist (30 years clinical experience), who managed the patient afterward, met a fully awake patient, without any complaints or pathological symptoms. After a second intravenous induction of 1.5 µg/kg fentanyl, 2 mg/kg propofol, and 1 mg/kg succinylcholine (a time lapse between the first and the second succinylcholine dose of approximately 5 to 7 min), limited mouth opening of approximately 2 cm was noted; however, the patient was successfully and atraumatically intubated. Thereafter, a balanced general anesthesia was started with sevoflurane. Mechanical ventilation was instituted with tidal volumes of 7 mL/kg, respiratory rate 12/min, minute ventilation 80 mL/kg/min, PEEP 5 mmH_2O, and P_{peak} 16 mmHg. An end-tidal carbon dioxide ($ETCO_2$) of 48 mmHg was noted on a monitor 3 min after ETI. The minute ventilation was increased to

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Table 1. Arterial blood gas analysis of a patient with malignant hyperthermia.

Parameter (units)	10 Min after ETI; FiO_2 50%	30 Min after ETI; FiO_2 50%	40 Min after ETI; FiO_2 50%	4 h after ETI – admission in ICU; FiO_2 50%	24 h after intubation; FiO_2 21%	Reference values
ctHb (mg/dL)	–	13.6	13.2	12.3	13.7	11.5-16
PO_2 (mmHg)	–	257.8	248.0	176.5	99.1	80-100
$ETCO_2$ (mmHg)	59	54.7	35	–	–	–
PCO_2 (mmHg)	–	59	37.1	25.1	36.5	35-45
pH	–	7.24	7.34	7.46	7.50	7.35-7.45
$SatO_2$	–	99.70%	99.80%	99.70%	98.40%	75-99
BE	–	-5.00	-3.80	-3.60	-0.60	-0 to +3
BB (mmol/L)	–	41.71	42.2	43.27	46.85	44-48
HCO_3 (mmol/L)	–	22.8	21.5	18.1	20.70	21-26
Lactate (mmol/L)	–	3.1	1.8	1.65	1.69	<2
Temperature (°C)	37.2	37.2	37.2	37.2	37.2	<37.5
INR		0.99	0.86	0.97	1.02	0.8-1.1

FiO_2 – fraction of inspired oxygen; ETI – endotracheal intubation; ICU – Intensive Care Unit; ctHb – concentration of total hemoglobin; PO_2 – partial oxygen pressure in arterial blood; PCO_2 – partial pressure of carbon dioxide in arterial blood; $ETCO_2$ – level of carbon dioxide released at the end of an exhaled breath; Sat O_2 – oxygen saturation in arterial blood; BE – base excess; BB – total buffer base; HCO_3 – concentration of bicarbonate; lactate – concentration of lactic acid; INR – international normalized ratio.

Table 2. Biochemical analysis of the patient with malignant hyperthermia.

Parameter (units)	30 Min. after ETI	40 Min. after ETI	4 h after ETI admission in ICU; FiO_2 50%	24 h after ETI; FiO_2 21%	48 h after ETI; FiO_2 21%	Postoperative Day 7	Reference values
Potassium (mmol/L)	5.1	4.9	3.7	3.5	3.4	3.7	3.5-5.1
Creatine kinase (U/L)	1579	2713	16 268	>37 000	>37 000	2658	25-170
Creatinine (umol/L)	102	101	101	68	68	88	40-120

FiO_2 – fraction of inspired oxygen; ETI – endotracheal intubation.

100 mL/kg/min, sevoflurane was discontinued (maximal minimum alveolar concentration achieved was 0.48), and additional 0.3 mg fentanyl was administered intravenously. Due to the unexpected and, at the time, unclear situation, the surgical staff were informed to stop the operation. During the next 10 min, $ETCO_2$ rose up to 59 mmHg. At that time, the diagnosis of MH was suspected, irrespective of the patient's stable vital signs: blood pressure 100/60 mmHg; heart rate 78 beats/min, sinus rhythm; peripheral oxygen saturation 98% at FiO_2 33%; and esophageal, axillary, and tympanic temperature of 37.2°C.

Local MH crisis protocol was started in the following order:

Priority actions: the inhalational anesthetic was already discontinued; all operating room staff were informed and mobilized; activated charcoal filters were placed on inspiratory and expiratory limbs of the breathing circuit; the anesthetic machine was replaced with a "vapour free" working station; propofol infusion was started at a rate of 100 µg/kg/min; hyperventilation 120 mL/kg/min was instituted with high fresh gas flow rate of 12 L/min; FiO_2 was raised to 50%; dantrolene was ordered and its reconstitution was considered; and laboratory

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check was ordered (**Tables 1,2**). At that point, around 25 min after intubation, in the face of steadily decreasing $ETCO_2$ around 50 mmHg and in the absence of pyrexia, the operative procedure proceeded. Its total duration was 3.5 h, including 50 min irradiation. During the next 10 min, $ETCO_2$ normalized.

Subsequent actions: forced diuresis of 3 mL/kg/h was maintained throughout the surgery by additional volume load of 15-20 mL/kg crystalloid solutions and 0.15 mg/kg furosemide, and serial blood gas analyses (**Tables 1, 2**) were arranged. After the operation, the patient was extubated with restored vital functions and admitted in the Intensive Care Unit with normal respiration but with an elevated CK level. In the absence of any complaints and pain, the patient was rehabilitated to the bedside upright position on the same day. Despite a maintained forced diuresis (3 mL/kg/h) over the next 3 days, a mild urine discoloration appeared, and as a preventive measure against acute renal injury, 2 hemodialysis sessions were performed due to extremely elevated CK levels, ranging from 1579 U/L at 30 min after intubation to >37 000 U/L at 48 min postoperatively (**Table 2**). With the patient in a stable condition, without alarming signs of organ failure and reporting only mild muscle weakness, she was transferred to the surgical ward on postoperative day 3 and discharged home on postoperative day 5 in very good health.

Later, a genetic test was performed, verifying a pathogenic variant of the *RYR1* gene – c.487C>T; p. (Arg163Cys), zygosity, heterozygous, which is associated with an autosomal recessive form of congenital myopathy, and is a dominantly inherited predisposition for MH. The patient was advised to arrange a genetic consultation for her children and relatives.

Discussion

The prevalence of MH is difficult to estimate. The reported range is about 1 in 50 000 to 100 000 general anesthetic procedures [1-5]; however, it is usually underestimated, because not all susceptible patients are exposed to the triggers. In contrast, the prevalence of gene mutations encoding the disease is much higher, ranging from 1 in 2000 to 1 in 3000 in the general population [5]. Both a genetic predisposition and one or more triggers are required for the development of an MH crisis during anesthesia [16]. Over 400 mutations have been identified in the *RYR1* gene located on chromosome 19q13.1, and at least 65 are causal for MH [4,5,9]. AIR, a breakdown of muscle fibers, releasing nephrotoxic intracellular contents and potassium into the systemic circulation, also represents an anesthetic crisis, with overlapping triggers and clinical picture. Volatiles and the depolarizing muscle relaxants are the strongest triggers for both crisis events. A variety of drugs could induce rhabdomyolysis in the perioperative settings, such as neuroleptics, antihistamines, corticosteroids, statins, anti-lipid drugs, alcohol, and substance abuse drugs (heroin, cocaine) [7,16]. Among the non-anesthetic causes are thermal or radiation body exposure, intensive physical activity, infection, emotional stress, caffeine, hyperglycemia, and muscle metabolic dysfunction [8,9,11,14]. Patients with comorbid neuromuscular diseases [14] are also at increased risk. The clinical presentation and classical first signs of MH crisis include an inexplicable and rapid elevation of $ETCO_2$ >55 mmHg, pyrexia >38.8°C, masseter spasm, generalized muscle rigidity, tachycardia and dysrhythmia, acidosis, rhabdomyolysis, and acute renal failure [1-3,7,8,16]. MH is characterized by rapid progression, and high mortality if unattended or untreated. There are also observed cases with occurrence of atypical reactions due to variable penetrance of this autosomal dominant inherited trait gene (97.3%), such as depression of consciousness and coma (9.8%), cardiac dysfunction (9.4%), pulmonary edema (8.4%), disseminated intravascular coagulation (7.2%), and hepatic dysfunction (5.6%) [9,17]. Since MH and AIR are rare conditions, only 2 case reports are available in the literature [18,19] concerning MH in patients with breast cancer, but our case is unique, raising further issues discussed below that need to be addressed.

Airway Management of a Patient with Mallampati III and Obesity with Expected Difficult Airways and General Anesthetic Choice

Unfortunately, there are not clear guidelines addressing this patient's population management. Given the obligatory ETI for securing the airways, particularly for TARGIT-IORT, during which all medical staff were outside the operating room for the irradiation procedure, rocuronium was unavailable, and there were difficult airways and a first unsuccessful intubation attempt, the second succinylcholine dose was inevitable. If a consultant anesthesiologist took the case from the beginning, with proper preparedness, the second induction and, respectively, the second succinylcholine dose could have been avoided, hence putting the patient, and other similar patients, at a lower risk of complications. To the best of our knowledge, this is the first reported case in the literature with MH crisis after a second full-induction succinylcholine dose, a strong MH and AIR trigger. Consequently, our general anesthetic choice was to rule out any AIR or MH trigger. Total intravenous anesthesia propofol + fentanyl is a treatment of choice in case of MH. Additionally, in the perioperative settings, rhabdomyolysis could be observed during neuroleptic malignant syndrome (thus excluding neuroleptics and antiemetics from the safe medication list), also during propofol infusion syndrome, linked to long-term (more than 48 h) and high dosage (above 4.0 mg/kg/h in stretch) propofol administration. Given the obligatory patient's motionlessness, especially during 20-Gy irradiation (55 min), and in the face of diagnosis uncertainty,

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it was not recommended to administer any muscle relaxant. Hence, the medical team chose opiate-based total intravenous anesthesia propofol+fentanyl, with a total fentanyl dose of 6 µg/kg and low total propofol dose of 3.8 mg/kg/h, without muscle relaxation.

The Dilemma: MH or AIR?

The reported patient had no clear history of MH predisposition, although upon further questioning, she remembered muscle weakness after a previous anesthesia. The potential crisis triggers for MH and AIR were the high total succinylcholine dose (2.0 mg/kg) administered in 5 to 7 min, the sevoflurane (administered shortly after ETI at a low minimum alveolar concentration of 0.48 achieved), and the radiation therapy [20]. The mild hypercarbia and the limited mouth opening during laryngoscopy were the first crisis symptoms and corner stones for suspecting MH, although there is no clear definition of masseter spasm [21]. They could also have been attributed to AIR or, as happens often in practice, were attributed to the obvious difficult airways: obesity, short neck, and unequivocal possibility for hypoventilation during the 2 anesthesia induction attempts. Hypercarbia was mild, self-limited, and lasted only 35 min in total. It would be extremely helpful to have the clear definition of masseter spasm or at least a record on the preoperative report of the interincisor gap in centimeters in every patient with planned general anesthesia and ETI. The picture of our patient became more complicated with the absence of pyrexia, hyperkalemia, lack of muscle rigidity signs throughout the body musculature, and hemodynamic stability maintained during the entire intra- and postoperative period, coupled with self-limited hyperlactatemia. All temperature measurements showed 37.2°C throughout the total hospital stay; later, the patient mentioned that this was her normal body temperature. Proving an AIR diagnosis is a time-dependent process, in which approximately 72 h are needed for CK and other enzymes' maximal elevation [12]. Consequently, in atypical cases, because of the requirement of prompt treatment, the better approach is to accept the MH diagnosis. Furthermore, the treatment of choice in MH is dantrolene, as opposed to antihyperkalemia treatment in cases with AIR [22]. Also, routine temperature measurement is not an obligatory part of the preoperative check-up. It is our opinion that this should be an indispensable part of preoperative check-up procedures, especially in those that change the body temperature, like irradiation or thermoablation.

Treatment

Because of the atypical, scarce, and obscured clinical presentation of our patient, 10 min after ETI (maximal $ETCO_2$ 59 mmHg, with upper normal limit minute ventilation of 100 mL/kg/min), we needed to switch the local MH crisis protocol on. Priority actions were implemented in the next 10 min. Intraoperative evaluation according to the Clinical Grading Scale for MH at 10 min revealed a score of 30 points (masseter spasm, 15 points; hypercarbia, 15 points), representing MH likelihood grade 4, "somewhat greater than likely" [23]. At 30 min, the MH clinical grading scale would have been 40, considering arterial pH <7.25 is 10 points; however, hypercarbia had already started to fall, and the values were below the limits. Although our medical facility stocks dantrolene, which is the etiologic mainstay of treatment [24-28], the typical time for reconstitution of an initial dose of 2.5 mg/kg (250 mg or 12.5 vials 20 mg each) would be 90 s per vial, or more than 20 min in total. During the next 10 min, $ETCO_2$ normalized; hence, dantrolene administration was withheld, and we administered a symptomatic rather than etiologic treatment with dantrolene [27-29]. Clear protocols with clear dantrolene administration guidelines are needed for treatment of atypical MH cases like ours. Whether dantrolene could have been applied with the aim to limit rhabdomyolysis remains a question for future consideration, provided the FDA has approved dantrolene only for MH treatment. Moreover, the FDA has warned about its carcinogenesis and mutagenesis [30], especially in breast cancer cases. Given the patient's stable vital signs, the operative procedure was not cancelled, and we decided to proceed with the surgical intervention, allowing the delivery of a single dose of 20 Gy in the tumor bed, using the Intrabeam System PRS 500 with XRS 4 Zeiss, thus extending the surgical procedure by 55 min. The advantages of TARGIT-IORT are indisputable and proven by multicentric studies from leading centers worldwide in respect to simultaneous application during surgery (1-step procedure), reduced irradiation of normal tissues, economic viability, better cosmetic outcomes, preferred choice by patients and specialists, and improved quality of life. A recent analysis estimates that at least 44 752 patients with breast cancer were treated with TARGIT-IORT in 260 centers in 35 countries, saving >20 million miles of travel and preventing about 2000 non-breast cancer deaths [13-15]. On the other hand, receiving a 20-Gy radiation dose at once is not indifferent to the organism, as the treatment targeted area temperature increases above 0.89±1.96°C during conventional external beam radiotherapy [20]. To alleviate the risk for developing next episodes of MH during the numerous courses of standard external beam radiotherapy in the irradiation department, we preferred to deliver radiation intraoperatively under constant monitoring. To the best of our knowledge, this is the first MH case successfully treated without dantrolene after a high total succinylcholine dose and uneventful intraoperative radiation therapy. Obviously, our patient developed rhabdomyolysis, proven by high CK levels [12]. Whether this rhabdomyolysis was aggravated by irradiation, and whether dantrolene administration at any time after $ETCO_2$ normalization could have prevented rhabdomyolysis are questions that need to be addressed further. Two hemodialysis sessions were administered to prevent

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further potential complications and acute renal injury [2,7,8]. Thanks to comprehensive care and monitoring of the patient's vital parameters throughout the whole procedure, our team was able to deliver IORT successfully during breast-conserving surgery to a patient with MH.

Conclusions

MH and AIR are rare intraoperative life-threatening anesthetic-induced reactions, with high rates of morbidity and mortality. Since MH exhibits highly variable clinical symptoms, in cases of obscure diagnostic dilemma MH or AIR, it is better to start MH crisis event treatment instead of waiting for diagnosis confirmation. To reduce misdiagnosis chances, it is our recommendation to record the patient's body temperature and interincisor distance in centimeters during the preoperative check-up if general anesthesia or a body temperature-affecting procedure is planned. Also, patients with difficult ETI signs and obligatory ETI should be treated by highly experienced anesthesiologists to avoid unnecessary risks related to the second induction and second potential trigger medication.

Ethic Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report was obtained from the patient.

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