Journal of
Medical Case Reports

CASE REPORT

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Malignant hyperthermia: patient undergoing limb debridement surgery—a case report

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Abstract

Background Malignant hyperthermia is a rare but potentially fatal clinical emergency, primarily triggered by inhaled volatile anesthetics. It is associated with inherited autosomal-dominant skeletal muscle disorders and typically caused by mutations in muscle calcium channel genes. Owing to its rapid onset and severe complications, prompt diagnosis and intervention are crucial. This case report highlights a unique instance of malignant hyperthermia, emphasizing the importance of early detection and timely treatment in saving a patient's life.

Case presentation A 30-year-old Han Chinese male underwent limb debridement surgery twice within 4 days, and, during the second surgery, he developed signs of malignant hyperthermia following the administration of inhaled anesthetics. The patient presented with hyperthermia, tachycardia, hypercapnia, and masseter spasm. Clinical diagnosis of malignant hyperthermia was confirmed, and immediate treatment with dantrolene was initiated. A multidisciplinary approach was employed to manage the condition, leading to successful stabilization and recovery. The patient ultimately made a full recovery without further complications. After the surgery, the patient underwent genetic testing, and no clear pathogenic genes were found; however, there were some suspicious related genes.

Conclusion This case underscores the critical importance of the early recognition of malignant hyperthermia and the prompt administration of dantrolene, which is vital in mitigating its life-threatening consequences. It also highlights the need for thorough preoperative screening for patients at risk of malignant hyperthermia and suggests improvements in treatment protocols to optimize patient outcomes.

Keywords Malignant hyperthermia, Dantrolene, Gene mutation, Volatile inhaled anesthetics

Background

Malignant hyperthermia (MH), a hypermetabolic syndrome, has drawn significant attention in the fields of anesthesiology and critical care medicine. Its onset is closely associated with the use of volatile inhaled anesthetics. The application of halothane, isoflurane, sevoflurane, desflurane, or succinylcholine may trigger this severe condition. Clinically, the typical characteristics of MH present a series of critical manifestations, including hypercapnia, accompanied by a rapid rise in body temperature, respiratory and metabolic acidosis, masseter muscle rigidity, tachycardia, and rhabdomyolysis [1]. Notably, the triggering factors of MH are not limited to the use of anesthetics. Strenuous exercise in high-temperature environments, infections, taking antipsychotic medications, and even overheating in infants can all act as "triggers" for malignant hyperthermia. According to relevant research, during the use of general anesthetics, the incidence of MH ranges from 1 in 10,000

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to 1 in 150,000 [2]. Particularly, the pediatric population has the highest incidence of MH. Moreover, compared with females, males have a significantly higher probability of experiencing malignant hyperthermia reactions [3].

On the basis of the complexity, high risk, and the urgency of the clinical diagnosis and treatment of MH, this case report aims to further deepen the understanding of this disease through an in-depth analysis of a patient undergoing limb debridement surgery. It provides more valuable references for clinicians when facing such complex conditions, helping to improve the early diagnosis rate and treatment success rate and, ultimately, improve the patient's prognosis.

Case presentation

The patient was a 30-year-old Han Chinese male who was hospitalized in the Second Affiliated Hospital of Wenzhou Medical University owing to "multiple body pain and limited mobility for 4 h after a car accident." On the day of admission, closed reduction and intramedullary nailing were performed for the right femoral fracture. During the perioperative period, redness and swelling of the wound occurred, and muscle debridement was planned. Apart from the above-mentioned conditions, the patient was basically in good health. There was no family history of malignant hyperthermia. Physical examination showed that the patient was conscious, with a height of 172 cm and a weight of 75 kg, and no abnormalities were found in the respiratory and circulatory systems. The preoperative laboratory test results were normal.

After the patient entered the operating room, vital signs were monitored: heart rate was 109 beats per minute, blood pressure was 135/78 mmHg, and oxygen saturation was 100%. During the operation, anesthesia was induced with propofol (120 mg), sufentanil (12.5 μg), and rocuronium bromide (50 mg). Oral tracheal intubation was performed, and anesthesia was maintained by inhaling sevoflurane and infusing remifentanil.

A total of 95 min after the start of anesthesia, the patient's blood pressure remained normal; however, the heart rate increased, and the body temperature rose slowly (from 36.7 °C to 37.4 °C), while the end-tidal carbon dioxide partial pressure increased from 40 to 50 mmHg. Even after adjusting the ventilator parameters, there was no improvement. Arterial blood gas analysis indicated respiratory acidosis (pCO_2 approximately 60 mmHg), and the blood potassium level was normal (5.0 mmol/L). Figure 1 shows the changes in vital signs of the patient throughout the entire surgical process.

A total of 130 min later, the patient's pCO_2 and body temperature increased sharply (the maximum body temperature reached 44.2 °C, and PCO_2 reached 120 mmHg). Blood gas analysis showed mixed acidosis (pH 6.93,

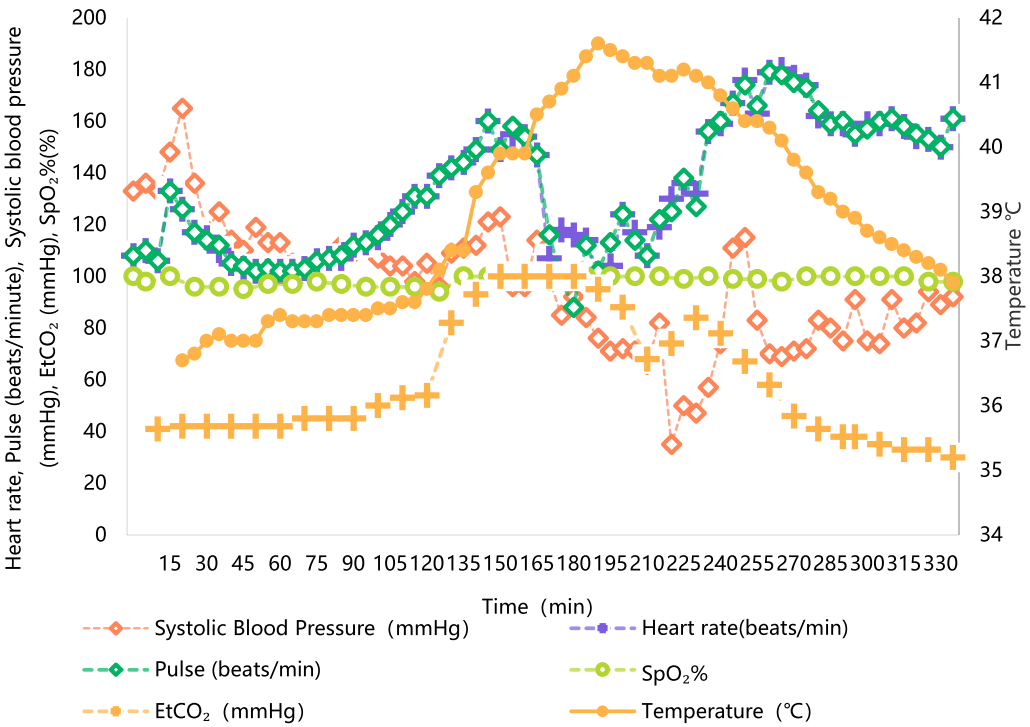

Fig. 1 Anesthesia record sheet

pCO_2 110 mmHg, base excess (BE) 9.3) and hyperkalemia (6.8 mmol/L). Malignant hyperthermia (MH) was highly suspected.

The sevoflurane was immediately discontinued, the fresh gas flow was increased, and propofol was used to maintain anesthesia instead. Dantrolene was urgently transported. During this period, cooling measures were taken (such as applying ice packs and using alcohol for cooling), blood pressure was increased (maintained with norepinephrine, dopamine, and adrenaline), acid–base imbalance was corrected (intravenous infusion of sodium bicarbonate and hyperventilation), blood potassium was reduced (intravenous infusion of calcium gluconate, intravenous infusion of 100 ml of 10% glucose solution + 2 units of insulin, and intravenous micropump infusion of 50 ml of 50% glucose + 8 units of insulin), and hormones were used for antiinflammation and other symptomatic supportive treatments.

Upon the arrival of dantrolene, 100 mg was slowly injected intravenously immediately, and an additional 60 mg was administered subsequently. After the patient's condition stabilized, close monitoring was continued, and symptomatic treatments were carried out.

After treatment, the patient's vital signs gradually stabilized. With the support of vasoactive drugs, the end-tidal carbon dioxide returned to normal, and the body temperature dropped to 38.1 °C. Subsequently, the patient was transferred to the intensive care unit (ICU) after the operation. Postoperative assessment showed that the white blood cell count (WBC) was 40.51×10^9/L, C-reactive protein (CRP) was 90.53 mg/L, hemoglobin (Hb) was 52 g/L, lactate was 18.69 mmol/L, creatine kinase (CK) was 15,595 IU/L, and myoglobin was > 2000 ng/ml. Considering the blood gas analysis and other indicators, it was diagnosed as fulminant malignant hyperthermia accompanied by rhabdomyolysis and multiple organ dysfunction (involving the brain, heart, lungs, kidneys, and liver). The treatment included assisted ventilation via tracheal intubation, bedside continuous renal replacement therapy (CRRT), antiinfection treatment with imipenem–cilastatin, and symptomatic support. On the second day after the operation (POD2), the patient's body temperature was stable (ranging from 35.8 °C to 36.6 °C), and the blood pressure was stable (97–152/57–72 mmHg) with the support of a low-dose vasopressor. The troponin level decreased after reaching its peak. On the third day, after discontinuing the vasopressor, the blood pressure did not drop significantly (110–146/49–69 mmHg), and the creatine kinase (CK) began to decline. Specific changes in CK and myoglobin are presented in Table 1. On the fourth day, with CRRT, the patient's vital signs and internal environment were stable. After gradually weaning from the ventilator and extubating, high-flow nasal oxygen therapy was used. The patient had active spontaneous breathing, and both the vital signs and the internal environment were stable. Overall, the patient's recovery was favorable.

After obtaining informed consent from the patient's family, a genetic test was completed. The results indicated the presence of certain suspected mutations in the *RYR1* gene: c.9758 T > C (p.Ile3253Thr), c.1144C > T(p.His382Tyr), and c.3124G > T(p.Val1042Leu).

Discussion

Malignant hyperthermia (MH), a hypermetabolic syndrome, has drawn significant attention in the fields of anesthesiology and critical care medicine. Its onset is closely associated with the use of volatile inhaled anesthetics. The application of halothane, isoflurane, sevoflurane, desflurane, or succinylcholine may trigger this severe condition [4]. Clinically, the typical characteristics of MH present a series of critical manifestations, including hypercapnia, accompanied by a rapid rise in body temperature, respiratory and metabolic acidosis, masseter muscle rigidity, tachycardia, and rhabdomyolysis.The fulminant type of MH, commonly seen in clinical practice, has an extremely rapid onset, and the progression of the disease is like a speeding train, posing a serious threat to the patient's life and health in a short time. If not diagnosed accurately and treated effectively in a timely manner, the prognosis for patients is often extremely poor, and it may even directly lead to death. Additionally, the other three types of MH, namely the masseter spasm type, the delayed-onset type, and the simple rhabdomyolysis type, are highly likely to transform into the most life-threatening fulminant type of MH under the continuous action of the inducing drugs. The Clinical Grading Scale (CGS) is currently the most commonly used MH evaluation form in China and is used to assist in diagnosis. For details, please refer to Tables 2 and 3. In this case, the patient scored 91 points. The breakdown is as follows:

Table 1 Changes in CK and myoglobin

Index	Before anesthesia	After anesthesia 4 h	POD1	POD2	POD3	POD4	POD5	POD10	POD16
CK (U/L)	354	15,595	63,416	69,001	32,905	21,609	7270	1882	998
Myoglobin (ng/L)	Not measured	Not measured	> 2000	> 2000	> 2000	> 2000	> 2000	1964	379

POD postoperative day

Table 2 Malignant hyperthermia Clinical Grading Scale (CGS)

Items	Indicators	Score
Muscle rigidity	Generalized muscle stiffness (excluding shivering caused by hypothermia, as well as that during and immediately after the recovery period from inhalation anesthesia)	15
	Masseter spasm after intravenous injection of succinylcholine	15
Myolysis	CK > 20,000 IU after intravenous injection of succinylcholine	15
	CK > 10,000 IU after anesthesia without the use of succinylcholine	15
	Myoglobinuria during the perioperative period	10
	Urinary myoglobin > 60 μg/L	5
	Serum myoglobin > 170 μg/L	5
	Whole blood/serum/plasma K^+ (potassium ion) > 6 mEq/L (excluding cases with combined renal failure)	3
Respiratory acidosis	End-tidal partial pressure of CO_2 > 55 mmHg with sufficient minute ventilation	15
	Arterial partial pressure of CO_2 > 60 mmHg with normal ventilation	15
	End-tidal partial pressure of CO_2 > 60 mmHg under spontaneous breathing conditions	15
	Arterial partial pressure of CO_2 > 65 mmHg under spontaneous breathing conditions	15
	Abnormal hypercapnia	15
	Abnormal tachypnea	10
Temperature increase	Abnormally rapid increase in body temperature during the perioperative period (judgment by the anesthesiologist is required)	15
	Abnormal increase in body temperature during the perioperative period (> 38.8 °C) (judgment by the anesthesiologist is required)	10
Cardiac arrhythmia	Abnormal tachycardia	3
	Ventricular tachycardia or fibrillation	3
Family history	MH family history among direct relatives	15
	MH family history among nondirect relatives	
Others	Base excess < −8 mEq/L shown in arterial blood gas	10
	pH value < 7.25 shown in arterial blood gas	10
	Quick correction of respiratory and metabolic acidosis after intravenous injection of dantrolene sodium	5
	Elevated CK at rest with MH family history	10
	Any of the above manifestations with MH family history	10

Table 3 The relationship between CGS score of MH and the probability of MH occurrence

Score	3–9	10–19	20–34	35–49	≥ 50
Level	2	3	4	5	6
Likelihood of MH occurrence	Impossible	Close to possible	Higher possibility	Very likely	Almost certain

generalized muscle stiffness accounted for 15 points; creatine kinase (CK) > 10,000 IU after anesthesia without the use of succinylcholine contributed 15 points; serum myoglobin > 170 μg/L was worth 5 points; serum potassium (K^+) > 6 mEq/L gave 3 points; end-tidal partial pressure of carbon dioxide ($PetCO_2$) > 55 mmHg with sufficient minute ventilation added 15 points; an abnormally rapid increase in body temperature during the perioperative period was 15 points; abnormal tachycardia counted for 3 points; base excess greater than 8 in arterial blood gas (ABG) analysis was 10 points; pH value < 7.25 was 10 points; and the rapid correction of respiratory and metabolic acidosis after intravenous injection of dantrolene sodium was 5 points.

The caffeine–halothane contracture test is the gold standard for the diagnosis of malignant hyperthermia (MH) [5]. The specific procedure is as follows: a 2–3 cm sample of the patient's thigh muscle fiber is taken and fixed in a balanced salt solution at a constant temperature of 37 °C. Under the condition of continuously introducing oxygen containing 5% carbon dioxide, the changes in muscle tension under the influence of different concentrations of halothane and caffeine are recorded by electrical stimulation. According to the North American MH

diagnostic criteria, for the caffeine test, when the caffeine concentration is 2 mmol/L, if the change in muscle tension is greater than 0.38 g, the caffeine–halothane contracture test is positive; if it is less than 0.2 g, the test is negative; and if it is between 0.2 g and 0.38 g, the result is considered equivocal. For the halothane test, after ventilation with 3% halothane for 10 min, if the change in muscle tension exceeds 0.78 g, the halothane–caffeine contracture test is positive; if it is less than 0.5 g, the test is negative; and if it is between 0.5 g and 0.78 g, the result is considered equivocal. A patient is diagnosed as being susceptible to MH if either test is positive and is diagnosed as nonsusceptible to MH only if both tests are negative [6]. The sensitivity of this experiment is 97% and the specificity is 78%. [7]. The caffeine–halothane skeletal muscle contracture test is an invasive procedure. It requires testing of the short-term *ex vivo* muscle tissue in a timely manner and is relatively costly. As a result, it has not been widely carried out and is only used for screening or definitive diagnosis.

It has now been confirmed that MH has the characteristic of autosomal dominant inheritance. More than 400 mutation sites have been identified in the RYR1 gene on chromosome 19q13.1, and at least 34 of them are clearly associated with MH [8, 21]. Mutations in related genes can cause abnormalities in the amino acid sequence of the encoded skeletal muscle sarcoplasmic reticulum calcium channel protein RYR1. Moreover, posttranslational modifications can generate hyperactive RyR1 channels. Both of these can lead to abnormal calcium ion regulation functions. When the Ca^{2+} content stored in the sarcoplasmic reticulum reaches a critical level, spontaneous Ca^{2+} release occurs. This process is called store-overload–induced Ca^{2+} release (SOICR) [9]. Alterations in RYR1 augment the propensity for spontaneous Ca^{2+} release during the overstorage of Ca^{2+} within the skeletal muscle sarcoplasmic reticulum. Put another way, this reduces the threshold of store-overload–induced Ca^{2+} release (SOICR). Consequently, calcium ions flow uncontrollably into the cell's cytoplasm, significantly enhancing the contractile force of skeletal muscles. If the sustained hypermetabolism of skeletal muscles remains unaddressed through active intervention, it may progress to rhabdomyolysis, an elevation in core body temperature, hypercapnia, metabolic acidosis, and multiple organ failure, and, in critical situations, it can even prove fatal. To date, numerous gene mutation sites associated with MH have been identified. These encompass the gene encoding RYR1 and others, such as genes encoding components related to the dihydropyridine receptor and genes associated with the encoding of various ion channels [10]. This may potentially explain a series of clinical syndromes with diverse manifestations. Additionally, phosphorylation, glutathionylation, oxidation, and nitrosylation of RyR1 have all been shown to regulate the release of Ca^{2+} from the sarcoplasmic reticulum (SR). However, the causes of these modifications and their functional consequences remain unclear [11–13]. Human genetic alterations are intricate. The sensitivity of DNA screening for detecting MH susceptibility is only approximately 50% [14]. Therefore, a negative test result cannot directly rule out the susceptibility to malignant hyperthermia. A definitive diagnosis requires a combination of the caffeine–halothane contracture test and the family history of the disease. After a high suspicion of MH in this patient, genetic testing was completed with the informed consent of the patient's family. The results indicated suspected mutations, as detailed in Table 4. The clinical significance of these suspected mutations remains unclear, and further research is needed to clarify their correlation with the patient's clinical phenotype. Since the caffeine–halothane contracture test is not available in this region, the patient will need to go to Beijing for the test on their own after recovery.

Dantrolene sodium is currently the only specific drug for the acute phase treatment of MH. It binds to specific sites on the RyR1 protein, reducing the activity of RyR1 channels in intact muscle cells [15]. It can effectively inhibit RyR1-mediated SOICR, reduce the calcium ion concentration in the cytoplasm, and weaken the contraction intensity of skeletal muscle tissues. When diagnosing malignant hyperthermia or having a high suspicion of its likelihood, aside from immediately discontinuing the inducing drugs, dantrolene sodium should be administered as early as possible. The instruction manual of injectable dantrolene sodium recommends an initial dose of 1 mg/kg, with an additional 1 mg/kg each time until the symptoms disappear or the maximum tolerated dose of 7 mg/kg is reached. Meanwhile, replace the soda-lime and breathing circuit and perform hyperventilation with high-flow oxygen to wash out the volatile anesthetics and reduce the end-tidal carbon dioxide partial pressure [16]. Typically, the above symptoms can be rapidly reversed after administration. In this case, the patient's intraoperative body temperature reached a maximum of 41.6 °C and the partial pressure of carbon dioxide (PCO_2) reached 120 mmHg; 160 mg of dantrolene was slowly injected intravenously, and, simultaneously, symptomatic and supportive treatments such as cooling, increasing blood pressure, correcting acidosis, reducing blood potassium, and using hormones for antiinflammation were carried out. Approximately 2 h later, the end-tidal carbon dioxide decreased to 33 mmHg, and the body temperature decreased to 38.1 °C. With the support of vasoactive drugs, the vital signs could basically be maintained stable. However, by contrast, dantrolene sodium has

Table 4 Results of genetic testing

Gene	Chromosome location	Transcript exon	Nucleotide-amino acid	Homozygous/heterozygous	Normal population frequency	Prediction	ACMG pathogenicity analysis (score)	Disease/phenotype (inheritance pattern)
RYR1	chr19:39,008,071	NM-000540.3:exon66	c.9758 T > C (p.Ile3253Thr)	Het.	0.0001997	D	Uncertain(2)	1. Autosomal recessive (AR) congenital myopathy type 1B 2. Malignant hyperthermia susceptibility type 1 (autosomal dominant, AD) 3. King—Denborough syndrome (AD) 4. Autosomal dominant congenital myopathy 1A with susceptibility to malignant hyperthermia (AD)
	chr19:38,942,425	NM-000540.3;exon12	c.1144C > T (p.His382Tyr)	Het.	–	D	Uncertain(2)	
	chr19:38,956,984	NM-000540.3:exon24	c.3124G > T (p.Val1042Leu)	Het.	0.0000367	U	Uncertain(0)	

Prediction, protein function prediction software REVEL: D, pathogenic; LD, likely pathogenic; U, uncertain significance; LB, likely benign; B, benign. spliceAI: T, affects splicing; F, does not affect splicing. En dash indicates unknown score. Bayesian framework uncertain site scores and corresponding pathogenic probability: < 0 (0.1%); 0 (10%); 1 (18.8%); 2 (32.5%); 3 (50%); 4 (67.5%); 5 (81.2%); ≥ 6 (≥ 90%)

disadvantages such as poor solubility, a long plasma half-life, hepatorenal toxicity, and thrombophlebitis. It may lead to adverse reactions such as muscle weakness and hepatorenal failure [17] and thus is generally not suitable for the long-term treatment of malignant hyperthermia (MH). Considering the significant harm, numerous complications, and long follow-up treatment period of malignant hyperthermia, finding a long-term treatment drug remains an urgent problem to be solved. Carvedilol is a beta blocker that can treat catecholamine-sensitive polymorphic ventricular tachycardia (CPVT) by inhibiting the store-overload–induced calcium release (SOICR) mediated by RyR2, which has a highly similar structure to RyR1. At present, it has been confirmed that carvedilol can also inhibit the enhanced SOICR mediated by RyR1; therefore, it may have the potential for the long-term treatment of MH. FKBP12 is a binding protein that can bind to RyR1 to stabilize the channel. Rycals (benzothiazole derivatives) can prevent FKBP12 from dissociating from the RyR1 channel and thereby prevent the increase of calcium ion concentration. In addition, there are other nonselective RyR inhibitors, such as high-concentration flecainide and EL20 (tetracaine derivative). At present, some scholars have used the high-throughput screening (HTS) assay method to select highly targeted RyR1 treatment drugs to reduce the risk of adverse reactions [18].

When MH typically occurs immediately upon exposure to triggering factors and presents with typical clinical symptoms, the diagnosis can be relatively quick and straightforward. However, clinical manifestations often vary from person to person. In cases where patients have mild initial symptoms, have a delayed onset, or are critically ill patients with comorbidities such as severe pneumonia or sepsis, it can be extremely challenging to distinguish MH from other diseases.

It is essential to be vigilant about other primary diseases that can cause symptoms such as tachycardia, high fever, and hypercapnia; in addition, it is important to conduct timely investigations. There are reports of patients who had undergone multiple general anesthetics before experiencing MH, yet no related discomfort symptoms were induced. The exact reasons for this remain incompletely understood [19]. Delayed onset of MH is rarely reported (ranging from 30 min after anesthetic induction to even 1 week), and sevoflurane is more likely to cause delayed-onset MH compared with other inhalants (with an average of 60 min) [20]. In this particular case, the patient received sevoflurane for induction anesthesia during the first surgery after admission. However, no typical MH manifestations were observed during or after the operation; both body temperature and end-tidal carbon dioxide partial pressure were normal. Only the surgical wound showed redness, swelling, and purulent exudation. It was not until the second anesthesia that an MH episode occurred. Whether this belongs to a rare MH subtype remains unclear. Currently, no relevant literature providing a clear explanation has been found, and further exploration within the industry is still needed.

Conclusion

MH is rare, with no detailed epidemiological data. Its rapid progression makes misdiagnosis likely among clinicians lacking relevant knowledge, especially in primary hospitals, thus missing treatment opportunities. Therefore, it is important to popularize MH knowledge, inquire about family history and prepare dantrolene sodium before general anesthesia, and suspect MH for unexplained symptoms during surgery. After onset, it is essential to diagnose and treat early with various measures including drug-related actions, supportive care, and life-support technologies, as needed. Monitoring closely to prevent complications is essential. After discharge, doctors should test the patient if possible, follow up, collect family history, and improve local databases and treatment centers. Moreover, there are still many limitations in the diagnosis and treatment of malignant hyperthermia at present. It must be mentioned that the pathogenic genes of malignant hyperthermia have not been fully decoded, and genetic discoveries alone are not sufficient for diagnosis. It is necessary to combine the patient's clinical manifestations and many tests for joint diagnosis.

Acknowledgements
Thanks to all medical staff at the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University for their meticulous care and support during the patient's treatment.

Author contributions
Z.G. and A.W. were responsible for case collection, collation, and analysis and wrote the first draft. J.Y. participated in the diagnosis and treatment of the case; X.C., R.C., and Z.L. revised and improved the manuscript. X.Z. provided professional guidance and suggestions and contributed significantly to the research design and result interpretation.

Funding
This study did not receive any external funding. All costs during the research process were borne by the authors' institutions or self-raised by the authors.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
All authors declare that there are no competing interests in this study. No financial, commercial, or other interests that may affect the objectivity and fairness of the research are involved.

Received: 15 January 2025 Accepted: 6 May 2025
Published online: 23 May 2025

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