



Case Report

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# A Death of Malignant Hyperthermia Performed Autopsy: A Case Report

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## Abstract

Malignant hyperthermia (MH) is a potentially lethal disorder triggered by certain anesthetics. MH is characterized by hypermetabolism, muscle rigidity, hypercapnia, tachycardia, hypoxaemia, respiratory and metabolic acidosis, and hyperthermia. Mutations in the RYR1 (account for about half of MH cases), CACNA1S, or STAC3 genes are associated with MH. We report on the case of a 19-year-old girl who is suffering from MH, without history of MH-susceptible and she died suddenly after cardiac arrest for more than 2 hours. The lack of clinical experience and vigilance resulted to the difficulty of early diagnosis. If MH is highly suspected during general anesthesia of potent volatile anaesthetics with or without succinylcholine, a collaborative treatment approach is mandatory, especially treated with dantrolene should begin as soon as possible. Autopsy of patients with MH, similar cases are infrequent in the literature, which is reviewed in this report, explore the pathophysiological changes, we hope that can be helpful for the prevention, diagnosis and treatment of similar cases in time.

**Keywords:** Malignant Hyperthermia, RYR1, Autopsy

## Introduction

As Malignant hyperthermia (MH), proportion ranging from 1:35,000 to 1:68,000, is extremely rare autosomal dominant pharmacogenetic disorder that triggered in genetically predisposed individuals by any of the potent volatile anaesthetics, such as isoflurane, desflurane, sevoflurane or enflurane, with or without succinylcholine [1,2]. Some literature indicates the mortality of a fulminant MH episode is >70% without treated, but increased awareness, advances in monitoring, and availability of dantrolene, have substantially reduced the mortality to <8% [3,4]. No clinical symptoms of MH are showed until patients, the MH susceptible, are exposed with triggering agents or excessive heat, extreme and unaccustomed exercise, flu-like illnesses [5,6]. Once exposed to triggering agents, an abnormally plentiful release of calcium from the sarcoplasmic reticulum is released, leading to hypermetabolism

shown by muscle rigidity, hypercapnia, tachycardia, hypoxaemia, respiratory and metabolic acidosis, and hyperthermia [7,8]. Failure to treat in time can lead to pulmonary edema, disseminated intravascular coagulation, and heart, liver, kidney and brain dysfunction [9]. Complications increase with every 10-min delay in treatment of dantrolene. Waited more than 50 minutes, complications increase to 100% [10]. Definitive diagnosis of MH mainly depends on muscle biopsy and genetic testing. The variants genes, such as ryanodine receptor 1 (RYR1) [11], calcium voltage-gated channel subunit alpha1 S (CACNA1S) [12], SH3 and cysteine rich domain 3 (STAC3) [13], are associated with MH. Autopsy of patients with MH, similar cases are infrequent in the literature, which is reviewed in this report, explore the pathophysiological changes, we hope that can be helpful for the prevention, diagnosis and treatment of similar cases in time.



## Case Report

A 19 years old female patient suspected MH, 50 kilogram(Kg), 153 centimeter(cm), was presented to out-patient department of Affiliated Hospital of Gui Zhou Medical University with fever (42oC) for more than 2 hours and cardiac arrest for more than a hour. The patient was scheduled for comprehensive shaping for ear cartilage nasal tip with the diagnose of saddle nose at Li Mei Kang Hospital. After one hour's rescue, the patient was finally declared clinically dead.

The patient was given general anaesthesia for operation time of 264 minutes, including Fentanyl 0.1mg, Propofol 100mg, Vecuronium Bromide 4mg, Atropine 0.05mg and Dexamethasone 5mg; maintaining anaesthesia with Isoflurane and intermittent injection of Vecuronium. After 6 minutes of the surgery, the patient showed suddenly skeletal muscle rigidity, heperthermia (41.6°C), low blood pressure (80/45mmHg), heart rate of 155 times, heavy sweating, 3.5mm pinpoint pupils on both sides, positive pupillary light reflex and abnormal blood gases and electrolytes. The patient was treated with controlled ventilation, positive transfusion with equilibrium liquid 1000ml, Dexamethasone 5mg; Norepinephrine; Deazepam 5mg; Dopamine 100mg; Furosemide 20mg; positive cooling with ice water until the patient's body temperature dropped. After rescuing for 83 minutes, the patient's condition continued to deteriorate with low blood pressure (50/22mmHg), heart rate of 25 times, SPO2 76%, 4mm pinpoint pupils on both sides, reduced pupillary light reflex. Finally, the patient suffered Cardiac arrest. MH was supposed by anesthetists of Li Mei Kang Hospital. Considering conditions got worse without treatment of dantrolene in Li Mei Kang Hospital, the patient was performed CPR and sent to out-patient department of Affiliated Hospital of Gui Zhou Medical University at the same time.

## Autopsy Report

An autopsy was performed to confirm the diagnosis. Approximately 10×5 cm of subscalp bleeding above the left auricle was found due to the surgery. There was no hemorrhage in the epidural/subarachnoid space without the skull and dura fractured. Laryngeal mucosa was mildly oedema as a result of the endotracheal tube. There was no injury and bleeding in subcutaneous, fat and muscle in the neck. Hyoid bone, thyroid cartilage and thymus were not abnormal. A small amount of reddish fluid adhesion was observed in the lower trachea and bilateral bronchi, which was considered to be pulmonary congestion, with smooth and complete mucosa. About 2x1 cm of bleeding was seen in the fat and muscle layer between 2-3 ribs on both sides of the sternum in the chest area, and the sternum flat 3-4 intercostal fracture, with less bleeding in the surrounding soft tissue, which was considered to be due to CPR. No fractures of the collarbones and ribs were found. A little light yellow effusion was observed in both ribcage. There was

no hemoperitoneum or effusion in the abdominal cavity or pelvic cavity.

## Main Organ Inspection

The brain gyrus widened on both sides with the sulci narrowed. There were not seen injury or bleeding in brain, cerebellum, brainstem surface and cut surface. The cerebrospinal fluid was clear. The left lung weighed 600g that was 150g lighter than the right, while both were smooth, intact, swollen and dark red. Pale yellow fluid was found in the pericardial cavity about 30ml with non-coagulated blood, while the heart weight was 240g. The thickness of the left ventricular wall was 1.0cm, which was 0.8cm thicker than the right side. The circumference of the tricuspid valve was 10.5cm, which was 2cm longer than the mitral valve. The circumference of the pulmonary valve was 5.5cm, which was 0.5cm longer than the aortic valve. There were multiple spotted bleeding points on the front and back of the heart. The gastric mucosa was not abnormal with empty stomach. There were no obvious abnormalities in the intestinal serous membrane, mucous membrane and contents. With a red dark color, the liver capsule was smooth and intact, while congestion was observed on the liver section. The gallbladder was filled with bile. Filled with blood in the cut surface, the membrane of the spleen was smooth and intact. The pancreatic capsule was smooth and intact, while no bleeding point was observed on the surface and section. With clear boundary of medulla, both kidney was smooth and intact.

## Histopathological Examination

Histopathological examinations, routine paraffin section and HE staining histological examination, were performed on vital organs Brain including heart, lung, liver, spleen, kidney and other tissues. With congested subarachnoid space and brain parenchyma, leakage hemorrhage was observed around some cerebral vessels, while the space between nerve cells and cerebral vessels widened. Neuronal meissner corpuscles were fuzzy, while the phenomenon of neurophagic phenomenon and satellite could be seen. Epithelial bleeding was seen in the epicardium and some areas of myocardium, while some cardiomyocytes were hypertrophic. The myocardial fibers were broken with disordered in some. It could be observed fat and a small amount of fibrous in the myocardium. Spotted lymphocytic infiltration could be seen in myocardial interstitial with dilated blood vessels. The proximal tubule epithelial cells had mild edema, while the collecting tubules were filled with raw urine. The blood vessels of the kidneys were congested as well as adrenal gland and gastric mucosa. The submucosa of the stomach was loose, while lymphocyte infiltration was seen in the mucous layer of the small intestine, accompanied by the formation of lymphatic follicles and a significant decrease in the number of glands. It could be noted focal hemorrhage in the brachial triceps, with the interstitial vasculature produces dilatated and congested.

A perivascular focal lymphocytic infiltration was noted. Some wavy and twisted muscle fibers could be seen in the longitudinal section, which were swollen and atrophic. The mesenchymal vasculature of the gastrocnemius muscle was dilated and congested with blood. Different in size, thyroid follicles were smooth, which filled with pink staining colloid. The blood vessels were dilated and filled with blood. The pancreas has dissolved, the outline of the pancreatic lobule remained, but the islets were hard to recognize. Lung with dense capsule, dilated congested interstitial vessels and alveolar wall capillaries. Additionally, alveoli were partially ectasia or compensatory ectasia, accumulation of red blood cells and fluid into the alveolar space. Part of the shed of bronchioles epithelium were observed. Red blood cells, serous effusion fluid and fibrous tissue can be seen partially into bronchiole. The splenic capsule was dense, with clear white and red medulla structures, at the same time, splenic sinus was congested. It could be seen that the pituitary blood vessels were dilated and congested, while focal bleeding has occurred in the pituitary. The liver's capsule is dense, and congestion can be seen in the liver sinus. Vacuoles of different sizes was observed in some hepatocytes, with a small amount of lymphocyte infiltration in the portal area.

### Biochemical Blood and Genetic Testing

The dead was performed biochemical blood and genetic testing. Inspection report form of guizhou jinyu medical examination center (sample barcode 2416911019) : creatine kinase 810U/L (reference value 40-200u/L); Myoglobin 1484.00ng/ml (reference value 25.00-58.00ng/ml). "Malignant Hyperthermia Susceptibility Gene Testing Report" of Ningbo Gene Technology Co., Ltd. pointed out that the patient had a heterozygous mutation in c.7084G>A site on the R1Y1 gene with the genotype GA. This patient carried a MH susceptibility gene who was a patient with MH.

### Discussion

According to the autopsy report, the wounds on the nasal and bilateral ears of the body conform to the characteristics of plastic surgery. It does not cause the manifestation of damage to important organs such as intracranial hemorrhage, thus the death of mechanical injury caused by surgical operation can be excluded. Bleeding under the scalp above the left auricle, with less bleeding, was consistent with the surgery, which was also not enough to cause death, as well as mid myocardial fat infiltration and chronic enteritis. In addition, it can be ruled out cause of death that no pathological signs of mechanical asphyxia and poisoning are detected throughout the body. During general anesthesia, the patient was treated with isoflurane for inhaled anesthesia, vecuronium for muscle relaxant, etc. Sudden symptoms appeared, such as skeletal muscle rigidity, rapid increase in body temperature, and tachycardia, which were in line with the clinical symptoms of MH. Then cardiac arrest ensued, leading to death. In addition, the

tests indicated that not only the concentrations of creatine kinase and myoglobin abnormally increased, but patient also carried MH susceptibility genes (R1Y1), which were consistent with the characteristics of blood biochemistry and genetic testing of MH. Therefore, we conclude that the patient died of cardiac arrest due to MH.

Here, we describe a fatal case of exposed to the potent volatile anaesthetics, isoflurane, with a potentially pathogenic RYR1 variant. No apparent abnormal signs were observed before the patient underwent anesthesia resuscitation. But within a few minutes the patient developed skeletal muscle rigidity, hyperthermia (41.6°C), low blood pressure(80/45mmHg), heart rate of 155 times, heavy sweating, 3.5mm pinpoint pupils on both sides, positive pupillary light reflex and abnormal blood gases and electrolytes. Considering possible cause as hypovolemia shock, allergies or MH, symptomatic treatments were given immediately. However, it was so fatal that the antidote drug, dantrolene, was not available in Li Mei Kang Hospital. One could imagine that the situation did not improve, then the patient developed hypoxemia and cardiac arrest. So that it added enormous difficulties to subsequent rescues, at the same time, missed the optimal time for treatment of dantrolene.

MH most often occurs intraoperatively with stimulated by triggering agents, but it also appear in the absence of a volatile agent or succinylcholine in recent research. Awake MH episode can be triggered by a combination of febrile illness (e.g., influenza type A) and physical exertion (e.g., dancing and weightlifting) with common clinical symptoms despite happened without any anesthetics [6,14]. Known to be positively-skewed, age distribution indicate younger people are most affected [15,16]. Multiple studies have shown that the clinical symptoms of children under 15 years of age account for 50% of all reactions [17,18], suggesting that the symptoms become more pronounced at younger age, which is consistent with our case report. Our case is also younger with typical clinical symptoms of MH. MH symptoms can present at any time, especially in the early postoperative period, with diagnostic clues appeared at the anesthetic record. Additional carbon dioxide should be an early indication of a potential MH crisis that anesthesiologist have to adjust ventilator parameters to elimination the addition. Due to the limited data collected, we have no way of knowing whether the end-respiratory carbon dioxide increased nor the corresponding measures taken in this case. Another early sign of MH is unexplained sinus tachycardia. It can interfere with our judgment for mistakenly believing a light plane of anesthesia or inadequate pain control. Hyperthermia is a key indicator of MH [19], presenting later or not, that increase the risk of morbidity from multiply organ failure, DIC about 39°C. General skeletal muscle rigidity is the most typical symptom of MH [20], then rhabdomyolysis appears, resulting in myoglobinuria and hyperkalemia, which is also a late sign of MH

[21]. Other clinical symptoms of MH may include hypoxemia, pulmonary edema, congestive heart failure, cardiac arrhythmias, electrolyte imbalances, and alterations in consciousness. Most of the representative signs are reflected in our case, such as skeletal muscle rigidity, rapid increase in body temperature, and tachycardia, which were in line with the clinical symptoms of MH.

Definitive diagnosis of MH mainly depends on muscle biopsy and genetic testing, with contracture testing being another one to diagnosis [22]. The variants genes, such as ryanodine receptor 1 (RYR1) [11], calcium voltage-gated channel subunit alpha1 S (CACNA1S) [12], SH3 and cysteine rich domain 3 (STAC3) [13], are associated with MH. Ryanodine receptors (RYRs) are a family of intracellular calcium release channels, with RYR1 being the isoform that is predominantly found in skeletal muscle. The patient carries a heterozygous mutation in c.7084G>A site on the R1Y1 gene with the genotype GA in this case, agreed with current research.

Treatment of MH requires a comprehensive approach including discontinuing triggering agents, hyperventilation, timely dantrolene administration, and alleviation of hyperthermia. Dantrolene is an effective antidote [23,24], approved by Health Canada (Ottawa, Ontario) and the U.S. Food and Drug Administration (Silver Spring, Maryland) for treatment of MH crisis in 1974 and 1979, respectively [25]. It plays a role as an antagonist at the ryanodine receptor to slow the release of calcium and to allow the cells to reincorporate it into the sarcoplasmic reticulum. Malignant Hyperthermia Association of the United States (MHAUS; Sherburne, New York) guidelines state that it must be available for dantrolene to treat MH within 10 min of the decision at where MH-triggering agents are used [26]. Giving an initial 2.5-mg/kg dantrolene dose, as MHAUS recommends, until adequate response is achieved. At least 720 mg of dantrolene should be stock to administer 10mg/kg to a 70kg patient for enough treatment at each hospital or institution, MHAUS mandates. Ryanodex is a more concentrated preparation that contains 250mg of dantrolene. Dantrolene has insufficient reserves in Chinese hospitals resulting from rich cost, limited shelf life (3-year) and low incidence of MH [26]. When the 19 years old girl was transferred to Affiliated Hospital of Gui Zhou Medical University for further treatment, cardiac arrest has happened. Considering the patient's critical condition, it was so late that missed the best time for rescue, we deeply regretted the failure to save the live of the young patient after more than an hour of hard rescue. Because it was not available at Li Mei Kang Hospital, this patient was not treated with dantrolene, which was not used after being transferred to Affiliated Hospital of Gui Zhou Medical University owing to be missed the best time for treatment.

## Conclusion

This case report reflects the clinician's lack of experience of early MH and the shortage of dantrolene in Chinese institutions, which ultimately results in death. Here, we describe the detailed

autopsy situation and the pathophysiological changes of MH. We hope attention should be paid for institutions to recognize the importance of reserve dantrolene, for clinicians to raise awareness of MH and treatment time to save lives.

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