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Malignant Hyperthermia in a Patient with Graves' Disease during Subtotal Thyroidectomy

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Abstract. We report the case of a 31-year-old man with Graves' disease who manifested malignant hyperthermia during subtotal thyroidectomy. His past medical history and family history were unremarkable. Before surgery, his condition was well controlled with propylthiouracil, β-adrenergic blocker and iodine. During the operation, anesthesia was induced by intravenous injection of vecuronium and thiopental, followed by suxamethonium for endotracheal intubation. Anesthesia was maintained with nitrous oxide and sevoflurane. One hour after induction of anesthesia, his end tidal carbon dioxide concentration (ET_{CO2}) increased from 40 to 50 mmHg, heart rate increased from 90 to 100 beats per min and body temperature began to rise at a rate of 0.3°C per 15 min. Suspecting thyroid storm, propranolol 0.4 mg and methylprednisolone 1,500 mg were administered, which, however, had little effect. Despite the lack of muscular rigidity, the diagnosis of malignant hyperthermia was made based on respiratory acidosis. Sevoflurane was discontinued and dantrolene was given by intravenous bolus. Soon after the treatment, ET_{CO2}, heart rate and body temperature started to fall to normal levels. His laboratory findings showed abnormally elevated serum creatine phosphokinase and myoglobin but normal thyroid hormone levels. Since dantrolene is efficacious in thyrotoxic crisis and malignant hyperthermia, an immediate intravenous administration of dantrolene should be considered when a hypermetabolic state occurs during anesthesia in surgical treatment for a patient with Graves' disease.

Key words: Graves' disease, Malignant hyperthermia, Subtotal thyroidectomy, Thyrotoxic crisis, Dantrolene
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THYROTOXIC crisis is a decompensated state of hyperthyroidism precipitated by excess release of thyroid hormones into the circulation. It is characterized by hyperpyrexia, marked tachycardia and susceptibility to severe hypotension (cardiovascular collapse). Before the introduction of antithyroid drugs and adrenergic blocking agents in the preparation of patients for thyroidectomy, surgical storm during the early postoperative period was the most common cause of thyrotoxic crisis [1]. Mortality rates of patients with thyrotoxic crisis have ranged from 10% to 75% [2].

Malignant hyperthermia is a genetic disorder characterized by a hypermetabolic crisis triggered by halogenated inhalational anesthetics and/or succinylcholine [3, 4]. Its signs and symptoms include fever, tachycardia, muscular rigidity, hypoxemia, myoglobinuria and an elevated serum creatine phosphokinase (CPK). None of the clinical features of malignant hyperthermia is specific to malignant hyperthermia. Diagnosis depends on recognition of the possible features that can occur during a malignant hyperthermia reaction and exclusion of other causes, such as sepsis, anaphylaxis, pheochromocytoma, thyroid storm and cerebral ischemia, that create clinical features similar to those of malignant hyperthermia [5]. Early diagnosis is important, as

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prompt, appropriate treatment leads to the best outcome.

Since both thyrotoxic crisis and malignant hyperthermia have similar clinical presentations, if thyrotoxic crisis occurs in an anesthetized patient with Graves' disease, differential diagnosis between them is not easy. We present here a case of malignant hyperthermia occurring in a patient with Graves' disease during subtotal thyroidectomy. Differential diagnosis and treatment for a hypermetabolic state encountered during anesthesia will be discussed.

Case Report

A 31-year-old man who had been aware of tremulous hands and goiter for six months was diagnosed with Graves' disease and was treated with thiamazole. Due to skin eruptions, thiamazole was discontinued and treatment was restarted with propylthiouracil (PTU). Under a regimen of PTU 600 mg daily and β-adrenergic antagonist nipradilol 12 mg daily, his condition was poorly controlled and thyroid function test ten months after PTU-treatment revealed a hyperthyroid state showing elevated free T4 (45 pmol/L, normal range 13–25 pmol/L) and elevated total T3 (5.0 pmol/L, normal range 1.2–2.8 pmol/L) and suppressed TSH (<0.02 mU/L, normal range 0.5–4.1 mU/L) with positive thyrotropin receptor antibody (TRAb 67.3%, normal range <10%) (Fig. 1). He was referred to our hospital to undergo subtotal thyroidectomy. He had a past history of aspermatism, had no previous general anesthetics and had no known family history of anesthetic-related death or serious complication.

On admission, he was 176 cm in height and weighed 69.7 kg. His blood pressure was 120/80 mmHg, pulse rate was 100 beats per minute (bpm) with a regular rhythm, and body temperature was 36.2°C. An elastic soft diffuse goiter was palpable without any tenderness or lymphadenopathy. His right lobe was 9.0×3.5 cm and the left was 9.5×3.5 cm. He had no lid retraction or exophthalmos. There were no abnormal findings upon chest, abdomen and neurological examinations. Laboratory findings on admission revealed that urine and peripheral blood cells were normal. Routine biochemical tests were normal except for moderate elevation of serum alkaline phosphatase level. Arterial blood gases were pH 7.382, $PaCO_2$ 43.9 mmHg, PaO_2 91.1 mmHg and bicarbonate 26.0 mmol/L. Thyroid function tests showed

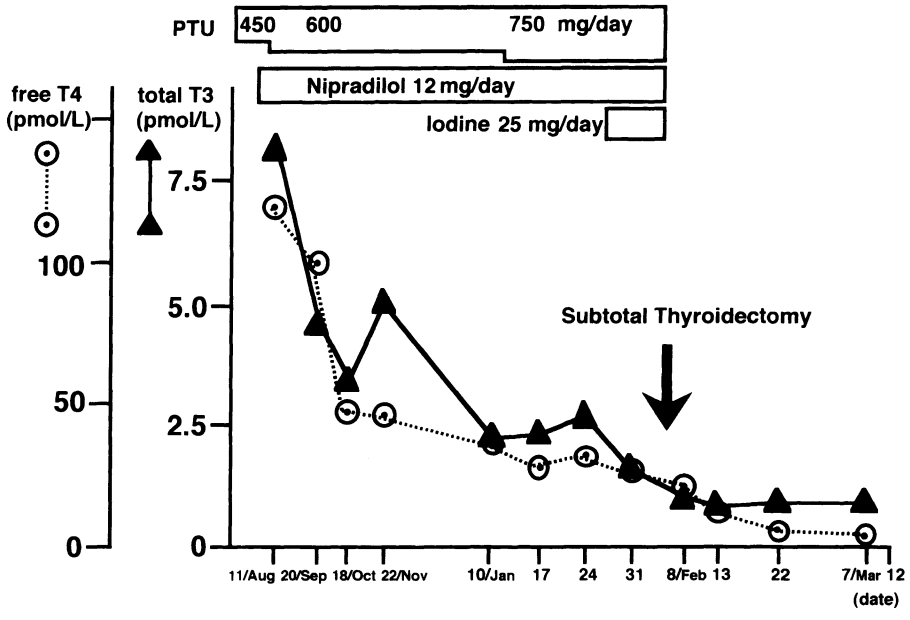

Fig. 1. Clinical course of the patient.
Open circle and closed triangle indicate the levels of serum free T4 and total T3, respectively. TSH had been undetectable since the outbreak of hyperthyroidism due to Graves' disease.

elevated free T4 (35 pmol/L) and normal total T3 (2.2 pmol/L) and suppressed TSH (<0.02 mU/L) with positive TRAb (68.8%).

After admission, the daily dose of PTU was increased to 750 mg, and nipradilol 12 mg daily was maintained for the treatment of hyperthyroidism. Aqueous iodine 25 mg daily was administered for 9 days before the subtotal thyroidectomy (Fig. 1). Six days before surgery, thyroid function tests showed slightly elevated free T4 (26 pmol/L) and normal total T3 (1.6 pmol/L), and serum CPK was within normal limits (131 IU/L, normal range 54–253 IU/L).

The patient underwent a subtotal thyroidectomy after 28 days of hospital treatment (Fig. 2). After premedication with hydroxyzine 50 mg, atropine 0.5 mg and famotidine 20 mg given intramuscularly, anesthesia was induced with vecuronium 1 mg and thiopental 350 mg at 0907 h and tracheal intubation was induced with suxamethonium 120 mg in rapid sequence. Anesthesia was maintained with nitrous oxide (3.2 L/min), oxygen (2.8 L/min) and sevoflurane (1–2.5%), and a spontaneous regular respiratory pattern was established 30 min after induction. At that time, the patient had rectal temperature of 37.7°C, blood pressure of 106/62 mmHg and heart rate of 90 bpm. Forty min after induction of anesthesia (just before starting surgery), the patient's end tidal carbon dioxide tension (ET_{CO2}) started to increase from 40 to 50 mmHg. Thirty min later, heart rate increased progressively from 90 to 100 bpm, and 15 min later, rectal temperature showed steady increases with persistent tachycardia of 110 to 120 bpm. One hour after the start of surgery, the thyroid was subtotally removed, but the patient was tachycardic and feverish. Suspecting thyroid crisis induced by surgical injury to the thyroid, propranolol 0.4 mg and methylprednisolone 1,500 mg were given by intravenous bolus. Treatment achieved a heart rate of 100 bpm, but had little effect on rectal temperature which increased to the maximum 38.8°C at a rate of 0.3°C per 15 min, or on ET_{CO2} which remained high at 60 mmHg. Arterial blood sample showed respiratory acidosis (pH 7.26, $PaCO_2$ 66.1 mmHg, PaO_2 282 mmHg, bicarbonate 29.4 mmol/L, FiO_2 0.8). A diagnosis of malignant hyperthermia was made based on hyperpyrexia, elevated ET_{CO2} and respiratory acidosis. Sevoflurane

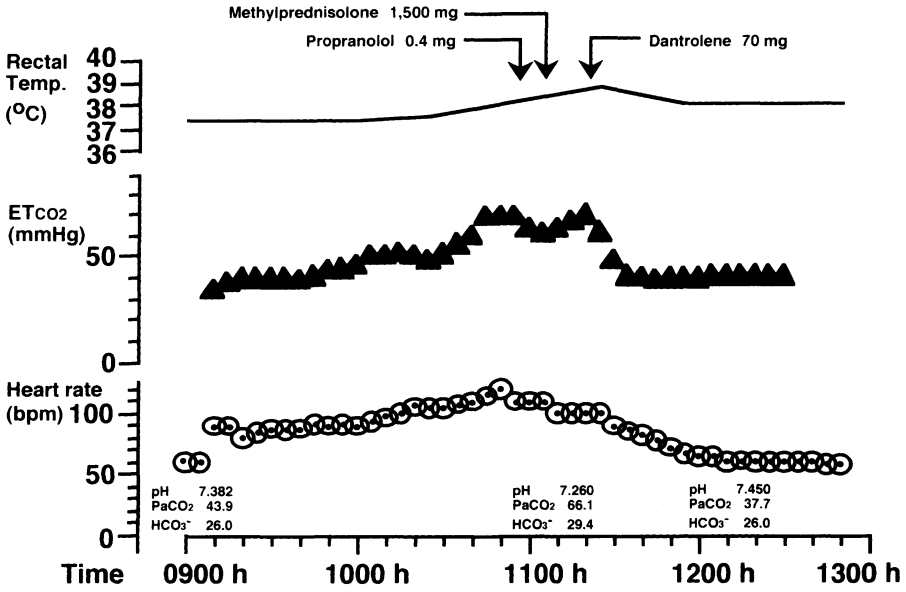

Fig. 2. Changes in rectal temperature, end tidal carbon dioxide concentration (ET_{CO2}) and heart rate during subtotal thyroidectomy.
Anesthesia was applied at 0907 h and the surgical operation started at 0948 h. The thyroid was subtotally removed at 1054 h. Propranolol 0.4 mg, methylprednisolone 1,500 mg and dantrolene 70 mg were administered intravenously at 1057 h, 1105 h and 1125 h, respectively. Arterial blood gases were analyzed at 1122 h and 1205 h under surgery. Operation was completed at 1238 h and anesthetic was discontinued at 1302 h.

was discontinued and bolus of 70 mg dantrolene was given. The inspiratory mixture was changed to 100% O_2 and active cooling of skin surface was done. Within 5 min after these procedures, the patient showed improvements and heart rate eventually decreased to 60 bpm, rectal temperature dropped to 37.2°C, and ET_{CO2} decreased and was maintained at 40 mmHg. Arterial blood gas analysis showed improvement of respiratory acidosis (pH 7.45, $PaCO_2$ 37.7 mmHg, PaO_2 573 mmHg, bicarbonate 26.0 mmol/L, FiO_2 1.0). The operation was completed in 2 h 50 min and the anesthetic was discontinued 25 min later. The patient soon emerged from anesthesia and the trachea was extubated. After transfer to intensive care unit, his blood pressure was 140/90 mmHg, heart rate 65 bpm, and rectal temperature 37.2°C. During the surgical procedure, muscular rigidity was absent, but intraoperative laboratory findings indicated noticeable elevation of serum CPK (5,313 IU/L), potassium (5.2 mEq/L, normal range 3.6–5.0 mEq/L) and myoglobin (762 nmol/L, normal range <2.9 nmol/L) levels and increased urinary excretion of myoglobin (1,802 nmol/L, normal range <1.2 nmol/L).

Thyroid function tests on the third postoperative day showed that serum free T4 remained at a normal level (21 pmol/L) and total T3 had decreased below normal range (1.0 pmol/L) (Fig. 1). During the early postoperative period, there was a transient increase in serum CPK, lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) (Fig. 3), being at the maximum levels of CPK (13,200 IU/L), LDH (329 IU/L, normal range 109–193 IU/L) and AST (216 IU/L, normal range 11–30 IU/L) on the third postoperative day. The remainder of the patient's hospital stay was uneventful and he was discharged on the seventh postoperative day, clinically euthyroid and with a normal serum CPK level (240 IU/L).

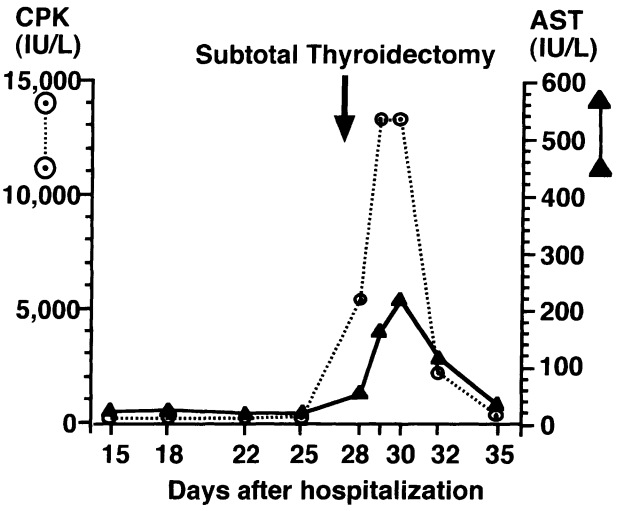

Fig. 3. Changes in serum CPK and AST while in the hospital.
Open circle and closed triangle indicate CPK and AST, respectively. CPK reached the highest value of 13,200 IU/L on the second and the third postoperative days. Perioperative laboratory findings indicated significantly elevated levels of serum and urine myoglobin (762 nmol/L and 1,802 nmol/L, respectively).

Discussion

Thyrotoxic crisis and malignant hyperthermia have marked clinical similarities [6–8]. There are several reports of cases of life-threatening thyrotoxicosis during anesthesia that have mimicked malignant hyperthermia [9–16]. After the introduction of antithyroid drugs, however, the incidence of perioperative thyroid crises was reduced. As can be seen from the reported cases, surgical stresses cause thyrotoxic crises during anesthesia in untreated or poorly treated thyrotoxic patients. Although the present patient had hyperthyroidism due to Graves' disease, his thyroid function was controlled at the time of surgery.

When we encountered unexpected tachycardia and hyperpyrexia during operation, initially we could not exclude the possibility of thyrotoxicosis. However, the hyperthyroid state was later discounted because the use of β-adrenergic blocking agent and a large dose of glucocorticoid did not ameliorate the symptoms. Since the present patient remained euthyroid before surgery by preoperative antithyroid drug-therapy, thyrotoxic crisis was unlikely. Furthermore, thyroid storm, when related to surgery, usually develops within 6–18 hours postoperatively [1]. In the present case, the patient's heart rate increased to over 100 bpm within 30 min after initiation of surgery, which was too rapid for thyrotoxic crisis. Laboratory findings of the patient during the intraoperative period revealed a remarkably increased level of serum CPK, that did not agree with hyperthyroidism [17]. Indeed, thyroid function tests two

days after surgery revealed normal serum free T4, indicating euthyroidism during the operation.

Although the patient lacked muscle rigidity and a rapid increase in body temperature (as great as 0.5°C/15 min), the diagnosis of abortive malignant hyperthermia was made based on the symptoms and signs such as tachycardia, increased body temperature (0.3°C/15 min), increased ET_{CO2}, increased arterial carbon dioxide pressure and respiratory acidosis [18]. Perioperative laboratory studies demonstrated marked increases in serum CPK and myoglobin and the presence of myoglobinuria, confirming the diagnosis.

Malignant hyperthermia is caused by abnormal Ca^{++} regulation in skeletal muscle cells [19]. The abnormality in the Ca^{++}-induced Ca^{++} release channels (ryanodine receptor) in skeletal muscle sarcoplasmic reticulum has been demonstrated in malignant hyperthermia [20]. There is a report that suggests a possible relation between hyperthyroidism and malignant hyperthermia. Kumar *et al.* [21] reported that the time to trigger malignant hyperthermia was significantly less in malignant hyperthermia-susceptible swine that were in thyrotoxicosis compared with swine in a non-thyrotoxic state. T3-induced elevation in body temperature or other unidentified T3-related factors may facilitate malignant hyperthermia. T3 increases Na^{+}-K^{+}-ATPase activity and the steady state levels of ryanodine receptor mRNA and sarcoplasmic reticulum Ca^{++}-ATPase mRNA in both heart and skeletal muscle [22–24]. The finding that T3 regulates the proteins that are involved in heat production and Ca^{++} homeostasis suggests that hyperthyroidism and malignant hyperthermia may have common pathogenic pathways to manifest hyperpyrexia and abnormalities in cardiac and muscular contractile properties.

Dantrolene exerted salient therapeutic effects with a rapid reduction in heart rate, ET_{CO2} and body temperature in the present patient. At one time, the mortality rate of malignant hyperthermia reached upward of 70%. However, since the advent of dantrolene, it has dropped to less than 5% [25]. In addition to the well defined role in the treatment of malignant hyperthermia, dantrolene has been used in the treatment of thyroid crisis, achieving clinical improvement without adverse effects [11, 12]. The clinical presentations are similar between thyroid crisis and malignant hyperthermia and to distinguish them is not easy especially when the muscle rigidity and the respiratory acidosis typical of malignant hyperthermia are not prominent. From these points of view, the immediate administration of dantrolene may be justified when hyperpyrexia and skeletal muscle abnormality occur during anesthesia in a patient with Graves' disease.

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