Thyroid storm with delayed hyperbilirubinemia and severe heart failure: indication and contraindication of plasma exchange

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Summary

Thyroid storm (TS) is a life-threatening condition that may suffer thyrotoxic patients. Therapeutic plasma exchange (TPE) is a rescue approach for TS with acute hepatic failure, but it should be initiated with careful considerations. We present a 55-year-old male patient with untreated Graves' disease who developed TS. Severe hyperthyroidism and refractory atrial fibrillation with congestive heart failure aggregated to multiple organ failure. The patient was recovered by intensive multimodal therapy, but we had difficulty in introducing TPE treatment considering the risk of exacerbation of congestive heart failure due to plasma volume overload. In addition, serum total bilirubin level was not elevated in the early phase to the level of indication for TPE. The clinical course of this patient instructed delayed elevation of bilirubin until the level of indication for TPE in some patients and also demonstrated the risk of exacerbation of congestive heart failure by TPE.

Learning points:

- Our patient with thyroid storm could be diagnosed and treated promptly using Japan Thyroid Association guidelines for thyroid storm.
- Delayed elevation of serum bilirubin levels could make the decision of introducing therapeutic plasma exchange difficult in cases of thyroid storm with acute hepatic failure.
- The risk of worsening congestive heart failure should be considered carefully when performing therapeutic plasma exchange.

Background

Thyroid storm (TS) is a life-threatening condition with multiple organ failure that is triggered in thyrotoxic patients by severe stress (1). Clinical manifestations of TS are unconsciousness, high fever, tachycardia, congestive heart failure, and gastrointestinal symptoms. Burch-Wartofsky Point Scale (BWPS) has been used for its diagnosis (2). Simple and useful diagnostic criteria and guidelines for TS were proposed by Japan Thyroid Association (JTA), and rapid diagnosis and

commencement of treatment were expected (3). Supportive therapy for multiple organ failure, especially for hepatic failure, is crucial for improving the prognosis of TS. Therapeutic plasma exchange (TPE) is recommended for TS with acute hepatic failure, but there is limited evidence on its application (4). Herein, we report a case of TS with acute hepatic failure that required a careful decision on introduction of TPE and discussed about the considerations for its application.

Case presentation

A 55-year-old man was referred to our hospital with watery diarrhea and dyspnea. The patient was a smoker and had no family history of thyroid disease. He felt finger tremor for 12 years and gradually lost body weight since its commencement. Intermittent recurring diarrhea began six years before this hospital visit. Two weeks prior, he had a fever, fatigue, and cough and was admitted to a nearby hospital because he felt diarrhea and dyspnea were worsening. The patient was diagnosed with heart failure due to atrial fibrillation and he was transferred to our hospital. He was alert and oriented on admission, body temperature was 36°C, blood pressure was 157/100 mmHg, and heart rate was 190 b.p.m. with irregular rhythm. He had orthopnea with respiratory rate of 18 breaths per minute and SpO₂ was 97% in room air. He presented swelling of eyelids, conjunctival injection and exophthalmos. On examination, he had a diffuse goiter without tenderness and had crackles with reduced breath sounds in the lungs. He also had pitting edema of his feet. We therefore suspected thyroid storm due to Graves' disease.

Investigation

The laboratory tests revealed mild dysfunction of the liver and the elevation of brain natriuretic peptide (BNP) on admission (Table 1, Day 1). The patient had thyrotoxicosis with elevated thyroid stimulating hormone receptor antibody (TRAb), so he was diagnosed with Graves' disease. ECG showed atrial fibrillation with tachycardia (Fig. 1A). Chest X-ray revealed cardiac enlargement and accumulation of pleural effusion that indicated heart failure (Fig. 1B). There was no obvious focus of infection by chest and abdominal CT (Fig. 1C). Ultrasonography of the neck revealed a diffusely enlarged thyroid gland with increased blood flow (Fig. 1D). According to the JTA guidelines for TS (3), the patient would be diagnosed with definite TS because he had thyrotoxicosis with tachycardia, heart failure, and gastrointestinal symptoms. BWPS of the patient (45 points) was highest category (≥45 points), which was also highly suggestive of TS (2).

Treatment

The patient was administered methimazole (MMI) 60 mg/day and hydrocortisone 300 mg/day

Table 1 Laboratory data during treatment for thyroid storm.

	Reference range	Day 1	Day 3	Day 5
White blood cells (/μL)	33–86 × 10 ²	59.3	191.5	202.4
Red blood cells (/μL)	435–555 × 10 ⁴	501	447	415
Platelets (/μL)	15.8–34.8 × 10 ⁴	11.2	6.9	4.8
Prothrombin time-international normalized ratio	0.8–1.2	1.3	5.2	3.0
Aspartate aminotransferase (IU/L)	13–30	36	2383	450
Alanin aminotransferase (IU/L)	10–42	22	1039	713
Lactate dehydrogenase (IU/L)	124–222	228	2645	362
Alkaline Phosphatase (IU/L)	106–322	367	288	304
Total Bilirubin (mg/dL)	0.4–1.5	1.6	2.2	5.3
Total Protein (g/dL)	6.6–8.1	6.4	5.7	5.9
Albumin (g/dL)	4.1–5.1	3.2	3.0	2.9
Urea nitrogen (mg/dL)	8–20	10.9	54.3	69.0
Creatinine (mg/dL)	0.65–1.07	0.45	3.33	3.60
Sodium (mEq/L)	138–145	138	137	133
Potassium (mEq/L)	3.6–4.8	4.2	5.8	5.7
Chloride (mEq/L)	101–108	107	97	98
Brain natriuretic peptide (pg/mL)	<18.4	193.3	ND	ND
Ketone bodies (μmol/L)	28–120	ND	328.8	244.6
Acetoacetic acid (μmol/L)	<76	ND	95.6	64.2
3-Hydroxybutyric acid (μmol/L)	0–74	ND	233.2	180.4
Thyroid stimulating hormone (μIU/mL)	0.5–5.0	<0.005	ND	ND
Free tri-iodothyronine (pg/mL)	2.3–4.0	28.0	16.0	ND
Free thyroxine (ng/dL)	0.9–1.7	>7.8	>7.8	ND
TSH receptor antibody (IU/L)	<2.0	11.4	31.6	ND

Laboratory data of the following key days are used in this table: on admission (day 1), on the day of transfer to intensive care unit (day 3), and on the day of withdrawal from ventilator (day 5).
ND, not determined.

Figure 1

Imaging studies and a physiological test of the patient on admission. Electrocardiogram shows the presence of atrial fibrillation (A). The heart was enlarged with pleural effusion on chest X-ray (B). CT shows no obvious focus of infection (C). The thyroid gland was diffusely enlarged with increased blood flow on ultrasonography, which is suggestive of Graves' disease (D).

intravenously, and potassium iodide 200 mg/day orally for hyperthyroidism (Fig. 2). He had a refractory atrial fibrillation despite treatment with landiolol, a beta-blocker. Respiratory status gradually worsened after a few hours, and he needed to receive supplemental oxygen via nasal cannula at 4 L/min. Systolic blood pressure reduced to approximately 80 mmHg and he had oliguria. Blood tests were examined after 18 h, which showed multiple organ failure with disseminated intravascular coagulation (DIC). Acute physiology and chronic health evaluation (APACHE)-II score was 14 points at that time. He was therefore transferred to the intensive care unit (ICU) to stabilize his cardiopulmonary status.

He was then intubated and received temporal mechanical ventilation for respiratory failure. Although we attempted to restore sinus rhythm, atrial fibrillation was refractory to cardioversion. We also had difficulty in controlling the heart rate, despite an increased dose of landiolol. Owing to worsening heart and renal failure, oliguria did not improve, despite treatment with diuretics. We began continuous hemodiafiltration (CHDF) to remove excess fluid on day 3. Continuous intravenous administration of noradrenaline was needed to maintain blood pressure when performing CHDF. Arterial oxygenation gradually increased due to improvement of respiratory failure followed by withdrawal from the ventilator on day 5.

Regarding treatment of acute hepatic failure, we considered introducing TPE because the patient's general condition did not improve within 48 h. On day 3, serum total bilirubin level did not fulfill the indication of TPE according to JTA guidelines for TS. The patient's serum total bilirubin level was 3.5 mg/dL, which was lower than that of the cut off values of 5.0 mg/dL (Table 1, Day 3). Serum total bilirubin increased to 5.3 mg/dL and fulfilled the indication for TPE treatment on day 5. Meanwhile, blood tests showed decrease in liver enzyme levels and thyroid hormone levels with improvement of general condition (Table 1, day 5 and Fig. 2). We consulted the adaptation of TPE with ICU staff and it was decided not to use it because plasma volume overload by TPE could exacerbate congestive heart failure. Cardiopulmonary condition was stabilized on day 8, and the patient was transferred to a general ward.

Outcome and follow-up

The doses of MMI, hydrocortisone and potassium iodine were gradually reduced in response to the improvement of hyperthyroidism. Thyroid hormone levels began to elevate when the doses of MMI were reduced to 20 mg/day on day 5, so its doses were increased again to 60 mg/day. He developed drug-induced agranulocytosis on day 50, so MMI was stopped and granulocyte colony

Figure 2

Clinical course during hospitalization of our patient with thyroid storm. Hyperthyroidism gradually improved under treatment with methimazole, potassium iodine, and hydrocortisone. Tachycardia was controlled with beta-blockers, and congestive heart failure was treated with continuous hemodiafiltration followed by intermittent hemodialysis. Respiratory failure was supported by mechanical ventilator. Serum total bilirubin levels gradually elevated and continued to increase until day 18, despite improvement of liver enzymes and the general condition. MMI, methimazole; KI, potassium iodide; FT3, free tri-iodothyronine; FT4, free thyroxine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T.Bil, total bilirubin; CHDF, continuous hemodiafiltration; IHD, intermittent hemodialysis.

stimulating factor (G-CSF) was administered immediately. He underwent total thyroidectomy on day 54, followed by thyroid hormone supplementation with 125 μg/day of levothyroxine. He was discharged from our hospital on day 72 and returned home.

Discussion

TS is a life-threatening condition with multiple organ failure that occurring in thyrotoxic patients. Prompt treatment is needed to save patients with TS, but the diagnosis of TS is difficult to ascertain because of its rarity and because it does not have specific symptoms. BWPS is the first diagnostic criteria of TS proposed by Burch and Wartofsky in 1993 (2). Recently, novel diagnostic criteria for TS were established by JTA followed by a nationwide

survey conducted in Japan (3). Our patient was successfully diagnosed with TS based on these criteria and immediate treatment could be started that would ultimately save his life.

The following mechanism has been reported as a cause of hepatic failure in TS: hepatic congestion due to congestive heart failure, hypoxia-induced centrilobular necrosis, direct damage of hepatocytes by thyroid hormone, and drug-induced hepatitis (5). The present patient had symptoms associated with hyperthyroidism for 12 years, so he may have had thyrotoxicosis without appropriate treatment. We therefore speculated that he already had underlying damage of hepatocytes before hospital admission. Hepatic congestion is another possible mechanism of the hepatic failure in our patient because he had congestive heart failure with refractory atrial fibrillation. His blood pressure was low during the treatment for heart failure, so there may have been hypoxia-induced liver damage. We could not perform liver biopsy to confirm the pathology because the patient's circulatory state was unstable when he was treated at ICU.

TPE is recommended for patients with TS when their general condition does not improve after 24–48 h of treatment for hyperthyroidism, according to the JTA guidelines for TS (4). TPE efficiently improves thyrotoxicosis by rapidly removing the serum proteins to which approximately 99% of thyroid hormones bind (6). TPE theoretically removes catecholamines, cytokines, and anti-thyroid stimulating hormone receptor antibodies, which can contribute to improvement of the general condition (7). Circulating plasma volume, on the other hand, increases up to 1.0–1.5 times when TPE is performed (8). Volume overload can deteriorate congestive heart failure. In our patient, we considered adaptation of TPE for uncontrolled hyperthyroidism with acute hepatic failure on day 2; but he had respiratory failure due to congestive heart failure. We therefore decided not to select TPE, with concern of worsening the congestion. Our patient's respiratory condition gradually improved thereafter, and he could be withdrawn from the ventilator.

JTA guidelines for TS recommend introducing TPE when TS patients with hepatic failure are unconscious and their laboratory data satisfy the following criteria: serum total bilirubin levels >5.0 mg/dL or hepaplastin time <30% and arterial ketone body ratio <0.7 (4). In our patient, serum bilirubin levels did not elevate rapidly in correspondence with elevation of liver enzymes. Liver enzymes and thyroid hormone levels had peaked out when serum total bilirubin levels increased above 5.0 mg/

dL. We therefore focused on the treatment of congestive heart failure prior to TPE at that time.

Delayed elevation of serum bilirubin levels has been reported in patients with multiple organ failure (9); disorder of bilirubin transportation due to hypoxia-induced mitochondrial dysfunction is one such estimated mechanism (10). Our patient exhibited a severe decrease in blood pressure during the treatment of heart failure and atrial fibrillation, so required vasopressor several times. We therefore speculate that there may have been circulatory failure followed by hepatic hypoxia leading to the delayed hyperbilirubinemia.

This is a report of just a single case, so further prospective surveys are needed to determine the criteria of indication for TPE for patients with TS. A prospective multicenter registry study of thyroid storm is currently in progress in Japan and we are looking for the new criteria according to this report.

In conclusion, the possibility of delayed hyperbilirubinemia and risk for worsening congestive heart failure should be considered when introducing TPE for TS patients with acute hepatic failure.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent was obtained from the patient for publication of this case report.

Author contribution statement

T Nakao is an endocrinologist physician who followed the patient during hospitalization and wrote the first draft. K Takeshima is the corresponding author and responsible for organizing this article. H Ariyasu is a senior advisor and revised the final draft. H Iwakura, C Kurimoto, S Uraki, S Morita, Y Furukawa are endocrinologist physicians who followed the

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