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Fulminant hepatitis and elevated levels of sIL-2R in thyroid storm

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Summary

We report the case of a 48-year-old man with thyroid storm associated with fulminant hepatitis and elevated levels of soluble interleukin-2 receptor (sIL-2R). Fatigue, low-grade fever, shortness of breath, and weight loss developed over several months. The patient was admitted to the hospital because of tachycardia-induced heart failure and liver dysfunction. Graves' disease with heart failure was diagnosed. He was treated with methimazole, inorganic iodide, and a β-blocker. On the day after admission, he became unconscious with a high fever and was transferred to the intensive care unit. Cardiogenic shock with atrial flutter was treated with intra-aortic balloon pumping and cardioversion. Hyperthyroidism decreased over 10 days, but hepatic failure developed. He was diagnosed with thyroid storm accompanied by fulminant hepatitis. Laboratory investigations revealed elevated levels of sIL-2R (9770 U/mL). The fulminant hepatitis was refractory to plasma exchange and plasma filtration with dialysis, and no donors for liver transplantation were available. He died of hemoperitoneum and gastrointestinal hemorrhage due to fulminant hepatitis 62 days after admission. Elevated circulating levels of sIL-2R might be a marker of poor prognosis in thyroid storm with fulminant hepatitis.

Learning points:

- The prognosis of thyroid storm when fulminant hepatitis occurs is poor.
- Liver transplantation is the preferred treatment for fulminant hepatitis induced by thyroid storm refractory to plasma exchange.
- Elevated levels of soluble interleukin-2 receptor might be a marker of poor prognosis in patients with thyroid storm.

Background

Thyroid storm is a rare, life-threatening complication of Graves' disease (1). Liver dysfunction in thyroid storm is induced by hepatic ischemia, dysfunction of hepatic metabolism, direct injury from thyrotoxicity, and anti-thyroid drugs (2). Fulminant hepatitis with thyroid storm causes multiple organ failure and is associated with poor prognosis.

Interleukin-2 (IL-2) is a cytokine produced by CD4-positive T cells. IL-2 binds to IL-2 receptor expressed on the cell surface, thereby activating T cells, B cells, natural killer cells, monocytes, and macrophages (3). Activated lymphocytes produce and release IL-2 receptor from the cell surface, which can be measured as soluble interleukin-2 receptor (sIL-2R). Multiple organ failure develops as a result of cytokine storm in some patients; circulating levels of sIL-2R are increased. Here, we report a case of thyroid storm with elevated levels of sIL-2R. The patient could not be rescued with plasma exchange for fulminant hepatitis.

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Case presentation

A 48-year-old man had fatigue for 3 months. One month before admission, he developed a low-grade fever, shortness of breath, and weight loss. He was admitted to the hospital because of tachycardia, liver dysfunction, hyperthyroidism, and cardiomegaly on chest x-ray. He had been prescribed antihypertensives for years. He had no history of heavy drinking, blood transfusion, or drug abuse. Blood tests revealed Graves' disease. Methimazole, inorganic iodide, hydrocortisone, and a β-blocker were started. On the day after admission, he became unconscious with a high fever and was transferred to the intensive care unit after tracheal intubation.

Table 1 Summary of laboratory testing results.

Laboratory test	Values	Reference range
Peripheral blood		
Leukoses (x 10^3/μL)	11.1	3.3–8.6
Erythrocytes (x 10^4/μL)	434	435–555
Hemoglobin (g/dL)	13.1	13.7–16.8
Platelets (x 10^4/μL)	28.9	15.8–34.8
Serum		
Albumin (g/dL)	2.56	4.1–5.1
Total bilirubin (mg/dL)	2.5	0.4–1.5
Direct bilirubin (mg/dL)	1.2	0.1–0.3
Aspartate transaminase (U/L)	1458	13–30
Alanine aminotransferase (U/L)	555	10–42
Lactate dehydrogenase (U/L)	3266	124–222
Alkaline phosphatase (U/L)	370	103–322
Glucose (mg/dL)	35	73–109
Blood urea nitrogen (mg/dL)	42.3	8–20
Creatinine (mg/dL)	2.16	0.7–1.1
Na (mmol/L)	141	138–145
K (mmol/L)	5.4	3.6–4.8
Ca (mg/dL)	7.6	8.8–10.1
CRP (mg/dL)	1.81	<0.14
PT (%)	19.1	80–100
Ammonia (μg/dL)	203	12–66
BNP (pg/mL)	397.3	<18.4
Free T3 (pg/mL)	7.5	1.9–3.2
Free T4 (ng/dL)	6.0	0.7–1.5
TSH (μIU/mL)	<0.01	0.4–5.0
TRAb (%)	40	<15%
TSAb (%)	645	<120%
Anti-TgAb (IU/mL)	40.0	141 10 6
Anti-TPOAb (IU/mL)	29.9	1.1–5.2
ANA	(–)	
AMA (units)	<1.5	<20
HBs Ag	(–)	
HCV Ab	(–)	
SIL-2R (U/mL)	9770	145–519

AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; Anti-TgAb., anti-thyroglobulin antibody; Anti-TPOAb, anti-thyroid peroxidase antibody; BNP, brain natriuretic peptide; CRP, C-reactive protein; HBs Ag, hepatitis B surface antigen; HCV Ab, anti-hepatitis C virus antibody; PT, prothrombin time; sIL-2R_ soluble interleukin-2 receptor; T3, triiodothyronine; T4, thyroxine; TRAb, thyroid-stimulating homione receptor antibody; TSAb, thyroid-stimulating antibody.

Investigation

On examination, height was 164 cm and weight was 59 kg. Temperature was 37.8°C, blood pressure was 77/56 mmHg, and heart rate was 141 beats per minute. The Glasgow Coma Scale score was E1VTM1 (sedated, T indicates endotracheal intubation). He had diffuse goiter without ophthalmopathy, abnormal sweating, distended jugular veins, and bilateral pretibial pitting edema. Blood tests showed extremely high levels of aspartate transaminase and alanine aminotransferase (1458 and 555 U/L, respectively), renal failure, hypoglycemia, coagulopathy, and hyperammonemia (Table 1). Arterial blood analysis revealed hypoxia and metabolic acidosis. Chest radiography demonstrated cardiomegaly and decreased pulmonary permeability in the right lung field (Fig. 1A). Electrocardiography showed atrial flutter. Echocardiography revealed a visual ejection fraction of 20% with diffuse hypokinesis. Computed tomography (CT) demonstrated an enlarged thyroid gland (Fig. 1B), but there were no abnormal lesions in the liver (Fig. 1C) or the brain. The patient was diagnosed with thyroid storm based on criteria from the Japan Thyroid Association and Burch–Wartofsky Point Scale (100 points).

Treatment

Cardiac arrest occurred 3 h after admission to the intensive care unit. Chest compressions and initiation of intra-aortic balloon pumping were performed for cardiogenic shock. Return of spontaneous circulation was achieved and cardioversion was performed for atrial flutter. Intravenous methimazole (30 mg/day), inorganic iodide (100 mg/day), hydrocortisone (200 mg/day), and landiolol hydrochloride (7.2γ) normalized thyroid function in 10 days (Fig. 2). Artificial respiratory management, intravenous glucose administration for hypoglycemia, and plasma exchange (including plasma filtration with dialysis and plasma adsorption) for hepatic failure resulted in the recovery of consciousness (E4V2M6). The patient was extubated on hospital day 10.

Outcome and follow-up

Transaminase levels decreased, but levels of total bilirubin increased and prothrombin time became prolonged (Fig. 2). The switch from methimazole to propylthiouracil was not effective. CT of the abdomen showed increased

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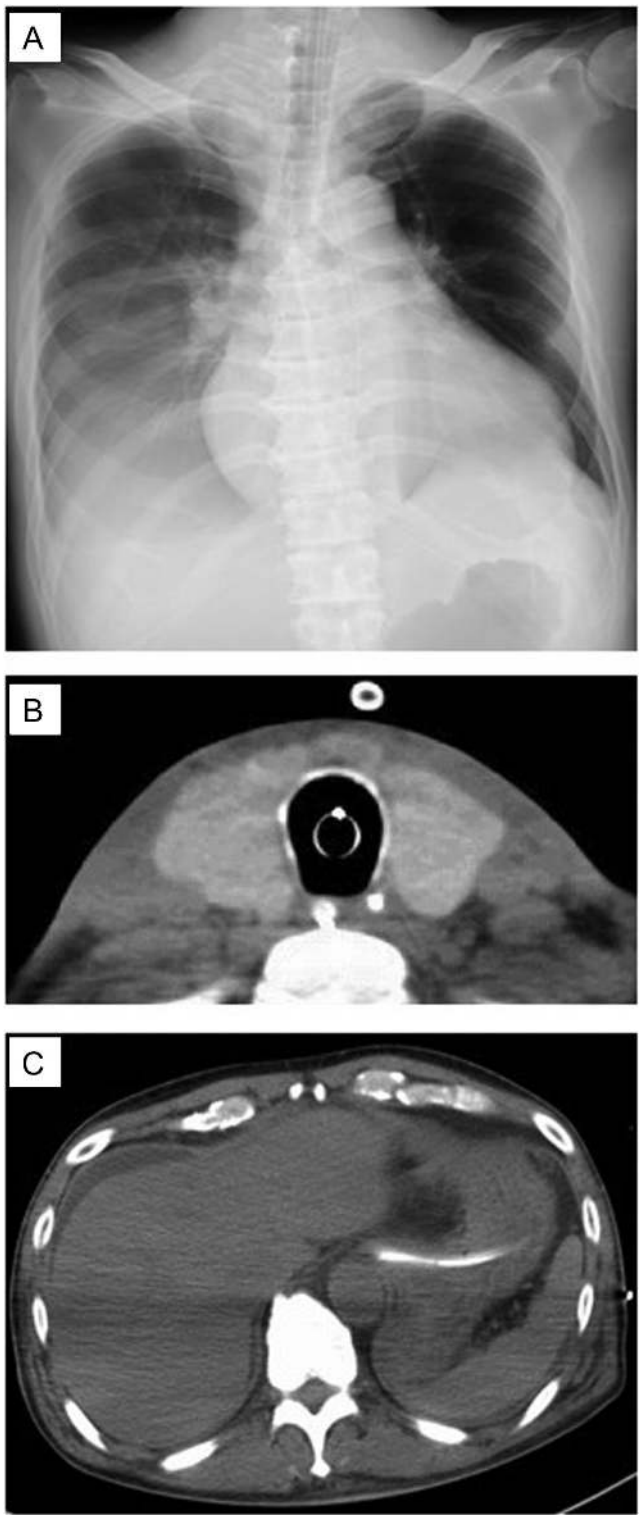
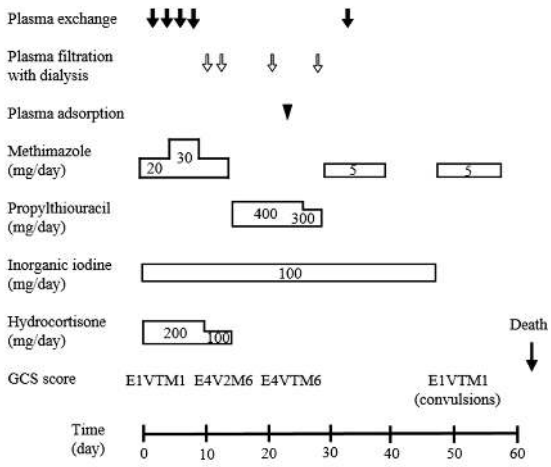


Figure 1
(A) Chest x-ray showed cardiomegaly and a pleural effusion. (B) Cervical computed tomography (CT) showed a swollen thyroid. (C) Abdominal CT showed ascites without any organic lesions in the liver.



Laboratory Test	Day2	Day10	Day27	Day39	Day56
Free T3 (pg/mL)	7.5	3.1	2.1	2.5	3.2
Free T4 (ng/dL)	6.0	2.3	1.3	1.6	1.5
Total bilirubin (mg/dL)	3.5	17.6	36.2	37.7	28.4
AST (U/L)	11960	65	46	22	24
ALT (U/L)	3087	67	49	14	2
PT (%)	8.9	37.3	28.6	26.6	20.7
Ammonia (μg/dL)	112	47	55	86	>500

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GCS, Glasgow Coma Scale; PT, prothrombin time; T3, triiodothyronine; T4, thyroxine.

Figure 2
Clinical course.

ascites. Coagulopathy and jaundice worsened. The patient was diagnosed with fulminant hepatitis. Investigations showed no evidence of viral hepatitis, congestive heart failure, or adverse drug effects, except for elevated levels of sIL2-R. Imaging studies and skin biopsy to detect intravascular lymphoma revealed no evidence of malignancy, suggesting that elevated sIL2-R levels were induced by thyroid storm. Fulminant hepatitis was refractory to plasma exchange. CT of the abdomen demonstrated exacerbation of liver atrophy. There were no suitable donors for orthotopic liver transplantation. Gastrointestinal bleeding, intra-abdominal hemorrhage, hematuria, subcutaneous bleeding, and endotracheal bleeding were not controlled. Red blood cell, platelet, and plasma transfusions were not effective in treating hemoperitoneum and gastrointestinal bleeding. The patient died on hospital day 62.

Discussion

We described a fatal case of thyroid storm complicated by fulminant hepatitis refractory to plasma exchange.

Fulminant hepatitis induced by thyroid storm is rare but life threatening. A previous report of thyroid storm with fulminant hepatitis showed four of ten patients died with heart failure and elevated levels of bilirubin (4, 5, 6). Orthotopic liver transplantation was performed in two of six patients who survived, but not in any patients who died (4, 5, 6). In thyroid storm, heart failure causes liver dysfunction via hepatic hypoxia. A nationwide survey in Japan found that the most common causes of death in patients with thyroid storm were multiple organ failure and congestive heart failure (7). In our patient, cardiogenic shock caused multiple organ failure and was the most important factor leading to fulminant hepatitis and death.

Hypoglycemia is rarely associated with thyroid storm. Excess levels of thyroid hormone increase levels of counterregulatory hormones and decrease the ability of insulin to bind to its receptor. Hypoglycemia with thyroid storm is caused by malnutrition, adrenal failure, decreased insulin clearance due to renal failure, and insufficient gluconeogenesis due to hepatic failure (8). Our patient had not eaten for 3 days before admission and developed cardiac and hepatic failure due to hyperthyroidism, which was associated with severe hypoglycemia.

Plasma exchange has been reported to be effective for thyroid storm by reducing levels of thyroid hormones, TSH receptor antibodies, catecholamines, and cytokines (9). Severe hepatic or renal dysfunction is a poor prognostic marker, suggesting disease refractory to plasma exchange (9). In our case, plasma exchange, plasma filtration with dialysis, and plasma adsorption normalized thyroid hormone levels, but not liver function.

This patient had abnormally high circulating levels of sIL-2R. Some hematologic malignancies and autoimmune diseases are associated with elevated levels of sIL-2R (3). Plasma levels of thyroxine are correlated with levels of sIL-2R in patients with Graves' disease. Thyroxine directly stimulates T cell activation and proliferation (10). Elevated sIL-2R has been reported in patients with disseminated intravascular coagulation caused by thyroid storm (11). Our patient had high levels of sIL-2R and free thyroxine as well as multiple organ failure, suggesting that the immune response stimulated by thyroid storm resulted in high levels of sIL-2R. Circulating sIL-2R is not involved in the development of fulminant hepatitis, but the immune-inflammatory response from thyroid storm could induce multiple organ failure and fulminant hepatitis.

We describe a fatal case of thyroid storm with fulminant hepatitis and elevated levels of sIL-2R. Orthotopic liver transplantation is the preferred treatment for fulminant hepatitis due to thyroid storm (4). Excessively high circulating levels of sIL-2R might be a marker of poor prognosis in thyroid storm with fulminant hepatitis.

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's wife.

Author contribution statement
Y Tanaka, T Uchida, and H Yamaguchi wrote the case report. Y Kudo, T Yonekawa, and M Nakazato contributed to the clinical management of this patient. K Shimizu and T Ideguchi were involved in the management of this case.

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