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A case of thyroid storm with a markedly elevated level of circulating soluble interleukin-2 receptor complicated by multiple organ failure and disseminated intravascular coagulation syndrome

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Abstract. Thyroid storm (TS) is a life-threatening endocrine emergency. However, the pathogenesis of TS is poorly understood. A 40-year-old man was admitted to a nearby hospital with body weight loss and jaundice. Five days after a contrasted abdominal computerized tomography (CT) scan, he exhibited high fever and disturbance of consciousness. He was diagnosed with TS originating from untreated Graves' disease and was transferred to the intensive care unit (ICU) of our hospital. The patient exhibited impaired consciousness (E4V1M4 in Glasgow coma scale), high fever (39.3°C), and atrial flutter with a pulse rate 162/min, and was complicated by heart failure, acute hepatic failure, and disseminated intravascular coagulation syndrome (DIC). His circulating level of soluble interleukin-2 receptor (sIL-2R), a serum marker of an activated immune response, was highly elevated (7,416 U/mL, reference range: 135-483). Multiple organ failure (MOF) and DIC were successfully managed by multimodality treatments using inorganized iodide, glucocorticoids, antithyroid drugs, beta-blockers, and diuretics as well as an anticoagulant agent and the transfusion of platelet concentrate and fresh frozen plasma. sIL-2R levels gradually decreased during the initial treatment, but were still above the reference range even after thyroidectomy. Mild elevations in serum levels of sIL-2R have previously been correlated with thyroid hormone levels in non-storm Graves' disease. The present study demonstrated, for the first time, that circulating sIL-2R levels could be markedly elevated in TS. The marked increase in sIL-2R levels was speculated to represent an inappropriate generalized immune response that plays an unknown role in the pathogenesis of TS.

Key words: Graves' disease, Thyroid storm, Multiple organ failure, Disseminated intravascular coagulation syndrome, Soluble interleukine-2 receptor (sIL-2R)

THYROID STORM (TS) is a life-threatening endocrine emergency originating almost exclusively from uncontrolled Graves' disease, typically in the presence of some triggering conditions [1]. Due to the decompensated functions of multiple organs, TS is characterized by severe clinical manifestations including disturbance of consciousness, high fever, marked tachycardia, congestive heart failure, and gastrointestinal and hepatic disturbances [1]. Nationwide surveys recently conducted in Japan revealed that the mortality of TS was still high (10.7%) because of fatal comorbidities such as shock, Multiple organ failure (MOF), and disseminated intravascular coagulation syndrome (DIC) [2]. These surveys also reported that there was no significant difference in thyroid hormone levels between TS patients and non-storm Graves' disease patients [2]. Several pathophysiological mechanisms have been proposed for the development of TS, including 1) an acute increase in the release of thyroid hormones, 2) activation of the sympathetic nervous system, 3) presence of relative adrenal insufficiency, and 4) augmentation in the peripheral cellular response to thyroid hormones; however, the precise mechanism still remains to be elucidated [1].

Interleukin-2 (IL-2) is a type 1 cytokine produced pri-

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marily by $CD4^+$ T cells following antigen stimulation. The proliferation and activation of various lymphocyte subsets including T cells, B cells, monocytes, macrophages, natural killer cells, and lymphokine-activated killer cells are induced when IL-2 binds its high-affinity cell surface receptor (IL-2R), which is composed of 3 subunits, IL-2Rα, IL-2Rβ, and IL-2Rγ chains [3, 4]. The α chain of IL-2R, which may be released by proteolytic cleavage from the cell surface, can be rapidly induced after T cell activation and is measurable at low levels in the sera of healthy subjects and at increased levels in various hematological and autoimmune disorders as soluble IL-2R (sIL-2R) by ELISA [5]. Serum levels of sIL-2R were previously shown to be markedly increased in hematological malignancies such as adult T cell leukemia, non-Hodgkin and Hodgkin lymphoma, and hairy cell leukemia [5, 6]. Nakase et al. proposed that hematological malignancies should be strongly suspected when a patient with a bulky mass lesion has an elevated sIL-2R level over 3,000 U/mL [6]. A mild elevation in sIL2-R has also been observed in several autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis, and could reflect disease activities [5, 7]. Circulating sIL-2R levels have also been reported to mildly increase in autoimmune Graves' disease and were positively correlated with thyroid hormone levels, but not with anti-thyroid autoantibodies [8-10]. Mild elevations in serum sIL-2R levels have also been reported in non-immunogenic thyroid disorders including toxic nodular goiter and toxic adenoma. In contrast, circulating sIL-2R levels were shown to be significantly lower in hypothyroid patients than in normal subjects [8-10]. Taken together, the production and/or release of sIL-2R in these thyroid disorders has been considered to be positively regulated by thyroid hormones rather than reflecting the autoimmune process. Nevertheless, circulating sIL-2R levels have never been evaluated in TS.

In the present study, we described a TS case with markedly elevated sIL-2R levels complicated by MOF and DIC, and monitored changes in sIL-2R levels during the treatment.

Patient

A 40-year-old man with no apparent previous medical history or family history of thyroid disease presented to a nearby hospital in February, 2012 with a loss in appetite and body weight loss that had worsened during the last 6 months. He never drank alcohol, smoked 30 cigarettes/day, and had no history of drug abuse. A physical examination revealed severe emaciation (body mass index 12.5 kg/m^2), small diffuse goiter without ophthalmopathy, and tachycardia. Laboratory findings showed liver dysfunction with jaundice (total bilirubin 6.5 mg/dL, prothrombin time 25%, AST 87 IU/L, ALT 90 IU/L, LDH 249 IU/L, and γGTP 35 IU/L) and he was emergently admitted to the hospital. Although a contrasted abdominal CT scan was performed to evaluate the cause of his liver dysfunction, the origin remained unknown in spite of the presence of moderate amounts of ascites caused by hypoalbuminemia. Increased levels of free triiodothyronine (FT3) (15.3 pg/mL), free thyroxin (FT4) (6.3 ng/dL), and anti-TSH receptor antibody (TRAb) (>30 IU/L) and undetectable TSH (<0.002 μL) were observed, and he was diagnosed with Graves' disease. Thiamozole (MMI) (30 mg/day), potassium iodide (KI) (100 mg/day), methyldigoxin (0.1 mg/day), and furosemide (20 mg/day) were promptly initiated orally. He exhibited high fever (38.4°C), restlessness, and marked tachycardia (250/min) on the 5th hospitalized day and was diagnosed with TS. Methylprednisolone (200 mg/day) was intravenously administered and KI and MMI doses were increased to 300 mg/day and 45 mg/day, respectively. He was transferred to the ICU of our hospital on the 7th hospitalized day because his consciousness level progressively deteriorated in spite of these treatments.

On admission to the ICU, the patient exhibited impaired consciousness (E4V1M4 in Glasgow coma scale) in the absence of focal signs, high fever (39.3 °C), and atrial flutter with a pulse rate 162/min. His blood pressure was 154/82 mmHg and SpO_2 was 95% in ambient air. An ultrasonography of neck revealed a diffusely enlarged goiter (the right lobe: transverse diameter 32 mm × thickness 17.3 mm and the left lobe: transverse diameter 23.5 mm × thickness 16.4 mm) with no nodular regions. Chest radiography showed mild cardiomegaly with moderate bilateral pleural effusion, and the ejection fraction on echocardiography was decreased to 43%. Brain CT and MRI scans revealed no apparent abnormal findings except mild diffuse brain atrophy. Physical and laboratory findings further indicated that he was complicated by heart failure, hepatic failure, and disseminated intravascular coagulation syndrome (DIC) (Table 1). FT3 and FT4 levels were slightly lower than those in the former hospital. The positive hepatitis B (HB) core and HB surface antibod-

ies with undetectable HB virus (HBV) DNA indicated that the patient had a past history of unrecognized HBV hepatitis. IgM antibodies against hepatitis A virus were negative. Increased levels of γ globulins and decreased levels of serum complements caused by severe liver dysfunction with hypoalbuminemia were also noted (Table 2). Based on these clinical findings, the diagnosis of TS originating from Graves' disease was confirmed according to the diagnostic criteria of Burch and Wartofsky (115 points) [1] and the Japan Thyroid Association (JTA) [2]. The sIL-2R level, measured on day 6 because hematological malignancies were suspected due to his severe emaciation, was found to be markedly elevated (7,416 U/mL, reference range: 135-483) even after the administration of corticosteroids.

Thiamazole (30 mg/day) and hydrocortisone (200 mg/day) were intravenously administered and an inorganized iodide preparation (120 mg/day) was administered *via* a nasal tube. Systemic cooling was performed using a cooling blanket. To control heart failure with marked tachycardia, propranolol and diuretics (furosemide and carperitide) were intravenously administered. DIC was treated with nafamostat mesilate, an anticoagulant agent, and the transfusion of platelet concentrate and fresh frozen plasma. Antibiotics were not administered because no signs of bacterial infection were observed, which was confirmed by a negative blood culture and endotoxin with slightly elevated C-reactive protein levels (Tables 1 and 2). His condition was successfully managed by these multimodality treatments, and he became non-febrile, was able to hold a conversation on the second hospitalized day, and was moved to the general ward the next day. His atrial flutter spontaneously returned to a sinus rhythm on the 6th hospitalized day. Further imaging studies including a whole body CT scan and gallium 67 scintigraphy ruled out the presence of malignant hematological disorders. A complication by primary biliary cirrhosis (PBC) was suspected from the positive anti-mitochondria M2 antibody on admission (Table 1) and ursodeoxycholic acid was added from day 12. However, a histopathological examination of a liver biopsy specimen obtained on day 23 revealed acute hepatitis with cholestasis, but not PBC. Total thyroidectomy was performed on day 65 after the recovery of hepatic and cardiac functions (total bilirubin 0.7 mg/dL, albumin 4.2 g/dL, prothrombin time 86%, and BNP 110.6 pg/mL) according to the wishes of the patient. We monitored changes in sIL-2R levels and found that they gradually decreased during the initial treatment, but were still above the reference range even after thyroidectomy (Fig. 1). He was discharged from hospital after rehabilitation for severe

Table 1 Laboratory findings on admission to the ICU (1)

Cell blood count		Blood chemistry			
Hct	34.0% (40.0-52.0)	TP	7.4 g/dL (6.3-7.9)	Na	149 mEq/L (137-145)
Hb	10.4 g/dL (13.2-17.3)	Alb	2.3 g/dL (3.9-5.0)	K	4.0 mEq/L (3.5-4.8)
RBC	401 × 10^4 /μL (402-570)	T-Bil	10.1 mg/dL (0.3-1.2)	Cl	106 mEq/L (100-107)
WBC	4,000 /μL (4,000-9,600)	D-Bil	7.1 mg/dL (0.0-0.2)	Ca	8.4 mg/dL (8.9-10.5)
Neutro	94% (42.2-73.2)	AST	39 IU/L (13-33)	BG	157 mg/dL (80-110)
Lymph	3% (20.1-47.3)	ALT	37 IU/L (8-42)	HbA1c	5.0% (4.3-5.8)
Plt	4.1 × 10^4 /μL (16-35)	LDH	211 IU/L (119-229)	T-Chol	64 mg/dL (128-219)
		ALP	345 IU/L (115-359)	TG	58 mg/dL (30-149)
Coagulation		γGPT	23 IU/L (10-47)	CRP	0.94 mg/dL (<0.1)
Fibrinogen	88 mg/dL (150-330)	CK	169 IU/L (62-287)	NH3	80 μg/dL (80-120)
PT	21% (70-130)	BUN	38 mg/dL (8-20)	BNP	3,249 g/mL (0-18.4)
APTT	58.9 sec (27.0-39.0)	Cr	0.58 mg/dL (0.8-1.3)	Ferritin	81.5 ng/mL (40.7-335.8)
FDP	25.7 μg/mL (0.0-4.0)	UA	9.5 mg/dL (3.2-7.0)	Procalcitonin	0.45 ng/mL (0-0.49)
D-dimer	19.3 μg/mL (0.0-1.0)		eGFR 102.6 ml/min/m^2	Endotoxin	negative
AT-III	23.5% (80-120)				

Hct, hematocrit; Hb, hemoglobin; RBC, red blood cell; WBC, white blood cell; Neutro, neutrophil; Lymph, lymphocyte; Plt, platelet; PT-INR, prothrombin time-international normalization ratio; APTT, activated partial thromboplastin time; FDP, fibrin/fibrinogen degradation product; AT-III, anti-thrombin III; TP, total protein; Alb, albumin; T-Bil, total bilirubin; D-Bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γGTP, γ-glutamyl transpeptidase; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; BG, blood glucose; T-Chol, total cholesterol; TG, triglyceride; CRP, C-reactive protein; BNP, brain natriuretic peptide. The normal range is shown in parentheses.

Table 2 Laboratory findings on admission to the ICU (2)

Immunological examination	
sIL-2R	7,416 U/mL (135-483)
IgG	3,088 mg/dL (870-1,700)
IgA	959 mg/dL (110-410)
IgM	138 mg/dL (35-220)
IgE	1,490 mg/dL (0-295)
CH50	14.4 IU/L (30.0-46.0)
C3	30.0 IU/L (65-135)
C4	9.3 IU/L (13-35)
ANA	20 × (negative)
AMA	19.7 (negative)
ASMA	negative

Urinalysis	
Protein	−
Ketone body	−
Sugar	−
Occult blood	2+

Thyroid function	
FT3	12.84 pg/mL (1.71-3.71)
FT4	4.27 ng/dL (0.7-1.48)
TSH	<0.05 μg/mL (0.35-4.94)
TRAb	73.9 IU/L (0-1.99)
MCHA	6400 × (<100)
TGHA	<100 (<100)
Anti-TPO Ab	170 IU/mL (<16.0)

Hepatitis virus infection	
HBs Ag	negative
HBc Ag	positive: 13.9
HBs Ab	positive: 1.3
HBV DNA	negative
HCV Ab	negative
HIV Ab	negative
IgM-HA Ab	negative

Blood culture	negative

International System of Units (SI) for free T4 to picomoles per liter (conversion factor, 12.87); for free T3 to picomoles per liter (0.0154).
sIL-2R, soluble interleukin-2 receptor; ANA, anti-nuclear antibody; AMA, anti-mitochondria M2 antibody; ASMA, anti-smooth muscle antibody; FT3, free T3; FT4, free T4; TRAb, anti-TSH receptor antibody; MCHA, microsome test; TGHA, thyroid test; TPO, thyroperoxidase; Ag, antigen; Ab, antibody; HBc Ab, hepatitis B core Ab; HBs Ab, HB surface Ab; HBV, HB virus; HCV, hepatitis C virus; HA, hepatitis A; HIV, human immunodeficiency virus type 1. The normal range is shown in parentheses.

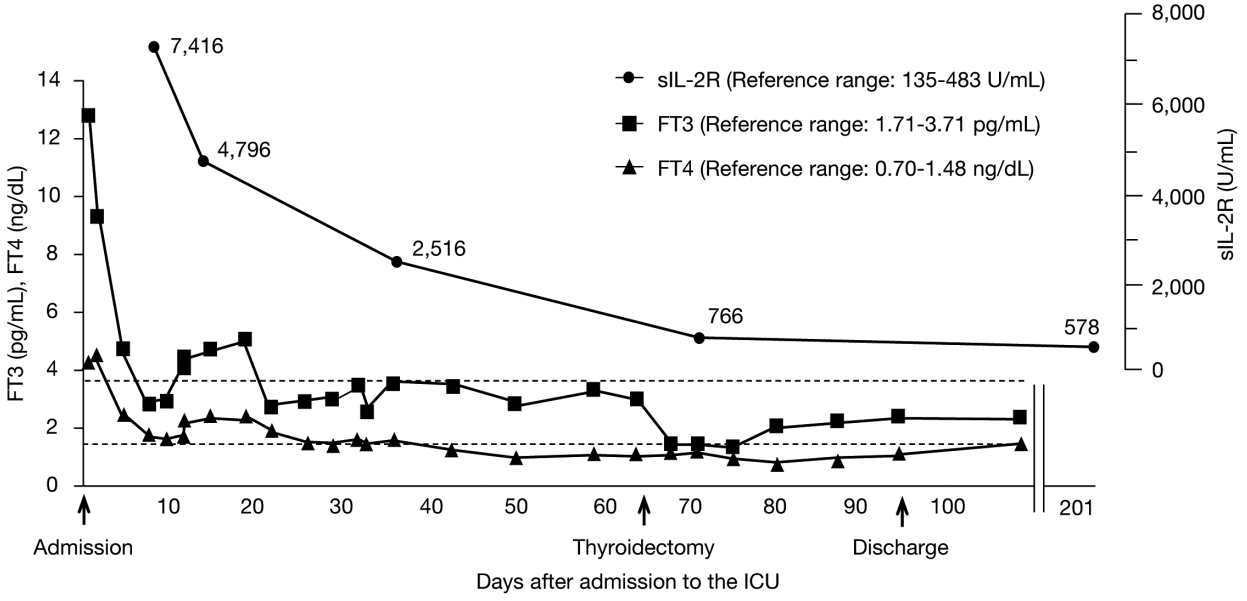

Fig. 1 Changes in sIL-2R, FT3, and FT4 levels during the treatment.
The upper and lower dashed lines indicate the upper normal limits of FT3 and FT4, respectively. sIL-2R levels measured at the indicated time points are indicated in actual numbers (U/mL).

muscle atrophy on day 94.

Discussion

We encountered a case of TS originating from untreated Graves' disease complicated by MOF and DIC that was successfully managed by multimodality treatments. Since the administration of iodinated contrast medium has rarely been reported to trigger TS in uncontrolled Graves' disease by unknown mechanisms [1, 2] and the patients had no other illness that could trigger TS such as infection, the contrast abdominal CT scan performed in this case may have contributed to the development of TS.

The circulating level of sIL-2R in this patient was markedly elevated to a level similar to that reported in adult T cell leukemia, which has been shown to have the highest level of sIL-2R among several malignant hematological disorders [5, 6]. Multiple imaging studies and the clinical course definitely ruled out a complication by hematological malignancies. An increase in circulating sIL-2R levels has previously been correlated with thyroid hormone levels in untreated Graves' disease and other thyrotoxic disorders [8-10]. However, FT3 and FT4 levels in this case were similar to those in TS cases reported in the nationwide survey, and were indistinguishable from those in non-storm Graves' disease patients [2]. Therefore, the marked elevation in sIL-2R in this patient was speculated to represent an exacerbated T cell-mediated immune response associated with MOF.

Emerging evidence has supported the pathogenic role of an aberrant immune response in the development of TS. MOF has been shown to develop from a heterogeneous disease population such as severe infection, shock, trauma, burns, and pancreatitis due to inappropriate generalized inflammatory responses in the host to various acute insults [12, 13]. Illnesses that lead to the development of MOF are well-known triggers for TS [1, 2]. Immunosuppressive glucocorticoids have been widely used and empirically established as essential for the treatment of TS [1, 11]. Moreover, therapeutic plasma apheresis, which can remove proinflammatory cytokines, has been shown to markedly improve severe clinical manifestations in many TS cases resistant to conventional drug therapies [14]. The markedly elevated sIL-2R levels observed in this case were still above the reference range even after thyroidectomy, which suggested that the immune-inflammatory response strongly activated in TS complicated by MOF could be prolonged even after the normalization of thyroid hormone levels.

Nationwide surveys recently performed by the JTA revealed that DIC was complicated by TS and was identified as one of the prognostic factors for the mortality of TS [2]. DIC can frequently be complicated in critically ill patients with systemic inflammatory response syndrome (SIRS), which develops due to infection or other illnesses and leads to MOF [15, 16]. TS can readily fulfill two of the four items in the diagnostic criteria for SIRS [15], fever (>38.0°C) and tachycardia (>90/min), because these symptoms are also diagnostic items for TS [1, 2]. Thus, TS may be to be complicated by DIC *via* pathophysiological mechanisms similar to those in SIRS, which include a cytokine-mediated imbalance between coagulant and anticoagulant pathways [17]. Nevertheless, it is important to note that sIL2-R levels were indistinguishable in the presence or absence of SIRS, severe sepsis, or septic shock in non-storm patients with acute onset medical conditions in an Emergency Department [18].

In summary, in addition to several already proposed pathophysiological mechanisms [1], the findings of the present TS case, in which a markedly elevated sIL-2R level was observed, suggest that the activated systemic immune response could be a novel pathogenic factor contributing to the development of TS complicated by MOF and/or DIC. Further evaluations of sIL-2R levels as well as proinflammatory cytokines are necessary in additional TS cases in order to confirm this hypothesis. Whether the levels of these parameters can be correlated with the severity of TS and serve as a prognostic factor also remain to be determined. Treatments specifically targeting deranged immune-inflammatory responses may be an alternative approach to improve the high mortality of TS.

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Disclosure Statement

The authors have no financial conflicts of interest to be disclosed.

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