Case Report

Thyroid storm with elevated presepsin without infection due to methimazole administration

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ABSTRACT

A 43-year-old woman was diagnosed with thyroid storm due to Graves' disease. Fever and inflammatory reactions were observed; however, the infectious focus was unclear. The patient was administered methimazole, potassium iodide, and meropenem. The presepsin levels increased and the fever persisted, but the C-reactive protein and procalcitonin (PCT) levels decreased. The meropenem and methimazole were discontinued, and propylthiouracil was initiated. The patient's presepsin levels and thyroid function decreased; however, her fever continued. A total thyroidectomy was performed, and the patient's fever improved while her presepsin and PCT levels normalized. Treatment with methimazole during thyroid storm may result in the secretion of presepsin without infection, which must be considered when diagnosing sepsis in patients with thyroid storm.

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Key Words
presepsin, procalcitonin, thyroid storm, methimazole

I. Introduction

Thyroid storm is a life-threatening endocrine emergency that originates from thyroid toxicosis. The condition manifests as the decompensation of multiple organs with a high fever, disturbed consciousness, heart failure, diarrhea, and jaundice [1]. Patients with thyroid storm and fever must be monitored carefully as severe thyroid storm may be complicated by pneumonia or urinary tract infections [2].

Presepsin and procalcitonin (PCT) are novel diagnostic and prognostic markers for sepsis. Presepsin is considered a promising biomarker for diagnosing sepsis and can be detected during sepsis earlier than C-reactive protein (CRP) and PCT [3].

This report presents a patient with thyroid storm who was treated with methimazole and experienced an increase in her plasma presepsin level without infection.

II. Case report

A 43-year-old woman was admitted to our hospital for thyroid toxicosis with a temperature of 39.2℃, blood pressure of 131/59 mmHg, heart rate of 145 /min, and nausea. Acute physiology and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score were 12 and two points, respectively. The thyroid gland was slightly enlarged. Ultrasonography of the thyroid gland revealed a heterogeneous internal echo with slightly increased blood flow (**Figure 1**). The TSH receptor antibody (TRAb) and thyroid stimulating antibody (TSAb) were elevated (5.1% and 685%, respectively). The patient was diagnosed with thyroid storm due to Graves' disease. The clinical course of the patient is shown in **Figure 2**. She was administered methimazole (60 mg/day), potassium iodide (0.2 g/day), landiolol (1 μg/kg/min for a total of 68 mg/day), hydrocortisone (200 mg/day for hospital days 1-3), and acet-

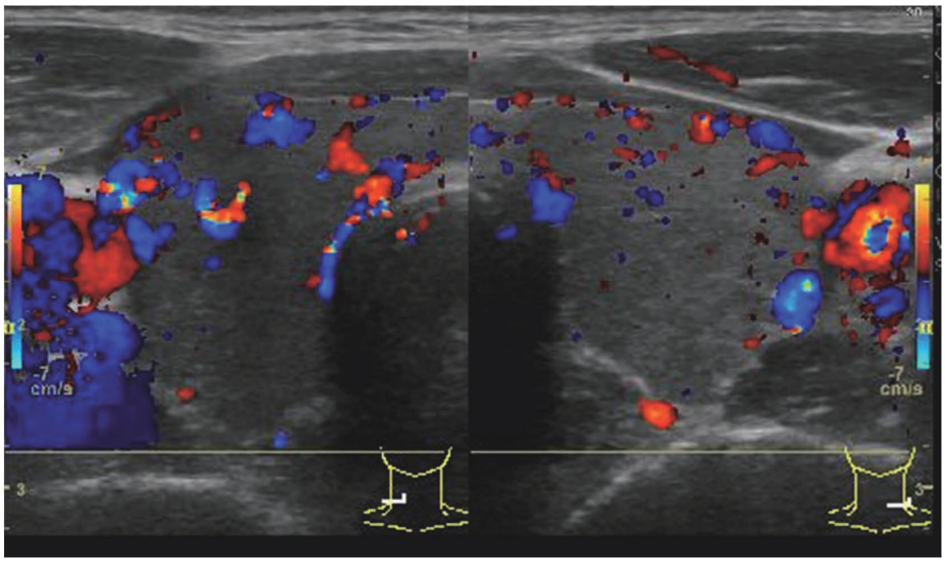
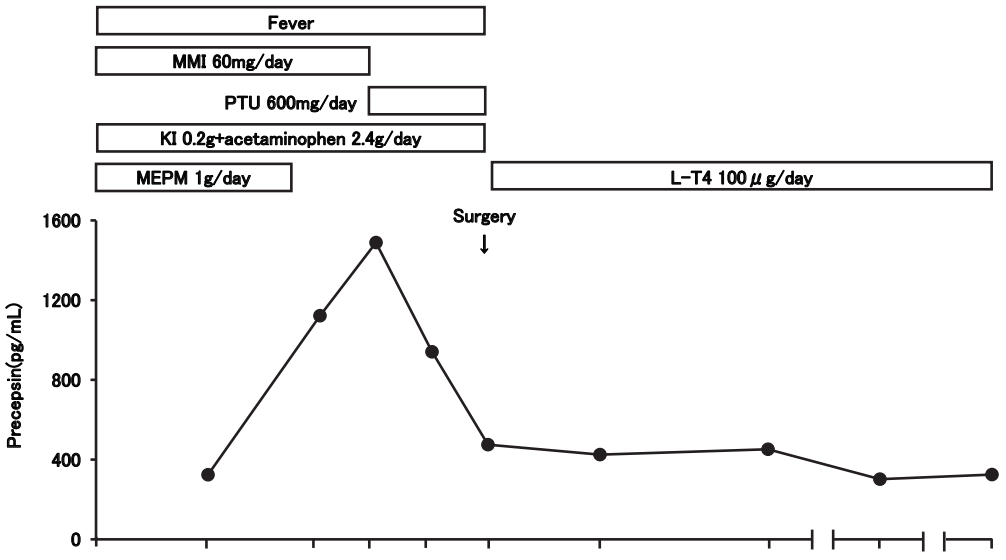


Figure 1 Ultrasonography of the thyroid gland showing heterogeneous internal echo and slightly increased of blood flow.



(Day)	1	9	16	20	23	27	35	44	65	93
PCT (ng/mL)	0.63	0.11	0.06	0.09	0.11	0.09	0.06	0.06	0.07	<0.05
CRP (mg/dL)	11.55	3.20	3.63	5.06	4.55	4.53	3.20	3.00	3.79	2.97
WBC (/μL)	10600	12700	10000	11000	7300	7600	7500	6600	5500	5200
FT3 (pg/mL)	14.6	4.6	5.4	7.3	5.1	2.4	1.1	1.0	1.2	1.8
FT4 (ng/dL)	9.3	2.0	2.3	3.2	2.4	1.5	0.5	0.4	0.6	1.2
TSH (μIU/mL)	<0.02	<0.02	<0.02	<0.02	<0.02	0.02	<0.02	0.77	20.32	7.53
ALP (U/L)	619	473	833	935	741	777	834	703	593	960
γ-GTP (U/L)	84	64	153	166	135	149	191	143	141	155
T.Bil (mg/dL)	1.3	0.4	0.4	0.5	0.3	0.3	0.5	0.4	0.4	0.3
eGFR (mL/min/1.73m^2)	90.1	79.4	106.3	104.0	99.6	95.6	91.9	88.4	82.2	86.8

Figure 2 Clinical course. Day 1 indicates admission. KI=potassium iodide, MEPM=meropenem, MMI=methimazole, PCT=procalcitonin, PTU=propylthiouracil.

aminophen (2.4 g/day). The patient's inflammatory responses, such as white blood cell (WBC) count and CRP and PCT levels, were also elevated. The blood cultures were negative. Whole-body computed tomography (CT) and echocardiography were conducted; however, the infection focus remained unclear. Thyroid storm complicated by bacterial infection was suspected, and meropenem (1 g/day) was administered. Palpitation and nausea improved immediately, but the fever persisted. The patient's CRP, PCT, and T.Bil levels decreased, but the presepsin, ALP, and γ-GTP levels increased. Renal function, AST, and ALT levels were within normal ranges. The infection focus was unclear on gallium scintigraphy and repeated whole-body CT. The blood culture results were negative. It was believed that the bacterial infection improved. The meropenem was discontinued on hospital day 12. The patient's CRP and PCT levels continued to decrease; however, her presepsin, ALP, and γ-GTP levels increased, and the fever continued. On hospital day 20, the methimazole was discontinued and propylthiouracil was initiated due to the possibility of fever secondary to methimazole. The patient's presepsin, ALP, and γ-GTP levels decreased. Thyroid function decreased, but her fever continued. It was believed that the fever was due to thyroid storm, and a total thyroidectomy was performed on hospital day 27. Histopathological features revealed fibrotic tissues, and the follicular epithelia exhibited local hyperplasia and papillary proliferation. Scalloping, formed by vacuoles in the colloid adjacent to the apex of the follicle cells, was increased locally. Lymphocytic infiltration with follicular formation was observed in the interstitial tissues. These findings are consistent with Graves' disease after treatment (**Figure 3**). The patient's fever resolved immediately after thyroidectomy. The presepsin and PCT levels normalized one and two months after surgery, respectively.

III. Discussion

Fever is reported in 63.5-64.9% of Japanese patients with thyroid storm [1]. The irregular use or discontinuation of antithyroid drugs and infections account for 44.7% and 31.4% of cases of thyroid storm, respectively [1]. Upper respiratory tract infections, acute bronchitis/pneumonia, and agranulocytosis/sepsis account for 41.5%, 20.7%, and 3.7% of the infections leading to thyroid storm, respectively [4].

In this patient, thyroid storm complicated by bacterial infections was suspected upon admission due to the patient's WBC count and CRP and PCT levels. The bacterial infection was believed to improve during the treatment as the CRP and PCT levels decreased; however, the presepsin levels increased. The patient's meropenem was discontinued and the methimazole was changed to propylthiouracil; however, the fever continued. The fever was believed to be due to the thyroid storm, and a total thyroidectomy was performed.

Presepsin is a 13-kDa protein that is the truncated N-terminal fragment of CD14 and is highly expressed on the membrane surfaces of monocytes [5]. Presepsin secretion by monocytes is triggered by bacterial phagocytosis or sterile phagocytic stimuli. Elastase in monocytes mediates CD14 cleavage to produce presepsin [6]. Presepsin levels are significantly elevated in patients with sepsis and hemophagocytic syndrome [6-8]. Presepsin levels may also increase with an increase in macrophage phagocytic activity. In a previous report, a patient with Graves' disease developed agranulocytosis and hemophagocytic syndrome after the administration of methimazole [9]; however, the patient's presepsin levels were not reported. PCT is secreted from multiple tissues during bacterial infec-

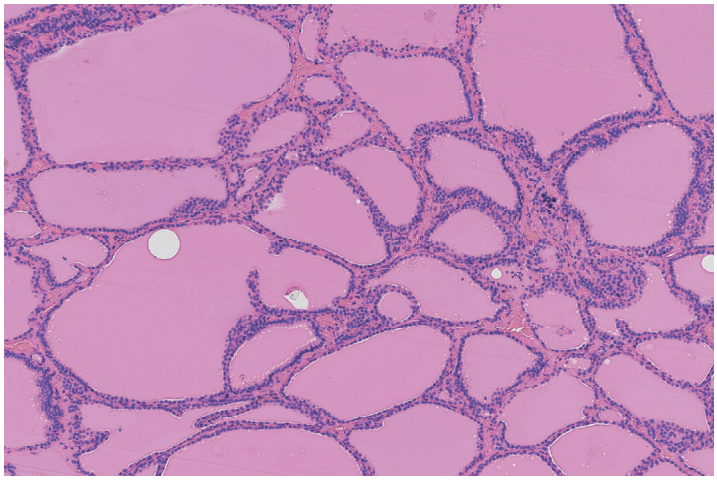


Figure 3 Histopathological features of thyroid specimen shown by hematoxylin and eosin staining (× 100).

tion, including the liver, kidneys, lungs, intestines, and muscles [10]. In the current patient, fever was observed without splenomegaly, cytopenia, hypertriglyceridemia, or hypofibrinogenemia. As the bone marrow, ferritin levels, and soluble interleukin-2 receptor levels were not examined, hemophagocytic syndrome could not be diagnosed.

Presepsin levels were correlated with the elevation of biliary enzymes in patients without renal dysfunction or sepsis. Presepsin production in liver Kupffer cells was confirmed by immunostaining [11]. These findings suggest that increased bile duct pressure results in presepsin over expression in the Kupffer cells, leading to elevated presepsin levels in both the bile and plasma [11]. In this patient, ALP and γ-GTP levels increased after the administration of methimazole, and decreased when methimazole was changed to propylthiouracil. It is possible that presepsin level increased due to the increase of bile duct pressure by methimazole; however, as we did not perform immunostaining of presepsin in the liver, this could not be proven. The frequency of severe liver injury, such as hepatic coma and hepatic failure, or mild liver injury to the use of methimazole was 0.05% or 0.09%, respectively. The frequency of severe or mild liver injury to the use of propylthiouracil was 0.17% or 0.04%, respectively [12]. Liver injury associated with methimazole is related to cholestasis, whereas the liver injury associated with propylthiouracil is related to hepatitis [12].

Presepsin levels have been shown to be significantly increased in patients with renal dysfunction [13,14]. As presepsin is a 13-kDa protein, it is freely filtered by the glomerulus and almost completely reabsorbed and catabolized with proximal tubular cells [14]. In this patient, renal function was within the normal range.

Presepsin is correlated with disease activity in patients with systemic lupus erythematosus (SLE), for which several reasons have been proposed [15]. The clearance ability of apoptotic body/cellular debris and neutrophil phagocytosis are impaired in these patients and the cathepsin D activity and neutrophil extracellular cell trap production are increased. In patients with thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome, the presepsin and alkaline phosphatase levels are increased [16]. Presepsin and troponin levels are significantly elevated in patients with acute myocardial infarction (AMI) [17]. However, the mechanisms underlying increased presepsin levels in patients with TAFRO syndrome and AMI are not well known.

In this patient, the presepsin level decreased when methimazole was changed to propylthiouracil. Treatment with methimazole during a thyroid storm may lead to presepsin secretion via a sterile phagocytic stimulus or an increase of bile duct pressure. We did not perform immunostaining of presepsin in the liver or thyroid gland. The precise mechanism underlying the methimazole-induced increase in presepsin levels is unclear. Further studies are needed to elucidate the mechanism by which methimazole increases the presepsin level in patients with thyroid storm without infection.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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