

## CASE REPORT

# Hemodynamic variation is a dominant contributing factor of Graves' hyperthyroidism complication: Heart failure and fatal liver dysfunction, a case report and analysis

Zhiyuan Li<sup>1</sup>  | Jinjing Wang<sup>1</sup>  | Jing Zeng<sup>1</sup>  | Jian Xue<sup>3</sup>  | Xinyu Li<sup>4</sup>  | Jianbing Su<sup>2</sup>  | Yi Fang<sup>1</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

<sup>2</sup>Outpatient Department, Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

<sup>3</sup>Department of Cardiovascular Medicine, Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

<sup>4</sup>Department of Preventive Medicine, School of Public Health, Capital Medical University, Beijing, China

## Correspondence

Jianbing Su, Outpatient Department, Fifth Medical Center of Chinese PLA General Hospital, No.8 Dongdajie Street, Fengtai District, Beijing, 100071 China.

Email: spinalsjb@sina.com

Yi Fang, Department of Endocrinology and Metabolism, Fifth Medical Center of Chinese PLA General Hospital, No.8 Dongdajie Street, Fengtai District, Beijing, 100071 China.

Email: fangyi307@163.com

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## Abstract

Tachycardia and atrial fibrillation, early symptoms of hyperthyroidism indicate significant hemodynamic variation in cardiovascular system, if left untreated and further deterioration in hemodynamics can result in chronic heart failure and liver dysfunction even a fatal event. We describe a female patient of Graves' hyperthyroidism to present the continuum of the pathophysiology development of the disease, to highlight the hemodynamic variation is a dominant contributing factor of Graves' hyperthyroidism complication, we wish to emphasize cardiac manifestations in the setting of thyrotoxicosis should be treated promptly and aggressively.

## KEYWORDS

atrial fibrillation, fatal liver dysfunction, Graves' hyperthyroidism, heart failure, hemodynamic variation, tachycardia

## 1 | INTRODUCTION

Graves' hyperthyroidism is an autoimmune disease resulting in excessive endogenous thyroid hormone production and release,<sup>1</sup> which is associated with multisystem involvement. Graves' hyperthyroidism presents with the features of palpitation, dyspnea, weight loss, tremors, and nausea. Excess amounts of thyroid hormone have a significant impact on cardiovascular hemodynamics through direct and indirect mechanisms.<sup>2</sup> Because of high frequency, increased mortality and morbidity, cardiovascular complications are important in hyperthyroidism.<sup>3</sup> We report a young female patient of long history Graves' hyperthyroidism with tachycardia, atrial fibrillation, congestive heart failure, and severe hepatic dysfunction, through reporting this case, we focus on the role of hemodynamics in severe complications of hyperthyroidism, analyze and discuss it according to our clinical practice and reviewing previous literature, present effective treatment strategies as well.

## 2 | CASE PRESENTATION

A 37-year-old female patient with intermittent palpitations, easy fatigability for 18 years was referred to our hospital; she had developed exertional dyspnea, lower extremity edema 6 weeks before entry. She was diagnosed with Graves' hyperthyroidism in 2001 and started on methimazole (MMI), but compliance taking the medication was low. She had taken herbal remedies for 2 years, but the detailed prescription could not be provided. She had admitted and received medical treatment at local hospital 4 weeks before, which include intravenous use of furosemide 40 mg/day, compound ammonium glycyrrhizinate 40 ml/day, metoprolol 50 mg/day, and aspirin 100 mg/day; however, her condition deteriorated and total bilirubin (TBil) was about five times higher than normal. Then, she was referred to our hospital. On physical examination, she was afebrile, heart beats at presentation were 105 per minute and blood pressure was 116/65 mmHg. She had mild generalized icterus but no consciousness disturbance, diffusely enlarged thyroid gland without pain. Two red spots on the upper chest were noticed that characterized by central arteriole with radiated blood vessels. Cardiovascular examination revealed an irregular rhythm, systolic murmur at the lower left sternal border, the jugular venous pressure was raised and neck veins engorged. Mild bilateral lower extremity edema was present. A workup for thyroid dysfunction demonstrated raised serum free thyroxine (FT4), triiodothyronine (FT3) levels with suppressed thyroid-stimulating hormone (TSH) level and high TSH receptor antibody titers (Table 1).

Differential complete blood count showed a low white blood cell count and low absolute neutrophil count. Increased brain natriuretic peptide (BNP) indicated congestive heart failure; cardiac biomarkers were negative for an acute coronary event. Liver chemistries showed mild elevations in aspartate aminotransferase (AST),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GTP), and blood ammonia. Notably, her TBil, direct bilirubin (DBil) elevated progressively, and coagulation disorders were confirmed. The patient also had negative serology for hepatitis A, B, and C. Autoimmunity markers (antinuclear antibody, antimitochondrial antibody, antineutrophil cytoplasmic antibody, anti-smooth-muscle antibody, and anti-liver-kidney microsome antibody) were all negative. The electrocardiogram (ECG) showed atrial fibrillation with ventricular rate at 80 beats/min (treated with metoprolol, 50 mg/day), chest radiography showed right pleural effusion and pulmonary congestion, and the cardiothoracic ratio was 72% (Figure 1). Transthoracic echocardiogram reported an left ventricular ejection fraction of 60% with bilateral atrial and right ventricle enlargement, elevated pulmonary artery pressure, severe mitral and tricuspid regurgitation (Figure 2). Abdominal ultrasonography, computed tomography, and magnetic resonance cholangiopancreatography showed no biliary ductal dilation, pancreatic, biliary, or intrahepatic mass, portal vein thrombosis, or findings concerning for primary sclerosing cholangitis. Moderate ascites was found in right-sided chest cavity, cavum pericardii, abdomen, and pelvic cavity. We evaluated renal function of our patient on the first day after admission. She had a urine output of 850ml/20h, and the creatinine clearance calculated by Cockcroft and Gault Equation indicated absence of acute kidney injury. A thyroid nuclear scan showed a diffuse homogenous increased uptake of radioactive iodine with no background uptake.

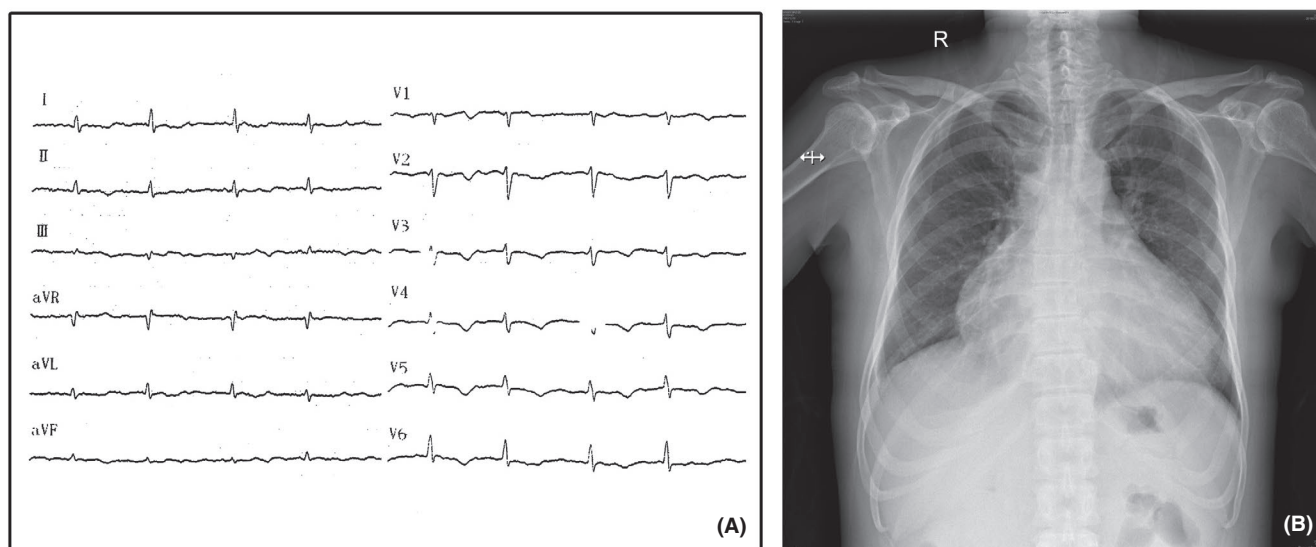
She was diagnosed with Graves' hyperthyroidism accompanied by atrial fibrillation, congestive heart failure (NYHA III), liver function and coagulation function supported the diagnosis of acute-on-chronic pre-liver failure. She was continued with furosemide intravenously 40 mg/day and metoprolol 50 mg/day; aspirin was ceased because of hemorrhagic tendency. However, symptoms of atrial fibrillation and heart failure did not improve significantly; BNP continued to rise. The treatment plan switched to methimazole cream 0.1 g (MMI 5 mg) 2/day to diminish levels of thyroid hormone (the concentration-time curves of the novel formulation in a preclinical study demonstrated the concentration of the methimazole cream of neck swearing group was higher than oral group in thyroid gland tissue and action time could be extended by percutaneous administration) bisoprolol 2.5 mg/day to control ventricular rate at 70–90 beats/min, torasemide injection at 20 mg/day and spironolactone tablets at 40 mg/day were

**TABLE 1** Laboratory data on admission

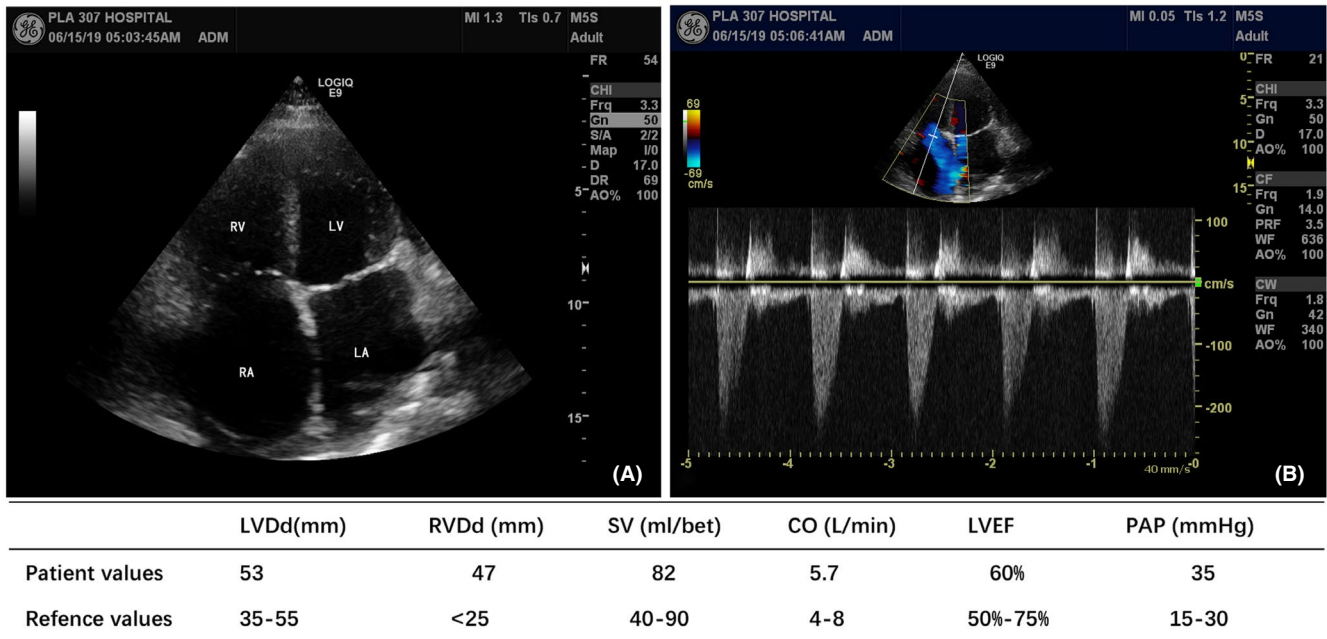
WBC ( $10^9/L$ )	2.7	(3.5–9.5)	Ca (mmol/L)	2.24	(2.15–2.57)
NEUT( $10^9/L$ )	1.13	(1.8–6.3)	BUN (mmol/L)	4.58	(1.4–8.3)
RBC ( $10^{12}/L$ )	3.68	(3.8–5.1)	Cre (mmol/L)	34	(55–110)
Hb (g/L)	105	(115–150)	LDH (U/L)	198	(109–245)
Plt ( $10^{12}/L$ )	97	(125–350)	LDL-C (mmol/L)	1.36	(1.9–3.8)
PT(s)	20.1	(8.8–12.8)	PG (mmol/L)	3.85	(3.9–6.1)
PTA(%)	47	(80–150)	Tn-I (ng/ml)	<0.012	(0–0.16)
APTT(s)	45.9	(24.9–36.8)	CK-MB (U/L)	22	( $\leq$ 25)
PT-INR	1.77	(0.8–1.5)	BNP (pg/ml)	1910	(0–125)
TP(g/L)	71	(65–85)	AMON ( $\mu$ mol/L)	54	(9–33)
Alb (g/L)	29	(40–55)	TSH ( $\mu$ IU/L)	<0.008	(0.55–4.78)
ALT (U/L)	13	(7–40)	FT3 (pmol /L)	24.1	(2.8–6.3)
AST (U/L)	56	(13–35)	FT4 (pmol/L)	109.13	(11.5–22.7)
TBil ( $\mu$ mol/L)	106.5	(2–20)	Trab (IU/L)	37.88	(<1.75)
DBil ( $\mu$ mol/L)	64.7	(0–6.8)	Blood gas analysis (nasal O <sub>2</sub> 3 L)		
TBA ( $\mu$ mol/L)	19.1	(0–15)	pH	7.435	(7.350–7.450)
ALP (U/L)	85	(40–150)	pCO <sub>2</sub> (mmHg)	31.3	(32–48)
$\gamma$ -GTP (U/L)	88	(7–45)	pO <sub>2</sub> (mmHg)	89.7	(80–100)
K (mmol/L)	4.29	(3.5–5.3)	HCO <sub>3</sub> (mmol/L)	22.4	(21–27)
Na (mmol/L)	134	(137–147)	BE (mmol/L)	–2.9	(–3 to 3)
Cl (mmol/L)	102	(99–110)	Lac (mmol/L)	1.9	(0.5–1.6)

Note: Numerals in parentheses are normal values.

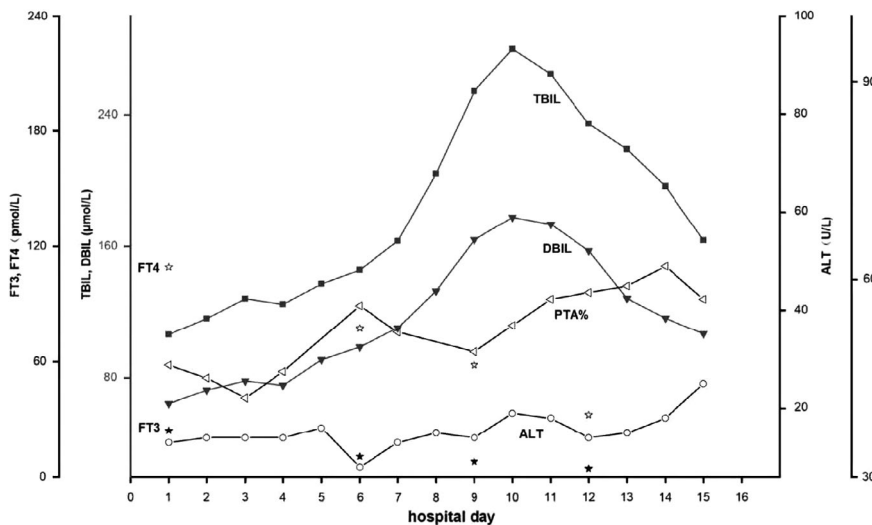
Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMON plasma ammonia; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BE, base excess; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CK, creatinine kinase; CK-MB, creatinine kinase-muscle-brain isozyme; Cr, creatinine; DBil, direct bilirubin; FT3, free triiodothyronine; FT4, free thyroxine; Hb, hemoglobin; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; NEUT neutrophile granulocyte; PG, plasma glucose; Plt, platelets; PT, prothrombin time; PTA, Prothrombin activity; PT-INR, prothrombin time international normalized ratio; RBC, red blood cells; TBA, total bile acid; TBil, total bilirubin; Tn-I, troponin I; TP, total protein; TRAb, thyrotrophin receptor antibody; TSH, thyroid-stimulating hormone; WBC, white blood cells;  $\gamma$ GTP,  $\gamma$ -glutamyl transpeptidase.



**FIGURE 1** ECG and chest radiography on admission. (A) ECG showing atrial fibrillation and a heart rate of 80 beats/min (treated with metoprolol, 25 mg 2/day). (B) Chest radiography showing right pleural effusion and pulmonary congestion, the cardiothoracic ratio was 72%



**FIGURE 2** Transthoracic echocardiogram reported (A) bilateral atrial and right ventricle enlargement with an left ventricular ejection fraction of 60%, (B) severe mitral and tricuspid regurgitation with elevated pulmonary artery pressure. CO, cardiac output; LA, left atrium; LV, left ventricle; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PAP, pulmonary arterial pressure; RA, right atrium; RV, right ventricle; RVDd, right ventricular end-diastolic dimension; SV, stroke volume



**FIGURE 3** Serial levels of biochemical parameters during hospitalization. ALT, alanine aminotransferase; DBil, direct bilirubin; FT3, free triiodothyronine; FT4, free thyroxine; PTA, prothrombin activity; TBIL, total bilirubin

admitted, maximum dose of torasemide reached at 80 mg/day. Consequently, her body mass steadily decreased from 63 kg to 56 kg; her dyspnea, lower limb edema, and other symptoms gradually alleviated. On the tenth day of admission, the ECG showed that sinus rhythm was restored and the ventricular rate was maintained at 60 beats/min.

Ademetionine for injection and capsule ursodeoxycholic acid were initiated on the second day of admission. Although her general condition was improving, TBil levels increased progressively (Figure 3). She was started on daily therapeutic plasma exchange (TPE) on hospital day four, replacement fluid contained half fresh frozen

plasma and half 5% albumin was equal in volume to her total plasma volume (about 4 L). Intravenous methylprednisolone at 40 mg/day was given for treatment of severe hepatic dysfunction, TBil levels peaked at 279.8  $\mu\text{mol/L}$  (DBil of 177.7  $\mu\text{mol/L}$ ) on hospital day eleven, and then, the TBil gradually decreased. The serum-free FT3 and FT4 levels were normalized on the twelfth day of admission. She was treated with radioactive iodine (RAI) at a dose of 50 mci as planned after the tenth course of TPE. The patient was discharged home on bisoprolol, oral diuretics, methylprednisolone tablet, and capsule

ursodeoxycholic acid. By 3 months postdischarge, her TBil had also normalized.

### 3 | DISCUSSION

Thyroid hormones have significant effects on cardiovascular system through nuclear genomic and extranuclear nongenomic mechanisms; both of them act together to regulate cardiac function and cardiovascular hemodynamics.<sup>4</sup> Excess thyroid hormones acting on the heart and peripheral vasculature induce decreased systemic vascular resistance, increased resting heart rate, left ventricular contractility, and blood volume.<sup>5</sup> The decreased systemic vascular resistance leads to reduction in renal perfusion pressure, further activation of the renin-angiotensin-aldosterone system (RAAS), thereby promotes sodium retention and blood volume in the body.<sup>6</sup> Hemodynamic variation combines to promote an increase in blood volume and preload, increase cardiac output 50%–300% higher than in normal individuals.<sup>7–9</sup>

Tachycardia is the most common rhythm disturbance, recorded in almost all patients with hyperthyroidism,<sup>10</sup> atrial fibrillation occurs in 10%–25% of patients with hyperthyroidism.<sup>11,12</sup> Investigations revealed that tachycardia  $\geq 150$  bpm in thyroid storm patients<sup>13</sup> and atrial fibrillation in patients with hyperthyroidism are associated with significant mortality.<sup>14</sup> Therefore, tachycardia and atrial fibrillation in the setting of thyrotoxicosis should be treated promptly and aggressively. Beta-blockers are selected as the first-line treatment for ventricular rate control of Graves' hyperthyroidism; they not only to help ameliorate cardiovascular symptoms and tremor, especially in the stage before antithyroid drugs (ATD) take effect but also to decrease the ventricular response to atrial fibrillation by action on the  $\beta_1$  receptors. Beta-blockers should be used in appropriate dose that control the heart rate to normal range in order to improve the tachycardia-mediated component of left ventricular dysfunction. Beta-blockers with higher selectivity in cardiovascular system have higher cardioprotective effects and superior prevention of atrial fibrillation, especially for patients with bronchospasm.<sup>15</sup>

If untreated tachycardia and atrial fibrillation last for a long period of time, hemodynamic variation predispose the patient to heart failure. Impaired ventricular relaxation, increased left ventricular mass caused by elevated left atrial pressure, ischemia resulting from raised resting heart rate and increased atrial ectopic activity,<sup>16</sup> these underlying factors relate to atrial fibrillation accelerate systemic hemodynamic deterioration. The concept of "tachycardia-induced cardiomyopathy" related to hyperthyroidism is more plausible, as heart failure commonly

improves with adequate control of the heart rate and atrial fibrillation when the euthyroid state is restored. Some reported cases of congestive heart failure with Graves' hyperthyroidism had increased pulmonary resistance, autoimmune mechanisms with subsequent endothelial damage may have an important role in its occurrence.<sup>17,18</sup> Our patient had features of high-output congestive heart failure with pulmonary hypertension, as evidenced by raised jugular venous pressure neck veins engorged and bilateral pedal edema. Echocardiogram reported right ventricular end-diastolic dimension increased significantly in our patients, but stroke volume and cardiac output of left ventricle almost normal (Figure 2), which means Graves' hyperthyroidism causes increased cardiac output and a hyperdynamic right ventricle, right ventricular function decreases more significantly than the left. The deteriorating of congestive heart failure due to hyperthyroidism in our patient means it is not limited to the elderly, it can develop even in young patients.

Brain natriuretic peptide is mainly synthesized and secreted by myocytes in the left ventricle as a response to myocytes stretched by pressure overload or volume expansion of the ventricle. Although BNP is steadily increased in heart failure, it may often be insufficient to reduce the sodium retention and vascular constriction due to activation of RAAS.<sup>19</sup> Therefore, use of diuretics is fundamental in the treatment of signs of fluid overload and congestion in patients with heart failure in hyperthyroidism. In comparison with furosemide, torsemide has higher bioavailability, longer half-life, higher degree of protein binding, these pharmacokinetic properties make torsemide works faster, longer, and better tolerated than furosemide.<sup>20,21</sup> Meanwhile, using the aldosterone receptor antagonist spironolactone to block RAAS, which acts primarily by competitive binding to the aldosterone-dependent sodium-potassium exchange sites located in the distal convoluted tubule and collecting duct. The effect of the blockade is to decrease sodium reabsorption with water retention and to increase potassium retention.

Compared with the increased cardiac output and peripheral circulation, the hepatic blood flow is little increased in the early stage of Graves' hyperthyroidism.<sup>22</sup> Under this condition, the growth of splanchnic oxygen consumption in hyperthyroidism is accomplished by an increased oxygen extraction. This could result in anoxia of the centro-lobular zones of the liver and may well be related to the centro-lobular necrosis.<sup>22</sup> It may lead to mild elevations in transaminases, which occur in up to 50% of patients with untreated hyperthyroidism. Thyrotoxicosis might also have a direct toxic effect on hepatic tissue; this may interfere with bile transport resulting in cholestasis with hyperthyroidism. In a rat model of thyrotoxicosis, plasmatic and intracellular organoid membranes of



hepatocytes in ultrastructure were significantly damaged, which has an adverse effect on the functionality of the liver.<sup>23</sup> The right heart failure in long-standing hyperthyroidism can cause passive liver congestion; liver dysfunction may range from mild hyperbilirubinemia, coagulopathy, and hepatomegaly to ascites and liver cirrhosis. Decreased cardiac output may be associated with acute hepatocellular necrosis with marked elevations in serum aminotransferases.<sup>24</sup> Therefore, the Japan Thyroid Association (JTA) guideline for the management of thyroid storm recommends that treatment of congestive heart failure could contribute to the recovery of normal liver function, which is one of the most common causes of hepatic damage and jaundice.<sup>12</sup>

We suspected the pre-existing chronic liver disease in this patient until the current episode, mainly because she had taken herbal remedies for 2 years, cases of herb-induced liver injury have been highlighted in many publications. Hyperthyroidism also reasonably consist of chronic liver injury as result of a long period of noncontrolled hyperthyroidism due to her poorly ATD compliance and the paucity of liver function tests.

Graves' hyperthyroidism patient should be rendered euthyroid before RAI therapy. Considering possibility of oral ATD-induced hepatotoxicity, methimazole cream was admitted to our patient for correcting hyperthyroidism, thyroxine concentration decreased and normalized on the twelfth day of admission. We also adopted TPE to remove harmful substances, circulating thyroid hormone and bilirubin, to replace coagulation factor and plasma factor, which is a useful adjunct as a bridge to the remedy when hyperbilirubinemia cannot be controlled effectively.

Another critical issue needed to be clarified is the presence or absence of thyroid storm. Our patient was evaluated carefully before admission, a negative diagnosis of thyroid storm was made according to an evidence-based diagnostic criteria for thyroid storm, which was formulated and established by JTA.<sup>13</sup> The criteria for congestive heart failure are defined to relatively severe manifestations: NYHA class IV and/or Killip class III/IV, pulmonary edema, moist rales in more than half the lung fields, or cardiogenic shock.<sup>12</sup> Tachycardia defined in thyroid storm of JTA criteria  $>130$  beats/min.<sup>12</sup> However, there was a tendency for our patient to experience further deterioration, such as infection or aggravated heart failure, which might induce thyroid storm, so we were vigilant in duration of her hospital stay and gave effective and active treatment.

In summary, as observed in our clinical practice and described in the previous literature, tachycardia and atrial fibrillation, early manifestations of hyperthyroidism indicate significant hemodynamic variation in cardiovascular system, hyperthyroidism, and untreated high-output

state can lead to persistent tachycardia and ventricular dilation; further deterioration in hemodynamics can result in chronic heart failure and liver dysfunction even a fatal event. A continuum of the disease present the pathophysiology development of Graves' hyperthyroidism, therefore, some conception has been formulated that hemodynamic variation is a dominant contributing factor of Graves' hyperthyroidism complication, the prompt identification and effective therapeutics of cardiac manifestations in hyperthyroidism patient are compulsory because the prognosis of it may be improved with the appropriate treatment.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

ZYL and JJW were involved in the diagnosis and management of the patient, proposed the study and writing of the manuscript, contributed equally to this work, and should be considered joint first author. YF and JBS are the communicating authors provided expert opinion for revisions, critically revised the manuscript. JZ and JX performed the literature search, gathered and organized information regarding the patient. XYL was involved in production, visualization of the diagram, and writing the manuscript.

## CONSENT

A written informed consent was obtained from the patient for publication; the use of personal health information is in accordance with the patient consent policy of the journal.

## DATA AVAILABILITY STATEMENT

The authors confirm data that support the findings of this report are available on request from the first corresponding author. The data are not publicly available due to privacy and ethical restrictions.

## ORCID

Zhiyuan Li  <https://orcid.org/0000-0002-1959-5820>

Jinjing Wang  <https://orcid.org/0000-0003-0805-580X>

Jing Zeng  <https://orcid.org/0000-0003-0569-2002>

Jian Xue  <https://orcid.org/0000-0002-4337-1704>

Xinyu Li  <https://orcid.org/0000-0001-8124-5533>

Jianbing Su  <https://orcid.org/0000-0001-6526-9623>

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