# Liver injury induced by levothyroxine tablets in a patient with hypothyroidism

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*To the Editor:* On March 9, 2018, a 31-year-old woman presented with liver dysfunction after thyroid cancer surgery. She was physically healthy; had no chronic diseases, such as hypertension and diabetes; had no history of infectious diseases, such as hepatitis and tuberculosis; had no history of drugs, food allergies, smoking, and alcohol consumption; and presented no obvious complaints during the disease course. B-ultrasound in the physical examination 3 years prior showed "left thyroid-occupying position." On February 5, 2018, she had undergone surgery at our hospital. Laboratory findings on February 6, 2018 revealed white blood cells (WBCs) $9.06 \times 10^9$/L ($3.50–9.50 \times 10^9$/L); neutrophils (NEs) $5.66 \times 10^9$/L ($1.80–6.30 \times 10^9$/L); triiodothyronine (T3) 0.94 (0.80–2.00) ng/mL; thyroxine (T4) 6.4 (5.1–14.1) μg/dL; free T3 (FT3) 3.95 (3.10–6.80) pmol/L; free T4 (FT4) 15.57 (12.00–22.00) pmol/L; thyroid-stimulating hormone (TSH) 2.56 (0.27–4.20) mU/L; thyroid peroxidase antibody (TPOAb) 8.2 (0–34.0) IU/mL; thyroglobulin antibody (TgAb) <10 (≤115) IU/mL; total bilirubin (T-BIL) 21.5 (5.0–22.0) μmol/L; direct bilirubin (D-BIL) 6.3 (0–10.2) μmol/L; alanine transaminase (ALT) 27.5 (7.0–40.0) U/L; aspartate transaminase (AST) 22.7 (13.0–35.0) U/L; and alkaline phosphatase (ALP), 48.9 (35.0–100.0) U/L. Hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody immunoglobulin M tested negative. On February 7, 2018, intra-operative pathology during left thyroidectomy indicated micro-papillary carcinoma. On February 11, 2018, she was discharged and prescribed levothyroxine tablets A (LTA; Merck KGaA, Darmstadt, Germany) 100 μg and calcium carbonate D3 tablets (CC-D3; Pfizer, China) 600 mg once daily.

On March 9, 2018, outpatient review laboratory findings revealed T3 1.11 ng/mL; T4 8.7 μg/dL; FT3 5.50 pmol/L; FT4 20.13 pmol/L; TSH 0.035 mU/L; thyroid-stimulating receptor antibody <0.3 IU/L; T-BIL 16.2 μmol/L; D-BIL 4.10 μmol/L; ALT 325.2 U/L; AST 144.9 U/L; and ALP 60.6 U/L. Anti-nuclear antibody (ANA), anti-mitochondrial antibody M2 sub-type (AMA-M2), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal antibody (LKM-1), anti-soluble liver antigen/liver-pancreatic antigen antibody (SLA/LP), and hepatocyte solute antigen (LC-1) tested negative. We suspected liver injury induced by LTA. The $R$ value [$R = (ALT_{measured\_value}/ALT_{normal\_upper\_limit})/(ALP_{measured\_value}/ALT_{normal\_upper\_limit})$] was 13.42.[1] Therefore, the admission diagnosis was drug-induced liver injury (hepatocyte injury type, acute, Roussel Uclaf causal relationship assessment method [RUCAM] 6 points, severity grade 1) and thyroid papillary cancer.

Admission examinations revealed body temperature 36.4°C; pulse 74 times/min; and blood pressure 120/65 mmHg. No yellow staining of the skin and mucous membranes and no liver area pain were noted. After admission, LTA was reduced to 75 μg once daily, and she continued to take CC-D3 tablets 600 mg once daily. Considering her hepatocyte injury type, magnesium isoglycyrrhizinate injection 100 mg with reduced glutathione for injection 2.4 g were intravenously dripped once daily for liver protection. Laboratory examinations on March 12, 2018 revealed the following: WBCs $5.46 \times 10^9$/L; NEs $2.60 \times 10^9$/L; and ANA, AMA-M2, ASMA, LKM-1, SLA/LP and LC-1, negative. Abdominal B-ultrasound presented no obvious abnormalities. Laboratory examinations on March 14, 2018 revealed the following: T-BIL 22.6 μmol/L; D-BIL 6.0 μmol/L; ALT 126.2 U/L; AST 43.3 U/L; and ALP, 52.9 U/L. The patient was discharged with the following prescriptions: LTA 75 μg and CC-D3 tablet 600 mg once daily, and glycyrrhizic acid diamine (GAD) capsules 100 mg and polyene phosphatidylcholine (PPC) capsules 456 mg 3 times/day.

Figure 1 presents the clinical course. On March 25, 2018, she presented with T-BIL 15.60 μmol/L; D-BIL 4.20 μmol. LTA was discontinued and switched to levothyroxine tablets B 75 μg (LTB; Berlin Chemie AG, Germany) once daily. GAD capsules, PPC capsules, and CC-D3 tablets were continued. On April 6, 2018, she presented with T-BIL

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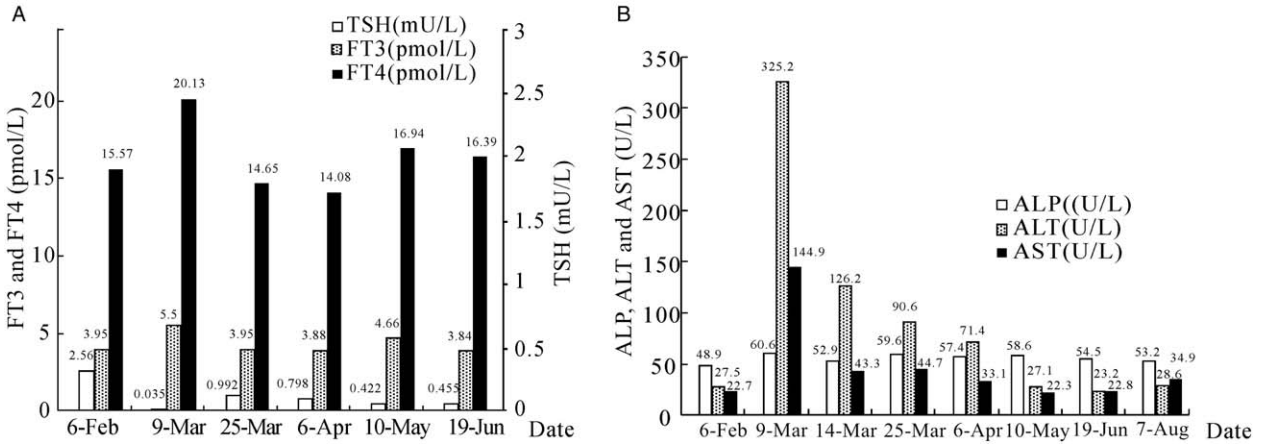


**Figure 1:** The clinical course of the case. (A) Changes in thyroid function. (B) Changes in liver enzymes. ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid stimulating hormone.

10.70 μmol/L; D-BIL 3.00 μmol/L. LTB was increased to 87.5 μg once daily, GAD capsules were reduced to 50 mg 3 times/day, PPC capsules were reduced to 228 mg 3 times/day, and CC-D3 tablets were continued. On May 10, 2018, she presented with T-BIL 15.30 μmol/L; D-BIL 3.90 μmol. LTB was increased to 87.5 μg and 100 μg, once daily alternately; GAD capsules and PPC capsules were discontinued. On June 19, 2018, she presented with T-BIL 16.00 μmol/L; D-BIL 4.60 μmol/L. LTB was increased to 100 μg once daily. On August 7, 2018, she presented with T-BIL 13.00 μmol/L; D-BIL 3.30 μmol/L. Abdominal B-ultrasound showed no obvious abnormalities.

The patient's liver function indicators before taking LTA were within normal ranges before treatment and were impaired after 26 days of treatment; transaminases decreased after 16 days of reduction and liver protection treatments. However, her liver function did not return to the pre-dose level, and we switched LTA to LTB. Transaminases decreased further after 12 days. She had no obvious abdominal B-ultrasound or autoimmune liver group abnormalities, liver dysfunction caused by liver parenchymal lesions were excluded, and TPOAb and TgAb tested negative, which could eliminate transient liver dysfunction caused by autoimmune thyroiditis. Since the main component of LTA and LTB is levothyroxine, their differences arise from their different additives. LTA additives are corn starch, gelatin, lactose, and stearic acid magnesium, while those of LTB are calcium bicarbonate, dextrin, long-chain glycerate, sodium carboxymethyl starch, and microcrystalline cellulose. Corn starch, gelatin, lactose, and stearic acid magnesium may have caused liver injury after considering RUCAM evaluation.[1]

In 1986, Shibata *et al*[2] reported that triiodothyronine (4 months) and levothyroxine (4 days) caused liver damage in a patient; Ohmori *et al*[3] and Kawakami *et al*[4] reported a case of liver injury caused by levothyroxine (27 days and 2 months, respectively). The mechanism may involve levothyroxine being a hapten-carrier protein complex where in the presenting cells are incorporated and digested. Some complexes are recognized by T lymphocytes, eventually causing liver damage. Recently, liver damage caused by levothyroxine tablets containing different additives has been reported. Per Toki *et al*,[5] liver damage may be caused by levothyroxine tablets containing $Fe_2O_3$.

In summary, the patient developed liver damage after taking LTA. Liver function gradually returned to normal after liver protection and switching to LTB. Liver dysfunction caused by additives is rare. We suggested that patients with adverse reactions to additives should avoid taking subsequent additive-containing treatments.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patient provided her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

## Conflicts of interest

None.

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