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 × 10⁹/L (3.50–9.50 × 10⁹/L); neutrophils (NEs) 5.66 × 10⁹/L (1.80–6.30 × 10⁹/L); triiodothyronine (T3) 0.94 (0.80–2.00) ng/mL; thyroid stimulating hormone (TSH) 4.4 (3.1–4.5) mIU/L; free T4 (FT4) 15.57 (12.00–22.00) pmol/L; thyroid-stimulating hormone (TSH) 2.56 (0.27–4.20) mU/L; 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; thyroid-globulin 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) 22.0 (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. We suspected liver injury induced by LTA.

On February 7, 2018, intra-operative pathology during left thyroidectomy indicated micro-papillary carcinoma. On March 9, 2018, outpatient review laboratory findings on February 6, 2018 revealed white blood cells (WBCs) 9.06 × 10⁹/L (3.50–9.50 × 10⁹/L); neutrophils (NEs) 5.66 × 10⁹/L (1.80–6.30 × 10⁹/L); triiodothyronine (T3) 0.94 (0.80–2.00) ng/mL; thyroid stimulating hormone (TSH) 4.4 (3.1–4.5) mIU/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; thyroid-globulin 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) 22.0 (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 April 6, 2018, she presented with T-BIL 15.60 g/dL; ALT 325.2 U/L; and ALP, 52.9 U/L. The patient was discharged and prescribed levothyroxine tablets (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; TSH 0.035 mIU/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-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. 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 × 10⁹/L; NEs 2.60 × 10⁹/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/L. LTA was discontinued and switched to levothyroxine tablets 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 15.60 μmol/L; D-BIL 4.20 μmol/L. LTA was discontinued and switched to levothyroxine tablets 75 μg (LTB; Berlin Chemie AG, Germany) once daily.
In 1986, Shibata et al. reported that triiodothyronine (4 months) and levothyroxine (4 days) caused liver damage in a patient; Ohmori et al. and Kawakami et al. 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. liver damage may be caused by levothyroxine tablets containing Fe2O3.

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.

References
