Liver Injury Induced by Levothyroxine in a Patient with Primary Hypothyroidism

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Abstract

We report a patient with primary hypothyroidism, who developed hepatocellular injury due to levothyroxine, synthetic thyroxine. A 63-year-old male was admitted to our hospital due to elevation of liver enzymes. The patient was diagnosed as having hypothyroidism and had been treated with levothyroxine for almost two months until admission. Drug-induced liver injury induced due to levothyroxine was suspected and liver enzymes were rapidly decreased after discontinuation of levothyroxine and dried thyroid powder, also containing thyroxine. Synthetic triiodothyronine, the deiodinated form of levothyroxine was administered instead, and was well tolerated by the patient. The drug-induced lymphocyte stimulation test (DLST) using levothyroxine was negative. Since triiodothyronine which structurally resembles levothyroxine did not cause liver injury, and DLST using levothyroxine was negative, it is unlikely that levothyroxine itself was targeted by the immune system. Rather, we assume that the complex of levothyroxine as the hapten and liver-related macromolecules in the body as the carrier might have acquired antigenicity in this patient and subsequently resulted in liver injury.

Key words: levothyroxine, drug-induced liver injury

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Introduction

Primary hypothyroidism, mainly caused by Hashimoto's thyroiditis, is mainly treated with replacement of thyroid hormones, especially oral administration of levothyroxine, i. e. synthetic thyroxine (T₄) (1). The use of levothyroxine for primary hypothyroidism has been well justified (2, 3), since levothyroxine, peripherally metabolized into triiodothyronine (T₃) through deiodination, can produce and maintain the proper amount of T₃ required under physiologic control (1). In general, levothyroxine is safe and well tolerated by patients, except for the possibility of developing osteoporosis in postmenopausal patients with excessive doses (1). However, it has been known that administration of levothyroxine could cause liver injury, although scarcely reported (4-6). Recently we encountered a male patient with primary hypo-

thyroidism, who developed liver injury due to levothyroxine.

Case Report

In October 2005, a 63-year-old male visited our hospital because of facial edema. Although there was a history of excess intake of alcohol beverage for 42 years, he quit drinking alcohol 4 months before his visit. On physical examination enlarged thyroid without tenderness was palpable, and facial and peripheral edema was noticed. Blood examination was compatible with primary hypothyroidism; serum levels of free T₃ and T₄ were decreased at 0.6 pg/ml and 0.1 ng/dl, respectively, and, by contrast, the serum level of thyroid stimulating hormone (TSH) was remarkably increased to 317.9 μ IU/ml. Both antithyroglobulin antibody and antithyroid peroxidase antibody were seropositive at 10.0 U/ml and 900.0 U/ml, respectively. Blood chemistry also demonstrated

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Figure 1. The clinical course of the present case after initiation of replacement therapy with levothyroxine.

elevation of total cholesterol, 258 mg/dl, aspartate aminotransferase (AST), 52 IU/l, creatine kinase, 1,835 IU/l, and a normal level of alanine aminotransferase (ALT), 20 IU/l; all of them were coincident with hypothyroidism. Ultrasonogram and CT scan of the neck demonstrated diffusely enlarged thyroid, without any nodularity. Thus, the diagnosis of primary hypothyroidism was made, and oral replacement therapy with 25 mg/day of levothyroxine was initiated on December 15, 2005, and the dosage was increased to 50 mg/day on January 5, 2006, 22 days later.

However, blood examination at a regular visit on February 2, 2006, almost two months after initiation of replacement therapy with levothyroxine, demonstrated elevation of liver enzymes, AST 670 IU/l and ALT 884 IU/l, and the patient was admitted for further evaluation and treatment on that day. On admission, the consciousness was clear, and no jaundice was noted on the skin or conjunctiva. Thyroid was not palpable at this time. Hepatosplenomegaly was not observed, either. Complete blood counts and other blood chemistry were as follows; white blood cell 6,600 /ml (eosinophil 16%), hemoglobin 13.3 g/dl, platelet counts 217,000/mm³, albumin 4.1 g/dl, total bilirubin 1.5 mg/dl, direct bilirubin 0.7 mg/dl, alkaline phosphatase 458 IU/l, gamma glutamyltranspeptidase 252 IU/l. Erythrocyte sedimentation rate was 12 mm/hr, slightly elevated. Blood markers indicating viral and autoimmune acute liver injury, including viral markers for hepatitis A/B/C virus, cytomegalovirus, Epstein Barr virus, and autoantibodies were negative. Although serum TSH level was 150.6 μ IU/ml, still high on admission, serum free T₃ and T₄ were within normal limit, 2.5 pg/ml and 0.8 ng/dl, respectively. Therefore, liver injury induced by hyperthyroidism due to overdose of levothyroxine was denied.

The clinical course after admission is shown in Fig. 1. Since drug-induced liver injury caused by levothyroxine was suggested as a possible etiology on admission, the administration of levothyroxine was discontinued soon after admission and we administered dried thyroid powder containing both natural T₃ and T₄ instead. However, the elevation of

ALT continued and jaundice developed along with administration of dried thyroid powder, and the results of blood test on admission suggested no other etiology of liver injury, as shown above. In addition, we performed liver biopsy for histological evaluation on the 12th hospital day. Liver histologies demonstrated marked infiltration of inflammatory cells, consisting of considerable eosinophils, within and in the vicinity of enlarged and edematous portal tracts (Fig. 2a). Focal necrosis and infiltration of eosinophils were observed within liver parenchyma (Fig. 2a), without predominancy in centrilobular zones (Fig. 2b). Taken together, we made a diagnosis as levothyroxine-induced liver injury, and changed replacement therapy from dried thyroid powder to liothyronine, synthetic T₃, at the 17th hospital day.

While the serum value of ALT decreased after discontinuation of dried thyroid powder, total bilirubin as well as jaundice became exacerbated, as shown in Fig. 1. Since the possibility that liothyronine also contributed to the liver injury was not excluded, liothyronine was discontinued at the 27th hospital day. Thereafter, liver enzymes and jaundice rapidly disappeared and the patient was discharged soon.

Meanwhile, hypothyroidism had not been treated at all after discharge and symptoms including peripheral edema developed again. Hence we administered liothyronine as a replacement therapy, and no liver injury has noted subsequently (Fig. 1). According to the criteria for drug-induced liver injury proposed by the Digestive Disease Week Japan in 2004, the score was 9, suggesting the causality of levothyroxine was 'highly probable' (7). Therefore, we finally concluded that only levothyroxine, not liothyronine, was responsible for liver injury.

During his admission, we performed a drug-induced lymphocyte stimulation test (DLST) (8, 9), using levothyroxine, dried thyroid powder, and liothyronine as candidate responsible drugs. The results are shown in Table 1 and none of them demonstrated a positive response.

Figure 2. Histopathological studies of the biopsied specimens of the liver demonstrated marked infiltration of inflammatory cells, consisting of considerable eosinophils, within and in the vicinity of the enlarged and edematous portal tracts. Mild proliferation of bile ducts and derangement of cholangiocytes were also seen. Focal necrosis and infiltration of eosinophils were observed within liver parenchyma (a, hematoxylin eosin stain, $\times 200$), even though necrosis and degeneration of hepatocytes was not remarkable in centrilobular zones (b, silver stain, $\times 400$).

Table 1. The Results of Drug-Induced Lymphocyte Stimulation Test (DLST)

Drug*		Values (cpm)	Stimulation index (%)**
Levothyroxine (Synthetic T ₄)	pt	259	87
	control	295	
Dried thyroid powder (T ₃ and T ₄)	pt	291	98
	control	295	
Liothyronine (Synthetic T ₃)	pt	215	114
	control	188	

* A dose per day of each drug (Levothyroxine 50 μ g, dried thyroid powder 40mg,

liothyronine 25 μ g) was diluted in 190 ml of phosphate buffer saline and used for assay

with serial dilutions. Values were counted at 3⁻⁴ dilution for levothyroxine and

liothyronine, and 3⁻³ for dried thyroid powder.

** The results of DLST are considered to be positive, if the S.I. is greater than 181%.

Discussion

For the treatment of hypothyroidism, either primary or central, levothyroxine, synthetic T₄, is primarily recommended (2, 3) due to several reasons. Orally administered levothyroxine is absorbed relatively slowly and equilibrates rapidly in its distribution volume, therefore avoiding large postabsorptive perturbations in free T₄ levels (1). In addition, levothyroxine is metabolized to its active form T₃ peripherally and thus it is rational to supply the “prohormone”, which is activated by physiologically regulated mechanisms (1). In the current case, levothyroxine, administered as a replacement therapy for hypothyroidism, caused liver injury. Dried thyroid powder, mixture of T₃ and T₄, also augmented

the elevation of liver enzymes, while liothyronine (synthetic T₃) did not demonstrate any liver damage.

In general, the replacement with synthetic T₄ for hypothyroidism increases the oxygen demand of hepatocytes. Thus, it would be possible to assume that liver injury in the current case developed due to relative ischemia of the liver, i.e. relatively reduced supply of oxygen to hepatocytes after oxygen demand was enhanced with replacement of thyroid hormone. However, if this would be the case, necrosis of hepatocytes would be mainly located at zone 3, the periportal area. In this case, focal necrosis and infiltration of eosinophils were mainly observed within liver parenchyma, even though also seen in the vicinity of the portal tracts. Therefore, it is implausible that ischemia due to replacement of thyroid hormone would be the reason for liver injury.

It should be considered how liver injury was caused by levothyroxine, identical to T₄, a low weight and generally present molecule in a body. Clearly, it is very unlikely that levothyroxine itself is targeted and recognized by T lymphocytes through presentation as antigens by antigen-presenting cells (APCs). This is supported by the fact that DLST, in which levothyroxine was added to mononuclear cells preparation of the patient (8, 9), showed negative results. In the demonstrated case, levothyroxine induced hepatocellular injury, while liothyronine was well tolerable without any elevation of liver enzymes. Since the molecular structures of levothyroxine and liothyronine are quite similar, conservation of liothyronine from liver injury also indicates that primary structure of levothyroxine was not targeted by the immune response.

Alternatively, we assumed that levothyroxine operated as a hapten. A complex of hapten and carrier protein would be incorporated and digested by APCs, and part of the complex would be recognized by T lymphocytes, leading to liver injury. In general, levothyroxine is bound to albumin, thyroxine binding globulin and transthyretin in sera (2); however, presumably carrier proteins in the current case may be closely related to the liver, and thus far liver injury devel-

oped. Interestingly, the safety of liothyronine in cases with levothyroxine-induced liver injury is a common feature among previous reports (4-6). Similarly, liothyronine caused no skin lesion to develop and was safely administered in a case with drug eruption caused by levothyroxine (10). It is likely that conformational epitopes derived from a complex of levothyroxine, not liothyronine, and carrier protein may be easily recognized by immune system in genetically sus-

ceptible individuals.

In conclusion, we reported a case with levothyroxine-induced liver injury. Since it is unlikely that levothyroxine itself was a target molecule of T lymphocytes, the diagnostic value of DLST might be limited for this drug. When liver injury develops during replacement therapy for patients with hypothyroidism, drug-induced liver injury should not be overlooked.

References

1. Larsen P, Davies T. Hypothyroidism and thyroiditis. in: Williams Textbook of Endocrinology Larsen P, Kronenberg H, Melmed S, Polonsky K, Eds. Saunders, Philadelphia 2003: 331-373.
2. Mandel S, Brent G, Larsen P. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med* **119**: 492-502, 1993.
3. Toft A. Thyroxine therapy. *N Engl J Med* **331**: 174-180, 1994.
4. Inui A, Ishikawa K, Mizuno N, Oimomi M, Baba S. Case of Hashimoto's disease with thyroxine induced allergic hepatitis. *Nippon Naika Gakkai Zasshi* **72**: 1407-1413, 1983 (in Japanese, abstract in English).
5. Shibata H, Hayakawa H, Hirukawa M, Tadokoro K, Ogata E. Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. *Arch Intern Med* **146**: 1624-1625, 1986.
6. Ohmori M, Harada K, Tsuruoka S, Sugimoto K, Kobayashi E, Fujimura A. Levothyroxine-induced liver dysfunction in a primary hypothyroid patient. *Endocr J* **46**: 579-583, 1999.
7. Takikawa H, Onji M. A proposal of the diagnostic scale of drug-induced liver injury. *Hepatol Res* **32**: 250-251, 2005.
8. Maria V, Pinto L, Victorino R. Lymphocyte reactivity to ex vivo drug antigens in drug-induced hepatitis. *J Hepatol* **21**: 151-158, 1994.
9. Maria V, Victorino R. Diagnostic value of specific T cell reactivity to drugs in 95 cases of drug induced liver injury. *Gut* **41**: 534-540, 1997.
10. Matsuno M, Sohmiya M, Nishiki M, Ohguni S, Kato Y. A case of chronic thyroiditis associated with drug eruption induced by levothyroxine sodium (Thyradin S). *Folia Endocrinol* **73**: 617-622, 1997 (in Japanese, abstract in English).