CASE REPORT

Case of acute mixed liver injury due to hypothyroidism

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SUMMARY

The effects of hypothyroidism on the liver are not well understood. A 77-year-old woman with Hashimoto's thyroiditis had stopped taking levothyroxine on her own for 6 months. Her thyroid stimulating hormone (TSH) level was consistent with severe hypothyroidism. She resumed thyroid replacement therapy. The following month, her liver function tests were significantly elevated. Seven weeks after resumption of therapy, her TSH and liver tests had returned to normal. We attribute the mixed hepatocellular injury to hypothyroidism that resolved on correction of the hypothyroid state. This case reminds us that thyroid disease should be considered when evaluating acute liver injury.

BACKGROUND

While the effects of hyperthyroidism on the liver have been well described in the literature,^{1–5} those related to hypothyroidism are less well understood. Because thyroxine and triiodothyronine play an important role in the basal metabolic rate and because the liver is important in the metabolism of thyroid hormones, these two organs are certainly expected to affect one another. Bohinc *et al* concluded that liver injury causes hepatic stromal cells to respond by downregulation of deiodinases leading to a hypothyroidism state, that is driven by the Hedgehog pathway.¹ Hyperthyroidism has been shown to cause hepatocellular injury with elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), especially in the setting of thyrotoxicosis, due to poor perfusion of hepatocytes when oxygen demand is increased.² Hypothyroidism can clinically mimic the signs and symptoms of chronic liver disease including myxedema ascites, myopathy and even myxedema coma.⁶ To our knowledge, there is only one case report describing hypothyroidism leading to hepatocellular injury in a paediatric patient with a genetic ring chromosome 18 syndrome defect. However, to date, other reports of hepatic injury due to hypothyroidism remain limited.⁷

Herein, we report a case of acute, asymptomatic mixed hepatocellular injury which we attribute to hypothyroidism that resolved on correction of the markedly hypothyroid state.

CASE PRESENTATION

A 77-year-old woman with a history significant for non-Hodgkin's lymphoma treated with total body radiation, and Hashimoto's thyroiditis diagnosed

in 2011 leading to hypothyroidism, was referred for evaluation of abnormal liver tests. Her history also included, ER-positive left breast cancer in 1993 treated with mastectomy, chemotherapy for 6 cycles and 10 years of tamoxifen and left nasal basal cell carcinoma, currently without evidence of active disease. She also developed in-situ carcinoma in a duodenal tubulovillous adenoma requiring a Whipple procedure approximately 2 years ago. Four years prior to presentation, she had normal aminotransferases, alkaline phosphatase (AP) and total bilirubin. Two months prior to presentation, she was found to have a mildly elevated AST, ALT, AP along with a significantly elevated thyroid stimulating hormone (TSH) level (see [table 1](#)). Total bilirubin, albumin, complete blood count and creatinine were all normal. At that time, she had stopped taking her levothyroxine for about 6 months as she had felt well. On her own, she had resumed the thyroid replacement 3–4 weeks later. Her lab tests done 4 weeks later (after a total of 7 weeks following resumption of her levothyroxine) were significant for further elevations in her ALT, AST and AP, although the bilirubin remained normal and she was asymptomatic. A repeat TSH level was not done at the time, and no liver tests were obtained in the weeks prior to these values. We were unsure what the peak values might have been. However, on the day of her Hepatology Clinic visit, her TSH had returned to normal range and the liver tests were back to near normal. As a result, it was decided to continue to monitor her liver tests, with the thought that they should remain normal. A biopsy was not indicated because her liver tests had improved significantly. Her only symptoms were chronic frequent bowel movements as well as epigastric and lower abdominal pain attributed to the Whipple procedure. She had no right upper quadrant pain, fever, weight loss, jaundice or abdominal fullness. Her current medications included pancrealipase 72 000 units three times per day, pantoprazole 40 mg per day, atorvastatin 20 mg per day, multivitamin daily, aspirin 81 mg per day and sertraline 100 mg per day, all of which she has taken for years, in addition to the levothyroxine. She denied alcohol use, herbal supplements or illicit drug use. She had normal vital signs and her physical examination was unremarkable, with no abdominal distention or hepatomegaly.

INVESTIGATIONS

A CT obtained prior to her clinic visit showed an enlarged liver, pneumobilia consistent with her

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Table 1 Liver function test results

Lab test	September 2013 (on levothyroxine 125 mcg per day)	January 2015 (on levothyroxine 125 mcg per day)	April 2017 (off of levothyroxine 125 mcg per day for 6 months)	May 2017 (just resumed levothyroxine 125 mcg per day)	June 2017 (date of liver clinic visit, still on levothyroxine 125 mcg per day)
Total protein	–	7.3 g/dL	7.2 g/dL	6.9 g/dL	6.7 g/dL
Albumin	4.0 g/dL	4.0 g/dL	4.1 g/dL	4.0 g/dL	3.9 g/dL
Total bilirubin	0.5 mg/dL	0.4 mg/dL	0.3 mg/dL	0.4 mg/dL	0.4 mg/dL
Direct bilirubin	–	–	–	0.17 mg/dL	0.14 mg/dL
Alkaline phosphatase	77 IU/L	70 IU/L	179 IU/L	211 IU/L	147 IU/L
AST	26 IU/L	19 IU/L	48 IU/L	333 IU/L	37 IU/L
ALT	33 IU/L	24 IU/L	42 IU/L	264 IU/L	47 IU/L
TSH	–	–	14.99 mIU/L	Not tested	1.96 mIU/L
Other	–	–	–	–	Positive thyroid peroxidase antibody

Reference ranges: total protein: 6–8.5 g/dL; albumin: 3.5–4.8 g/dL; total bilirubin: <1.2 mg/dL; direct bilirubin: <0.4 mg/dL; alkaline phosphatase: 39–117 IU/L; AST: <40 IU/L; ALT: <32 IU/L; TSH: <4.5 mIU/L.

ALT, alanine transaminase; AST, aspartate transaminase; TSH, thyroid stimulating hormone.

Whipple procedure and surgically absent pancreas, gallbladder and spleen and was negative for fatty liver disease.

The viral hepatitis panel was positive for hepatitis A total antibody indicating immunity and negative for hepatitis B surface antibody, antigen and hepatitis C antibody. Antinuclear antibody screen was negative.

OUTCOME AND FOLLOW-UP

In this patient, a 6-month absence of not taking her levothyroxine resulted in a significant rise in TSH with subsequent elevations in liver tests and we surmise that the elevations in AST, ALT and AP were likely the result of her relapse of hypothyroidism off of her thyroid replacement therapy which she had been taking for years. While we may have missed the peak values when her TSH was highest, the elevations seen on presentation suggested a mixed, but predominantly hepatocellular injury based on an R value of 4.73.⁸

This patient did not develop other signs of acute hypothyroidism, such as myxedema. We understand that antinuclear antibodies are not the only diagnostic criteria for autoimmune hepatitis; however, given that her liver enzyme values improved back to near normal within several weeks after resuming levothyroxine therapy and with normalisation of the TSH, this strongly suggests that the subacute liver injury was in fact associated with her untreated hypothyroidism.

DISCUSSION

The liver is responsible for the deiodination of T4 to T3 and serves as a reservoir for T4 and T3. The literature has established that patients with cirrhosis have normal or low serum T4 and decreased T3 levels.^{8–14} The likely reason for this includes a diminished amount of thyroxine-binding prealbumin and albumin. However, free T4 and free T3 levels are often normal.

A case-controlled study of hypothyroid subjects from India demonstrated that serum bilirubin, AST, ALT and AP were higher in patients with hypothyroidism compared with euthyroid subjects, although not statistically significant.⁷ That study noted that the elevated liver enzymes normalised when a euthyroid state was achieved with thyroid replacement therapy, similar to our case. Other reports also have also noted that hypothyroidism-related abnormalities in hepatic function are usually reversible with treatment.^{8,9}

Our case, although not the first, is a significant reminder of the importance behind consideration of liver injury due to hypothyroidism. Arora *et al* described a case series of adults similar to our case here.⁷ Their group also postulated that the state of low circulating thyroid hormone levels might exert a direct injurious effect on the liver. Mechanisms include hepatic congestion from possible cardiac abnormalities or increased vascular endothelial permeability due to hypothyroidism.^{6,10,15–18} A study involving rats showed decreased biliary excretion in hypothyroidism.¹¹

Learning points

- Our case may serve as a reminder to clinicians that thyroid disease, in addition to drug-induced liver injury, viruses and autoimmune disease, should be considered in evaluation of acute liver injury.
- We already know that hyperthyroidism has been associated with liver disease but little is known about the effects of hypothyroidism.
- This is an interesting case report of an adult patient who had mixed type liver injury from hypothyroidism.

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