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Case Report

Clinical Case Report: Dissociation of Clinical Course of Coexisting Autoimmune Hepatitis and Graves Disease

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ABSTRACT

Objective: Concurrent autoimmune disorders, including autoimmune hepatitis (AIH), with Graves disease have been reported. Glucocorticoids can simultaneously lower thyroid hormone levels and treat AIH. Recurrence of hyperthyroidism is associated with recurrence of hepatitis. We present a case of coexisting AIH and Graves thyrotoxicosis, which improved with prednisone, but the thyrotoxicosis recurred during a prednisone taper while the hepatitis stayed in remission.

Methods: Evaluation included measurements of liver enzyme levels, thyroid function tests, and thyroid-stimulating antibodies as well as abdominal ultrasound, magnetic resonance imaging, and liver biopsy.

Results: A 47-year-old woman presented with nausea and jaundice. Workup showed an aspartate aminotransferase level of 1956 (reference, 10-42) U/L and alanine aminotransferase level of 1634 (reference, 14-54) IU/L. The liver biopsy was consistent with AIH. Nine months later, she reported palpitations, heat intolerance, and weight loss and was diagnosed with Graves disease. The patient received prednisone at 60 mg daily, and the liver and thyroid functions normalized after 1 month. Prednisone was tapered to 5 mg daily. Seven months later, she presented with a thyroid-stimulating hormone level of 0.049 (reference, 0.340-5.6) μIU/mL) and free thyroxine level of 3.96 (reference, 0.58-1.64) ng/dL. Liver enzymes remained at normal levels. Prednisone was increased from 5 to 20 mg to treat hyperthyroidism. The patient was referred for thyroidectomy for a diagnosis of Graves disease with thyrotoxicosis.

Conclusion: This case is an example of coexisting autoimmune diseases, Graves disease and AIH, with different clinical courses. Despite initial resolution with glucocorticoid therapy, Graves disease recurred, while AIH stayed in remission.

Introduction

Graves disease is the most common cause of thyrotoxicosis. In this autoimmune disease, stimulating autoantibodies against the thyrotropin receptor lead to excess production of thyroid hormone. An association between Graves disease and coexisting autoimmune disorders, such as autoimmune hepatitis (AIH), has been reported.[1] AIH is characterized by an elevated level of liver enzymes and interface hepatitis with plasma cell infiltration.[2] In cases of coexisting AIH and Graves disease, glucocorticoids improve liver enzyme and thyroid hormone levels. Corticosteroids inhibit thyroid-stimulating hormone (TSH) secretion and decrease conversion of thyroxine (T4) to triiodothyronine (T3) by type 2 deiodinase.[3] Accordingly, case reports have shown that recurrence of hyperthyroidism is associated with recurrence of AIH.[2,4] We present a case of a patient with AIH and Graves thyrotoxicosis, which initially improved with prednisone therapy, but the thyrotoxicosis recurred with a prednisone taper, while the hepatitis stayed in remission.

Case Report

A 47-year-old woman with a history of recurrent kidney stones presented with a 1-month history of fatigue, nausea, yellow discoloration of the eyes, and dry, itchy skin. Her aspartate aminotransferase level was 1956 (reference, 10-42) U/L, alanine aminotransferase level was 1634 (reference, 14-54) IU/L, and total bilirubin level was 15.1 (reference, 0.3-1.6) mg/dL. Her gamma-

Abbreviations: AIH, autoimmune hepatitis; FT4, free thyroxine; PTH, parathyroid hormone; RAI, radioactive iodine ablation; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

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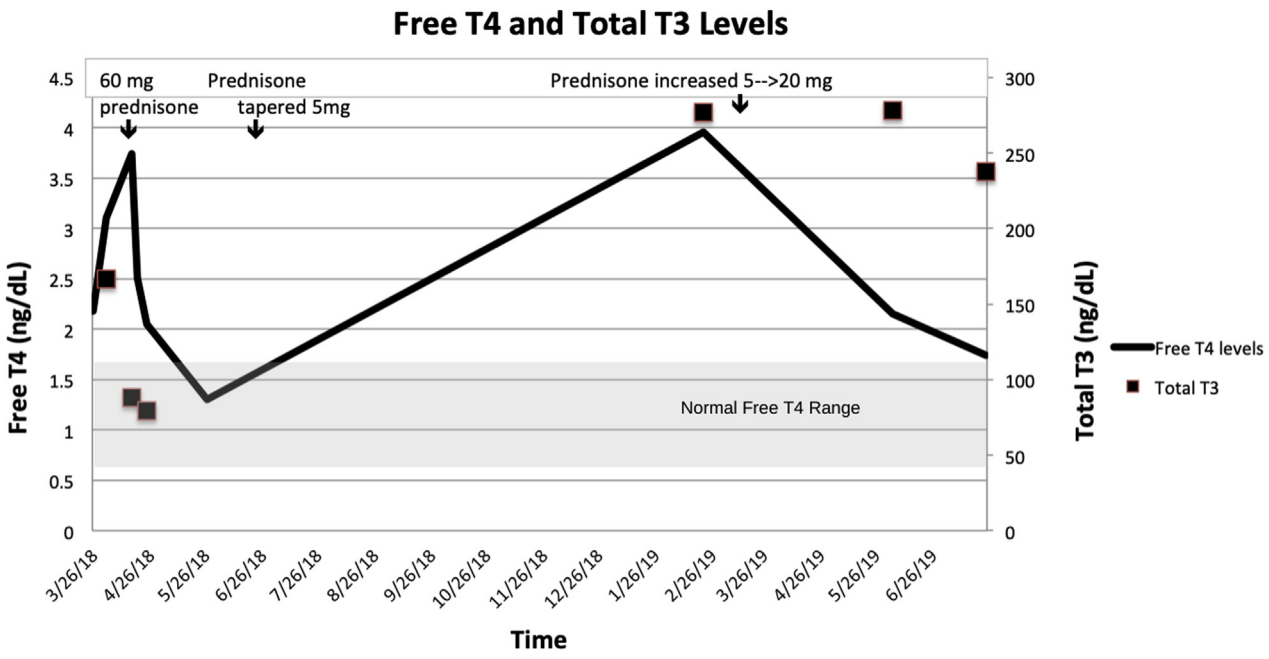

Fig. 1. FT4 and total T3 levels. *FT4* = free thyroxine; *T3* = triiodothyronine; *T4* = thyroxine.

glutamyl transferase level was 71 (reference, 7-64) U/L, and alkaline phosphatase level was 195 (reference, 38-126) IU/L. Abdominal ultrasound showed a hypoechoic liver without any intrahepatic biliary ductal dilation. Follow-up abdominal magnetic resonance imaging revealed nonspecific, mild periportal edema. The liver was normal in size, contour, and enhancement. No intra- or extrahepatic biliary ductal dilation was noted. Ultrasound-guided liver biopsy showed portal and periportal fibrosis and moderate chronic inflammation consisting predominantly of lymphocytes, plasma cells, and rare eosinophils, with evidence of interface activity. The findings were consistent with AIH, and treatment was initiated with ursodeoxycholic acid at 300 mg 3 times daily. The liver enzyme levels improved (Fig. 1 and 2); thus, corticosteroids were not given.

Nine months later, she presented with worsening upper- and lower-extremity weakness, slurred speech, abdominal pain, and nausea and vomiting. Her aspartate aminotransferase level was 2783 (reference, 10-42) U/L, and alanine aminotransferase level was 1780 (reference, 14-54) IU/L. She was tachycardic and reported heat intolerance, amenorrhea, palpitations, and a 13.6-kg weight loss. Her TSH level was 0.024 (reference, 0.340-5.6) μIU/mL, with an elevated free thyroxine (FT4) level of 3.74 (reference, 0.58-1.64) ng/dL. Thyroid-stimulating immunoglobulin level was 435% (reference, <140%). She was treated with prednisone at 60 mg daily, propranolol at 20 mg 3 times daily, and cholestyramine at 4 g 3 times daily. She was discharged on a 1-month prednisone taper starting at 60 mg daily. Liver function test and thyroid function test results normalized on a follow-up 1 month later. Cholestyramine was discontinued, and prednisone was tapered to 5 mg daily (Fig. 1).

The patient was lost to follow-up for 7 months. She was seen at an endocrine clinic, where she reported palpitations and heat intolerance. The thyroid function test results were consistent with hyperthyroidism (TSH, 0.049 μIU/mL, FT4, 3.96 ng/dL). The liver function test results remained in the normal range. Due to a risk of hepatotoxicity with thionamides, propylthiouracil or methimazole was not initiated. Prednisone was increased from 5 to 20 mg daily, and cholestyramine was resumed to treat hyperthyroidism. After the initiation of prednisone, the patient had fasting as well as postprandial hyperglycemia, which was treated with insulin. Though the TSH level remained suppressed, prednisone was not increased further because the FT4 level improved. She was started on beta-blockade with atenolol at 50 mg daily. Atenolol was used rather than propranolol during outpatient management due to the convenience of once-daily dosing. The patient was ultimately referred for total thyroidectomy. Radioiodine was not proposed because she had concurrent hypercalcemia and an elevated parathyroid hormone (PTH) level in the setting of recurrent nephrolithiasis. High calcium levels were noted after she presented with Graves disease recurrence, which persisted even after improvement of the FT4 levels. The PTH level before surgery was 60.3 (reference, 12.0-88.0) pg/mL, with an albumin-adjusted calcium level of 12.1 (reference, 8.9-10.3) mg/dL. Thus, she was referred for a surgery for diagnoses of Graves disease and primary hyperparathyroidism. A week prior to the surgery, the patient was started on a saturated solution of 3 drops (150 mg) of potassium iodide every 8 hours. She underwent right inferior parathyroidectomy in conjunction with total thyroidectomy. After the surgery, the patient had postsurgical hypoparathyroidism, with a PTH level of <1.2 (reference, 12.0-88.0) pg/mL and albumin-adjusted calcium level of 7.6 (reference, 8.9-10.3) mg/dL. She was treated with calcium carbonate at 2500 mg twice daily (total 2000 mg of elemental calcium), calcitriol at 0.25 μg twice daily, and cholecalciferol at 2000 IU daily. The calcium level improved to an albumin-adjusted level of 8.1 (reference, 8.9-10.3) mg/dL. Repeat PTH level was 3.4 (reference, 12.0-88.0) pg/mL. AIH remained in remission without prednisone after the surgery.

Discussion

Our case report describes a patient who had recurrence of thyrotoxicosis on a prednisone taper, while AIH remained in remission, which has rarely been reported. We present a long-term follow-up of this patient's clinical course over a 2-year period. Ultimately, she required surgery for a definitive treatment of her

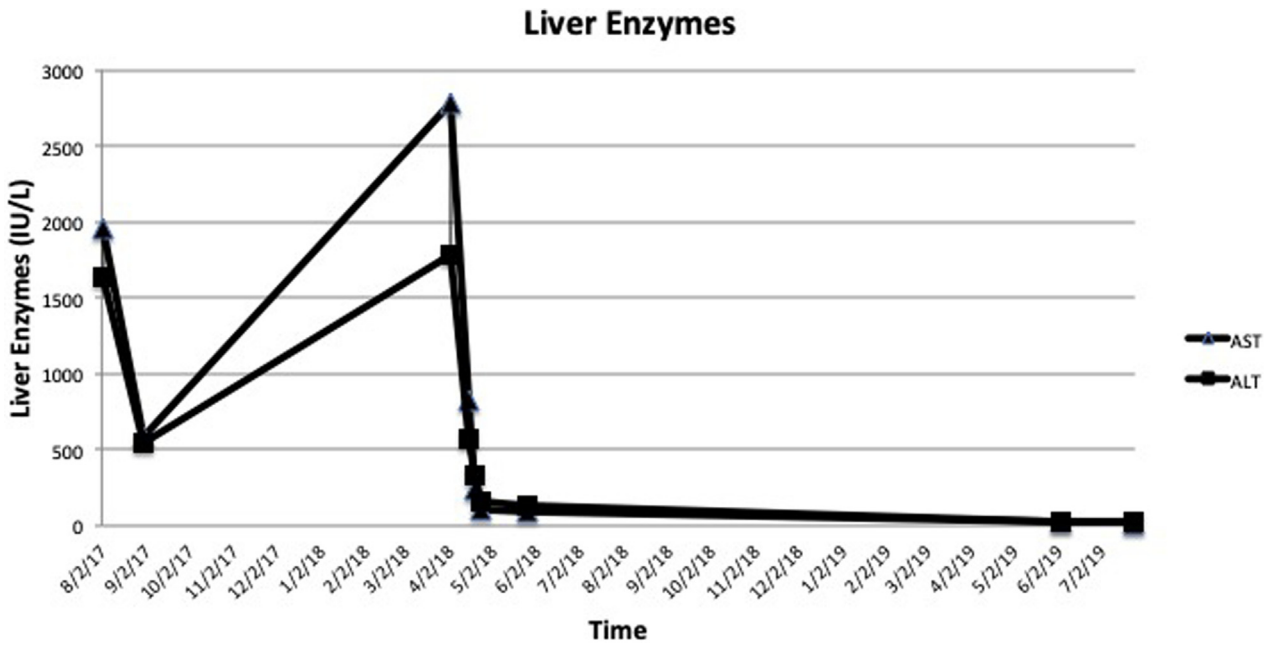

Fig. 2. Liver enzymes. *ALT* = alanine aminotransferase; *AST* = aspartate aminotransferase.

Table
Description of Previously Reported Cases of Coexisting Graves Disease and AIH

Case report	Description/timeline	Outcome
Rana et al[2]	15-year-old female MMI first → RAI → oral prednisone for persistent AIH → normal LFT results 1 month later	Progression of AIH despite stable thyroid function
	21-year-old female RAI first → immunosuppression including steroids for progression of AIH → LFT results did not improve, eventual liver transplant	Persistent hepatitis despite normalization of thyroid function
	39-year-old female Prednisone and MMI both started first → RAI ablation → remission of both → recurrent AIH → liver transplant	Recurrence of AIH despite stable thyroid function
	38-year-old female Immunosuppression first for AIH → LFT results normalized → MMI started for Graves → acute liver injury → pulse dose steroids → LFT results normal → RAI → TFT and LFT results normalized	Both remained stable after steroids and RAI
Bokhari et al[4]	38-year-old female Steroids started first → LFT and TFT results normalized with steroids → Graves disease recurred on prednisone taper	Graves disease recurred on prednisone taper, hepatitis remained stable
Yamada et al[8]	12-year-old female MMI first → elevated LFT results → AIH diagnosed → prednisone and immunosuppressant → LFT results normalized, TFT results remained normalized → prednisone tapered to 5 mg → LFT and TFT results stable	Both Graves disease and AIH remained in remission on prednisone at 5 mg
Jhee et al[9]	25-year-old female MMI first → no improvement in LFT results → prednisone → LFT and TFT results normal after 1 week	Graves disease and AIH in remission on prednisone at 60 mg, no data given after 1 week
Coy et al[7]	22-year-old female MMI first (on and off for 1.5 years) → AIH dx → RAI. No steroids	Graves disease remission after RAI. No follow-up data given for AIH
Sawhney et al[6]	24-year-old female Steroids and immunosuppression first for AIH → diagnosed with Graves disease → high-dose hydrocortisone → LFT results improved → RAI ablation → AIH went into complete remission → stayed on 20 mg prednisone	Both AIH and Graves disease went into remission after steroids and RAI, stayed in remission on prednisone at 20 mg
Cui et al[10]	31-year-old female PTU and KI first → admitted with hepatitis → steroids started (1 g of methylprednisone) → LFT and TFT results normalized → patient tapered to prednisone at 10 mg daily → unclear follow-up	Both Graves disease and AIH went into remission with steroids. No follow-up data after taper
Papdakis et al[11]	28-year-old female Prednisone first → LFT results normal → prednisone tapered and azathioprine started → LFT and TFT results normal after 1 month of treatment	Both Graves disease and AIH had remission, no long-term follow-up data

Abbreviations: AIH = autoimmune hepatitis; LFTs = liver function tests; MMI = methimazole; RAI = radioactive iodine ablation; TFTs = thyroid function tests.

Graves disease. Reports on Graves disease with concurrent AIH are relatively rare.[2,5] In most cases, AIH was not diagnosed at initial presentation because of a broad differential of elevated liver enzyme levels in the setting of thyroid disease. Thyrotoxicosis can cause hepatic dysfunction in both cholestatic and hepatic enzymes.[5] Therefore, identifying the etiology of elevated liver enzyme levels in an autoimmune thyroid disease remains a diagnostic challenge.[5] The treatment of concurrent AIH and Graves disease

remains a challenge because thionamides have the potential to cause hepatic injury.

On review of literature, we found 11 reported cases of patients with coexisting Graves disease and AIH (Table). All the reported cases were in women between 12 and 39 years of age. Unless there was a known diagnosis of hepatitis,[6] the patients received first-line therapy with methimazole or propylthiouracil until liver disease was accurately diagnosed. Seven of the 11 cases received definitive treatment with radioactive iodine ablation (RAI), and in 2 of these cases, the patient received RAI prior to any corticosteroids.[2] However in both the cases, AIH progressed, and the patients required eventual initiation of glucocorticoids.[2] In 1 case, the patient was treated with RAI and did not require any corticosteroids.[7] In 4 reports, the patients only received corticosteroids, and both Graves disease and AIH remained in remission.[8-11] Only 1 case was similar to that of our patient, where both Graves disease and AIH were initially treated with corticosteroids, but Graves disease recurred on a prednisone taper, while the hepatitis remained in remission.[4] However, data about the length of remission was not provided for those cases beyond a few months. Glucocorticoids are not typically included in the long-term management of Graves disease because of the risk of adverse effects such as hyperglycemia, weight gain, and fluid retention. While corticosteroids can be used in the treatment of both Graves disease and AIH, 5 cases in the literature have shown that the progression of AIH can occur apart from the clinical course of Graves disease.[2,4]

The use of prednisone improved Graves disease in our patient. Cholestyramine was used in conjunction with corticosteroids to improve the patient's thyrotoxicosis. Bile-acid sequestrants bind thyroid hormone in the intestines and increase fecal excretion of T4.[12] However, cholestyramine was discontinued once the acute hyperthyroid state improved and the patient remained in remission. In our case, the patient had a recurrence of thyrotoxicosis on a prednisone taper while the hepatitis remained in remission. Given our patient's history of steroid-induced hyperglycemia requiring insulin, we were hesitant to use high doses of glucocorticoids. Our patient's hepatitis remained in remission despite the relatively low dose of prednisone. AIH is thought to be due to a T-cell mediated immune response against liver antigens, leading to progressive inflammation.[13] Similar to Graves disease, the presence of elevated serum autoantibodies is characteristic of AIH.[14] Glucocorticoids remain a mainstay of the treatment of AIH, and the benefit is thought to be conferred by their anti-inflammatory effects.[15] In Graves disease, the autoantibodies bind to the TSH receptor and stimulate follicular cell growth, causing diffuse thyroid enlargement and excess production of thyroid hormones.[16] Glucocorticoids inhibit peripheral conversion of T4 to T3. Graves disease probably did not stay in remission on a low dose of prednisone because it does not have a direct effect on the antibody activation of thyroid follicular cells. It is also possible that at lower doses of glucocorticoids, the peripheral conversion of T4 to T3 is decreased.

Conclusion

The course of the patient presented here indicates that in patients with concurrent autoimmune hepatic and thyroid diseases, thyroid disease may have a different clinical course from that of AIH after corticosteroid treatment. Given the limited options for medical management of hyperthyroidism in the setting of liver disease, early definitive therapy is recommended with either RAI ablation or thyroidectomy.

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Disclosure

The authors have no multiplicity of interest to disclose.

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