

“Painless Thyroiditis”: The Rare Phenomenon of Lithium-Associated Thyrotoxicosis

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According to data from the U.S. National Comorbidity Survey, the lifetime prevalence of bipolar I disorder in the United States is 0.4%.¹ Lithium carbonate is the mainstay of therapy for bipolar disorder and is widely prescribed.² The drug produces striking long-term reduction of depression as well as manic morbidity in both bipolar I and bipolar II disorders. The association of lithium therapy with hypothyroidism is universally acknowledged. As many as 30% of patients taking lithium can present with biochemical hypothyroidism, sometimes as early as the first year of treatment.³ The association of lithium therapy with hyperthyroidism, however, is much more rare. By 1994, only 44 cases of lithium-associated thyrotoxicosis had been reported in the medical literature.⁴ Scant additional cases have been reported since 1994, one of which occurred following withdrawal of lithium therapy.⁵⁻⁷ The mechanism of lithium-induced thyroid dysregulation remains conjectural, but evidence points to immune dysregulation of the thyroid gland synthetic apparatus by certain identified antithyroid antibodies.⁸ This article describes a case of lithium-associated thyrotoxicosis in a 47-year-old homeless man with a 10-year history of lithium treatment for bipolar disorder.

CASE PRESENTATION

Initial Presentation

A 47-year-old homeless man was evaluated in the Emergency Department of the Greater Baltimore Medical Center after several days of worsening depression, increasing tremors, unsteady gait, and polyuria.

History

The patient reported that he was diagnosed with bipolar disorder in the 1970s and had been on lithium therapy for more than 10 years. Other past medical his-

tory included thyroid surgery for a “benign nodule” in the left thyroid lobe in 1970, pericarditis in 1979, and a head injury due to a motor vehicular accident in 1985. The patient’s self-reported history suggested that he was euthyroid after his thyroid surgery in 1970, that he never received thyroid hormone replacement therapy, and that he remained euthyroid before the initiation of lithium therapy. Efforts to obtain results from recent thyroid function testing were unsuccessful, as the patient had generally been homeless.

The patient denied any fever, chills, chest pain, shortness of breath, weakness, visual symptoms, cold intolerance, nausea, vomiting, constipation, diarrhea, weight loss, headache, palpitations, or lightheadedness. The only medication he reported taking was lithium carbonate (600 mg twice daily). He stated that he had been on paroxetine (20 mg once daily) but had not taken the drug for many months. The patient was allergic to penicillin. He reported no family history of depression, thyroid disease, or autoimmune disease. The patient had a 23 pack-year history of tobacco use. He denied use of recreational drugs and stated that he drank uncertain quantities of beer. He further reported drinking 4 beers the night prior to admission. The patient was a divorced telemarketer, with no children.

Physical Examination

Physical examination revealed a well-nourished man who was alert and oriented to person, place, and time. He was afebrile but tachycardic, with a heart rate of

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108 bpm. Blood pressure was 146/85 mm Hg, with no orthostatic change. The remainder of the cardiovascular and chest examinations were normal.

The patient's speech was slurred, his mood was depressed, and his affect was flat. However, he was cooperative and answered questions appropriately. His pupils were normal and equally reactive, his neck was supple, and there was no jugular venous distension. The thyroid gland was not enlarged, but a left thyroid lobe scar was noted. There was no nystagmus, and the fundi appeared normal. However, the patient demonstrated resting tremors, ataxia on finger-to-nose testing, and ataxic gait. Deep tendon reflexes were minimally increased. The remainder of the neurologic exam was normal.

Routine Laboratory Studies

Abnormal findings on laboratory evaluation included a urine specific gravity less than 1005 and a toxic plasma lithium level of 1.9 mEq/L. Ethanol was not detected in the plasma, and urine toxicity screen was negative. Electrocardiography revealed sinus tachycardia of 102 bpm, with normal PR and QT intervals and nonspecific ST-T wave changes. A chest radiograph was normal.

Initial Diagnosis and Management

The patient was admitted to the telemetry unit with a presumptive diagnosis of bipolar disorder with lithium toxicity. Lithium was withheld, and intravenous fluid (0.9% saline) was started at 250 mL/hr. A prophylactic alcohol withdrawal assessment (AWAS) protocol for ethanol detoxification was initiated using chlordiazepoxide (50 to 100 mg every 4 hours as per AWAS scores). Following psychiatric evaluation, the patient was restarted on paroxetine (10 mg once daily). By hospital day 2, his plasma lithium level was 0.4 mEq/L, and lithium carbonate therapy was resumed (300 mg 3 times daily).

Thyroid Function Testing

In view of the patient's past thyroid surgery and risk for hypothyroidism from chronic lithium therapy,³ a thyroid-stimulating hormone (TSH) level was obtained and found to be below 0.06 μ U/mL (0.38 to 4.70 μ U/mL). The TSH assay was repeated twice; both repeat values were less than 0.06 μ U/mL. Additional thyroid function studies were subsequently ordered and revealed the following findings: free thyroxine index (FTI), 5.77 (normal range, 1.26 to 5.64); resin triiodothyronine (T_3) uptake, 39.5% (normal range, 28% to 47%); total thyroxine (T_4), 14.6 μ g/dL (nor-

mal range, 4.5 to 12.0 μ g/dL); and free T_4 , 5.7 ng/dL (normal range, 2.3 to 4.2 ng/dL). A radionuclide thyroid scan demonstrated no measurable uptake even at 24 hours; antibodies to thyroid peroxidase (TPOAb) were less than 20 U/mL (normal range, 0 to 20 U/mL), and antibodies to thyroglobulin (TgAb) were 17 ng/mL (normal range, 0 to 59.4 ng/mL). The erythrocyte sedimentation rate was 7 mm/hr.

Final Diagnosis, Management, and Outcome

The diagnosis of lithium-associated thyrotoxicosis of the "painless thyroiditis" subtype⁹ was made on day 3, while the patient was in the telemetry unit. Atenolol (25 mg once daily) was started on day 4, and the patient was moved to the medical/psychiatric floor. By day 5, the patient's tremors were virtually gone, and his heart rate had decreased to 70 bpm. The patient was discharged after day 6. Uncertainty regarding the patient's ability to comply with follow-up office visits raised concern about starting antithyroid medicines, considering the need to monitor the patient's leukocyte count. Instead, the patient was scheduled for a follow-up visit to the Department of Medicine outpatient practice office 1 week after discharge to start tapazole. However, the patient did not keep the appointment and was subsequently lost to follow-up.

DISCUSSION

This patient was peculiar in his initial presentation, because his tremors and tachycardia could have been the result of 3 independent causes: reversible lithium toxicity, alcohol withdrawal, or hyperthyroidism. The fact that these clinical features persisted into the fourth hospital day, despite normalization of plasma lithium levels and chlordiazepoxide treatment, supported hyperthyroidism as the underlying cause of the tremors and tachycardia. These facts, taken together with the biochemical indicators of hyperthyroidism, led to lithium-associated thyrotoxicosis as the most likely diagnosis.

This patient's presentation resembled that of other reported cases of lithium-associated thyrotoxicosis. In 5 of 14 patients reported in a case series of lithium-associated thyrotoxicosis, neither TPOAb nor TgAb levels were raised.⁹ In 2 of the 14 patients, there was an absence of thyroid visualization on nuclear scanning, a phenomenon referred to as "painless thyroiditis;" 1 of the 2 patients had no detectable antibodies.⁹ (This patient had thyroid antibodies in the normal range.) Low radioiodine uptake in lithium-associated thyrotoxicosis was recently described in a 26-year old woman; in this case, the thyrotoxicosis remitted following discontinuation of lithium treatment.⁶

The phenomenon of lithium-associated thyrotoxicosis was first reported in 1974.¹⁰ By 1994, a review of the medical literature disclosed only 44 reported cases of hyperthyroidism in lithium-treated patients.⁴ It has been argued that the report of thyrotoxicosis in lithium-treated patients can be explained as simply a chance phenomenon, given that as many as 600,000 patients with bipolar disorder take lithium carbonate in the United States.¹¹ However, a recent statistical analysis of local thyrotoxicosis incidence figures and lithium prescription data carried out in Christchurch, New Zealand, demonstrated that long-term lithium therapy is clearly associated with an increased risk of thyrotoxicosis.⁹

The mechanism of lithium-associated thyrotoxicosis remains conjectural and is an apparent paradox, because lithium is a known goitrogen that blocks the synthesis and release of thyroid hormone.¹² This generally leads to iodine retention and the expansion of intrathyroidal iodine stores. Some maladaptation to disturbed iodine kinetics with a possible *escape phenomenon* after the expansion of the intrathyroidal iodine pool has been postulated to explain lithium-associated thyrotoxicosis.⁹ It has also been hypothesized that the thyrotoxic state is induced via an immune mechanism. Antithyroid antibodies (ie, TgAb and TPOAb) have been variously described in patients with lithium-associated thyrotoxicosis.⁹ The possible interplay of antithyroid antibodies, the human leukocyte antigen system, lymphocytes, and cytokines in the pathogenesis of autoimmune thyroid disease remains to be clearly elucidated.⁸

SUMMARY

Given that bipolar I disorder has a lifetime prevalence of 0.4% in the United States¹ and that most treated patients receive lithium carbonate,² it can be estimated that well over 500,000 individuals in the United States are on lithium therapy. All such patients should have pretreatment baseline thyroid function studies and regular thyroid monitoring during lithium therapy. Physicians should be alert for features of *both* hypothyroidism *and* hyperthyroidism. It is the authors' belief

that some cases of "breakthrough mania" in bipolar patients on lithium therapy could be explained by the occurrence of lithium-associated thyrotoxicosis. HP

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