Lithium-induced parathyroid dysfunction: A new case

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ABSTRACT
Lithium salts are widely used in psychiatric practice and are known to induce thyroid dysfunction. Lithium-induced parathyroid dysfunction is rare. We are reporting a case of hyperparathyroidism in a 28-year-old female patient who was on lithium carbonate for 2 years, when she developed osteopenia and girdle girdle-type muscle weakness. Biochemical parameters showed hyperparathyroidism with shift of calcium creatinine clearance ratio to 0.013, indicating an error in threshold of calcium sensing receptor. The patient eventually required parathyroidectomy and the histology of the gland showed atypical features.

Key words: Atypical adenoma, calcium sensing receptor, hyperparathyroidism, lithium

INTRODUCTION
Parathyroid dysfunction is well known in long duration lithium treatment, though it is less frequent when compared to hypothyroidism. About 40 cases of parathyroid adenomas have been detected in patients on lithium treatment. We are reporting a patient who developed hypercalcemia while on treatment with lithium, requiring surgical treatment.

CASE REPORT
A 28-year-old lady reported to the endocrinology department for evaluation of hypercalcemia detected at a local hospital. She was receiving 600 mg of lithium carbonate for bipolar mood disorder for last 2 years. She had a history of weight gain, polyarthralgia, and generalized weakness since 6 months. Clinical examination revealed an obese [body mass index (BMI) 36.30Kg], depressed lady with proximal girdle muscle weakness and generalized bone tenderness. Investigations revealed altered thyroid function: FT4 0.77 ng/dl (0.94-1.71 ng/dl) and thyroid stimulating hormone (TSH) 1.45 μIU/ml (0.45-4.5 μIU/ml). Serum corrected calcium levels were 11 mg/dl (8.5-10.2 mg/dl) on repeated assessment and serum phosphate was 2.4 mg/dl (2.7-4.5 mg/dl). Serum intact parathyroid hormone (PTH) was 489.6 pg/ml (16-62 pg/ml). Serum alkaline phosphatase was 1073 IU/l (39-117 IU/l) and Bone Mineral Density (BMD) studies showed Z scores of −2.5 and −2.9 on hip bones and lumbar spines, respectively. Serum albumin and creatinine remained in the normal ranges (4.1 g/dl and 0.8 mg/dl, respectively). 24-h urinary calcium was reduced to 75 mg (normal 100-300 mg), phosphorus was reduced to 288 mg (400-1300 mg), and creatinine was 408 mg (urine volume 1750 ml). The calcium creatinine clearance ratio was 0.013. Serum magnesium was 2.4 ng/dl (1.7-2.55 ng/dl). Serum 25-OH vitamin D estimation showed a normal level of 69 nmol/l (25-125 nmol/l). The serum prolactin (pooled and diluted) was 14.90 ng/ml (1.67-16.11 ng/ml), and serum insulin (total) was 5.80 μIU/ml (4-30 μIU/ml).

Since the clinical and biochemical features were suggestive of lithium-induced hyperparathyroidism, lithium was discontinued. The clinical features and biochemical parameters did not normalize after 3 months of cessation of lithium treatment (serum calcium was 11.4 mg/dl and PTH 882.5 pg/ml). So, the patient was prepared for surgical
treatment after localization studies. 99 mTc-sestamibi dual phase scintigraphy showed significant tracer retention in delayed images, suggestive of hyperfunctioning left inferior parathyroid gland. The patient was subjected to routine total neck exploration since lithium-induced parathyroid hyperplasia was still a possibility. The left inferior parathyroid gland was enlarged and hard in consistency. This was removed en bloc with neighboring soft tissue since parathyroid carcinoma was suspected. The other parathyroid glands appeared normal. Rapid intraoperative PTH assay showed a fall from 1063 to 89.84 pg/ml after 10 min of the excision, ensuring completeness of resection.

The excised tissue showed a well-encapsulated tumor measuring 2 cm in size and weighing 3.9 g. Microscopy revealed diffuse sheets of cells separated by thin fibrovascular septa. Cells were round or oval with eosinophilic cytoplasm and focal areas of necrosis. Capsular infiltration and vascular invasion were seen. Immunostaining for Ki 67 showed less than 3% positive staining and so was diagnosed as atypical adenoma.

The patient received oral calcium supplementation for 12 months since the BMD studies showed osteopenia 6 months after the operation. The patient has been reviewed periodically for the last 31 months and the serum corrected calcium level remains within normal ranges. She is on thyroxine supplementation even though lithium was discontinued.

**DISCUSSION**

Lithium has been in clinical use since 1950 as a very effective treatment in bipolar affective disorders. It alters multiple steps in thyroxine synthesis apart from iodine trapping, organic binding to tyrosine, and coupling of iodosotyrosines. Thyroid dysfunction is noted in 50% patients receiving lithium salts. Hypercalcemia following lithium treatment was first reported in 1973. A thyroid disease in a first-degree relative was noted as a risk factor for the development of hyperparathyroidism during lithium treatment. Both *in vitro* studies and *in vivo* studies in healthy volunteers demonstrated direct action of lithium on parathyroid cells in releasing intact PTH. Lithium can shift the set point of calcium-sensing receptors (CaSR) in parathyroid cells, leading onto excess release of PTH.

The extracellular CaSR, described first by Brown *et al.* in 1993, plays a major role in the maintenance of physiological serum ionized calcium ($Ca^{2+}$) concentration by regulating the circulating levels of PTH. CaSR controls important aspects of parathyroid function by increasing PTH synthesis, PTH secretion, and cellular proliferation. There is widespread distribution of the CaSR along the nephron and plays a major role in calcium/inorganic phosphate homeostasis, cation transport, urine concentration, and renin release. Presence of CaSR expression has been observed in tissues like intestine, bone, thyroid C cells, lactating breast, and placenta. Familial hypocalciuric hypercalcemia (FHH) is a benign, autosomal dominant form of hypercalcemia with abnormalities in the regulation of parathyroid and renal function by calcium homeostasis caused due to heterozygous inactivating mutations of the CaSR gene. These patients have hypercalcemia and low calcium creatinine clearance ratio. These patients are asymptomatic and seldom express osteopenia. The intact PTH levels are either normal or marginally elevated. The index patient was symptomatic and hypercalcemia appeared to be PTH dependent. Mother of the patient was screened and was found to be normocalcemic.

Epithelial cells of ascending loop of Henle cause less urinary excretion of calcium despite hypercalcemia. Calcium creatinine clearance ratio is always >0.02 in primary hyperparathyroidism, but is shifted to <0.01 in conditions of impaired CaSR sensitivity. Patient had decreased level of 24-h urinary calcium as opposed to the usual feature of hypercalciuria seen in primary hyperparathyroidism. There are about 40 cases of lithium-induced hyperparathyroidism reported in the literature since 1973. The reports show incidences of single gland adenomas as well as diseases of multiple glands. A retrospective analysis of 15 cases showed 14 patients (92%) with adenomas, but 3 patients had double adenomas. The decision to operate is individualized, but symptomatic patient after cessation of lithium requires parathyroidectomy. Total neck exploration is usually preferred over focused parathyroidectomy. The excised parathyroid showed macroscopic features such as hard texture and adhesions to the neighboring tissue. There were few histological features such as focal capsular penetration and vascular invasion. Proliferation marker above 5% is indicative of malignancy but was low in the index case and so suits with the description of atypical adenoma. The patient requires 50 μg of L-thyroxine despite discontinuing lithium.

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