Histological features of the thyroid gland in a patient with lithium induced thyrotoxicosis

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Abstract
A 26 year old woman with lithium induced thyrotoxicosis was reported. The thyrotoxicosis was associated with a non-tender diffuse goitre and a low radioactive iodine uptake by the gland. The thyrotoxicosis was reversible and remitted on withdrawal of the drug. The histopathological alterations of the thyroid gland were characterised by extensive follicular cell disunion with no lymphocytic infiltration. It is postulated that lithium might directly damage thyroid follicular cells and that subsequent release of thyroglobulin into the circulation might be a cause of transient thyrotoxicosis.

Keywords: Thyrotoxicosis, lithium, thyroid histology.

Case report
A 26 year old woman was referred to us because of a week history of sweating, palpitations, and anorexia. She had a three year history of manic depressive psychosis and had been taking lithium carbonate, 800 mg/day, for the preceding two years. She had no history of thyroid disease and there was no family history of thyroid disorders. She was clinically euthyroid six months before this episode, and serum values at that time including a thyroxine (T4) of 90 nmol/l (normal 59-142), a free T4 of 19-6 pmol/l (normal 9-20-7), and a triiodothyronine (T3) of 1.7 nmol/l (normal 1.2-2.9). Physical examination revealed warm moist hands and fine finger tremor, but ophthalmoscopy was not evident. The thyroid gland was diffusely enlarged and was non-tender. No nodules were palpable. The serum thyroid hormone concentrations were raised: free T4 87-5 pmol/l, T3 3-5 nmol/l, and free T3 13-6 pmol/l (normal 3-4-8-2). TSH was suppressed at <2.0 mU/l (normal <10-0). Radioactive iodine uptake was markedly reduced to only 1-0% at 24 hours (normal 10-40%). Serum antithyroglobulin and antimicrosome autoantibodies were negative. TSH binding inhibitor immunoglobulin (TBI) was also negative. These clinical and laboratory findings suggested a diagnosis of silent (painless) thyroiditis. Large needle biopsy (Silverman) of both lobes of the thyroid gland was performed. Lithium therapy was stopped and the patient was given propranolol for the control of thyrotoxic symptoms. The values of the serum thyroid hormones continued to rise for two...
Thyroid histology in lithium-thyrotoxicosis

weeks and then returned to normal limits. The serum values of thyroid hormones three months after lithium withdrawal were: T4 92·6 nmol/l, free T4 21·9 pmol/l, T3 1·3 nmol/l, and free T3 6·3 pmol/l. The goitre disappeared and was no longer palpable.

Pathology

Microscopically the thyroid gland was composed of large distended follicles with abundant colloid. In most of the follicles, follicular lining cells were desquamated, with cytoplasmic vacuolation (figure). These desquamated follicular cells were present in the follicular colloid, and occasionally thyroid follicles were filled with aggregates of these desquamated follicular cells and macrophages. Some follicles were disrupted, and at the points of disruption there was minimal lymphocytic infiltration. In another focus, a considerable amount of stromal fibrosis was noted in close association with follicular disruption and rather small atrophied follicles (figure). Lymphocytic infiltration, suggesting the presence of chronic thyroiditis, was not evident anywhere in the specimen.

Discussion

The mechanism of action of lithium on the biosynthesis of thyroid hormone has not been elucidated completely, but the drug has been shown to inhibit iodine uptake into the thyroid gland, impair coupling of iodotyrosines, and interfere with the release of hormone from the gland. Considering the suppressive effects of lithium on thyroid function, the occurrence of lithium induced thyrotoxicosis is surprising, and the causal mechanisms are still uncertain.

The present case was characterised by hyperthyroidism which remitted on cessation of the lithium treatment, by goitre with no tenderness, and by low radioactive iodine uptake by the gland. Histologically the thyroid gland showed a marked follicular disruption. These clinical, laboratory, and histological features resembled those found in patients with silent thyroiditis or postpartum thyroiditis, which are considered to represent a destructive phase of chronic thyroiditis and to be due to enhancement of autoimmunity. In the present case, however, circulating autoantibodies for thyroid antigens were negative and chronic thyroiditis was not evident histologically. Lithium itself may directly injure thyroid follicular cells and cause thyroid follicular destruction. Subsequent release of thyroglobulin increases the serum thyroid hormone concentration, causing hyperthyroidism and low radioactive iodine uptake by the gland. Such a follicular destruction has also been reported in amiodarone induced hyperthyroidism. Follicular disruption may also occur in association with physical examination (palpation) or surgical procedures of the thyroid gland. In our experience of more than 2000 large needle biopsies of the thyroid gland, we were unable to find such non-specific follicular disruption in a single case. The histological changes found in the present case are thus unlikely to have been caused by the needle biopsy procedure. In addition, the patient had no history of trauma to the neck preceding the episode.

To date, eight cases of lithium induced thyrotoxicosis have been reported. Three of the four patients with lithium associated thyrotoxicosis reported by Brownlie et al had a past history of thyroid diseases, including Graves' disease. These four patients were treated with antithyroid drugs and radiiodine. On the other hand, Rosser et al reported a patient who became euthyroid spontaneously with cessation of lithium treatment. Radioactive iodine uptake was not increased in either case, and the clinical laboratory findings suggested a causal relationship between the transient thyrotoxicosis and follicular destruction, although histological examination of the thyroid gland was not performed in either case.

Although histological examination of the thyroid gland in patients with lithium induced thyrotoxicosis has rarely been performed, the present study suggests that lithium causes direct damage to the thyroid follicles and that the follicular disruption contributes to the transient thyrotoxicosis.

(A) Thyroid follicles are rather distended. Many desquamated follicular cells with vacuolated cytoplasm are present in the colloid of the follicles. Follicular disruption (arrow) is also noted (haematoxylin-eosin). (B) In another focus of the specimen, disrupted follicles (arrows) and rather small atrophied follicles are noted associated with significant stromal fibrosis (haematoxylin-eosin).
Splenic lymphoma with circulating villous lymphocytes

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Abstract
This report describes the occurrence of splenic lymphoma with villous lymphocytes (SLVL) in a 56 year old white female with a family history of chronic lymphocytic leukaemia. Other unusual features included a marked lymphocytosis with counts up to 224 × 10⁹/l and marked clumping of lymphocytes in EDTA anticoagulated blood. The neoplastic cells were CD19+, CD20+, CD22+, CD23+, IgM +, λ +, κ −, CD5− and CD10−. The spleen had nodular infiltrates of B lymphocytes in the region of the white pulp with minimal red pulp involvement. Electron microscopy of peripheral blood lymphocytes revealed cells with polar cytoplasmic processes. This report underlines the need for detailed analysis, including morphology and immunophenotyping, for each patient with a small B cell lymphoproliferative disorder.

Keywords: Splenic lymphoma with villous lymphocytes, immunophenotype, familial, electron microscopy.

The disease now referred to as splenic lymphoma with villous lymphocytes (SLVL)³ was previously described by Neiman et al² under the rubric malignant lymphoma simulating leukemic reticuloendotheliosis. In their study of 10 cases, Neiman et al compared and contrasted this disorder with hairy cell leukaemia (HCL) and prolymphocytic leukaemia (PLL) and emphasised the importance of a histological examination of the spleen in making the distinction. The patient described here was initially thought to have B chronic lymphocytic leukaemia (CLL) based on her family history. A diagnosis of SLVL was later made by correlating the morphology and immunophenotype of peripheral blood lymphocytes and histology of the resected spleen.

Case report
A 56 year old white female presented with progressively increasing abdominal girth in November 1993. On physical examination, the spleen was massively enlarged, being palpable 13 cm below the left costal margin. There was no peripheral lymphadenopathy. Abdominal computed tomography scans confirmed massive splenomegaly with hypodense areas suggestive of leukemic or lymphomatous infiltrate, or both. No mediastinal or abdominal lymphadenopathy was observed.

Examination of the peripheral blood revealed a haemoglobin concentration of 104 g/l; a platelet count of 121 × 10⁹/l; a white blood cell count (WBC) of 69 × 10⁹/l, with 98% lymphocytes. The lymphocytes were larger than small lymphocytes and had a moderate amount of cytoplasm. The nuclei were round, with few clefted and irregular forms and had a clumped chromatin pattern (fig 1). Small but distinct nucleoli were present in some of the cells. Irregularly distributed surface projections, which were sometimes concentrated at one or both poles of the cell, were seen in some cells. An unusual feature noticed in the smears was marked clumping of the lymphocytes (fig 1). The leukemic cells were tartrate resistant acid phosphatase (TRAP) negative. Electron microscopic studies were carried out on buffy coated preparations of peripheral blood. Small villous