- 1 Cupps TR, Fauci AS. The vasculitides. In: Smith LH, ed. *Major problems in internal medicine*, vol 21. Philadelphia: WB Saunders, 1981: 26-49 and 72-87.
- 2 Gaffey CM, Chun B, Harvey JC, Manz HJ. Phenytoin-induced systemic granulomatous vasculitis. *Arch Pathol Lab Med* 1986;110:131-5.
- 3 Lie JT. Disseminated visceral giant cell arteritis. Histopathologic description and differentiation from other granulomatous vasculitides. *Am J Clin Pathol* 1978;69:299-305.
- 4 Petersen OMF, Frankel SR. Idiopathic granulomatous vasculitis. In: Churg A, Churg J, eds. *Systemic vasculitides*. New York: Igaku-Shoin, 1991:181-91.
- 5 Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. *Arthritis Rheum* 1990;33:1065-144.
- 6 Berk JE, Cohen M. Granulomas hepaticos. In: Berk JE, ed. *Bockus: Gastroenterologia*, 4th Spanish edition. Barcelona: Salvat, 1987:3475-90.
- 7 Mullick FG, McAllister HA, Wagner BM, Fenoglio JJ. Drug related vasculitis. Clinicopathologic correlations in 30 patients. *Hum Pathol* 1979;10:313-25.
- 8 Haber MM, Marboe CC, Fenoglio JJ. Vasculitis in drug reactions and serum sickness. In: Churg A, Churg J, eds. *Systemic vasculitides*. New York: Igaku-Shoin, 1991:305-13.
- 9 Bloodworth JMB, Hamwi GJ. Histopathologic lesions associated with sulfonylurea administration. *Diabetes* 1961;10:90-9.
- 10 Ingelmo M, Vivancos J, Bruguera M, Sierra J, Balcells A. Angiitis por hipersensibilidad y hepatitis granulomatosa inducida por glibenclámda: a proposito de un caso. *Med Clin (Barc)* 1980;75:306-8.

J Clin Pathol 1995;48:582-584

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

Y Mizukami, T Michigishi, A Nonomura, S Nakamura, M Noguchi, E Takazakura

Abstract

A 26 year old woman with lithium induced thyrotoxicosis is reported. The thyrotoxicosis was associated with a non-tender diffuse goitre and a low radioiodine 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 disruption 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.

(*J Clin Pathol* 1995;48:582-584)

Keywords: Thyrotoxicosis, lithium, thyroid histology.

Lithium is increasingly used for the treatment of manic depressive illness. Thyroid disturbances during lithium treatment have been noted. These commonly present as a goitre with or without hypothyroidism¹⁻³; more rarely there is a goitre with hyperthyroidism.^{2,4-6} There have, however, been few reports describing the histological alterations of the thyroid gland during lithium treatment.^{2,3,5,7,8}

In the present report, we describe the histopathological features of the thyroid gland in a patient with lithium induced thyrotoxicosis which remitted on withdrawal of the drug.

Case report

A 26 year old woman was referred to us because of a two 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 9.0-27.0), 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 exophthalmos 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 (TBII) 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

Kanazawa
University Hospital,
Kanazawa, Japan
Y Mizukami
A Nonomura

Department
of Nuclear Medicine
T Michigishi

Department
of Internal Medicine
S Nakamura

Department
of Surgery
M Noguchi

Kurobe Citizens
Hospital, Kurobe,
Japan: Department
of Internal Medicine
E Takazakura

Correspondence to:
Dr Yuji Mizukami MD,
Pathology Section,
Kanazawa University
Hospital,
13-1 Takara-machi,
Kanazawa 920, Japan.

Accepted for publication
13 October 1994

(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).

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 vacuolisation (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.⁹ 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.¹⁰ 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.⁸ 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.¹¹ Follicular disruption may also occur in association with physical examination (palpation) or surgical procedures of the thyroid gland.¹² 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.¹³ 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.²⁻⁶ Three of the four patients with lithium associated thyrotoxicosis reported by Brownlie *et al*² had a past history of thyroid diseases, including Graves' disease. These four patients were treated with antithyroid drugs and radioiodine. On the other hand, Rosser⁴ and Reus *et al*⁶ each reported one 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.

- Schou M, Amdisen A, Jensen SE, Olsen T. Occurrence of goitre during lithium treatment. *BMJ* 1968;iii:710-3.
- Brownlie BEW, Chambers ST, Sandler WA, Donald RA. Lithium associated thyroid disease - a report of 14 cases of hypothyroidism and 4 cases of thyrotoxicosis. *Aust NZ J Med* 1976;6:223-9.
- Lindstedt G, Nilsson LA, Walinder J, Skott A, Ohman R. On the prevalence, diagnosis and management of lithium-induced hypothyroidism in psychiatric patients. *Br J Psychiatry* 1977;130:452-8.
- Rosser R. Thyrotoxicosis and lithium. *Br J Psychiatry* 1976;128:61-6.
- Franklin LM. Thyrotoxicosis developing during lithium treatment: case report. *NZ Med J* 1974;79:782.
- Reus VI, Gold P, Post R. Lithium-induced thyrotoxicosis. *Am J Psychiatry* 1979;136:724-5.
- Kontozoglou T, Mambo N. The histopathologic features of lithium-associated thyroiditis. *Hum Pathol* 1983;14:737-9.
- Fauerholdt L, Vendsborg P. Thyroid gland morphology after lithium treatment. *Acta Pathol Microbiol Scand Sect A* 1981;89:339-41.
- Berens SC, Bernstein RS, Robbins J, Wolff J. Antithyroid effects of lithium. *J Clin Invest* 1970;49:1357-67.
- Mizukami Y, Michigishi T, Nonomura A, et al. Postpartum thyroiditis - a clinical, histologic and immunopathological study of 15 cases. *Am J Clin Pathol* 1993;100:200-5.
- Smyrk TC, Goellner JR, Brennan MD, Carney JA. Pathology of the thyroid in amiodarone-associated thyrotoxicosis. *Am J Surg Pathol* 1987;11:197-204.
- Carney JA, Moore SB, Nothcatt RC, Woolner LB, Stillwell GK. Palpation thyroiditis (multifocal granulomatous folliculitis). *Am J Clin Pathol* 1975;64:639-47.
- Mizukami Y, Michigishi T, Nonomura A, Nakamura S, Ishizaki T. Pathology of chronic thyroiditis: A new clinically relevant classification. *Pathol Annu* 1994;29:135-58.

J Clin Pathol 1995;48:584-587

Splenic lymphoma with circulating villous lymphocytes

F Imbing Jr, D Kumar, S Kumar, G Yuoh, F Gardner

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 $224 \times 10^9/l$ and marked clumping of lymphocytes in EDTA anticoagulated blood. The neoplastic cells were CD19+, CD20+, CD22+, CD22+, 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

(*J Clin Pathol* 1995;48:584-587)

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

The disease now referred to as splenic lymphoma with villous lymphocytes (SLVL)¹ was previously described by Neiman *et al*² under the rubric malignant lymphoma simulating leukaemic 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 ini-

tially 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 leukaemic 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 $121 \times 10^9/l$; a white blood cell count (WBC) of $69 \times 10^9/l$, 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 leukaemic cells were tartrate resistant acid phosphatase (TRAP) negative. Electron microscopic studies were carried out on buffy coated preparations of peripheral blood. Small villous

Department of Pathology, The University of Texas Medical Branch, Texas, USA
F Imbing Jr
D Kumar
S Kumar
G Yuoh

Department of Internal Medicine
F Gardner

Correspondence to:
Dr D Kumar,
Department of Pathology,
Division of Anatomical
Pathology, 22 South
Greene Street, Baltimore,
MD 21201-1595, USA.

Accepted for publication
13 October 1994