Clinical Reports

Myxoedema followed by TSAb-induced hyperthyroidism: Report of 2 cases

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Summary: The development of spontaneous hyperthyroidism following primary hypothyroidism is an unusual occurrence. We report two cases of confirmed primary hypothyroidism who subsequently became hyperthyroid. Thyroid stimulating antibodies were present in the sera of both patients during the hyperthyroid state. The significance of this sequence of events is discussed and a possible explanation proposed.

Introduction

The progression from primary hypothyroidism to hyperthyroidism has been described previously but not fully explained (Olczak *et al.*, 1978; Irvine *et al.*, 1979; Guansing *et al.*, 1980). Here we report two patients, in both of whom the serum contained immunoglobulins capable of stimulating the secretion of tri-iodothyronine (T₃) from thyroid slices incubated *in vitro*.

Case histories

Case 1

In September 1969 a 29 year old woman presented with an 18 month history of tiredness, hair loss, intermittent swelling of the legs and puffiness around the eyes. On examination she was pale with periorbital puffiness and bilateral ankle oedema. The thyroid was not palpable. Investigations were consistent with hypothyroidism: protein bound iodine (PBI) 2.4 µg/100 ml (normal range 4–8 µg/100 ml), total cholesterol 9.4 mmol/l (normal range 4.7–7.8 mmol/l). Thyroid microsomal and thyroglobulin antibodies were negative. A ^{99m}Tc scan showed minimal uptake in the neck and the thyroid outline was not discernible. ¹³¹I uptake was greatly reduced, being 5% at 2 h, 3% at 24 h and 2% at 48 h. She was commenced on L-

thyroxine with marked clinical and biochemical improvement. She was maintained on L-thyroxine 200 µg/d for 11 y. In October 1980 she returned, complaining of tiredness, irritability, weight loss, heat intolerance and excessive sweating. On examination clinical features of hyperthyroidism were present and there was exophthalmos and lid retraction; a small firm goitre had developed. The free thyroxine index (FT₄I) was elevated at 304 (normal 55–160). L-thyroxine therapy was stopped but the features of hyperthyroidism persisted. Results of repeat testing in February 1981 are shown in Table I. The thyrotrophin (TSH) was not elevated and the serum was strongly positive for thyroid stimulating antibodies (TSAb; Table II). She was treated with propylthiouracil and sub-

Table I Thyroid function tests

	Patient 1 Feb 1981	Patient 2 Aug 1978	Normal range
Free thyroxine index (FT ₄ I)	182	168	55–160
Tri-iodothyronine (T ₃) (nmol/l)	4.2	3.5	1.1–3.1
Thyroid binding globulin capacity (mg/l)	18	—	12–32
Microsomal antibody titre	1:100,000	1:25,000	
Thyroglobulin antibody titre	1:20	1:640	

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Table II Results of TSAb assay

	Free T ₃ released (pmol/l)*	TSAb index† (%)
Pooled normal serum (PNS)	52.9 ± 8.7	21.4
Patient 1	291.7 ± 18.2	118.2
Patient 2	301.7 ± 44.5	122.2
bTSH 1 mU/ml (in PNS)	246.8 ± 32.2	100

* Mean ± s.e.m.

† TSAb index is the free T₃ release expressed as a percentage of the free T₃ released in response to bTSH 1 mU/ml in pooled normal serum. Values over 100% indicate a high titre of TSAb.

sequently underwent partial thyroidectomy. The thyroid tissue was not examined histologically.

Case 2

In 1941 a female patient, then aged 34, had a partial thyroidectomy for thyrotoxicosis. In 1964 she developed weakness, lethargy and vomiting. There was pigmentation in exposed areas of skin and in palmar creases and hypotension was noted. The diagnosis of Addison's disease was confirmed by finding very low 24 h urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids and by the absence of a cortisol response to 8 days stimulation with ACTH gel. No adrenal calcification was seen on X-ray and no evidence of intra-abdominal tuberculosis was found. She was treated with cortisone acetate 12.5 mg b.d. and fludrocortisone 0.1 mg/d. She remained well until January 1973 when a diagnosis of polymyalgia rheumatica was made. She was given prednisolone 5 mg b.d. in addition to her normal dose of cortisone acetate and within a month symptoms had improved. At routine attendance at the endocrine clinic 3 weeks before commencing prednisolone, slight puffiness of the face prompted a check of thyroid function tests; a low protein bound iodine of 3.0 µg/100 ml (normal 3.5–7.5 µg/100 ml) and a high T₃ resin uptake (labelled T₃ taken up by serum proteins) of 145% (normal 99–123) confirmed hypothyroidism. No goitre was palpable. L-thyroxine was commenced and the dose gradually increased to 150 µg/d; this was associated with clinical improvement.

In 1976 she complained of weight loss, palpitations and dyspnoea. The total T₄ was 155 nmol/l (normal 70–150 nmol/l) and the FT₄I was 191 (normal 55–147). The thyroxine was reduced and then discontinued altogether in January 1977 after which she became euthyroid. In September 1977 she developed

diabetes mellitus, which was treated with a carbohydrate restricted diet and glibenclamide. In August 1978 she complained of recent weight loss and a pulse rate of 120/min was noted. Thyroid function tests (Table I) confirmed hyperthyroidism. A ^{99m}Tc scan showed functioning thyroid tissue in both lobes, the right being larger and more active than the left. Thyroid antibodies (Professor D. Doniach) were positive and were present in higher titres than when previously measured in 1976. She was treated with carbimazole 45 mg/d and later received 6 mCi ¹³¹I therapy with a satisfactory clinical response. The patient regained weight, she felt generally more energetic, was less sweaty and the pulse rate fell to 80/min. In January 1980 she developed pre-tibial myxoedema which responded to topical fluocinolone cream. By March 1980 she had become biochemically hypothyroid (T₄ 47 nmol/l and TSH 35 mU/l) and was started on replacement thyroxine. Serum, examined when subsequently euthyroid, was strongly positive for TSAb.

Assay of TSAb

The bioassay method has been previously described (Atkinson & Kendall-Taylor, 1981) and measures the release of T₃ from thyroid tissue maintained *in vitro*. Two slices of porcine thyroid tissue, of uniform size (1 × 1 × 0.5 mm) were placed with 100 µl of heat-inactivated serum on a Visking dialysis membrane in a two compartmental diffusion pot containing 5 ml of buffer (Hepes/gelatin/Earles balanced salts, pH 7.4). The pots were incubated at 37°C for 5 h. The tissue was then washed with 200 µl of buffer and removed. The pots were sealed and incubated for a further 18 h at 37°C in a shaking waterbath; free thyroid hormones released by the thyroid tissue in response to stimulation were allowed to dialyse across the membrane. Free tri-iodothyronine in the dialysate was measured by radioimmunoassay. Five replicates of each sample were assayed. Result were compared with the response to a standard TSH preparation (bTSH 1 mU/ml) and to a pool of serum obtained from normal subjects. Results are shown in Table II and are corrected for the amount of free tri-iodothyronine present when the test serum was incubated in the absence of thyroid tissue.

Discussion

The development of hyperthyroidism following primary hypothyroidism is a rare event, and few cases have been adequately documented in whom spontaneous thyrotoxicosis followed an initial diagnosis of primary hypothyroidism (Olczak *et al.*, 1978; Irvine *et al.*, 1977; Guansing *et al.*, 1980). That such an event

does occur, however, may shed further light on the understanding of the pathogenesis of auto-immune thyroid disorders.

The frequent familial association of Graves' disease and primary hypothyroidism and the occasional development of hypothyroidism during the course of Graves' disease, either spontaneously or following antithyroid drug therapy (Irvine *et al.*, 1977; Wood & Ingbar, 1979) suggest a close similarity of the pathogenesis of each disorder. Spontaneous primary hypothyroidism in adults is most commonly the end-result of the destructive process of chronic auto-immune thyroiditis. Once established, auto-immune thyroiditis has been regarded as a stable or gradually deteriorating condition for which life-long replacement therapy is required. However, transient hypothyroidism does occur post-partum (Amino *et al.*, 1982). In most patients a temporary aggravation of previous subclinical auto-immune thyroiditis has been considered to be the likely aetiology and Jansson *et al.* (1984), using fine needle aspiration biopsy, reported lymphocytic thyroiditis in all their cases. Neither of the patients reported here had a pregnancy within the 12 months preceding the development of either hypothyroidism or hyperthyroidism. The hyperthyroidism of Graves' disease results from the presence in the serum of abnormal immunoglobulins referred to as thyroid stimulating antibodies (TSAb), which bind to the thyroid cell membrane at or near the TSH receptor, leading to stimulation of thyroid hormone secretion (Kidd *et al.*, 1980).

Several methods have been used to detect these Graves'-specific immunoglobulins (Ig), based either on binding or on functional properties. Other reported cases (6 in all) of spontaneous hyperthyroidism developing after hypothyroidism have been examined for Graves' Ig using either the thyrotrophin binding inhibiting immunoglobulin (TBII) assay (Olczak *et al.*, 1978; Irvine *et al.*, 1977) or a long-acting thyroid stimulator (LATS) assay (Guansing *et al.*, 1980; Sung & McDougall, 1978) and there is doubt about the biological significance of both these techniques. LATS has been regarded as an epiphenomenon whereas TBII is a measure of Ig binding to, not stimulation of, thyroid tissue. Furthermore TBII is occasionally found in patients with hypothyroidism (Endo *et al.*, 1978). Sera from both the cases reported here were strongly positive for thyroid stimulating activity, when assessed by their capacity to stimulate the release of thyroid hormones from thyroid tissue *in vitro*. The

thyroid stimulating activity shown by this technique is associated with the IgG fraction (Atkinson, 1982). There can therefore be little doubt that TSAb was responsible for the hyperthyroidism in these 2 patients who previously were hypothyroid.

In the two cases reported here the thyroid was not palpable during the hypothyroid phase, presumed atrophic as a consequence of chronic thyroiditis, radioisotope uptake in case 1 was negligible and in both cases, thyroid tissue was unresponsive to stimulation by elevated endogenous TSH. Although glucocorticoids can restore thyroxine levels in some patients with combined adrenal and thyroid deficiency (Barnett *et al.*, 1982), patient 2 had been on a satisfactory dose of replacement steroids for several years. Corticosteroids may influence immune regulation in auto-immune thyroid disorders (Volpé, 1981) but whether the prednisolone therapy in case 2 had any effect must remain speculative. Subsequently, after an interval of 11 y and 5 y, respectively, the thyroid was able to respond to stimulation by TSAb, producing both thyrotoxicosis and associated glandular enlargement.

A possible explanation for this transition from hypothyroidism to TSAb-induced hyperthyroidism is that the auto-immune tissue damage, initially severe enough to cause thyroid hypofunction, recovered sufficiently to allow subsequent stimulation by TSAb. Alternatively primary hypothyroidism may be associated with the presence of blocking antibodies, i.e. immunoglobulins binding at or near the TSH receptor, thereby inhibiting the effects of TSH on both thyroid growth and hormone synthesis (Lamberg, 1979; Christy & Morse, 1977; Irvine *et al.*, 1977). Hypothyroidism associated with blocking antibodies has been documented (Endo *et al.*, 1978; Matsuura *et al.*, 1980; Konishi *et al.*, 1983; Steel *et al.*, 1984), although other work (Yamada *et al.*, 1978) suggested that inhibitory factors are not common and are not a major cause of hypothyroidism. The ensuing hyperthyroidism may then be attributed to a decline in the titre of the blocking antibodies and the emergence of thyroid stimulating antibodies.

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