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A CASE OF HASHIMOTO'S THYROIDITIS WITH THYROID IMMUNOLOGICAL ABNORMALITY MANIFESTED AFTER HABITUAL INGESTION OF SEAWEED

By

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ABSTRACT

An interesting case of iodide induced goitre with immunological abnormalities is described. The patient who was sensitive to synthetic penicillin had previously been treated for exudative pleuritis, congestive heart failure and acute renal failure. Following recovery, he began to ingest large amounts of seaweed after which he developed goitrous hypothyroidism. It was of interest that the serum level of gamma-globulin increased, and subsequently the antithyroid microsomal antibody became strongly positive, suggesting that thyroidal autoimmune processes had been precipitated. Biopsy of the thyroid gland revealed chronic thyroiditis, with evidence suggesting extreme stimulation by TSH. High thyroidal uptake of ^{131}I, positive perchlorate discharge test and biochemical analysis of the thyroidal soluble protein showed severe impairment of hormone synthesis following continuous accumulation of excess iodide. While there is evidence suggesting that increased iodide may be an important factor in the initiation of Hashimoto's thyroiditis, this may result from the marked increased sensitivity of Hashimoto's gland to the effects of iodine. Thus an occult lesion could be unmasked in this manner. The mechanism by which iodide mediates this effect is not clear.

The predisposition to immunological abnormalities may play an important role in the pathogenesis of chronic thyroiditis (*DeGroot et al.* 1962; *Volpé* 1977). Whether the condition may be induced by thyroidal antigenic stimulation on the one hand, or is due solely to a defect in immune surveillance with inability to suppress a "forbidden" clone of lymphocytes on the other, has not been finally established. It has been reported that iodide may be related to the

pathogenesis of chronic thyroiditis (*Follis* 1959, 1964; *Weaver et al.* 1966, 1969; *Beierwaltes* 1969). The present study reports an interesting case of chronic thyroiditis initiated by excess iodide administration with a clinical picture of iodide myxoedema. Iodide induced not only the functional abnormality, but also appeared to precipitate the immunological manifestations of Hashimoto's disease. It is thus suggested that under certain conditions, habitual ingestion of large doses of iodide may play an important role in the pathogenesis of chronic thyroiditis in the human.

CASE REPORT

A 44 year old male was first admitted to our hospital on July 2, 1974, suffering from lacunar tonsillitis, exudative pleuritis, congestive heart failure and acute renal failure. Culture of the sputum showed a growth of pseudomonas aeruginosa. Moderate proteinuria (400–800 mg/day) was associated with an elevation of the serum level of creatinine (5.8 mg/100 ml) and blood urea nitrogen (80 mg/100 ml), although the urinary sediment contained only 2–3 red blood cells and 1–2 white blood cells per high-power field and no casts. These nephrological abnormalities disappeared rather promptly one or two weeks after initiation of treatment. Eczematoid dermatitis with pruritus, arthralgia and eosinophilia appeared intermittently. The sensitivity test for antibiotics such as carbenicillin or sulbenicillin was strongly positive at this time. Thyroid function tests were not performed at the initial admission, although the patient seemed to be euthyroid and goitre was not noticed.

He recovered and was discharged from the hospital on November 2, 1974. Later, he began taking large amounts of seaweed. He gradually gained 11 kg in weight and complained of anorexia. On December 28, 1974, he visited our hospital again.

Physical examination revealed a puffy face, hypohydrosis, bradycardia (57/min), and a soft and diffuse goitre enlarged to a moderate degree. At that time, the following studies were all within normal limits; urinalysis, RA test, LE test, antinuclear antibody, renal function tests and liver function tests. The white blood cell count was 6300 with 52 % lymphocytes. Total serum protein was 8.2 g/100 ml with gammaglobulin of 26 %. Total cholesterol was 281 mg/100 ml. Lymphocytosis and hypergammaglobulinaemia had not been observed on the initial admission.

Thyroid function tests were as follows: T_3 resin sponge uptake was 21.2 % (Triosorb, Dainabot Radioisotope Lab., Ltd., Tokyo, normal 25–35 %), serum triiodothyronine 109 ng/100 ml (Radioimmunoassay, Kaken Chemical Co., Ltd., Tokyo, normal 98–188 ng/100 ml) and thyroxine (T_4) 0.6 μg/100 ml (Competitive protein binding analysis, Tetrasorb, Dainabot Radioisotope Lab., Ltd., Tokyo, normal 5.9–11.5 μg/100 ml). Serum thyroid stimulating hormone (TSH) was 125 μU/ml (Radioimmunoassay, Daiichi Radioisotope Lab., Ltd., Tokyo, normal < 4 μU/ml), and showed an exaggerated response to the intravenous injection of 500 μg of TSH releasing hormone (TRH). Thyroidal uptake of ^{131}I was 66.2 % (4 h) and 69.5 % (24 h) on January 6, one week after restricting his iodide intake. Thyroid scanning showed diffuse uptake of radioactivity in an enlarged gland. A perchlorate discharge test was performed on January 24. Administration of 400 mg of $KClO_4$ orally 1 h after the ingestion of ^{131}I discharged 31.4 % of the thyroidal ^{131}I, suggesting the presence of an impaired organification of iodide accumulated in the thyroid gland.

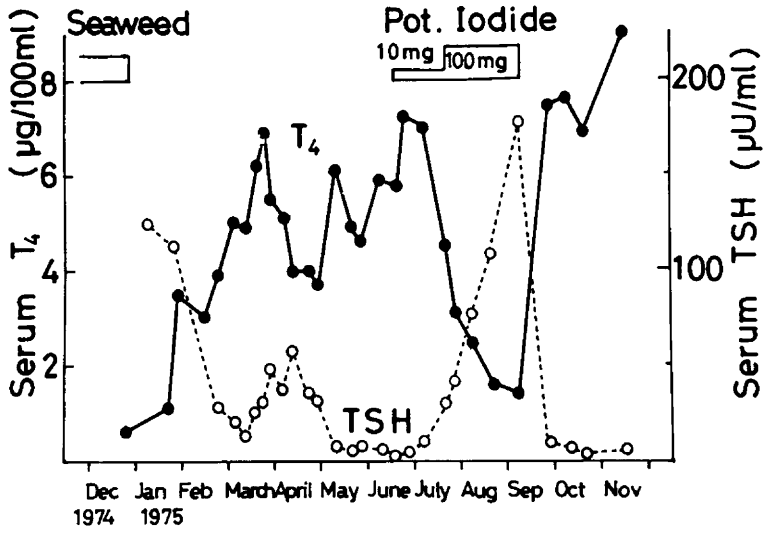


Fig. 1.
Changes of serum levels of thyroxine and TSH in the clinical course of the patient.

The patient was treated simply by iodide restriction and no drugs were used. The serum T_4 level gradually rose and the TSH level gradually declined at the same time. About 3 months later, both reached almost normal levels (Fig. 1). He improved subjectively, lost weight and the goitre decreased markedly. Iodide loading test was performed with the consent of the patient. Oral administration of 10 to 100 mg of potassium iodide (KI) in saturated solution again induced goitrous hypothyroidism (Fig. 1). The result of an ^{131}I uptake test, performed on September 9 when the patient was still taking iodides (100 mg/day), was 33.1 % (2 h), 31.8 % (4 h) and 14.7 % (24 h), a surprisingly high uptake for such large doses of iodide. After discontinuing KI loading, he promptly returned to a euthyroid state.

The most interesting phenomenon in this case was the observation that the abnormal immunological findings developed coincidently with the administration of the excess iodide (Table 1). Serum gamma-globulin concentration, thymol turbidity test (TTT) and zinc sulphate test (Kunkel) were entirely normal before the onset of the iodide goitre. Tests for thyroid auto-antibodies to thyroglobulin (TGHA) and microsomes (MCHA) (tanned sheep red cell haemagglutination technique, Thyroid test and Microsome test, Fujizoki Pharmaceutical Co., Ltd., Tokyo) were not tested at that time. However, they were negative immediately after the onset of the iodide goitre. Although TGHA remained negative throughout the course, the serum gammaglobulin concentration rose and the MCHA became strongly positive soon after the onset of the iodide goitre. As he again became euthyroid with iodide restriction, these immunological abnormalities gradually regressed. In contrast to the first attack of iodide goitre, the serum gamma-globulin concentration did not rise again, and antithyroid microsomal antibody titer did not increase at the time of the second occurrence of iodide goitre after KI loading.

Table 1.
Changes of ESR, anti-thyroid antibodies, serum gamma-globulin, Kunkel and TTT in the clinical course of the patient.

	ESR 1 h/2 h (mm)	MCHA	TGHA	Serum gamma-globulin (g/100 ml)	Kunkel (unit)	TTT (unit)
July 2, 1974	13/31	/	/	1.14	7.0	2.7
	Ingestion of large amounts of seaweed					
December 28, 1974	3/14	/	/	2.13	15.0	10.0
January 7, 1975	34/65	negative	negative	2.55	15.5	10.2
January 21	12/40	6400	negative	2.60	15.6	9.4
February 15	30/61	409 600 ↑	negative	2.79	14.6	6.4
February 24	13/35	409 600 ↑	negative	2.33	12.5	6.2
March 10	9/25	409 600 ↑	negative	2.16	12.0	6.7
June 16	4/12	102 400	negative	2.08	12.1	4.8
	Potassium iodide loading (10–100 mg/day)					
August 25	7/15	6400	negative	2.00	12.5	6.2
October 20		6400	negative	1.85	11.2	5.1
February 23, 1976	4/13	6400	negative	1.61	11.4	6.6
November 7, 1977	7/17	400	negative	1.36	10.9	3.8

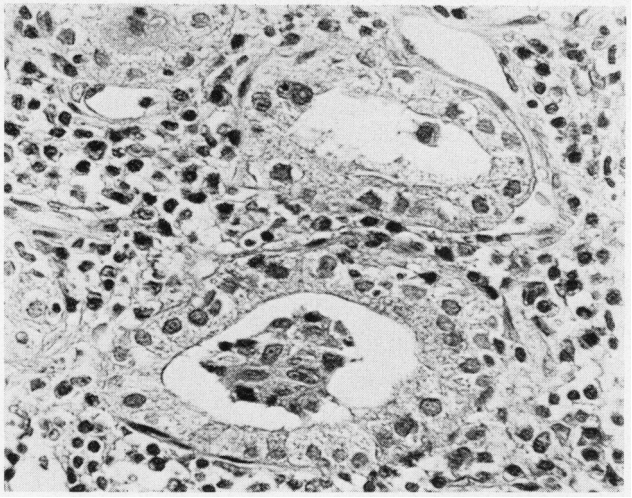
ESR = erythrocyte sedimentation rate, MCHA = anti-thyroid microsomal haemagglutination antibodies (MCHA value is indicated by the maximum dilution of the serum for positive haemagglutination), TGHA = anti-thyroglobulin haemagglutination antibodies, Kunkel = zinc sulphate test, TTT = thymol turbidity test.

An open biopsy of the thyroid gland, performed on February 3, 1975, when the patient was still hypothyroid and goitrous, revealed Hashimoto's thyroiditis with cellular changes suggesting extreme stimulation by TSH, although fibrosis was very slight (Fig. 2). Soluble thyroidal protein obtained from the biopsy was analyzed by a modification of the method reported by *Inoue & Taurog* (1968). About 90.2 % of the thyroidal soluble protein was 4S component, and 19S thyroglobulin comprised only 6.8 %, which was about 0.37 % of the wet weight of the thyroid (normal 8 %). The degree of iodination of this thyroglobulin was only 0.11 % (normal 0.5 %). These findings were quite similar to those found in the iodine deficient thyroids of rats (*Inoue & Taurog* 1968) and in Hashimoto's thyroiditis (*DeGroot et al.* 1962; *Nakashima et al.* 1978). The lack of 19S thyroglobulin seemed compatible with the histological finding of colloid depletion (Fig. 2).

DISCUSSION

In the present study, a case of primary goitrous hypothyroidism induced by excess iodide was observed. Iodide goitre is not a particularly rare disease in itself, over 200 cases having been reported (*Wolff* 1969). However, antithyroid antibodies are generally absent or of low titer (*Wolff* 1969; *Begg & Hall* 1963), although a high titer of antithyroid antibodies has been detected in some cases (*Begg & Hall* 1963; *Buchanan et al.* 1965; *Hall et al.* 1966). Histological examination has generally revealed epithelial hyperplasia or parenchymatous hypertrophy of the thyroid gland. In some cases of iodide goitre, the histological findings have been those of chronic thyroiditis (*Turner* 1956; *Paris et al.* 1961; *Liewendahl & Turula* 1972) as in our case. It is known that excess iodide induces goitre and/or hypothyroidism in chronic thyroiditis (*Braverman et al.* 1971). Thus, it might be that, in our case, chronic thyroiditis had already been present when the patient began to ingest excess iodide. However, in the case of chronic thyroiditis, the antithyroid antibodies did not seem to change in spite of a development of functional abnormalities, when excess iodide was given (*Braverman et al.* 1971). In addition, the recovery from iodide-induced hypothyroidism in the case of chronic thyroiditis was rapid, and the patient became euthyroid within 3–5 weeks after discontinuation of iodide therapy, similar to the course observed in our own case at the time of KI loading (Fig. 1). On the other hand, the first episode of iodide goitre required a much longer time for the recovery of the thyroid function. Hence, the first occurrence of iodide goitre, accompanied by the appearance of antithyroid microsomal antibody (MCHA) and hypergammaglobulinaemia, may have represented a different quality of thyroidal response when compared to the subsequent KI loading study. It should be emphasized that in our case the serum gamma-globulin concentration did not increase, nor did MCHA become positive until after the onset of iodide goitre.

A



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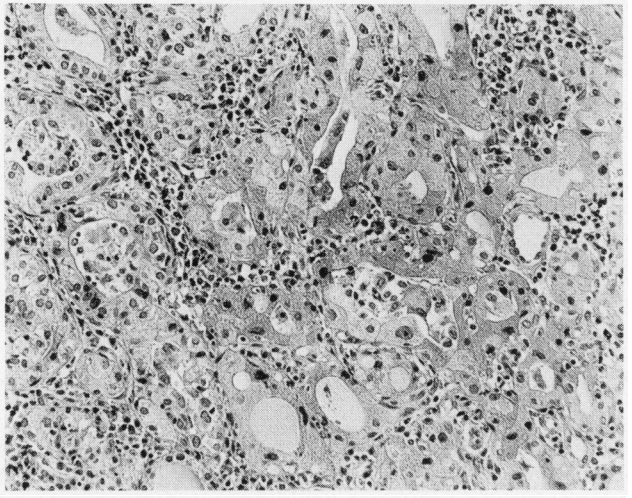

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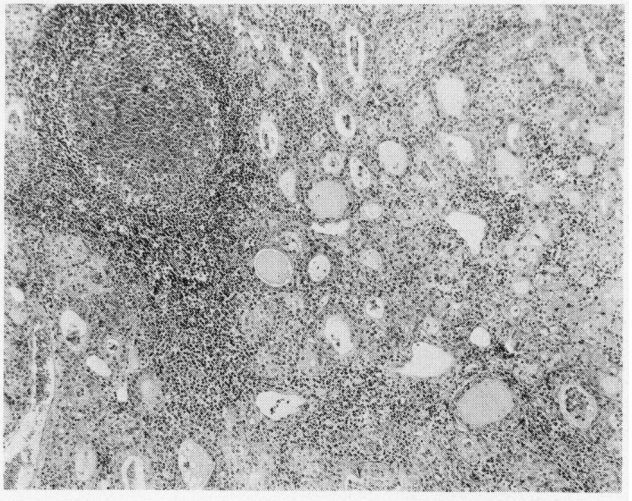

Hypothyroidism itself may be associated with gamma-globulin abnormalities (*Lewis & McCullagh* 1944). However, the change in the concentration of serum gamma-globulin was not in parallel with that of thyroid function only (Table 1). Liver function tests were normal. Therefore, the remarkable elevation in serum gamma-globulin concentration, together with the appearance of lymphocytosis, seemed to suggest some immunological change. Although Hashimoto's thyroiditis has been associated with immune complex deposition in the renal glomeruli (*O'Regan et al.* 1976), renal biopsy revealed no such depositions in our case and the participation of immunological mechanisms in the renal lesions seemed to be only slight if present at all.

From the epidemiological point of view, a steadily increasing incidence of thyroiditis has been reported after the initiation of the therapeutic use of iodine in Michigan (*Weaver et al.* 1966, 1969). It was proposed that in genetically predisposed patients iodide could induce chronic lymphocytic thyroiditis. It was also noted that increased lymphocytic infiltrates were found in the thyroid glands which had been removed surgically after the prior use of iodine.

Recently, iodide has been found to be cytotoxic to the hyperplastic iodide-deficient thyroid glands of dogs (*Belshaw & Becker* 1973) and rats (*Valenta & Wong* 1976) and has sometimes been found to induce acute thyroiditis in human thyroids (*Edmunds* 1955). Necrosis of thyroid follicular cells induced by pre-operative iodine treatment of thyrotoxicosis in humans has also been noted. It is conceivable that these effects may act as precipitant of chronic thyroiditis. Actually, *Follis* (1959, 1964) reported that when hamsters with hyperplastic iodine deficient goitres were given large amounts of iodine, an inflammatory reaction developed in the gland, although excess iodide did not damage the thyroid gland of normal hamsters. *Evans et al.* (1969) reported that thyroiditis induced in dogs by the combination of iodine injection and immunization more closely resembled classic human Hashimoto's thyroiditis.

Association of Hashimoto's thyroiditis and other diseases possibly of autoimmune aetiology has been reported. *Blizzard et al.* (1959) reported a high incidence of penicillin sensitivity and penicillin antibodies in patients with

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Fig. 2.

Histology of the thyroid gland of the patient. Haematoxylin and eosin stain.

Fig. 2 A: Thyroid follicles were small and colloid was scarce surrounded by tall epithelial cells. × 370.

Fig. 2 B: Eosinophilic degeneration of the epithelial cells. × 160.

Fig. 2 C: Infiltration of lymphocytes and the formation of the germinal centre × 65.

Hashimoto's thyroidits. *Beare* (1958) has commented on the frequency of allergic diseases in Hashimoto's thyroiditis. Sensitivity test given for carbenicillin or sulbenicillin was also strongly positive in our case. As *Beare* (1958) pointed out, a defective immune mechanism of this type might have led to progressive autoimmunity and facilitated the occurrence of autoimmune thyroiditis in response to the thyroid damage caused by excess iodide. In a thyroid gland with marked epithelial hyperplasia and extreme reduction in thyroglobulin content, antigenicity to microsomal fraction may predominate over that to thyroglobulin. As to the initially negative antibodies in spite of high TSH and iodide ingestion, there might be a latent period before the appearance of such antibodies (*McMaster et al.* 1961; *Miescher et al.* 1961; *Hall et al.* 1966). On the other hand, *Volpé* (1977) has pointed out that there is little evidence in favour of antigenic change as an initiation of Hashimoto's thyroiditis, and it may be that the mechanism by which iodides precipitate the disorder in presumably genetically predisposed subjects may not relate to any antigenic alteration.

Our observation strongly support the view of *Weaver et al.* (1966, 1969) that the use of iodide could be the precipitating factor of thyroiditis. Our contention concerning the aetiological role of iodide in Hashimoto's thyroiditis is schematically shown in Fig. 3. However, there is no evidence that iodide in

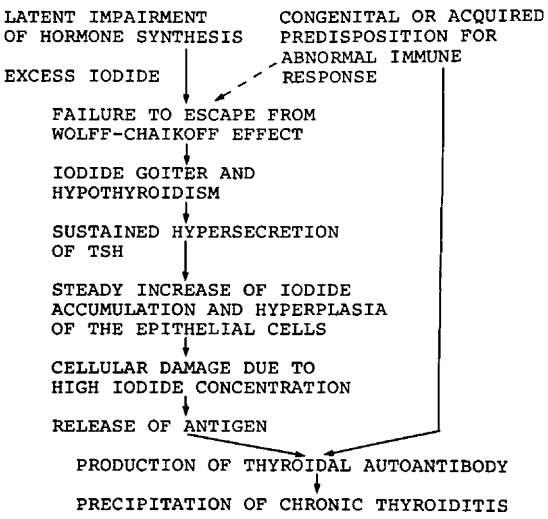

Fig. 3.
Hypothetical scheme showing the induction of thyroidal autoimmune mechanism in this case.

doses taken have directly induced any cytotoxic effect in humans, or that cytotoxicity causes the immunological events. Where there is tremendous cytotoxicity, such as in subacute thyroiditis, there is only a minimal immune response, and Hashimoto's thyroiditis does not usually occur (*Volpé* 1977). Thus, congenital or acquired predisposition for abnormal immune response seemed to play an important role together with the excess iodide in this case.

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