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THYROID FUNCTION AFTER POSTOPERATIVE RADIATION THERAPY IN PATIENTS WITH BREAST CANCER

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Abstract

Thyroid stimulating hormone (S-TSH) and thyroxine (S-T_4) were measured in sera from 80 patients with breast cancer using radioimmunoassay. The patients had been irradiated after mastectomy 7.2±1.0 years earlier with 45 Gy in 3 to 4 weeks to parasternal, ipsilateral supraclavicular and axillary areas. Five patients (6%) had hypothyroidism with low S-T_4 and elevated S-TSH levels. In addition, 12 patients (15%) had elevated (>5 mU/l) S-TSH levels and normal S-T_4 values. Shielding of the thyroid during irradiation and long-term follow-up of thyroid function with repeated hormone assays are recommended.

Key words: Radiation, injurious effects, complications of therapeutic radiology, hypothyroidism.

Radiation-induced primary hypothyroidism has been reported to occur rather frequently after mantle irradiation in Hodgkin's disease (10) and following treatment of head and neck cancer (12). In view of these reports and of the occasional observation of breast cancer patients with primary hypothyroidism at this hospital, an investigation was carried out on the effect on thyroid function of postoperative radiation therapy following mastectomy, and the results are now presented.

Material and Methods

Ninety-three female patients with breast cancer who had been irradiated postoperatively after mastectomy 5 to 10 years previously (in 1975–1979) were invited to participate in S-T_4 (serum thyroxine) and S-TSH (serum thyroid stimulating hormone) measurements. Eighty-three patients took part in the investigation (89%). The patients were not consecutive, because most of them also participated in another study, in which the long-term effects of irraditation to the healthy heart were investigated. The mean age of the patients was 54.9±8.2 years (range 39–75 years) at examination.

Two patients who had thyroxine medication because of thyroid surgery and one patient who had hypothyroidism after treatment with radioactive iodide for hyperthyroidism were excluded.

Among the remaining 80 patients, 3 cases of primary hypothyroidism had been diagnosed during the follow-up after postoperative radiation therapy, but the rest were unaware of any endocrinologic disease. None of the patients had received cytotoxic therapy. One patient was receiving tamoxifen and 2 others nandrolone because of disseminated disease. Although steroids may change the serum thyroxine concentration by changing the level of circulating sex hormone-binding globulin, they do not change the S-TSH levels, and therefore the 3 patients receiving hormonal therapy were also included in the analysis.

All patients had been irradiated postoperatively after mastectomy 7.2±1.0 years previously. Although photographs and roentgen films of the treatment field were available in each case it was difficult to assess how large a part of the thyroid volume had been irradiated, due to variations in anatomy. A typical treatment field is shown in the Figure. Only a part of the thyroid is normally located within the radiation field. A dose of 45 Gy was delivered to this anterior field with a 6 MeV linear accelerator in fifteen 3 Gy fractions on five days a week in 21 to 25 days (CRE about 1 650). The dose within the thyroid tissue in the field was thus about 45 Gy. However, a few patients received 45 Gy in eighteen 2.5 Gy fractions (CRE about 1 570), and in some cases an extra pause of a few

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Table 1

Characteristics of patients with hypothyroidism

Case No.	Age at diagnosis (years)	Time elapsed from irradiation to clinical hypothyroidism (years)	S-T_4 at diagnosis (nmol/l)	S-TSH at diagnosis (mU/l)	Antithyreo-globulin antibodies	Antimicrosomal antibodies
1	41	0.5	<20	>10	1:160	1:100
2	47	5.5	45	34	–	1:400
3	51	4.0	30	58	1:80	1:1600
4	52	9.0	31	>50	–	–
5	62	6.5	60	45	–	1:100

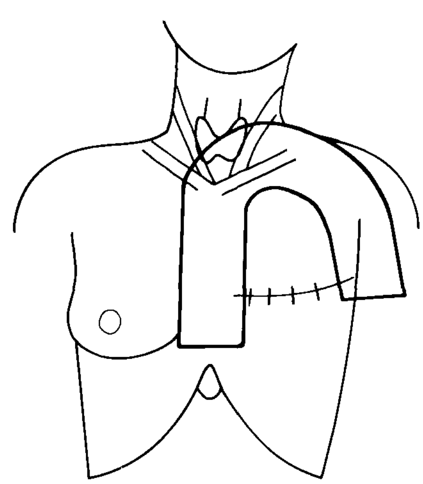
Table 2

Characteristics of patients with normal S-T_4 and elevated S-TSH

Case No.	Age at analysis (years)	Time elapsed from irradiation (years)	S-T_4 (nmol/l)	S-TSH (mU/l)	Anti-thyreo-globulin antibodies	Anti-microsomal antibodies
6	64	8	76	15.6	–	1:1 600
7	64	9	76	15.1	–	–
8	72	6	83	12.2	–	1:1 600
9	70	6	108	12.0	–	1:100
10	50	6.5	105	10.5	–	–
11	57	7.5	97	7.5	Not determined	
12	58	8	86	7.0	Not determined	
13	54	7	117	5.9	–	–
14	48	8	81	5.6	–	–
15	50	8	93	5.6	–	–
16	56	8.5	79	5.3	–	–
17	54	8	109	5.2	1:20	–

days was made. Two patients with hypothyroidism had an extra pause in irradiation (case 1 because of gastroenteritis, CRE 1300; Case 4 because of skin desquamation, CRE 1470).

Peripheral blood samples were drawn and serum S-T_4 and S-TSH were analysed by radioimmunoassay (RIA). The reference value for S-T_4 is from 70 to 150 nmol/l and for S-TSH <5.0 mU/l at this hospital. Serum antimicrosomal and antithyreoglobulin antibody titres were measured using a passive haemagglutination technique, in cases with elevated S-TSH levels, in order to exclude chronic autoimmune thyroiditis. For antimicrosomal antibodies the titre ≥1:1600 and for antithyreoglobulin antibodies ≥1:640 were considered elevated.



A typical treatment field.

Results

Five patients (6%) had hypothyroidism (S-T_4 <70 nmol/l and S-TSH >5.0 mU/l; Table 1). The time interval from irradiation to detection of hypothyroidism ranged from 6 months to 9 years (mean 5 years). In 3 cases (Nos 1–3) with symptoms compatible with hypothyroidism the diagnosis had been made during out-patient follow-up and 2 more cases (Nos 4 and 5) were found during the present study. In addition, 5 patients (6%) had clearly elevated S-TSH levels (range 10.5–15.6 mU/l; Table 2) and another 7 patients (9%) mildly elevated S-TSH levels (5.2–7.5 mU/l). Thus, 17 out of 80 patients (21%) had thyroid hypofunction detectable by S-TSH assay.

Three cases (Nos 3, 6 and 8) had moderately elevated serum antimicrosomal antibody titres, but increased serum antithyreoglobulin antibody titres were not found in patients with hypothyroidism or with an elevated S-TSH level. Asymptomatic autoimmune thyroiditis as a major cause of the thyroid hypofunction in these patients was thus very unlikely.

The mean age of the patients with hypothyroidism at examination (53.0 years) did not differ significantly from that of the rest of the patients (55.0 years).

Discussion

Hypothyroidism following external irradiation is a well-documented complication after mantle irradiation in Hodgkin's disease. The reported frequency of hypothyroidism after this type of treatment has varied markedly. In two large investigations (5, 8) about 20 per cent of the patients had low S-T_4 and elevated S-TSH levels, indicating biochemical hypothyroidism, and in addition about 40 per cent of the cases had an elevated S-TSH level indicating subclinical hypothyroidism after irradiation with 40 to 50 Gy to the neck in 4 to 5 weeks. A TRH stimulation test has revealed another group of patients with normal S-T_4 and S-TSH values but an exaggerated S-TSH response to TRH (10).

It has been suggested that lymphography performed before irradiation in lymphoma patients may increase the incidence of hypothyroidism due to prolonged iodine release from the contrast substance ethiodol (5, 6), but not all investigators have been able to confirm this finding (11). Surgery of the thyroid gland before irradiation increases the occurrence of hypothyroidism considerably (12). Children may run a greater risk than adults of developing radiation-induced hypothyroidism (9).

In the treatment of cancer in the head and neck area, radiation-induced hypothyroidism has been reported to occur less frequently than in lymphoma patients. VRABEC & HEFFRON (12) reported elevated S-TSH levels in 14 per cent of cases when irradiation, 50 Gy, without surgery was delivered to at least half of the thyroid gland, whereas DE JONG et coll. (3) found hypothyroidism to occur only if irradiation had been combined with surgery.

BRUNING et coll. (1) have recently reported hypothyroidism in 2 to 3 per cent and elevated S-TSH values in 10 to 25 per cent of patients with breast cancer, depending on the treatment fields used. The patients received postoperative irradiation to the supraclavicular fossa with radiation fields comprising only a minor part of the thyroid. Our observation of 6 per cent hypothyroidism in addition to 15 per cent of patients having elevated S-TSH levels was very similar to the findings of these authors. The occurrence of hypothyroidism in 6 per cent of our irradiated breast cancer patients is much higher than the reported prevalence of hypothyroidism in Finland, which has been found to be 0.5 to 1 per cent in two large populations with a mean age of about 40 years (7).

SCHIMPFF et coll. (8) and TAMURA et coll. (11) have reported an increasing prevalence of patients with elevated S-TSH levels with increasing time after neck irradiation. VRABEC & HEFFRON (12) and GLATSTEIN et coll. (6) have noted that elevation of the S-TSH level most often occurs already within the first year after radiation therapy. In the present investigation, two previously undiagnosed cases with hypothyroidism were detected 6.5 and 9 years after neck irradiation. It is probable that the cumulative incidence rate of hypothyroidism after external thyroid irradiation increases slowly for years and even decades, following the irradiation, and these patients thus need continuous follow-up. However, a spontaneous return of S-TSH to normal levels (2), and even spontaneous disappearance of hypothyroidism (4), has been described in children irradiated for Hodgkin's disease.

Whenever possible, the thyroid should be excluded from the treatment field. As the clinical diagnosis of hypothyroidism is often difficult, and as this condition commonly occurs after neck irradiation, we recommend that all patients with a history of thyroid irradiation should be examined concerning the S-TSH level, first annually, and later every second year.

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