Hyperthyroidism with Low Radioiodine Uptake After Head and Neck Irradiation for Hodgkin's Disease

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Abnormalities of thyroid function are well documented in patients who have had external irradiation to the neck for neoplastic disorders (*1–10*). The most common form of thyroid dysfunction is compensated biochemical hypothyroidism diagnosed by a raised serum thyrotropin (TSH) with normal thyroxine (T4). Overt clinical hypothyroidism, radiation thyroiditis, Graves' hyperthyroidism with and without ophthalmopathy (*11*), hypothyroidism followed by hyperthyroidism (*12*), thyroid adenoma, thyroid carcinoma (*13*), Hashimoto's thyroiditis and granulomatous thyroiditis (*9*) have all been described, but less commonly.

Below we report three patients with transient hyperthyroidism and low radioiodine uptake. Each patient had Hodgkin's disease and had mantle radiation therapy. In our review of the literature we were only able to find two reports of three patients with this combination of test results. They were considered to have painless or silent thyroiditis after neck irradiation (*14, 15*).

CASE REPORTS

Case 1

A 34-yr-old woman presented in December 1982 with shortness of breath and prominent neck veins. Chest x-ray and computed tomographic (CT) scan revealed a large mediastinal mass. Biopsy of a supraclavicular node demonstrated Nodular Sclerosing Hodgkin's lymphoma. Prior to the staging laparotomy she had a bipedal lymphangiogram and 1,500 rad of mantle irradiation to reduce the mediastinal mass. At laparotomy in January 1983, Stage 11A Nodular Sclerosing Hodgkin's Disease was diagnosed. She chose to have radiotherapy alone and by June 1983, had completed sub-total lymphoid irradiation including 4,400 rad to the mantle area. She was well in December 1983, and thyroid function tests were normal. In March 1984, she became tired and lethargic and lost 10 lb in weight in spite of eating well. She had a tachycardia and her skin was warm, but her thyroid was impalpable. Serum Free T4 was >5.0 ng/dl (normal 0.8–2.0 ng/dl) and T3 was 260 ng/dl (normal 70–200 ng/dl). Twenty-four-hour-iodine-123 (^{123}I) uptake was 1% (normal 10–30%). She was treated with Propranolol 20 mg T.I.D. Four months later she became clinically hypothyroid (FT4 was 0.2 ng/dl), and was started on L thyroxine. All attempts to discontinue the thyroxine have resulted in clinical and biochemical hypothyroidism with a rise in TSH. She has had no recurrence of Hodgkin's disease.

Case 2

A 44-yr-old man was diagnosed with Stage IVB Hodgkin's disease in June, 1984. He had bilateral hilar lymphadenopathy, a right paratracheal mass, extensive disease below the diaphragm and involvement of the lumbar spine and multiple extranodal sites. He was treated with three cycles of MOPP chemotherapy (nitrogen mustard, vincristine, procarbazine, and prednisone).

He received 4,400 rad external beam radiation therapy to the pelvis and 1,800 rad to the mantle area between September and November 1984. Then he had a further three cycles of chemotherapy and further radiation therapy to the para aortic, splenic, and mantle areas including 1,900 rad to the neck with completion of treatment in August 1985.

In September, 1986 TSH was <2.0 μ/ml and total T4 7.9 ng/dl. From December 1986 to February 1987, he developed weight loss, tachycardia, palpitations, hand tremor, and leg weakness. To ensure he had no recurrence of Hodgkin's disease, an abdominal CT with 150 ml contrast was done and was normal. He was then suspected to be hyperthyroid in March and serum-free T4 was 3.1 ng/dl (normal 0.8–2.0), sensitive TSH was <0.05, μU/ml (normal 0.4–3.4 μU/ml). The thyroid gland was palpable at the lower border of both poles and because of the recent contrast media, a technetium-99m pertechnetate thyroid scan was performed instead of ^{123}I. This demonstrated a slightly enlarged thyroid gland. He was treated with propranolol 40 mg T.I.D. Four weeks later, by which time the contrast should have been excreted, ^{123}I uptake

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at 6 hr was 2% and TSH was 0.05 μU/ml with a FT4 of 1.1 ng/dl. In May 1987, he was hypothyroid and FT4 was 0.7 ng/dl and TSH was > 60 μU/ml and he was clinically hypothyroid. He was treated briefly with thyroxine, and thyroid function tests returned to normal. There was no evidence of Hodgkin's disease.

Case 3

A 37-yr-old woman was diagnosed as having Stage 111 A s Nodular Sclerosing Hodgkin's disease in March 1986. Prior to laparotomy she had bipedal lymphangiography and 3 days later was treated with 1,500 rad to the mantle area preoperatively. She was treated with six cycles of chemotherapy comprising alkeran, procarbazine, and velban (PAVe). Serum TSH was <2 μU/ml (normal <6 μU/ml). In June 1986, she had a further 2,900 rad to the mantle area and in December 1986, an additional 4,350 rad to the abdomen and pelvis.

In August 1987, she complained of hot flashes, amenorrhea, irritability, and loss of weight despite increased appetite. Clinically she appeared mildly hyperthyroid. The thyroid gland was impalpable. Free T4 was 5.0 ng/dl, serum TSH was 0.05 μU/ml and ^{123}I scan demonstrated nonvisualization of the thyroid with a 24-hr uptake of 1%. She was treated with propranolol 20 mg T.I.D. However, within a few weeks she became clinically and biochemically hypothyroid requiring L thyroxine 0.125 mg daily which she now continues.

DISCUSSION

Although none of the three cases presented above underwent thyroid biopsy, because there was no palpable thyroid tissue, the laboratory evidence and natural histories of the disorders support the diagnosis of silent thyroiditis. The differential diagnosis includes thyrotoxicosis factitia but in each case we were satisfied this did not apply. It is also unlikely that the iodine contrast alone would have caused transient hyperthyroidism then hypothyroidism, which in two of the three patients has been prolonged. It is probable the patients have silent thyroiditis.

This syndrome was first reported in 1975 (*16,17*) and is characterized by a transient hyperthyroidism accompanied by a low radioactive iodine uptake. Estimates of prevalence vary from 4–30% of all cases of hyperthyroidism (*18,19*) and there is evidence of a geographic variation in frequency of the syndrome (*18*). It is uncommon in California. Women in the third and fourth decade are most commonly affected and tend to present more acutely than is the case with hyperthyroidism due to Graves' disease. The thyroid is of normal size or slightly enlarged and there is no pain or tenderness. The initial phase of thyrotoxicosis usually lasts 4 to 8 wk before returning to a euthyroid state. In 25–40% of patients there is a hypothyroid phase which can last several months or can be permanent (*20*). Treatment of the hyperthyroid phase in symptomatic, with beta adrenergic blocking agents such as propranolol. If hypothyroidism occurs thyroxine is advised. The patients described had characteristic features.

The etiology of this disorder is unknown but the histopathology of the gland is similar to that seen in Hashimoto's thyroiditis with focal or diffuse lymphocytic infiltration, occasionally Askanazy cells, and varying degrees of fibrosis. Silent thyroiditis is most probably an autoimmune disease (*21*).

Although none of the three cases presented above underwent thyroid biopsy, the laboratory evidence and natural histories of the disorders strongly support the diagnoses of silent thyroiditis. The differential diagnosis would have to include thyrotoxicosis factitia but in each case we were satisfied that this did not apply. We did not measure thyroid antibodies since they are not diagnostically valuable and would not have altered management.

In the reports of hypothyroidism after head and neck irradiation the severity of thyroid dysfunction is related to the radiation dose to the neck (*4*). In our patients the doses were 4,400 rad, 3,700 rad, and 4,400 rad. In addition, each patient underwent bipedal lymphangiography with an interval prior to radiation therapy of 3 days, 9 mo, and 8 days, respectively. The role of lymphangiography in producing thyroid dysfunction is still unclear. Shalet et al. (*10*) found significantly greater thyroid dysfunction in patients who had lymphangiography, in addition, to radiation therapy than those who had neck irradiation alone. Smith et al. (*2*) found that decreased thyroid function was inversely proportional to the length of time between a diagnostic lymphangiogram and the radiation therapy (*2*). Fuks et al. (*8*) documented thyroid dysfunction in two of 14 lymphoma patients who had undergone lymphangiography but had not received neck irradiation. Other authors have failed to show any difference between irradiated patients who had lymphangiograms and those who did not (*6,9*). In children with Hodgkin's disease Constine et al. (*4*) found no time relationship between hypothyroidism and the interval between the lymphangiogram and radiation therapy. Most investigators find that age, sex, and the addition of chemotherapy to the regime have no effect on the incidence of postradiation thyroid abnormalities (*1,2,4*). Tamura et al. (*6*) actually found that chemotherapy appeared to have a protective effect and in their group of 126 patients, 31% of those who received radiation therapy developed positive thyroid antibodies in contrast to 21% of those who received no neck irradiation (*6*).

Most of the factors so far studied in relation to thyroid dysfunction have been applied to those patients who develop biochemical or clinical hypothyroidism. Since so few cases of hyperthyroidism with low uptake have been reported in this setting it is impossible to say what factors are causal. It may also be possible that there is no relationship in these patients between the thyroid abnormalities and neck irradiation or lymphangiography. However, in view of the other well-recognized

effects of radiation on thyroid function, it seems likely that a relationship does in fact exist. It is possible that some patients who appear to have classic primary hypothyroidism after neck irradiation are presenting with the final hypothyroid stage of silent thyroiditis. This cannot be proven by our data. We recommend that all patients who have had therapeutic radiation over the thyroid area have routine evaluation of thyroid function (preferably FT4 and sensitive TSH) at least yearly. We also recommend that an ^{123}I uptake is measured in patients who thyroid function tests after radiation therapy are high. This will ensure that patients with low uptake thyroiditis are not treated as if they have Graves' hyperthyroidism.

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