Thyroid Abnormalities after Therapy for Hodgkin’s Disease in Childhood

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Key Words. Thyroid abnormalities · Hodgkin’s disease in childhood

Abstract

Background. Involvement of the thyroid gland is an important morbidity of therapy for Hodgkin’s disease, which should be well recognized by caretakers of these patients. However, the roles of age at the time of therapy for Hodgkin’s disease, chemotherapy, treatment with reduced dose of radiation and lymphangiography in causing thyroid abnormalities have not been defined.

Materials and Methods. Eighty-nine pediatric and young adult patients (less than 21 years old at diagnosis) with Hodgkin’s disease who were treated with either radiation alone (57 patients), radiation and chemotherapy (20 patients), or chemotherapy alone (12 patients) at the University of Minnesota between 1971 and 1986 were periodically evaluated.

Results. The median age at diagnosis was 14 years, and the median duration of follow up was 11 years. Of 89 patients evaluable for thyroid abnormalities, 51 patients developed biochemical hypothyroidism. The median time to development of hypothyroidism was six years. The estimated actuarial risk of developing hypothyroidism was 60% at 11 years. Radiation to the thyroid region was associated with an elevated risk of development of hypothyroidism (relative risk = 9.9), with patients receiving mantle irradiation alone developing hypothyroidism earlier (median time 2.5 years) than patients receiving combined modality treatment (median time 6 years; \( p = 0.001 \)). Dose of radiation was the chief correlate for the development of hypothyroidism (relative risk increasing by 1.02/Gy; \( p < 0.001 \)). Age, gender, chemotherapy and prior lymphangiography were not shown to be significant risk factors for the development of hypothyroidism. Four patients were diagnosed with thyroid nodules, (diagnosed 7.6 to 14.3 years after treatment of Hodgkin’s disease), with histology showing multinodular goiter (2), single colloid nodule (1) and papillary carcinoma (1). Transient hyperthyroidism developed in two patients 8 and 13 months after treatment for Hodgkin’s disease.

Conclusions. There is a high risk for development of thyroid disease after patients have received radiation therapy for Hodgkin’s disease, reinforcing the need for continued clinical and biochemical evaluation of such patients.

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Introduction

Radiation therapy is an important component of the treatment of Hodgkin’s disease, either alone or in combination with chemotherapy. Currently, 75% of children and adults with newly diagnosed Hodgkin’s disease achieve long-term survival [1], and are therefore at risk for long-term complications resulting from the disease and its treatment. Potential complications of therapy for Hodgkin’s disease include mediastinitis, pneumonitis, pericardial fibrosis, cardiovascular disease (including coronary artery disease), scoliosis, growth retardation, thyroid dysfunction, gonadal failure and second malignancies [2-4]. A variety of thyroid diseases have been diagnosed in patients treated for Hodgkin’s disease; among them hypothyroidism is the most common [5-13]. Iodinated radiographic contrast agents may or may not [5-7, 9, 12] contribute to the risk of hypothyroidism, and the role of chemotherapy as a risk factor for thyroid dysfunction has not been established. Hyperthyroidism, with transient thyrotoxicosis, has also been described [14, 15], as have thyroid nodular disease and thyroid cancer, following therapy for Hodgkin’s disease [16-20]. We studied a cohort of Hodgkin’s disease survivors who were treated at the University of Minnesota Hospital and Clinics in order to obtain further information about the spectrum and incidence of benign and malignant thyroid diseases in such patients, and also to delineate further what risk factors (such as age, sex, chemotherapy

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and lymphangiography) might be involved in the development of thyroid dysfunction after treatment for Hodgkin’s disease.

**MATERIALS AND METHODS**

The patient population consisted of all patients diagnosed with Hodgkin’s disease between March 1970 and August 1986 and who were less than 21 years of age at diagnosis. One hundred and six patients met the eligibility criteria. A small subgroup of this patient population had been evaluated previously for thyroid abnormalities and that report is published elsewhere [21]. The present study contains an updated version of this original cohort and additional patients who met the eligibility criteria. We reviewed the records of these 106 patients. Seventeen patients did not have thyroid function tests after finishing therapy for Hodgkin’s disease and were excluded from further analysis.

For the remaining 89 patients, the median age at the time of diagnosis of Hodgkin’s disease was 14 years (range, 3.9 to 20.9 years). There were 47 females and 42 males.

Seventy-three of the 89 evaluable patients had lymphangiography prior to initiating therapy. Eighty patients underwent a staging laparotomy. The stage of disease at diagnosis was: I in 15 patients, II in 44 patients, III in 26 patients and IV in four patients. Histologically, 72 patients were found to have nodular sclerosis, nine had mixed cellularity and eight had lymphocyte predominance.

Twelve patients received combination chemotherapy only: cyclophosphamide, vinblastine, procarbazine and prednisone (CVPP) in 10 patients; mechloretamine, vincristine, procarbazine and prednisone (MOPP) in one patient; and MOPP alternating with ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) in one patient. Twenty patients received both radiation and chemotherapy. Fifty-seven patients received only radiation therapy. The duration of treatment ranged from three weeks for patients receiving involved field radiation to as long as 49 months for those receiving combination chemotherapy. The extent of radiation therapy ranged from treatment of the involved fields to total lymphoid irradiation, but included the mantle area, the cervical area, or the mediastinum in 76 of the 77 irradiated patients. The mean dose of radiation was 43.8 Gy for patients with mantle radiation alone (midplane central axis), compared to 28.6 Gy for those with mantle radiation and chemotherapy.

The endpoints of the study included the development of thyroid abnormalities (hypothyroidism, hyperthyroidism, palpable thyroid abnormalities) and their time to development. The time to development of thyroid disease was measured from diagnosis of Hodgkin’s disease. Generally, patients were followed bimonthly during the first year after completing therapy, every three months during the second year, every four months during the third year, twice annually during the fourth and fifth years and annually thereafter.

Thyroid function studies, including plasma total thyroxine (T4), T3 resin uptake, T4 index and thyroid stimulating hormone (TSH) were obtained in the 89 patients approximately once every year. Both T4 and TSH were measured by standard radioimmunoassay techniques. T4 resin uptake results were normalized using pooled normal serum to 1.00. T3 index was calculated by multiplying T4 by normalized T3 resin uptake. Normal values were T4: 5.0 to 11.5 µg/dl; T3 resin uptake: 0.85 to 1.15; T4 index: 5.0 to 11.5 µg/dl; and TSH: <6 µU/l.

Hyperthyroxemia was defined as an elevated T4 index. Compensated hypothyroidism was defined as a normal T4 index with an elevated TSH value. Uncompensated hypothyroidism was defined as a low T4 index and an elevated TSH.

All data are expressed as mean ± standard error unless otherwise noted. Statistical methods included the Student t-test, chi-square test for homogeneity of proportions and Cox regression analysis. Life tables were constructed using the Kaplan-Meier technique. The data for patients who had no specific thyroid disease were censored at the time of the last follow up, or on the date of death. Potential risk factors for thyroid disease, such as age, sex, dose of radiation, exposure to chemotherapy, stage of disease, recurrence and prior lymphangiography were assessed by univariate and multivariate analysis, using Cox regression analysis.

**RESULTS**

Patients were followed for a median of 11 years (range, 1.0 to 23 years). At the time of the last follow up, 81 patients were alive without disease, one patient was alive with disease and seven patients had died. The causes of death included second malignant neoplasms (two patients), myocardial infarction (two patients) and progressive Hodgkin’s disease (three patients).

Of the 89 patients at risk for thyroid disease, 52 were found to have thyroid abnormalities (Table 1). The actuarial risk of developing any thyroid abnormality (hypothyroidism, hyperthyroidism, palpable thyroid disease) 11 years after therapy for Hodgkin’s disease was 63%.

**Hypothyroidism**

Hypothyroidism was the most common finding, affecting 51 of the 89 evaluable patients. The actuarial risk of developing either overt or subclinical hypothyroidism was 60% by 11 years. Of the 51 patients with hypothyroidism, 39 had undergone mantle irradiation only (median dose 45 Gy; range, 20 to 49.5 Gy), 11 had received mantle irradiation and chemotherapy (median dose 31 Gy; range, 19.5 to 45 Gy), while one patient had not received radiation to the mantle region (p = 0.001). The age at diagnosis (13.9 versus 13.7...
versus late) and effects of lymphangiography are shown in Table 2. Of the 47 females, 60% developed hypothyroidism as compared to 55% of the 42 males ($p = 0.3$). Age at diagnosis of Hodgkin’s disease ($p = 0.8$), stage of disease at presentation ($p = 0.6$), prior lymphangiogram ($p = 0.1$) and recurrence ($p = 0.4$) did not appear to be significant risk factors. Mantle irradiation was associated with an estimated relative risk (RR) of 9.9 for the development of biochemical hypothyroidism ($p = 0.001$), whereas mantle irradiation and chemotherapy were associated with an estimated RR of 6.0 for the development of hypothyroidism ($p = 0.027$). Dose of radiation was the chief correlate for the development of hypothyroidism (using Cox regression), with the RR increasing by 1.02/Gy ($p < 0.001$). The actuarial risk of developing hypothyroidism at 11 years was 74% for patients who had received more than 45 Gy, 64% for those who had received 30 to 45 Gy, 54% for those who had received less than 30 Gy and 8.3% for those who had not undergone irradiation to the thyroid gland ($p = 0.002$) (Fig. 2B).

### Thyroid Nodular Disease

Palpable abnormalities of the thyroid gland were identified in five patients, seven months to 14.3 years after therapy. Four patients had nodules and one patient had symmetric thyroid enlargement. Histology of the nodules revealed multinodular goiter without any evidence of malignancy in two patients, a single colloid nodule in one patient and papillary carcinoma of the thyroid gland in one patient.

### Hyperthyroxemia

Two of the 89 evaluable patients developed hyperthyroxemia and symptomatic hyperthyroidism. One patient had

<table>
<thead>
<tr>
<th>Disease</th>
<th># Patients/Total #</th>
<th>Percent</th>
<th>Time to Occurrence (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>51/89</td>
<td>57%</td>
<td>6.0</td>
</tr>
<tr>
<td>Hyperthyroxemia</td>
<td>2/89</td>
<td>2%</td>
<td>0.9</td>
</tr>
<tr>
<td>Thyroid Nodules</td>
<td>4/89</td>
<td>4%</td>
<td>7.6-14.3</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>4/89</td>
<td>3%</td>
<td>13.9</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>1/89</td>
<td>1%</td>
<td>14.3</td>
</tr>
<tr>
<td>Single colloid nodule</td>
<td>1/89</td>
<td>1%</td>
<td>7.6</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>2/89</td>
<td>2%</td>
<td>12.6</td>
</tr>
</tbody>
</table>

* A total of 89 patients were evaluable for biochemical abnormalities

Figure 1. Actuarial risk of hypothyroidism in 89 children treated for Hodgkin’s disease from diagnosis of Hodgkin’s disease.
received radiation to the mantle region and developed hyperthyroidism eight months after initiating treatment. She subsequently developed uncompensated hypothyroidism after two years, requiring thyroid replacement therapy. The second patient had received chemotherapy only and developed hyperthyroidism 13 months after initiating treatment. She subsequently became euthyroid within one year.

**Discussion**

The outcome in patients with Hodgkin’s disease has improved dramatically in the last three decades, with long-term survival now seen in the majority of patients. Thyroid disease is one of the most common problems requiring evaluation and intervention during follow up. Several studies have documented a high incidence of impaired thyroid function in both children and adults after therapy for Hodgkin’s disease [6, 8, 9, 22, 23]. The proportion of affected patients has varied greatly, depending on several variables including the sensitivity of the procedures, and the length of follow up [6, 24]. We observed that 65% of the irradiated patients developed thyroid hypofunction, compared to 37% [22], 69% [6] and 88% [21] in the three other reports of thyroid dysfunction in children after treatment for Hodgkin’s disease. The median time to development of hypothyroidism was six years after initiating treatment.

Chemotherapy was not shown to be a risk factor for the development of thyroid dysfunction in the present study, and thus confirmed the observations reported by Schimpff et al. [8] in adults, and Devney et al. [21] in children. Patients receiving radiation and chemotherapy were at a slightly reduced risk, compared to patients who received radiation alone. This was probably due to a significantly lower dose of radiation received by patients in the former group (28.6 Gy versus 43.8 Gy; *p* < 0.001).

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**Table 2. Risk factors for hypothyroidism following treatment of Hodgkin’s disease**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Relative Risk</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy alone (<em>n</em> = 12)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy alone (<em>n</em> = 57)</td>
<td>9.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Radiation and Chemotherapy (<em>n</em> = 20)</td>
<td>6.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Radiation dose (risk/Gy)</td>
<td>1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (risk/yr)</td>
<td>1.02</td>
<td>0.8</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females* (<em>n</em> = 47)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Males (<em>n</em> = 42)</td>
<td>0.96</td>
<td>0.8</td>
</tr>
<tr>
<td>Lymphangiogram (<em>n</em> = 73)</td>
<td>1.92</td>
<td>0.1</td>
</tr>
<tr>
<td>Stage at Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II* (<em>n</em> = 59)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>III-IV (<em>n</em> = 30)</td>
<td>0.85</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Reference group
There continues to be considerable controversy regarding the effect of age at the time of irradiation on the subsequent development of hypothyroidism. An increased incidence of hypothyroidism in younger patients was reported by Glatstein et al. [5] and Green et al. [22], whereas Hancock et al. [16] reported an increased probability of hypothyroidism with increasing age in children largely as a function of the increasing dose of radiation to the thyroid gland. In contrast, our data as well as those of other investigators [8, 9] did not show a relationship between age at treatment and eventual evidence of biochemical thyroid dysfunction.

Transient hyperthyroidism was seen in two patients, reverting to euthyroid state in one and progressing to a hypothyroid state in the other. There have been several case reports of hyperthyroidism after treatment for Hodgkin’s disease [14, 15, 25-27], with the mechanism being unclear.

Four patients were found to have palpable thyroid nodules, with papillary carcinoma of the thyroid gland in one patient, developing 15 years after the initiation of therapy for Hodgkin’s disease. The data from Connecticut Tumor Registry showed the RR of thyroid cancer to be 6.7 in patients with Hodgkin’s disease, with the risk increasing 10 years after the diagnosis of Hodgkin’s disease and remaining increased thereafter [28]. In Hancock’s series [16], thyroid cancer developed in 6 of the 1,677 irradiated patients, 9 to 18 years after irradiation, for an overall RR of 15.6. The mean age of this group was 28 (range, 2 to 82 years).

There has been considerable controversy regarding the interaction between lymphangiography and radiation in the development of thyroid dysfunction. Several studies have documented an increased incidence of hypothyroidism among patients undergoing lymphangiograms prior to radiation therapy [6, 9, 23], while others have been unable to show such an association [7]. Seventy-three (82%) of the patients underwent lymphangiograms as part of their staging procedure, prior to starting therapy. We could not demonstrate a significant effect of lymphangiography on the risk of developing hypothyroidism, either on univariate or multivariate analysis.

The dose of radiation appeared to be the chief correlate for the development of hypothyroidism in our study. To decrease the risk of thyroid injury, exclusion of the thyroid from the fields of irradiation has been suggested [29]. However, this does not seem to be a practical option because of the frequent involvement of low cervical lymph nodes in close proximity to the thyroid gland and the occasional involvement of the thyroid gland itself. Suppression of the thyroid gland with thyroxine administration prior to irradiation did not prevent the subsequent development of hypothyroidism [30].

The results of our study confirm the high prevalence of thyroid dysfunction in children after treatment for Hodgkin’s disease. Our data show that radiation remains the major risk factor for development of hypothyroidism, with the risk increasing with the dose of radiation. Continued follow up of patients to detect development of hypothyroidism is important.

ACKNOWLEDGMENTS
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