Hypothyroidism After Radiotherapy for Primary Thyroid Lymphoma

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Abstract. Background: Thyroid lymphoma is rare, with no standard therapeutic protocol. Radiotherapy is often employed. Patients and Methods: Nine patients who had received radiotherapy for thyroid lymphoma in our Institute, from September 2005 to August 2013, were reviewed for hypothyroidism. The median radiation dose was 40 Gy. Thyroid-stimulating hormone (TSH) levels were measured before and after radiotherapy, and hypothyroidism was defined as a TSH level exceeding 10 mIU/l. Peak TSH was defined as the highest TSH level during the follow-up period. Results: The complete response rate was 77.8%, and the 5-year overall survival rate was 74.1%. The median time-to-peak TSH was 162.5 days after the start of radiotherapy. Hypothyroidism was diagnosed in three (37.5%) out of eight patients without thyroidectomy. Conclusion: Hypothyroidism is a frequent complication of radiotherapy for thyroid lymphoma.

Primary thyroid lymphoma is a rare malignancy that accounts for 1-5% of all thyroid malignancies and 1-2% of all extranodal lymphomas (1-3). According to an epidemiological study from Denmark, the annual incidence is estimated to be 2.1 per million people (4). Because of the rarity of this disease, there are no randomized controlled trials comparing surgery, radiotherapy, and chemotherapy. Thus, a standard-of-care has yet to be established. Thyroid lymphoma is highly invasive. Diffuse large B-cell lymphoma (DLBCL) is associated with extraglandular invasion in 85% of cases and vascular invasion in 49%, making radical surgery difficult (5, 6). Moreover, surgery inevitably leads to hypothyroidism, and there are also risks of recurrent laryngeal nerve palsy, esophageal injury, and hypoparathyroidism. Pyke et al. reported no difference in outcomes between patients undergoing radiotherapy after debulking or excision of a tumor and those undergoing radiotherapy after biopsy only (7). In recent years, radiotherapy and chemotherapy have been the favored treatments. Thyroid lymphoma is a disease with a relatively good prognosis that has a 5-year crude survival rate of 66% based on the therapeutic outcomes of 1408 cases in the database of the National Cancer Institute (8). There is concern about the impact, as a late adverse event, of radiotherapy on thyroid function. To our knowledge, this is the first longitudinal study on hypothyroidism as an adverse reaction to radiotherapy for thyroid lymphoma.

Patients and Methods

Patients’ characteristics. The cases of nine patients with thyroid lymphoma who received radiotherapy at our Institute from September 2005 to August 2013 were retrospectively reviewed (Table I). There were four males and five females, with a median age of 73 (range=57-78) years. Diagnosis was confirmed by thyroid biopsy (eight patients) or thyroidectomy (one patient). The pathological subtypes were DLBCL in six patients and mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) in two. One patient was diagnosed as having “malignant lymphoma” only. The Ann Arbor staging system was used for clinical staging: In stage I, the tumor is limited to the thyroid gland; in stage II, the tumor involves the gland and regional lymph nodes above the diaphragm. There were six and three patients, respectively, with disease of stages IE and IIE.

Treatment. The patients with DLBCL, which is a high-grade lymphoma, were given radiotherapy after two to six courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP chemotherapy), or the above agents plus rituximab (R-CHOP chemotherapy). One patient initially received radiotherapy and then...
Another patient, who is shown as patient no. 3 in Table I, received radiotherapy because of a positive surgical margin after total thyroidectomy plus lymph node dissection. One patient with MALT lymphoma, which is a low-grade lymphoma, was treated with radiotherapy after two courses of CHOP chemotherapy, and the other patient with MALT lymphoma was treated with radiotherapy alone. In the patient who was diagnosed as having “malignant lymphoma” only, because the tumor was large and associated with severe dysphagia, radiotherapy was initially administered, followed by two courses of vincristine, cyclophosphamide, prednisolone, and Adriamycin (doxorubicin); R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Hypothyroidism before any treatment. Because the surgical margin was positive after total thyroidectomy plus lymph node dissection, prophylactic irradiation was delivered.

The method of radiotherapy was antero-posterior opposing field irradiation in all patients, with a dose of 1.8-2.0 Gy per fraction, five fractions per week. Radiation was initially delivered to a wide area including the primary lesion, the entire thyroid gland, and lymph nodes in both lateral regions of the neck and the superior mediastinum for prophylactic nodal irradiation, and the radiation field was then limited to the primary lesion. In one patient with DLBCL, the prophylactic nodal irradiation field was set to include only the two lateral regions of the neck, while the superior mediastinum was not irradiated. In another patient with DLBCL who underwent total thyroidectomy, prophylactic nodal irradiation was delivered to a wide area including lymph node areas in both lateral regions of the neck and the superior mediastinum. In one patient with MALT lymphoma, only the primary lesion and the entire thyroid gland were irradiated from the beginning. In one patient with DLBCL, the radiation field was limited to the primary lesion after a radiation dose of 40 Gy had been delivered because of a past history of interstitial pneumonitis. In all patients except this one and the patient who underwent total thyroidectomy, the entire thyroid gland was included in the radiation field from the start until the completion of irradiation. The median radiation dose was 40 Gy (range=36-66 Gy). The radiation doses were 50 Gy in one and 40 Gy in five patients with DLBCL, and the doses in the two patients with MALT lymphoma were 50 Gy in one and 36 Gy in the other. The dose in the patient who was diagnosed as having “malignant lymphoma” only was 66 Gy.

Assessment of thyroid function. Thyroid function was assessed using thyroid-stimulating hormone (TSH) levels in peripheral blood before and after radiotherapy as an index. While the cut-off level for TSH was set at 10 mIU/l (normal value=0.34-3.8 mIU/l), hypothyroidism was defined as a TSH level exceeding 10 mIU/l. Because thyroid hormone replacement therapy is generally recommended when TSH exceeds 10 mIU/l (9), our decision to treat was based on this recommendation. Peak TSH was defined as the highest measured TSH level during the follow-up period after the start of radiotherapy. There were two patients who had already presented with hypothyroidism before radiotherapy or chemotherapy. One of them, a patient with MALT lymphoma, had been diagnosed as having chronic lymphocytic thyroiditis. The patient who underwent total thyroidectomy was excluded from assessment (patient in no.3 in Table I).
Statistical analysis. SPSS ver. 21.0 (IBM, Armonk NY, USA) was used for statistical analysis. A Kaplan–Meier curve was generated for the 5-year overall survival percentages (10). Overall survival (OS) was defined as the time between the start of radiotherapy and death or last follow-up for surviving patients. Disease-free survival (DFS) was defined as the time from the start of radiotherapy to the complete response.

Results

The median follow-up was 317 days (range=126-2850 days). After all treatment was completed, all the patients were assessed for response both clinically and radiologically. As per the RECIST criteria (11), seven patients (77.8%) had a CR. The two remaining patients without CR had DLBCL. One of them died of acute respiratory distress syndrome during treatment, and the other died of DLBCL recurrence in the small intestine. The 5-year overall survival (OS) rate was 74.1% (Figure 1). Acute-phase radiation toxicity occurred in the form of grade 1 dermatitis and mucositis. In patients whose upper mediastinum was irradiated, late-phase radiation toxicity occurred in the form of grade 1 pneumonitis, but none of our cases experienced grade 2 or higher toxicity. The median time-to-peak TSH after radiotherapy commenced was 162.5 (range=58-1279) days and the TSH level was 6.97 (range=2.53-123.9) mIU/l (Figure 2). In three (37.5%) out of eight patients, excluding the one who underwent total thyroidectomy, TSH levels were elevated, exceeding 10 mIU/l, after radiotherapy; hypothyroidism was diagnosed, and administration of levothyroxine sodium hydrate was started. In the patient who received the lowest radiation dose of 36 Gy to the smallest radiation field including only the thyroid gland, the TSH level most rapidly increased, and this patient reported general malaise. This patient was the only one to describe a symptom, i.e. general malaise, associated with hypothyroidism. The radiation field and radiation dose were not apparent risk factors for hypothyroidism after radiotherapy.

Discussion

The most common thyroid lymphoma is B-cell type non-Hodgkin’s lymphoma, and the most common histological subtype is DLBCL, followed by MALT lymphoma (12). Six of our patients had DLBCL, and two had MALT lymphoma. There was one patient who was diagnosed as having “malignant lymphoma” only. Thyroid lymphoma, especially MALT, has been associated with chronic inflammation of the thyroid gland, such as in chronic lymphocytic thyroiditis (Hashimoto thyroiditis). The risk of thyroid lymphoma has been described as being at least 60-times higher in patients with chronic lymphocytic thyroiditis than in those without (13). Among our patients, there were two who already presented with hypothyroidism before treatment, and, as
mentioned above, one of them, with MALT lymphoma, had a history of chronic lymphocytic thyroiditis. As is the case with other types of malignant lymphomas, different treatment procedures are used for thyroid lymphoma depending on histological subtype. While monotherapy, such as radiotherapy, is applied to low-grade lymphomas, chemoradiotherapy is often used for high-grade lymphomas. A combination of radiotherapy and chemotherapy such as CHOP chemotherapy, or chemotherapy alone, for DLBCL and follicular lymphoma reportedly resulted in a CR rate of 62.5%, a 5-year disease-free survival (DFS) rate of 40%, and a 5-year OS rate of 41% (14). The outcomes of treatment procedures including surgery for other types of thyroid lymphomas have been reported to lead to a 5-year DFS rate of 100% and a 5-year OS rate of 100% for MALT lymphoma and 73.6 and 75.6%, respectively, for high-grade lymphomas, a majority of which are DLBCL (15). In Japan, the DFS and OS rates achieved with treatment procedures for thyroid lymphoma including surgery were 100 and 100% for MALT lymphoma and 83.3 and 100% for DLBCL, respectively (16). Limited-stage MALT lymphoma is a low-grade malignancy, in which favorable therapeutic outcomes can be achieved with radiotherapy alone. Previous reports on MALT lymphoma indicate that irradiation at 25-30 Gy achieves nearly 100% CR and 5-year DFS rates. In primary thyroidal and gastric lymphomas especially, the 5-year DFS rate is reported to be better at 93%, than in primary lymphomas involving other sites (17). For our entire patient group, the post-treatment CR rate was 77.8%, and the post-treatment 5-year OS rate was 74.1%. These rates are comparable to those of previous reports. Neither the optimal field nor the optimal dose has been established for administering radiotherapy for thyroid lymphoma. In previous reports, the radiation field included the primary lesion and the entire thyroid gland, as well as bilateral neck nodes and the upper mediastinum for prophylactic nodal irradiation (15, 16). In a previous report comparing radiation fields between involved-field radiotherapy (IFRT), which includes the entire thyroid gland and local neck nodes, and extended-field radiotherapy (EFRT), which includes the entire thyroid gland, neck, and mediastinal nodes, the 5-year OS for stage I disease was significantly better with EFRT than IFRT (18). We initially delivered radiotherapy to a wide area including the primary lesion, the entire thyroid gland, and lymph node areas on both sides of the neck and the superior mediastinum for prophylactic nodal irradiation, and then limited the radiation field to the primary lesion. In one patient with MALT lymphoma, which is often at a limited stage, only the primary lesion and the entire thyroid gland were irradiated from the start. For all but one patient, the entire thyroid gland was included in the radiation field from the start until the completion of irradiation. There are various reports on radiation doses ranging from 24 to 72 Gy, and, reportedly, the prognosis may also be better with a radiation dose of more than 40 Gy (18, 19). In our patients, the median radiation dose was 40 Gy (range=36-66 Gy). In the present study, we examined hypothyroidism associated with radiotherapy for thyroid lymphoma by measuring TSH levels in peripheral blood. Many clinical symptoms of hypothyroidism, such as general malaise, hypodrosis, dry skin, constipation, and weight gain, are non-specific, which makes early detection based on clinical symptoms difficult. Sub-clinical hypothyroidism is recognized as possibly exacerbating hypercholesterolemia (20). Thus, regular assessment of thyroid function is essential for early detection and treatment of subclinical hypothyroidism. Hypothyroidism after radiotherapy to the head and neck region is a well-known late adverse event. Rubin et al. reported previously that if the entire thyroid gland is irradiated with 45 Gy, hypothyroidism will develop in 1-5% of cases five years after irradiation (21). In Japan, Hayabuchi et al. reported that the majority of patients with hypothyroidism caused by radiotherapy to the neck present with abnormal TSH levels within 3 years (22). Vogelius et al. performed a statistical analysis of 44 articles published between 1990 and 2010 that were identified using the key words “radiotherapy” and “hypothyroidism,” and found that the risk of hypothyroidism from a radiation dose of 45 Gy or more to be 50% (23). Although they also reported that chemotherapy was not found to be a risk factor, there is a view that hypothyroidism caused by radiation is an antigen-antibody reaction, which would tend to be suppressed by concurrent chemotherapy (24). In Japan, Yoden et al. analyzed statistically 169 patients who had undergone radiotherapy to the neck with the thyroid gland included in the radiation field, reporting that hypothyroidism was observed in 33 patients (19.5%) (25). Regarding hypothyroidism after radiotherapy for thyroid lymphoma, a previous report showed that hypothyroidism was only diagnosed at 2 years 3 months after radiotherapy with a median dose of 30.6 Gy in one of eight patients with MALT lymphoma and at 4 years 5 months after chemotherapy followed by radiotherapy with a median dose of 42.5 Gy in one of 21 patients with high-grade lymphoma (15). Compared with the results described in these previous reports on hypothyroidism caused by radiotherapy, increased TSH levels were observed earlier at a higher frequency of 37.5% (three out of the eight patients) in our patients. Moreover, in a patient who received the lowest radiation dose of 36 Gy to the smallest field including only the thyroid gland, the TSH level rose most rapidly, and this patient complained of general malaise. In our eight patients, neither the radiation field size nor the radiation dose was an apparent risk factor for hypothyroidism after radiotherapy.
Conclusion

In the present study, we examined radiotherapy performed for thyroid lymphoma at our Institute. The post-treatment CR and 5-year OS rates were comparable to those of previous reports. When thyroid function was assessed by measuring TSH levels in peripheral blood before and after radiotherapy as an index, increased TSH levels were observed earlier at a higher frequency than in previous reports on hypothyroidism associated with radiotherapy. Even when a low radiation dose is administered for thyroid lymphoma, the possibility of hypothyroidism as a common adverse reaction should be kept in mind.

References