

Case Report

Thyroid nodules and long-term follow-up among childhood cancer survivors who underwent hematopoietic stem cell transplantation

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Abstract. Thyroid nodules have been observed in childhood cancer survivors (CCS) treated with chemotherapy and radiotherapy. We report four patients with thyroid nodules identified during the long-term follow-up of children who underwent hematopoietic stem cell transplantation (HSCT). The thyroid nodules were diagnosed as adenomatous goiter in all four patients. The interval between the primary cancer diagnosis and the occurrence of the thyroid nodules was more than 10 yr. Furthermore, all four patients underwent HSCT in conditioning with total body irradiation (TBI) before the age of 10 yr. Two of four patients commenced treatment with levothyroxine due to elevated TSH levels. Only two patients showed elevated thyroglobulin levels ($> 70 \mu\text{g/L}$). In conclusion, we suggest that CCS who have undergone HSCT in conditioning with TBI more than 10 yr previously should be followed up carefully for thyroid nodules using ultrasound.

Key words: childhood cancer survivors (CCS), hematopoietic stem cell transplantation (HSCT), total body irradiation (TBI), adenomatous goiter

Introduction

The 5-yr survival rates in childhood cancer now exceed 80% due to improved treatments. Secondary malignant tumors are one of the late effects among childhood cancer survivors (CCS) treated with chemotherapy and radiotherapy. Hypothyroidism and thyroid nodules have been reported in patients treated

with hematopoietic stem cell transplantation (HSCT) (1, 2). Brignardello *et al.* (3) performed thyroid ultrasound on 129 CCS and detected solid thyroid nodules in 35 of them. Among 19 patients in whom fine-needle aspiration (FNA) was conducted, seven were diagnosed with nodular hyperplasia. In five patients, all malignant tumors detected were confirmed as papillary thyroid carcinoma, based on cytology.

We report on four patients having undergone HSCT previously who were identified with thyroid nodules after a long-term follow-up. Our purpose was to investigate the need for thyroid ultrasound in CCS who have been treated with HSCT more than 10 yr previously.

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Table 1 Characteristics of patients with thyroid nodules

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	M	M	M	M
Age at thyroid nodule diagnosis (yr)	24	15	23	13
Primary cancer	ALL	Neuroblastoma	NHL	ALL
Age at primary cancer diagnosis (yr)	1	2	8	2
Radiation therapy	TBI (12 Gy)	TBI (12 Gy)	Abd (30 Gy) + TBI (12 Gy)	TBI (12 Gy)
Type of transplantation	Autologous + Related sibling	Autologous	Unrelated	Unrelated
Stem cell source	BM + CB	PBSC	CB	CB
Elapsed time between primary cancer and thyroid nodule (yr)	18	13	13	11
Serum Thyroglobulin (ng/ml)	105	117	0.3	31.0
Thyroid diagnosis	AG	AG	AG	AG
Palpable (yes/no)	No	No	No	Yes
Number of nodule	1	1	1	2
Volume of thyroid gland (ml) Right lobe + Left lobe	2.9 + 3.0	3.8 + 2.7	4.1 + 4.2	3.2 + 7.8
Maximum size of nodule (mm)	17	11	10	20

Abd, abdominal; AG, adenomatous goiter; ALL, acute lymphoblastic leukemia; BM, bone marrow; CB, cord blood; NHL, Non-Hodgkin lymphoma; PBSC, peripheral blood stem cell; TBI, total body irradiation.

Case Report

We examined the laboratory data on the blood test results of CCS two to three times yearly and performed thyroid ultrasound when thyroid nodules were palpable or when thyroid dysfunction was suspected, based on the laboratory data and physical findings, or when CCS were likely to undergo transition to adult health care. We assessed their thyroid volume based on ultrasound (4).

Patient 1

Patient 1 was a 26-yr-old male who had been diagnosed with acute lymphoblastic leukemia (ALL) when he was 2 yr old (Table 1). He had been treated in line with the Tokyo children's cancer study group (TCCSG) L92-13 protocol. However, at 4 yr of age, he experienced a relapse, for which he received autologous bone marrow

transplantation in conditioning with busulfan 4 mg/kg, etoposide 950 mg, and melphalan 126 mg. He also received umbilical cord blood transplantation (CBT) in conditioning with cytalabine 8000 mg, melphalan 180 mg/m², and total body irradiation (TBI) 12 Gy (six fractions of 2 Gy each) due to recurrence at 5 yr. Following the transplantation, the patient developed chronic graft versus host disease. At age 15, testosterone replacement therapy was administered due to primary hypogonadism resulting from high gonadotropin and low testosterone levels. At age 24, laboratory findings revealed normal thyroid function (TSH 2.04 μ IU/ml, free T₃ 2.64 pg/ml, free T₄ 0.80 ng/dl, and thyroglobulin [Tg] 105 ng/ml [\leq 33.7 ng/ml]). Thyroid ultrasound was then performed prior to possible transitioning of the patient to adult health care. We found a multilocular nodule in the left lobe and cysts in both lobes of the thyroid on ultrasound. We

suspected that the nodules were adenomatous goiter and therefore referred him to another hospital. Based on the histological diagnosis, adenomatous goiter was confirmed using FNA.

Patient 2

Patient 2 was a 16-yr-old male who had been diagnosed with neuroblastoma as a 1-yr-old. He was initially treated with cisplatin, vincristine, ifosfamide, and pirarubicin. At 2 yr of age, he underwent peripheral blood stem cell transplantation (PBSCT) in conditioning with cyclophosphamide and thiopeta. Two months afterwards, he underwent PBSCT again, this time in conditioning with TBI and melphalan. After the transplantation, he was started on 13 cis-retinoic acid. At age 9, following his relocation to our city, he was referred to our hospital. We performed a thyroid ultrasound at age 15 because of a slightly elevated TSH level; however, the free T_4 level remained within the normal range (TSH 5.617 μ IU/ml, free T_3 3.70 pg/ml, free T_4 0.96 ng/dl, Tg 117 ng/ml) with no clinical symptoms. We found small cysts scattered throughout the thyroid gland, with a multilocular nodule measuring 11 mm in diameter in the right lobe of the thyroid. As such, treatment commenced with levothyroxine. He was referred to the Department of Endocrine Surgery at the University Hospital where FNA was performed. The cytological investigation confirmed the diagnosis of adenomatous goiter.

Patient 3

Patient 3 was a 26-yr-old male who had been diagnosed with non-Hodgkin's lymphoma (NHL) at 8 yr of age. He started treatment under the TCCSG NHL96-04 and NHLB96-04 protocols with abdominal radiation at a dose of 30 Gy (20 fractions of 1.5 Gy each). When he was 9 yr old, he received CBT in conditioning with etoposide 60 mg/kg, melphalan 90 mg/m², and TBI 12 Gy (six fractions of 2 Gy each). At age 16, the TSH level was slightly elevated although the free T_4 level remained within the

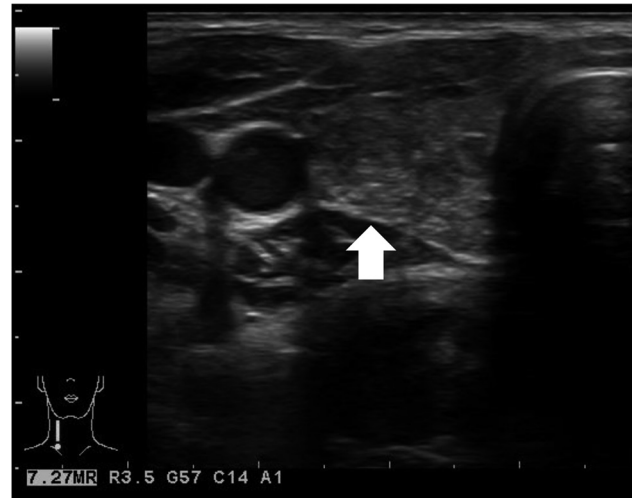


Fig. 1. Ultrasound thyroid image of Patient 3. A multilocular nodule can be seen in the right lobe.

normal range. He commenced treatment at age 17 with levothyroxine because the TSH level was elevated (TSH 17.2 μ IU/ml, free T_3 2.3 pg/ml, free T_4 0.9 ng/dl, and Tg 0.3 ng/ml) with no clinical symptoms. Both Tg and TPO autoantibodies were positive based on the laboratory findings. We performed thyroid ultrasound when he was 23 yr old and found cysts in both lobes and a 10 mm multilocular nodule in the right lobe of the thyroid (Fig. 1). He was subsequently referred to the Department of Endocrinology in another hospital and diagnosed with adenomatous goiter using ultrasound.

Patient 4

Patient 4 was a 13-yr-old male, diagnosed with ALL at the age of 2. He had been treated under the TCCSG L06-04 protocol and the infant ALL protocol. At 3 yr of age, he underwent CBT in conditioning with cyclophosphamide 120 mg/kg, etoposide 60 mg/kg, and TBI 12 Gy (six fractions of 2 Gy each). We performed a thyroid ultrasound because of a palpable thyroid nodule detected when he was 13 yr old, which showed multilocular nodules in both lobes of the thyroid. His thyroid function test was normal (TSH 1.641 μ IU/ml, free

T₃ 3.19 pg/ml, free T₄ 0.96 ng/dl, Tg 31.0 ng/ml). He was then referred to the Department of Breast and Thyroid Surgery in another hospital where, based on cytological diagnosis, adenomatous goiter was confirmed using FNA.

Discussion

All four of our patients were treated with radiation therapy, but received only 12 Gy to the thyroid (Table 1). Sklar *et al.* (5) reported that patients who received higher doses of radiation (> 25 Gy) to the thyroid were more likely to develop thyroid nodules. However, more recently, it has been reported that the risk of thyroid cancer increased with increasing radiation doses but declined at high doses (> 30 Gy or > 40 Gy) because of its cell-killing effect (6, 7).

Some studies have reported that the risk of thyroid nodules was higher in CCS diagnosed with primary cancer before the age of 10 than in those older than 10 yr (5, 6). It is believed that when thyroid cells become slightly damaged with radiation therapy, they tend to grow more actively among younger children compared to older children. A higher risk of thyroid nodules has also been reported among those treated with HSCT before the age of 10 in another study (8) and our four patients had all undergone HSCT before the age of 10.

Previous studies have reported that thyroid nodules were found in CCS who had undergone HSCT in conditioning with TBI (9–11), and all our patients were conditioned with TBI (Table 1). Sanders *et al.* (2) also reported that 18 out of 791 patients who had undergone HSCT before they turned 18 had thyroid nodules. Among those 18 patients, all had received TBI, and 13 had been diagnosed with papillary carcinoma, while the remaining 5 patients were classified as having benign thyroid nodules. The median time from HSCT to the diagnosis of thyroid nodules in these 18 patients was 9.9 yr (range, 4.5–22.3 yr). This was similar to the interval between the primary cancer diagnosis and the occurrence of thyroid

nodules in our patients, where the interval was more than 10 yr.

Adenomatous goiter are benign thyroid nodules; however, they need to be carefully monitored. The cytological diagnosis for thyroid nodules using FNA has been shown to have a false-negative rate of between 1% and 11% in the general population (12), while Acharya *et al.* (13) reported a false-negative rate of 33% in patients after radiation therapy.

In two of our four patients, the TSH levels were elevated, and both patients commenced treatment with levothyroxine. Sanders *et al.* (2) reported that the risk of thyroid dysfunction was higher in CCS treated with HSCT before the age of 10. The prevalence of hypothyroidism in those treated with HSCT has been reported to be between 23.2% and 34% (14, 15).

Tg is one of the globulins produced in the follicular cells of the thyroid gland. Tg becomes elevated due to its production in benign thyroid nodules and in thyroid cancers, and following the destruction of the thyroid. The levels of Tg in CCS who received thyroid irradiation were higher than in those not receiving irradiation. Moreover, the risk of thyroid tumor was higher in CCS whose Tg levels were above 70 µg/L (16). Serum Tg as a marker of thyroid tumor had limitations, with only two of our patients showing elevated Tg levels (> 70 µg/L). The TSH level was elevated in Patient 3; however, his Tg level was not elevated. As reported, the Tg autoantibody interferes with the measurements of Tg in the immunoassay method (17). The thyroid nodule was palpable in only one of our four patients. However, Brignardello *et al.* (3) reported that thyroid cancer had been identified on ultrasound despite not being palpable clinically.

In conclusion, CCS who underwent HSCT in conditioning with TBI are at a high risk of developing thyroid nodules and dysfunction. We suggest that screening for thyroid nodules, using ultrasound for long-term follow-up of CCS who had undergone HSCT in conditioning with TBI over 10 yr previously, is beneficial.

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