Autoimmune thyroid disease following hematopoietic stem cell transplantation in childhood cancer survivors

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Highlights

● Childhood cancer survivors (CCSs) who received hematopoietic stem cell transplantation (HSCT) rarely developed autoimmune thyroid disease (AITD).
● Thyroid function of CCSs treated with anti-thymocyte globulin (ATG) may reveal AITD.
● Thyroid function of CCSs experiencing the onset of chronic graft versus host disease (GVHD) may reveal AITD.

Abstract. Thyroid dysfunction has been observed in childhood cancer survivors (CCSs) who have undergone hematopoietic stem cell transplantation (HSCT). We retrospectively analyzed the thyroid function of 54 CCSs who underwent HSCT and were referred to our endocrinology department at Chiba Children’s Hospital between January 1, 2008, and December 31, 2019. Three patients developed autoimmune thyroid disease (AITD) after HSCT. Two of these patients had Graves’ disease (GD), and the third had autoimmune thyroiditis. The association between HSCT and AITD remains unclear. All three patients had chronic graft versus host disease (GVHD). AITD was reported to be induced by the transmission of abnormal T or B lymphocyte clones from the donor to the recipient. One patient with GD was treated with a high dose of anti-thymocyte globulin (ATG). Some studies have reported that ATG is associated with a risk of severe T cell depletion and GD onset. In conclusion, CCSs who received HSCT rarely developed AITD. We suggest that CCSs treated with ATG and/or experiencing an onset of chronic GVHD should be carefully monitored for thyroid function because it might reveal AITD.

Key words: autoimmune thyroid disease, autoimmune thyroiditis, childhood cancer survivors, Graves’ disease, hematopoietic stem cell transplantation
Introduction

Hematopoietic stem cell transplantation (HSCT) is an important treatment option for various diseases (1). Thyroid dysfunction is one of the late effects that occur in childhood cancer survivors (CCSs) who undergo HSCT (2), and autoimmune thyroid disease (AITD) has rarely been reported in these patients (3). The mechanism by which HSCT triggers AITD development remains unclear. This study aimed to examine the association between AITD and CCSs who underwent HSCT.

Patients and Methods

Patients

We retrospectively reviewed the medical records of 54 CCSs who had undergone HSCT and were referred to the endocrinology department of Chiba Children’s Hospital between January 1, 2008, and December 31, 2019, to evaluate the association between AITD and HSCT.

Thyroid function

Thyroid function was evaluated in accordance with a previous report (4). We defined primary hypothyroidism as a TSH level of ≥ 10 μIU/mL and a free T4 level of < 0.75 ng/dL, and central hypothyroidism as a free T4 level of < 0.75 ng/dL with non-elevated TSH levels. We defined subclinical hypothyroidism as a TSH level of ≥ 5 μIU/mL and a normal free T4 level, and hyperthyroidism as a TSH level of ≤ 0.10 μIU/mL with elevated free T3 and/or free T4 level. We defined AITD as a symptomatic thyroid dysfunction with elevated levels of the anti-TSH receptor (TR), anti-thyroid peroxidase (TPO), or anti-thyroglobulin (Tg) antibodies. We evaluated the thyroid volume using ultrasound (5).

Statistical analysis

Relationships between clinical factors of CCSs and AITD were evaluated using Fisher’s test. The Mann-Whitney U test was used to assess intergroup differences. Statistical significance was set at \( p < 0.05 \). All statistical analyses were performed using EZR (version 1.27; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (R Foundation for Statistical Computing, Vienna, Austria) which includes frequently used biostatistical functions (6).

The retrospective study protocol was approved by the ethics committee of Chiba Children’s Hospital (2019-042) and complied with the principles of the Declaration of Helsinki.

Results

Characteristics of patients

We examined 54 CCSs (26 men and 28 women) who underwent HSCT. Their median age at the diagnosis of primary cancer was 3.3 yr (range: 0–15.6 yr), and at HSCT was 5.0 yr (range: 0.3–19.0 yr).

The diagnoses included hematological diseases (43 patients), solid tumors (8 patients), and brain tumors (3 patients). The hematological diseases included acute lymphoblastic leukemia (18 patients), acute myelocytic leukemia (12 patients), non-Hodgkin lymphoma (NHL) (5 patients), aplastic anemia (AA) (3 patients), Wiskott-Aldrich syndrome (1 patient), chronic myelocytic leukemia (1 patient), juvenile myelomonocytic leukemia (1 patient), transient abnormal myelopoiesis (1 patient), and hemophagocytic syndrome (1 patient). The solid tumors included neuroblastoma (3 patients), rhabdomyosarcoma (3 patients), and hepatoblastoma (2 patients). The brain tumors included medulloblastoma (1 patient), primitive neuroectodermal tumors (1 patient), and myeloid sarcoma (1 patient).

Thyroid function

Eleven patients had thyroid dysfunction. Of these, 9 had hypothyroidism, including 5 with primary hypothyroidism and 4 with subclinical hypothyroidism. Four patients were diagnosed with AITD based on our criteria, but we excluded one patient who had been diagnosed with autoimmune thyroiditis before HSCT. Thus, we reviewed 53 patients and divided them into two groups: AITD (3 patients) and non-AITD (50 patients).

The association between HSCT and AITD

We evaluated the association between CCSs who underwent HSCT and AITD (Table 1), but there were no significant differences in sex, age at primary cancer diagnosis, and HSCT. Moreover, we evaluated the components of the conditioning regimen but did not find any significant differences. The dose of anti-thymocyte globulin (ATG), differed according to the primary cancer. Patient 1, who exhibited Grave’s disease (GD), was treated with a high dose (10 mg/kg) of ATG for AA (Table 2). Three patients in the non-AITD group were treated with ATG. One patient was treated with a high dose (20 mg/kg) of ATG for AA, and two patients were treated with low doses (2.5 mg/kg) for NHL. There was no significant difference in the rates of acute and chronic graft versus host disease (GVHD).

CCSs with HSCT developing AITD

Three patients developed AITD after HSCT (Table 2). The elapsed time between the diagnosis of the primary cancer and the development of AITD was 9 years (range: 3–12 yr). All three patients tested positive for anti-Tg...
antibodies. Both patients with GD showed signs of irritable behavior and palpitations and were treated with methimazole. The symptoms improved after treatment, and thyroid tests were normal. Another patient with autoimmune thyroiditis revealed no clinical symptoms and was treated with levothyroxine. His thyroid test results were normal after initiation of levothyroxine treatment. Two patients had no endocrine abnormalities except for thyroid dysfunction, but patient 2 was treated with estrogen and progesterone replacement therapy for primary hypogonadism.

Table 1. Characteristics of childhood cancer survivors (CCSs)

|                        | AITD (n = 3) | Non-AITD (n = 50) | Odds ratio | 95% CI     | p-value |
|------------------------|--------------|-------------------|------------|------------|---------|
| **Sex**                |              |                   | 1.825      | 0.089–113.305 | 1       |
| Male                   | 1            | 24                |            |            |         |
| Female                 | 2            | 26                |            |            |         |
| **Age at primary cancer diagnosis (yr)** | (4.6–15.6) | (0.0–15.6) | 0.693 | | |
| **Age at HSCT (yr)**   | 5            | 4.7               | 0.884      |           |         |
| **Primary cancer**     |              |                   |            |            |         |
| Hematological disease  | 3            | 40                |            |            |         |
| Brain tumor            | 0            | 2                 |            |            |         |
| Solid cancer           | 0            | 8                 |            |            |         |
| **Conditioning regimen** |        |                   |            |            |         |
| TBI                    | 2            | 34                | 0.637      | 0.030–40.332 | 1       |
| Chemotherapy           |              |                   |            |            |         |
| Cyclophosphamide       | 2            | 30                | 1.065      | 0.051–66.787 | 1       |
| Busulfan               | 0            | 17                |            |            |         |
| Melphalan              | 1            | 22                | 0.551      | 0.008–11.301 | 1       |
| Etoposide              | 1            | 25                | 0.427      | 0.006–8.749 | 0.594   |
| Anti-thymocyte globulin| 1            | 3                 | 6.627      | 0.091–167.771 | 0.230   |
| Acute GVHD             | 1            | 26                | 0.430      | 0.006–8.783 | 0.595   |
| Chronic GVHD           | 3            | 33                | 0.546      |           |         |

AITD, autoimmune thyroid disease; CI, confidence interval; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

Table 2. Characteristics of childhood cancer survivors (CCSs) with autoimmune thyroid disease (AITD)

| Patient 1 | Patient 2 | Patient 3 |
|-----------|-----------|-----------|
| **Sex**   | F         | F         | M         |
| **Age at primary cancer diagnosis (yr)** | 4 | 4 | 8 |
| **Primary cancer** | Aplastic anemia | Acute lymphoblastic leukemia | Non-Hodgkin lymphoma |
| **Age at AITD diagnosis (yr)** | 7 | 16 | 17 |
| **TSH (µIU/mL) / free T₃ (pg/mL) / free T₄ (µg/dL) at AITD diagnosis** | <0.01 / 14.6 / 2.19 | <0.01 / 7.09 / 1.85 | 17.2 / 2.3 / 0.9 |
| **Anti-TR (>2 IU/mL) / anti-TPO (>16 IU/mL) / anti-Tg antibodies (>28 IU/mL)** | 9.4 / 7 / 586 | 3.6 / 180 / 83 | <1.0 / >50 / >100 |
| **Volume of thyroid gland (mL)** | 1.9 + 3.2 | 4.6 + 3.4 | 4.1 + 4.2 |
| **AITD** | Graves’ disease | Graves’ disease | Autoimmune thyroiditis |
| **Age at HSCT (yr)** | 4 | 5 | 9 |
| **Stem cell source** | Bone marrow | Bone marrow | Cord blood |
| **HLA of recipient** | A24/26 B7/61 DR9/14 | A2/11 B48/67 DR4 | A11/31 B61/62 DR4/8 |
| **HLA of donor** | A24/26 B7/61 DR9/14 | A210/11 B61/87 DR4/16 | A11/31 B54/61 DR4/8 |
| **Conditioning regimen for HSCT** | Cy 200 mg/kg + ATG 10 mg/kg | TBI 12 Gy + Cy 120 mg/kg | TBI 12 Gy + VP-16 60 mg/kg + L-PAM 90 mg/m² |
| **Acute GVHD** | No | Grade 1 | Grade 1 |
| **Chronic GVHD** | Mild | Moderate | Mild |
| **Treatment of chronic GVHD** | Prednisolone + Tacrolimus | Prednisolone | Prednisolone + Cyclosporine |
| **Treatment of AITD** | Methimazole | Methimazole | Levothyroxine |

ATG, anti-thymocyte globulin; Cy, cyclophosphamide; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; Tg, thyroglobulin; TPO, thyroid peroxidase; TR, TSH receptor.
Discussion

We previously confirmed that HSCT and chronic GVHD are risk factors for primary hypothyroidism and subclinical hypothyroidism (7). Previous studies have reported that HSCT is associated with a risk of thyroid dysfunction, and the prevalence of primary hypothyroidism among CCSs who have undergone HSCT is 23.1–45.1% (8, 9). However, the mechanisms underlyingAITD development after HSCT are unclear becauseAITD is rare in CCSs (3).

In this study, there was no significant difference, but three of our patients withAITD had chronic GVHD. Chronic GVHD may be a risk factor forAITD. However, some studies have reported a small number of patients who developed AITD (10–12). According to a previous hypothesis, AITD develops as a result of the transmission of abnormal T or B lymphocyte clones from the donor to the recipient. A previous study reported that autoimmune hyperthyroidism is associated with chronic GVHD (13).

Au et al. (3) reported that some human leukocyte antigen (HLA) types were associated withAITD in CCSs who underwent HSCT; however, the association was not clear in our study. Hawkins et al. (14) reported a strong association between DR9 and GD, whereas Vita et al. (15) reported that DR4 was associated with GD. In patient 1, both the donor and recipient had DR9. In patient 2, both the donor and recipient had DR4 and not DR9. We did not evaluate HLA types in non-AITD patients. Further studies are needed to evaluate the association between HLA type andAITD.

A few pediatric cases of GD development followingAA have been reported (16, 17). The process that leads to GD is unclear, but a hypothesis has been proposed. According to this hypothesis, ATG treatment leads to severe depletion of T cells and development of GD (16, 18). Among the 54 CCSs, four were treated with ATG. A patient diagnosed with AA was treated with a high dose (10 mg/kg/day) of ATG. Among the three patients with non-AITD, one patient diagnosed with AA had been treated with a high dose (20 mg/kg/d) of ATG. Two patients had been treated with a low dose (2.5 mg/kg/d) of ATG. We hypothesized that GD was caused by a high dose of ATG but did not find a significant association in this study.

ATG was administered for the depletion of chronic GVHD in HSCT outside of treatment for AA (19). A previous study reported that the depletion of T cells by ATG was thought to play a role in the development of many autoimmune diseases (20). A recent study reported that a low dose of ATG plays a useful role in the depletion of T cells (21). Further studies are needed to determine the optimal ATG dose.

There were some limitations to our study. First, our study was performed at a single hospital, and we evaluated only a small sample of patients with AITD. Second, the thyroid function of CCSs was not routinely assessed before HSCT. Third, we reviewed CCSs who had been referred to our department by oncologists at our hospital. We could not examine all CCSs who had undergone HSCT at our hospital.

Conclusion

In conclusion, CCSs who underwent HSCT rarely developed AITD. We suggest that the thyroid function of CCSs who have been treated with ATG and/or developed chronic GVHD must be carefully monitored because it might reveal AITD.

Conflicts of interests: None of the authors reports financial relationships relevant to this article.

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