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Original Article

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

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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 T_4 level of < 0.75 ng/dL, and central hypothyroidism as a free T_4 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 T_4 level, and hyperthyroidism as a TSH level of ≤ 0.10 μIU/mL with elevated free T_3 and/or free T_4 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

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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) median (range)	4.6 (4.6–8.9)	3 (0–15.6)			0.693
Age at HSCT (yr) median (range)	5 (4.8–9.7)	4.7 (0.3–19)			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 T_3 (pg/mL) / free T_4 (ng/dL) at AITD diagnosis	< 0.01/ 14.63/ 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) Right lobe + Left lobe	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 B61/67 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/m^2
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.

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.

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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 underlying AITD development after HSCT are unclear because AITD is rare in CCSs (3).

In this study, there was no significant difference, but three of our patients with AITD had chronic GVHD. Chronic GVHD may be a risk factor for AITD. 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 with AITD 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 and AITD.

A few pediatric cases of GD development following AA 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.

References

1. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, *et al*. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 2010;363: 2091–101. [Medline] [CrossRef]
2. Matsumoto M, Ishiguro H, Tomita Y, Inoue H, Yasuda Y, Shimizu T, *et al*. Changes in thyroid function after bone marrow transplant in young patients. Pediatr Int 2004;46: 291–5. [Medline] [CrossRef]
3. Au WY, Lie AKW, Kung AWC, Liang R, Hawkins BR, Kwong YL. Autoimmune thyroid dysfunction after hematopoietic stem cell transplantation. Bone Marrow Transplant 2005;35: 383–8. [Medline] [CrossRef]
4. Iwaku K, Noh JY, Minagawa A, Kosuga Y, Suzuki M, Sekiya K, *et al*. Determination of pediatric reference levels of FT3, FT4 and TSH measured with ECLusys kits. Endocr J 2013;60: 799–804. [Medline] [CrossRef]
5. Suzuki S, Midorikawa S, Fukushima T, Shimura H, Ohira T, Ohtsuru A, *et al*. Thyroid Examination Unit of the Radiation Medical Science Center for the Fukushima Health Management Survey. Systematic determination of thyroid volume by ultrasound examination from infancy to adolescence in Japan: the Fukushima Health Management Survey. Endocr J 2015;62: 261–8. [Medline] [CrossRef]
6. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48: 452–8. [Medline] [CrossRef]
7. Shimazaki S, Kazukawa I, Mori K, Kihara M, Minagawa M. Factors predicting endocrine late effects in childhood cancer survivors from a Japanese hospital. Endocr J 2020;67: 131–40. [Medline] [CrossRef]
8. Baker KS, Ness KK, Weisdorf D, Francisco L, Sun CL, Forman S, *et al*. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. Leukemia 2010;24:

doi: 10.1297/cpe.31.2021-0059

2039–47. [Medline] [CrossRef]
9. Leung W, Ahn H, Rose SR, Phipps S, Smith T, Gan K, *et al*. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. Medicine (Baltimore) 2007;86: 215–24. [Medline] [CrossRef]
10. Law A, Rifkind J, Rosen F, Lipton JH. Hyperthyroidism six years post-BMT for acute myeloblastic leukemia in a patient on long-term lithium therapy for bipolar affective disorder. Leuk Lymphoma 2004;45: 807–9. [Medline] [CrossRef]
11. Lee WY, Oh ES, Min CK, Kim DW, Lee JW, Kang MI, *et al*. Changes in autoimmune thyroid disease following allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28: 63–6. [Medline] [CrossRef]
12. Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. Front Biosci 2001;6: G17–22. [Medline] [CrossRef]
13. Mulligan SP, Joshua DE, Joasoo A, Kronenberg H. Autoimmune hyperthyroidism associated with chronic graft-versus-host disease. Transplantation 1987;44: 463–4. [Medline] [CrossRef]
14. Hawkins BR, Ma JT, Lam KS, Wang CC, Yeung RT. Association of HLA antigens with thyrotoxic Graves' disease and periodic paralysis in Hong Kong Chinese. Clin Endocrinol (Oxf) 1985;23: 245–52. [Medline] [CrossRef]
15. Vita R, Lapa D, Trimarchi F, Vita G, Fallahi P, Antonelli A, *et al*. Certain HLA alleles are associated with stress-triggered Graves' disease and influence its course. Endocrine 2017;55: 93–100. [Medline] [CrossRef]
16. Paketçi A, Demir K, Tüfekçi Ö, Acar S, Abacı A, Yılmaz Ş, *et al*. Graves' disease following allogenic hematopoietic stem cell transplantation for severe aplastic anemia: case report and literature review. J Pediatr Endocrinol Metab 2018;31: 589–93. [Medline] [CrossRef]
17. Kumar M, Goldman J. Severe aplastic anaemia and Grave's disease in a paediatric patient. Br J Haematol 2002;118: 327–9. [Medline] [CrossRef]
18. Todd A, Todd J. Graves' disease following successful treatment of severe aplastic anaemia with antilymphocyte globulin. Clin Lab Haematol 1999;21: 69–70. [Medline] [CrossRef]
19. Kröger N, Solano C, Wolschke C, Bandini G, Patriarca F, Pini M, *et al*. Antilymphocyte globulin for prevention of chronic graft-versus-host disease. N Engl J Med 2016;374: 43–53. [Medline] [CrossRef]
20. Teramura M, Kobayashi S, Iwabe K, Yoshinaga K, Mizoguchi H. Mechanism of action of antithymocyte globulin in the treatment of aplastic anaemia: in vitro evidence for the presence of immunosuppressive mechanism. Br J Haematol 1997;96: 80–4. [Medline] [CrossRef]
21. Shiratori S, Kosugi-Kanaya M, Hayase E, Okada K, Goto H, Sugita J, *et al*. T-cell depletion effects of low-dose antithymocyte globulin for GVHD prophylaxis in HLA-matched allogeneic peripheral blood stem cell transplantation. Transpl Immunol 2018;46: 21–2. [Medline] [CrossRef]