Cytomegalovirus reactivation triggers the late onset of hyperthyroidism after autologous peripheral blood transplantation

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ABSTRACT

Thyroid dysfunction is an important issue in patients receiving autologous and allogenic hematopoietic stem cell transplantation (HSCT). However, the exact mechanisms underlying thyrotoxicosis secondary to HSCT remain unclear. The present case exhibited a reversed imbalance in helper/suppressor T-cell populations and B-cell dysregulation for a long time after transplantation, and the reactivation of cytomegalovirus may have been associated with the development of clinical hyperthyroidism. The long-term monitoring of thyroid function, T-cell populations, and cytomegalovirus after HSCT is important.

1. Case report

A 53-year-old female was diagnosed with mantle cell lymphoma (Stage IIIB). Autoimmune antibodies, including thyroid receptor-stimulating, thyroid-stimulating hormone (TSH) receptor-blocking, TSH receptor-stimulating, thyroid peroxidase, and antinuclear antibodies, were not detected prior to therapy (Table 1). The patient received rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (R-HCVAD/MA) chemotherapy. After 3 courses of chemotherapy, she was mobilized with G-CSF at 10 μg/kg and harvested when her WBC count was 10.0 × 10⁹/L. She was conditioned with ranimustine, etoposide, cytarabine, and melphanal, followed by the infusion of CD34 on day 11, and the last platelet transfusion was on day 12. The complete remission of lymphoma was confirmed in fluoro-deoxy-glucose positron emission tomography/computed tomography scans. On day 120, thrombocytopenia had progressed and she presented with goiter. She did not have ocular symptoms, compressive symptoms, or other symptoms of hyperthyroidism. As shown in Table 1, thyroid function tests revealed normal FT3 (3.27 pg/mL), FT4 (1.08 ng/dL), and thyroglobulin (36 ng/mL) levels and a suppressed TSH level (<0.01 μU/mL). Elevations in the anti-thyroid peroxidase antibody (28.2 IU/mL), anti-thyroglobulin (70 ng/mL), and IgM levels were all reduced. Cytomegalovirus (CMV) serology showed positivity for the IgG antibody at 6.1 (negative, <2.0; borderline, 2.0–3.9; and positive, ≥4.0 index) and negativity for the IgM antibody (<0.8, negative, <0.8; borderline, 0.8–1.2; and positive, ≥1.2 index) using an enzyme immunoassay (EIA) (SRL, Tokyo, Japan). Thyroid function, the CD4/CD8 ratio, serum immunoglobulin levels, and CMV serology were followed up every 3 months, and her clinical course was uneventful until 3 years. At that time, the patient presented with fatigue and laboratory data showed the progression of thrombocytopenia (Table 1). Thyroid function tests revealed elevated FT3 (11.18 pg/mL), FT4 (4.65 ng/dL), and thyroglobulin (70 ng/mL) levels and a suppressed TSH level (<0.01 μU/mL). Ultrasonography showed an enlarged thyroid gland. The CD4/CD8 + T cell ratio was inverted to 0.47. Serum immunoglobulin, IgG, IgA, and IgM levels were all reduced. CMV serology showed positivity for the IgG antibody at 6.1 and a high level of the IgM antibody (3.21). Real-time PCR assays for the detection of CMV-deoxyribonucleic acid (DNA) in serum (SRL, Tokyo, Japan) (positive, ≥2.0 × 10⁴ copies/mL) showed 5.4 × 10⁴ copies/mL. CMV reactivation as a consequence of this immunocompromised state may have contributed to the development of clinical hyperthyroidism. She was administered 20 mg of methimazole per day and ganciclovir. After one month, the patient’s condition improved and CMV-DNA was no longer detectable. She has remained stable with the administration of methimazole (10 mg/day).

Thyroid dysfunction is an important issue in patients receiving autologous peripheral blood transplantation (HSCT). The immunophenotyping of peripheral blood mononuclear cells showed a reversed CD4:CD8 ratio. Serum immunoglobulin, IgG, IgA, and IgM levels were all reduced. Cytomegalovirus (CMV) serology showed positivity for the IgG antibody at 6.1 (negative, <2.0; borderline, 2.0–3.9; and positive, ≥4.0 index) and negativity for the IgM antibody (<0.8, negative, <0.8; borderline, 0.8–1.2; and positive, ≥1.2 index) using an enzyme immunoassay (EIA) (SRL, Tokyo, Japan). Thyroid function, the CD4/CD8 ratio, serum immunoglobulin levels, and CMV serology were followed up every 3 months, and her clinical course was uneventful until 3 years. At that time, the patient presented with fatigue and laboratory data showed the progression of thrombocytopenia. Thyroid function tests revealed elevated FT3 and FT4 levels and a suppressed TSH level. Ultrasonography showed an enlarged thyroid gland. The CD4/CD8 + T cell ratio was inverted to 0.47. Serum immunoglobulin, IgG, IgA, and IgM levels were all reduced. CMV serology showed positivity for the IgG antibody at 6.1 and a high level of the IgM antibody. Real-time PCR assays for the detection of CMV-deoxyribonucleic acid (DNA) in serum showed positive results. Thyroid function, the CD4/CD8 ratio, serum immunoglobulin levels, and CMV serology were followed up every 3 months, and her clinical course was uneventful until 3 years. At that time, the patient presented with fatigue and laboratory data showed the progression of thrombocytopenia. Thyroid function tests revealed elevated FT3 and FT4 levels and a suppressed TSH level. Ultrasonography showed an enlarged thyroid gland. The CD4/CD8 + T cell ratio was inverted to 0.47. Serum immunoglobulin, IgG, IgA, and IgM levels were all reduced. CMV serology showed positivity for the IgG antibody at 6.1 and a high level of the IgM antibody. Real-time PCR assays for the detection of CMV-deoxyribonucleic acid (DNA) in serum showed positive results.
autologous (auto) and allogenic (allo) HSCT, and several types of thyroid disorders have been reported, including hypothyroidism, euthyroid sick syndrome, and hyperthyroidism [1]. Most cases of thyroid disorders are euthyroid syndrome and hypothyroidism. A previous study reported that the prevalence of subclinical hyperthyroidism within 3 months of auto-HSCT was 16% and all cases of subclinical hyperthyroidism had disappeared within 6 months [2]. However, clinical hyperthyroidism is a rare complication after transplantation, with few cases reported being published in the literature [2–4].

Post-transplant thyroid ultrasonography showed a non-homogenous hypoechoic pattern in 30% of patients with subclinical hyperthyroidism that was sometimes associated with a mild increase in auto-antibodies, suggesting chronic autoimmune thyroiditis. In HSCT patients, discrepancies between functional and ultrasound results and the appearance or absence of thyroid auto-antibodies may be related to the immunological conditions of patients or immunological effects of immunosuppressive therapies. Transient hyperthyroidism was generally non-symptomatic, particularly in auto-HSCT patients, and did not require any treatment. Feng et al. reported two hyperthyroid cases that developed more than 2 years after auto-HSCT [3]. In their cases, a pre-transplant assessment showed normal thyroid function; however, details on thyroid function after HSCT to the onset of hyperthyroidism were not shown. Transplanted patients with transient hyperthyroidism and those with no evidence of thyroiditis need to be monitored every 3 to 4 months after transplantation until their endocrine parameters normalize.

The exact mechanisms underlying thyrotoxicosis secondary to HSCT remain unclear. In the present case, familial Graves’ disease and drug-induced hyperthyroidism were excluded. Several mechanisms, such as the toxic effects of irradiation or intense chemotherapy and donor-derived autoimmunity, have been proposed for the generation of autoimmune antibodies after HSCT [1]. Au et al. demonstrated that post-HSCT thyrotoxicosis was strongly associated with the HLA B46 and DR9 antigens [5], and DR9 may have been one of the causes of the onset of hyperthyroidism in our patient.

Tauchmanova et al. showed that an imbalance in the lymphocyte CD4/CD8 ratio was associated with increased circulating levels of the Th1 cytokines interferon-γ and tumor necrosis factor-α after transplantation, and suggested that these changes contributed to immune system deregulation and the development of early post-HSCT euthyroid sick syndrome [6]. Although autoimmune diseases have been reported in patients after HSCT, the mechanisms responsible for this relationship have not yet been elucidated. Chemoradiotherapy and bone marrow/peripheral blood reinfusion may lead to a dysfunction in the immune system, and this may be related to impaired suppressor T-cell function in the post-transplant period. Suppressor T cells are important regulators of immune responses to self-antigens, and defective suppressor T-cell function may allow the emergence of auto-reactive lymphocytes with consequent auto-antibody production. Immune deregulation may also be caused by compromised thymic function as a result of irradiation and chemotherapy. It has been shown in experimental models that various organ-specific autoimmune diseases may develop by depleting T-cell subsets, including CD4 and CD8 cells [7]. Impaired B-cell regulation as a result of quantitative or qualitative T-cell abnormalities may also lead to auto-antibody formation. Winiarski et al. reported four cases of Evans syndrome among 28 children undergoing bone marrow transplantation who received immunotherapy [8]. The high incidence of Evans syndrome in their study may have been related to vigorous T-cell suppression, leading to B-cell deregulation and autoimmune diseases. Michinton et al. suggested that viral infections that occur during the post-transplant period play a role by damaging or combining with self-antigens and forming “altered self” antigens [9]. A previous study reported that CMV infection may cause autoimmune phenomena after transplantation [10]. However, CMV alone per se is not sufficient, and other contributory factors towards autoimmune phenomena are required. The present case of hyperthyroidism with auto-antibodies showed evidence of a T-cell imbalance, such as a reversed CD4:CD8 ratio in peripheral blood for a long time after HSCT, and an immune system imbalance may have contributed to thyroid dysfunction. Moreover, the reactivation of CMV may have been associated with the development of clinical hyperthyroidism.

In conclusion, the long-term monitoring of thyroid function, T-cell populations, and CMV after HSCT is important. Further studies are needed to confirm immune system imbalances, CMV, and thyroid function in HSCT patients.

Conflicts of interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.11.002.

References

[1] M. Kami, Y. Tanaka, S. Chiba, et al., Thyroid function after bone marrow

Table 1

|                | Before | Day 120 | Day 360 | Day 720 | Day 900 | Day 1102 | Day 1140 | Day 1300 |
|----------------|--------|---------|---------|---------|---------|----------|----------|----------|
| WBC (×10^9/L) | 4.1    | 1.6     | 2.7     | 2.1     | 1.9     | 1.9      | 2.7      | 3.2      |
| RBC (×10^12/L)| 459    | 324     | 330     | 340     | 358     | 339      | 348      | 386      |
| Hb (g/dL)     | 12.5   | 10.8    | 11.5    | 11.8    | 12.4    | 11.4     | 11.8     | 12.8     |
| Plt (×10^9/L) | 30.4   | 3.9     | 6.2     | 7.5     | 7.9     | 4.9      | 6.4      | 12.6     |
| Free T3 (pg/mL) (normal range: 2.39–3.86 pg/mL) | 3.12 | 1.82    | 3.12    | 3.36    | 3.45    | 11.18    | 5.69     | 3.77     |
| Free T4 (ng/mL) (normal range: 0.87–1.72 ng/dL) | 1.68 | 1.08    | 1.22    | 1.57    | 1.7     | 4.65     | 2.76     | 1.69     |
| TSH (μU/mL) (normal range: 0.43–4.82 μU/mL) | 3.02 | 0.13    | 0.04    | 0.04    | 0.01    | <0.01    | <0.01    | 0.36     |
| Thyroglobulin (ng/mL) (normal range: 2.0–37.7 ng/mL) | 23   | 36      | 40      | 44      | 50      | 70       | 52       | 38       |
| Anti-thyroid peroxidase antibody (IU/mL) (normal range: < 9.4 IU/mL) | –    | 28.2    | 30      | 31      | 53      | 60.9     | 54       | 32.3     |
| anti-TSH receptor antibody (IU/mL) (normal range: < 2.0 IU/mL) | –    | 4.2     | 4.4     | 5.1     | 7.3     | 13.3     | 11.7     | 3.2      |
| Serum immunoglobulin (Ig) |             |          |          |          |          |          |          |          |
| IgG (mg/dL) (normal range: 870–1700 mg/dL) | 1120 | 450     | 553     | 662     | 540     | 558      | 621      | 920      |
| IgA (mg/dL) (normal range: 110–410 mg/dL) | 340  | 70      | 60      | 70      | 71      | 63       | 66       | 90       |
| IgM (mg/dL) (normal range: 35–220 mg/dL) | 60   | 28      | 30      | 31      | 56      | 33       | 35       | 41       |
| CD4/CD8 ratio | ND     | 0.26    | 0.32    | 0.47    | 0.44    | 0.47     | 0.51     | 0.83     |
| CMV-IgG antibody (index) | 4.7   | 4.5     | 5       | 5.3     | 5.4     | 6.1      | 8.8      | 10.2     |
| CMV-IgM antibody (index) | negative | negative | negative | negative | negative | 3.21 | 3.24 | 2 |
| CMV-DNA (copies/mL) | ND   | ND      | ND      | ND      | ND      | 5.4×10^3 | <2×10^3 | <2×10^3 |

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Plt, platelets; ND, not done; TSH, thyroid-stimulating hormone.
transplantation: possible association between immune-mediated thyrotoxicosis and hypothyroidism, Transplantation 71 (3) (2001) 406–411.

[2] L. Tauchmanová, C. Selleri, G. De Rosa, et al., Endocrine disorders during the first year after autologous stem-cell transplant, Am. J. Med. 118 (6) (2005) 664–670.

[3] Y.H. Feng, B.A. Su, C.Y. Lin, et al., Hyperthyroidism as a latent complication of autologous hematopoietic stem cell transplantation, Int. J. Hematol. 88 (2) (2008) 237–239.

[4] F. Ishikawa, H. Shigematsu, H. Gondo, et al., Autoreactive antibodies following autologous peripheral blood stem cell transplantation, Bone Marrow Transplant. 22 (7) (1998) 729–731.

[5] W.Y. Au, A.K. Lie, A.W. Kung, et al., Thyrotoxic periodic paralysis after allogeneic hematopoietic stem cell transplantation, Br. J. Haematol. 129 (1) (2005) 160–161.

[6] L. Tauchmanova, A. Colao, C. Selleri, et al., Thyroid dysfunction after autologous hematopoietic stem cell transplant, Am. J. Med. 119 (6) (2006) e5–e6.

[7] K. Atkinson, J.A. Hansen, R. Storb, et al., T-cell subpopulations identified by monoclonal antibodies after human marrow transplantation. I. Helper-inducer and cytotoxic-suppressor subsets, Blood 59 (1982) 1292–1298.

[8] J. Winiarski, O. Ringdén, M. Remberger, et al., Bone marrow transplantation in children using unrelated donors at Huddinge Hospital, Acta Paediatr. 85 (3) (1996) 327–335.

[9] R.M. Minchinton, A.H. Waters, J.S. Malpas, et al., Selective thrombocytopenia and neutropenia occurring after bone marrow transplantation-evidence of an auto-immune basis, Clin. Lab. Haematol. 6 (1984) 157–163.

[10] T. Kamisako, K. Taubaki, Y. Adachi, Autoimmune hepatitis after cytomegalovirus infection in a bone marrow-transplanted patient, Am. J. Gastroenterol. 92 (7) (1997) 1238–1239.