Circulating IL-8 and IL-10 in Euthyroid Sick Syndromes following Bone Marrow Transplantation

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INTRODUCTION

The euthyroid sick syndromes (ESS) refer to changes in thyroid hormone metabolism and regulation in the patients with nonthyroidal illness (1). The observed abnormalities are usually reversible and have been attributed to disturbances in peripheral metabolism, tissue uptake, binding, and receptor occupancy of thyroid hormones. The hypothalamic-pituitary-thyroid axis could be suppressed in more severe and prolonged nonthyroidal illness (2-9). Despite the description of the syndrome some 38 yr ago, its pathogenesis remains elusive. Recently, particular attention was paid to the role of cytokines in the pathogenesis of ESS. It is currently agreed that ESS is related with an increased production of cytokines, however, there has been scarce data on the relationship between cytokines and thyroid hormones in the patients undergoing bone marrow transplantation (BMT). Because interleukin-8 (IL-8) has been identified as a potent proinflammatory and interleukin-10 (IL-10) as an antiinflammatory cytokine, we studied the relation between thyroid hormone parameters and these cytokines following BMT. We studied 80 patients undergoing allogeneic BMT. Serum T3 decreased to nadir at post-BMT 3 weeks. Serum T4 was the lowest at the post-BMT 3 months. Serum TSH sharply decreased to nadir at 1 week and gradually recovered. Serum free T4 significantly increased during 3 weeks and then returned to basal level. Mean levels of serum IL-8 significantly increased at 1 week after BMT. Mean levels of serum IL-10 significantly increased until 4 weeks after BMT. No significant correlation was found between serum thyroid hormone parameters and cytokines (IL-8, IL-10) after adjusting steroid doses during the entire study period. In conclusion, ESS developed frequently following allogeneic BMT and cytokine levels were increased in post-BMT patients. However, no significant correlation was found between serum thyroid hormone parameters and these cytokines.

Key Words: Euthyroid Sick Syndromes; Bone Marrow Transplantation; Interleukin-8; Interleukin-10

It is generally agreed that euthyroid sick syndromes (ESS) are associated with an increased production of cytokines. However, there have been scarce data on the relationship between cytokines and thyroid hormones in the patients undergoing bone marrow transplantation (BMT). Because interleukin-8 (IL-8) has been identified as a potent proinflammatory and interleukin-10 (IL-10) as an antiinflammatory cytokine, we studied the relation between thyroid hormone parameters and these cytokines following BMT. We studied 80 patients undergoing allogeneic BMT. Serum T3 decreased to nadir at post-BMT 3 weeks. Serum T4 was the lowest at the post-BMT 3 months. Serum TSH sharply decreased to nadir at 1 week and gradually recovered. Serum free T4 significantly increased during 3 weeks and then returned to basal level. Mean levels of serum IL-8 significantly increased at 1 week after BMT. Mean levels of serum IL-10 significantly increased until 4 weeks after BMT. No significant correlation was found between serum thyroid hormone parameters and cytokines (IL-8, IL-10) after adjusting steroid doses during the entire study period. In conclusion, ESS developed frequently following allogeneic BMT and cytokine levels were increased in post-BMT patients. However, no significant correlation was found between serum thyroid hormone parameters and these cytokines.
MATERIALS AND METHODS

Patients

We prospectively enrolled 80 patients (30 females, 50 males) undergoing allogeneic BMT for hematologic diseases from October 1998 to August 1999 in St. Mary's Hospital in Korea. Exclusion criteria were previous thyroid disease and the use of thyroid hormones or thyrostatic medication before BMT. Patients who died before 1 month after BMT were also excluded. Underlying diseases among the 80 patients were 27 chronic myelogenous leukemia, 23 acute myelogenous leukemia, 13 acute lymphoblastic leukemia, 8 severe aplastic anemia, 7 myelodysplastic syndrome, 1 multiple myeloma, and 1 paroxysmal nocturnal hemoglobinuria. The mean age of the patients was 32.7 ± 7.8 yr (mean ± SD, range 19-54) at the time of BMT.

Fifty three patients received TBI (10-13.2 Gy) as a conditioning regimen. Intravenous cyclosporin A, 5 mg/kg/day one day before BMT and 3 mg/kg/day until the 20th day after BMT, was administered to all patients in order to prevent graft versus host disease (GVHD). Thereafter, oral cyclosporin A at 6 mg/kg/day was begun and continued for 6-12 months. Established GVHD was treated with a combination of intravenous methylprednisolone or oral prednisolone and cyclosporin A. Doses were tapered when clinical control of GVHD was achieved. Most patients received steroid as a premedication, when platelet transfusions were performed for the prevention of bleeding owing to thrombocytopenia. Some patients received high dose steroid therapy and oral prednisolone, so this particular group of patients was classified as a high dose steroid group (40 patients). The causes for the administration of high dose steroid among the particular patients were GVHD and BOOP (Bronchiolitis Obliterans Organizing Pneumonia), and *Pneumocystis carinii* pneumonia. The mean dose of prednisolone which was administered during post-BMT 1 month was 35.4 ± 4.8 mg/day and 11.2 ± 2.4 mg/day among the high dose steroid group (n=40) and the non-high dose steroid group (n=40), respectively. The high-dose steroid group was arbitrarily defined as the patients with prednisolone dose above the mean of 15 mg/day during post-BMT 1 month.

Blood was sampled from all patients to determine serum levels of T3, T4, FT4, and TSH before BMT, at 1, 2, 3, 4 weeks and 3 months after BMT. The serial changes of thyroid hormone levels were evaluated at each time point before, and serially after BMT. Thyroid hormone parameters among the patients with TBI or the high dose steroid group were compared to those in the patients without TBI or high dose steroid therapy. We also analyzed the incidence of ESS. Low T3 syndrome was defined as serum T3 level is below normal range at any time point and low T4, T3 syndrome was defined in which both serum T3 and T4 are below normal range at any time point until post-BMT 3 months.

The protocol was approved by the Institutional Review Board of St. Mary's Hospital and informed consents were obtained from all participants.

Methods

All assays were performed in serum samples. Serum T3 (RIA-mat T3, Byk-Sangtec Diagnostica, Germany, normal values: 1.1-2.9 nmol/L) and serum T4 (RIA-mat T4, Byk-Sangtec Diagnostica, Germany, normal values: 64-154 nmol/L) were determined in duplication by radioimmunoassay. The intra- and inter-assay coefficients of variation (CV) for the range of concentrations evaluated were 3.0% and 5.0% for T3; and 2.8% and 5.1% for T4, respectively. Serum TSH (IRMA-mat TSH, Byk-Sangtec Diagnostica, Germany, normal values: 0.3-3.0 mU/L) was determined by immunoradiometric assay. The intra-assay and inter-assay CV of TSH were 2.5% and 5.7%, respectively. Serum FT4 (RIA-mat FT4, Byk-Sangtec Diagnostica, Germany, normal values : 9-24 pmol/L) were determined in duplication by radioimmunoassay. Intra-assay and Inter-assay CV of FT4 were 2.4% and 7.8%.

ELISA was used to measure serum IL-8 and IL-10 (ELISA kit, Hyundae Pharm. Institute, Incheon, Korea). The detection limits for IL-8 and IL-10 were 10 and 10.4 pg/mL, respectively. The maximum inter- and intra-assay CV for the range of concentrations evaluated were 7.4% and 7.6% for IL-8 and 9.8% and 5.6% for IL-10. Blood samples were taken between 7 a.m. and 9 a.m. following an overnight fast. After centrifugation (1,500 x g) for 10 min, aliquots of serum were stored at -20°C until analysis.

Statistical analysis

All values are given as the mean±SEM. The data were analyzed by ANOVA for repeated measures, followed by post-hoc analysis for pairwise comparisons. Spearman rank test was used to examine the bivariate correlations between two variables. Significance was accepted at p<0.05.

RESULTS

The serial changes of thyroid hormones levels after BMT

The mean levels of serum T3, T4 and TSH before BMT were 1.57 ± 0.07 nmol/L, 79.4 ± 3.3 nmol/L, 0.81 ± 0.07 mU/L, respectively. For all patients analyzed, mean levels of serum TSH sharply decreased to nadir at 1 week (p<0.01 against basal value), and gradually recovered until 6 months, at which TSH level is not significantly different from basal values. Mean levels of serum T3 decreased significantly at 1 week, and
declined more until the nadir of 3 weeks \((p<0.01\) against basal value). It began to increase after 4 weeks, and gradually reached pre-BMT basal values until 6 months. Mean levels of serum T4 increased within normal range during initial 2 weeks following BMT, but thereafter decreased significantly at 3 months compared to basal values \((p<0.05\) against basal value). Then it recovered to basal values at 6 months. Serum FT4 significantly increased within normal range during 3 weeks following BMT \((p<0.01)\) and then returned to basal level until 3 months (Fig. 1). Low T3 syndrome was found among 47 out of the 80 patients \((58.8\%)\), and low T3, T4 syndrome was found in other 26 patients \((32.5\%)\).

The serial changes of serum cytokines (IL-8, IL-10) after BMT

Mean levels of serum IL-8 significantly increased at 1 weeks after BMT \((p<0.05\) vs baseline), and declined thereafter. Mean levels of serum IL-10 significantly increased at 2, 3 and 4 weeks after BMT \((p<0.01\) vs baseline) and declined thereafter (Fig. 2).

The correlations between serum thyroid hormone levels and serum cytokines (IL-8, IL-10) after BMT

Spearman rank test revealed no significant correlation between serum thyroid hormone parameters (T3, T4, FT4, TSH) and cytokines (IL-8, IL-10) before BMT, and at 1, 2, 3, 4 weeks and 3 months after BMT, respectively, except for 3 cases. There were significant inverse relationships between IL-8 and T3 at 2 weeks \((r=-0.48, p<0.05)\), IL-8 and FT4 at 3 months \((r=-0.83, p<0.05)\), and IL-10 and T3 at 1 week \((r=-0.45, p<0.05)\), respectively (Table 1). However, these relations became insignificant after adjusting steroid doses.

The differences in thyroid hormone parameters between the patients with and without TBI or high dose steroid therapy

There were no significant differences in serum T3, T4 and TSH levels between the patients with and without TBI except for serum T4 levels at post-BMT 3 weeks. Serum TSH levels in the patients with TBI tended to be lower than those without our TBI during the entire observation period, but without statistical significance (Fig. 3A). Patients from both groups did not display any differences in serum FT4 level during the entire period.

Table 1. Correlation coefficients between cytokine concentrations (IL-8, IL-10) and thyroid hormone parameters following BMT (Spearman rank test)

|          | Pre-BMT | 1 W | 2 W | 3 W | 4 W | 3 M |
|----------|---------|-----|-----|-----|-----|-----|
| IL-8     |         |     |     |     |     |     |
| (pg/mL)  |         |     |     |     |     |     |
| serum T3 | 0.33    | -0.28 | -0.48* | 0.01 | -0.02 | 0.26 |
| (nmol/L) |         |     |     |     |     |     |
| serum T4 | 0.27    | 0.11  | 0.08  | 0.08  | -0.41 | 0.49 |
| (nmol/L) |         |     |     |     |     |     |
| serum TSH| -0.04   | -0.24 | -0.08 | -0.07 | -0.54 | -0.26 |
| (mU/L)   |         |     |     |     |     |     |
| serum FT4| 0.03    | 0.15  | -0.07 | 0.27  | -0.10 | -0.83* |
| (pmol/L) |         |     |     |     |     |     |
| IL-10    |         |     |     |     |     |     |
| (pg/mL)  |         |     |     |     |     |     |
| serum T3 | -0.16   | -0.45* | -0.30 | -0.30 | -0.29 | -0.10 |
| (nmol/L) |         |     |     |     |     |     |
| serum T4 | -0.23   | -0.10 | -0.28 | -0.18 | -0.57 | -0.10 |
| (nmol/L) |         |     |     |     |     |     |
| serum TSH| 0.28    | -0.16 | 0.1   | 0.10  | -0.02 | -0.67 |
| (mU/L)   |         |     |     |     |     |     |
| serum FT4| -0.21   | -0.10 | -0.24 | -0.39 | -0.31 | 0.21  |
| (pmol/L) |         |     |     |     |     |     |

*p < 0.05
Patients with high dose steroid represented lower levels of T3 at 3 week (p<0.05), and TSH at 2 and 3 week (p<0.05) than those with low dose steroid with statistical significance. Serum T3, T4 and TSH levels in the patients with high dose steroid tended to be lower than those with low dose steroid during the entire period, but without significance (Fig. 3B). Patients from both groups did not display any differences in serum FT4 level during the entire period.

The differences in IL-8 and IL-10 levels between the patients with and without TBI or high dose steroid therapy

There were no significant differences in serum IL-8 and IL-10 levels between the patients with and without TBI during the entire period (Fig. 4A).

There were no significant differences in serum IL-8 and IL-10 levels between the patients with high dose steroid therapy and without it, except for serum IL-10 levels at 2 and 3 weeks (Fig. 4B).

**DISCUSSION**

In this study, we found the rapid change of thyroid function and IL-8, IL-10 following allogeneic BMT, and also observed that thyroid hormone levels were not related with IL-8 and IL-10. In a study of 27 patients undergoing BMT, serum TSH and T3 levels decreased significantly at the first months after BMT compared to basal values, but serum T4 levels declined in less degree and more slowly than serum T3 levels (18). Our data are in agreement with those reported previously (18, 19). In general, serum TSH level in ESS is usually normal, but
often decreased or increased in ESS. In this study, serum TSH decreased significantly during the early period of BMT, and recovered gradually and spontaneously until 3 months. Initial decrease of TSH might be related to the prednisolone therapy and TBI-related hypothalamic dysfunction. It is noteworthy that acute changes of T3 and T4 concentrations in these BMT recipients gradually recovered to the pre-BMT levels at 6 months. This reversibility in thyroid function indicates that acute changes in thyroid hormone levels in the early period of the post-BMT represent only the reactive change in response to BMT, confirming the presence of ESS.

The incidence of ESS after BMT is reported to be 43% at the post-BMT 3 months (20), but there has been no study showing the serial changes of thyroid hormone parameters during the earlier period of the post-BMT, during which more development of ESS is expected to occur. In our study, total 91.3% patients had ESS during the post-BMT 6 months. Low T3 syndrome was found in 58.8% patients and low T4, T3 syndrome in other 32.5% patients during 6 months after BMT. It suggests that ESS develops frequently in the early period of post-BMT, especially during the first month after BMT.

IL-8 is well known pro-inflammatory cytokine, which is involved in local and systemic inflammatory reactions including GVHD or severe hepatic veno-occlusive disease (VOD) (21, 22). In addition, IL-8 is abundantly produced by normal hepatocytes. And endothelial injury occurring in the liver during VOD may elevate systemic IL-8 concentrations (21). Within the cytokine network, the activation of pro-inflammatory mediators is followed by the increased production of endogenous inhibitory molecules, including the antagonistic cytokines. The serum IL-10 concentration is correlated with the production of inflammatory cytokines, such as IL-1, IL-6 and TNF-α (13, 14). Indeed, systemic TNF-α release during pre-transplant conditioning, which was previously reported to be an indicator of poor outcome, was inhibited among the patients with high IL-10 production (15, 16, 23). IL-10 is a Th2 cytokine that inhibits cytokine production by Th1 cell. High spontaneous IL-10 production in transplant recipients is associated with fewer transplant related complications. However, Hempel et al. reported that high IL-10 serum levels among the patients after BMT were significantly associated with a fatal outcome (24). There have been several studies regarding the changes of thyroid function or cytokines following BMT. Increased circulating cytokine levels are associated with several complications of BMT, such as GVHD or infectious episodes (25-27). However, there was no study regarding the relation between thyroid hormone changes and cytokines among the patients undergoing BMT, to our knowledge. Because IL-8 has been identified as a potent pro-inflammatory and IL-10 as an anti-inflammatory cytokine, we studied the relation between serum concentration of thyroid hormone parameters and these cytokines, and as a result, we observed no significant correlation between serum thyroid hormone parameters (T3, T4, TSH) and cytokines (IL-8, IL-10) before BMT and during the 3 months following BMT. Boelen et al. studied the level of IL-8 and IL-10 among the patients with ESS and found no evidence that they had a pathologic role (17), which was consistent with our result. It has been shown that human thyrocytes can synthesize cytokines which activate T and B lymphocytes. These immune cells play important roles during the initiation and continuation of thyroid autoimmune. It was reported that cytokines (IL-6, sIL-6R, IL-8) could play an important role in the development of Graves’ disease, and that their levels are modulated by thyrostatic treatment (28). In this study, it is interesting that serum IL-10 levels are significantly higher at 2 and 3 weeks in the high dose steroid group than the low dose group on the view point that immune function and the production of inflammatory cytokines are generally reduced by steroid treatment (29). IL-10 is known to be higher in the patients with the post-BMT complications (e.g. GVHD) (24, 30), thus larger amounts of steroid might be administrated to these complicated cases. We think that it could explain why IL-10 levels were higher in the patients with high dose steroid therapy.

Our study implies that ESS develops frequently following allogeneic BMT and these changes gradually recover until post-BMT 3 months. Increased levels of cytokines, including IL-8 and IL-10, were found among the post-BMT patients, and no significant correlation was found between serum thyroid hormone parameters.

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REFERENCES

1. Larry J, Anthony PW. Disorders of the thyroid gland. In: Braunwald, Fauci, Kasper, Longo, Jameson, eds. Principles of Internal medicine. 15th ed. New York: McGraw-Hill. 2001: 2060-83.
2. Watofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the “euthyroid sick syndrome.” Endocr Rev 1982; 3: 164-217.
3. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf) 1993: 39: 499-518.
4. Vagenakis AG. Alterations of thyroid function in non-thyroidal illness:
the euthyroid sick syndrome. In: Grossman A, ed. Clinical endocrinology, 2nd eds. London: Blackwell 1997: 383-91.
5. Chopra JI. Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab 1997; 82: 329-34.
6. DeGroot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999; 84: 151-64.
7. Van den Bergh G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 1998; 143: 1-13.
8. Brauner R. Hypothalamo-hypophysal function after treatment of cancers. Ann Endocrinol (Paris) 1995; 56: 127-31.
9. Bartalena L, Brogioni S, Grasso L, Martino E. Thyroid function. Eur J Endocrinol 2000; 153: 214-25.
10. Oh KW, Kang MI, Lee WY, Son HS, Yoon KH, Cha BY, Lee KW, Son HY, Kang SK, Shin WS, Min WS, Kim CC, Ahn BY, Sohn HS. The nonthyroidal illness syndrome: prognostic value and circulating cytokines after allogeneic bone marrow transplantation. J Korean Soc Endocrinol 2000; 132: 386-93.
11. Van Damme J. Interleukin-8 and related molecules In: Thomson AW (Ed), The cytokine handbook. Academic Press, New York 1991: 201.
12. Wensisch C, Parchalk B, Looareesuwan S, Graninger W. Elevated levels of IL-10 and IFN-γ in patients with acute Plasmodium falciparum malaria. Clin Immunol Immunopathol 1995; 74: 1157.
13. Moore KW, O’Garra A, de Waal Malefyt R, Vieira P, Mosmann TR. Interleukin-10. Annu Rev Immunol 1993; 11: 165-90.
14. de Waal Malefyt R, Yssel H, de Vries JE. Direct effects of IL-10 on subsets of human CD4 T cell clones and resting T cells. Specific inhibition of IL-2 production and proliferation. J Immunol 1993; 150: 4754-65.
15. Holler E, Roncarolo MG, Hintermeier-Knabe R, Eissner G, Ertl B, Schulte U, Knabe H, Kolb HJ, Andreesen R, Wilmanns W. Prognostic significance of increased IL-10 production in patients prior to allogeneic bone marrow transplantation. Bone Marrow Transplant 2000; 25: 237-41.
16. Baker KS, Roncarolo MG, Peters C, Bigler M, DeFor T, Blazar BR. High spontaneous IL-10 production in unrelated bone marrow transplant recipients is associated with fewer transplant-related complications and early deaths. Bone Marrow Transplant 1999; 23: 1123-9.
17. Boelen A, Schiphorst MC, Wiersinga WM. Relationship between serum 3, 5′-triiodothyronine and serum interleukin-8, interleukin-10 or interferon-γ in patients with nonthyroidal illness. J Endocrinol Invest 1996; 19: 480-3.
18. Hershman JM, Enkisen E, Kaufman N, Champlin RE. Thyroid function tests in patients undergoing bone marrow transplantation. Bone Marrow Transplant 1990; 6: 49-51.
19. Wehmann RE, Gregerman RI, Burns WH, Saral R, Santos GW. Suppression of thyrotropin in the low-thyroxine state of severe nonthyroidal illness. N Engl J Med 1985; 312: 546-52.
20. Vexiau P, Perez-Castiglioni P, Socie G, Devergje A, Toubert ME, Aractingi S, Gluckman E. The ‘euthyroid sick syndrome’: incidence, risk factors and prognostic value soon after allogeneic bone marrow transplantation. Br J Haematol 1993; 85: 778-82.
21. Remberger M, Ringden O. Serum levels of cytokines after bone marrow transplantation: increased IL-8 levels during severe veno-occlusive disease of the liver. Eur J Haematol 1997; 59: 254-62.
22. Uguccioni M, Meliconi R, Nesci S, Lucarelli G, Ceska M, Gasharrini G, Facchin A. Elevated interleukin-8 serum concentrations in β-thalassemia and graft-versus-host disease. Blood 1993; 81: 2252-6.
23. Takatsuka H, Takemoto Y, Okamoto T, Fujimoto Y, Tamura S, Wada H, Okada M, Yamada S, Kanamaru A, Kakishita E. Predicting the severity of graft-versus-host disease from interleukin-10 levels after bone marrow transplantation. Bone Marrow Transplant 1999; 24: 1005-7.
24. Hempel L, Korholz D, Nussbaurn P, Bonig H, Burdach S, Zintl F. High interleukin-10 serum levels are associated with fatal outcome in patients after bone marrow transplantation. Bone Marrow Transplant 1997; 20: 365-8.
25. Rowbottom AW, Riches PG, Downie C, Hobbs JR. Monitoring cytokine production in peripheral blood during acute graft-versus-host disease following allogeneic bone marrow transplantation. Bone Marrow Transplant 1993; 12: 635-41.
26. Imamura M, Hashino S, Kobayashi S, Tanaka J, Imai K, Kasai M, Sakurada K, Miyazaki T. Hyperacuic graft-versus-host disease accompanied by increased serum interleukin-6 levels. Int J Hematol 1994; 60: 85-9.
27. Remberger M, Ringden O, Markling L. TNF alpha levels are increased during bone marrow transplantation conditioning in patients who develop acute GVHD. Bone Marrow Transplant 1995; 15: 99-104.
28. Bossovski A, Urban M. Serum levels of cytokines in children and adolescents with Graves’ disease and non-toxic nodular goiter. J Pediatr Endocrinol Metab 2001; 14: 741-7.
29. El Azab SR, Rosseel PM, de Lange JJ, Groeneveld AB, van Strik R, van Wijk EM, Scheffer GJ. Dexamethasone decreases the pro-to anti-inflammatory cytokine ratio during cardiac surgery. Br J Anaesth 2002; 88: 496-501.
30. Min CK, Lee WY, Min DJ, Lee DG, Kim YJ, Park YH, Kim HJ, Lee S, Kim DW, Lee JW, Min WS, Kim CC. The kinetics of circulating cytokines including IL-6, TNF-alpha, IL-8 and IL-10 following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2001; 28: 935-40.