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

It is generally agreed that euthyroid sick syndromes (ESS) are associated with an increased production of cytokines. However, there has been scarce data on the relationship thyroid hormone changes and cytokines among 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 T_3 decreased to nadir at post-BMT 3 weeks. Serum T_4 was the lowest at the post-BMT 3 months. Serum TSH sharply decreased to nadir at 1 week and gradually recovered. Serum free T_4 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*

Won Young Lee, Jung Yul Suh, Sun Woo Kim, Eun Sook Oh*, Ki Won Oh* Ki Hyun Baek†, Moo Il Kang†, Kwang Woo Lee†, Choon Choo Kim†

Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; Mizmedi Hospital*, Seoul; Department of Internal Medicine, The Catholic University of Korea†, Seoul, Korea

(Won Young Lee and Jung Yul Suh contributed equally to the work)

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Address for correspondence
Won-Young Lee, M.D.
Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108 Pyung-dong, Jongro-gu, Seoul 110-746, Korea
Tel : +82-2-2001-2075, Fax : +82-2-2001-2049
E-mail : Drlwy@samsung.co.kr

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, but the degree of cytokine involvement and their specific role in the pathogenesis of ESS remain to be elucidated.

Bone marrow transplantation (BMT) is currently the treatment of choice for many hematologic diseases. Thyroid dysfunction is one of the most common endocrine abnormalities occurring after BMT. Among the patients undergoing BMT, the development of ESS indicates a poor prognosis. There have been several studies regarding the change of thyroid function following BMT. However, there were few studies about the relation of thyroid hormone changes and cytokines in the patients undergoing BMT. We previously reported negative relationship between serum thyroid hormone levels and interleukin-6 (IL-6), or tumor necrosis factor-α (TNF-α) (10). Because cytokines were operative in an extensive network, we wondered if other cytokines are involved. Interleukin-8 (IL-8) has been identified as a potent proinflammatory and interleukin 10 (IL-10) as an anti-inflammatory cytokine (11, 12). IL-10 is reported to block the production of proinflmamatory cytokines in response to lipopolysaccharide or other stimuli (13, 14). High IL-10 production in transplant recipients is believed to have a major role in maintaining immunobalance (15, 16). However, there have been scarce data on the role of IL-8 and IL-10 in the pathogenesis of ESS (17).

Thus, we intended to identify whether IL-8 and IL-10 could contribute to the development of ESS after BMT. We also observed the effect of total body irradiation (TBI) and high dose steroid therapy through the changes of thyroid function and cytokine profiles after allogeneic BMT.

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 T_3, T_4, FT_4, and TSH before BMT, at 1, 2, 3, 4 weeks and 3, 6 months after BMT, respectively. From 24 out of the 80 patients, serum cytokines (IL-8, IL-10) were measured before BMT, at 1, 2, 3, 4 weeks and 3 months after BMT. The correlation of serum thyroid hormone levels and cytokines was 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 T_3 syndrome was defined as serum T_3 level is below normal range at any time point and low T_3, T_4 syndrome was defined in which both serum T_3 and T_3 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 T_3 (RIA-mat T_3, Byk-Sangtec Diagnostica, Germany, normal values: 1.1-2.9 nmol/L) and serum T_4 (RIA-mat T_4, 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 T_3 and 2.8% and 5.1% for T_4, 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 FT_4 (RIA-mat FT_4, Byk-Sangtec Diagnostica, Germany, normal values : 9-24 pmol/L) were determined in duplication by radioimmunoassay. Intra-assay and Inter-assay CV of FT_4 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×*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 T_3, T_4 and TSH before BMT were 1.37±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 T_3 decreased significantly at 1 week, and

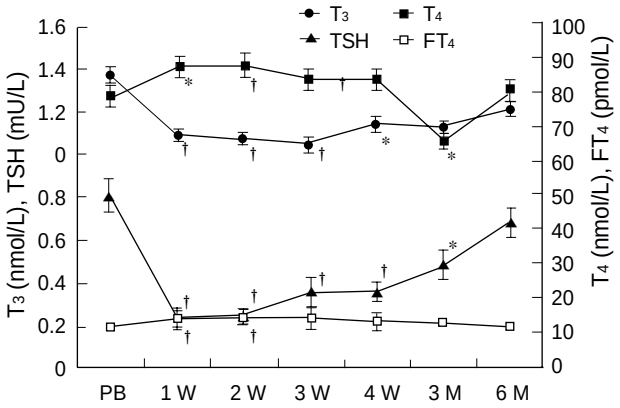

Fig. 1. The serial changes of thyroid hormones and TSH levels after BMT. Data are given as mean values (±SEM). *p<0.05 and †p<0.01 against basal values. PB: pre-BMT, W: weeks, M: months.

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 T_4 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 FT_4 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 T_3 syndrome was found among 47 out of the 80 patients (58.8%), and low T_3, T_4 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 (T_3, T_4, FT_4, 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 T_3 at 2 weeks (r=-0.48, p<0.05), IL-8 and FT_4 at 3 months (r=-0.83, p<0.05), and IL-10 and T_3 at 1 week (r=-0.45, p<0.05), respectively (Table 1). However, these relations became insignificant after adjusting steroid doses.

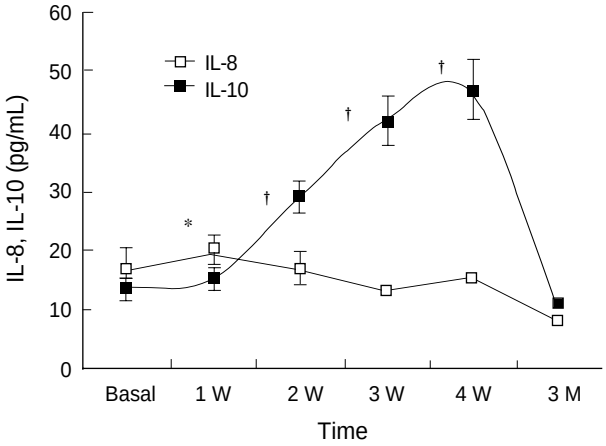

Fig. 2. The changes of serum IL-8 and IL-10 levels in peripheral blood, before and after allogeneic BMT. Data is given as mean values (±SEM). *p<0.05, †p<0.01 against basal value. Following BMT, serum IL-8 increases at 1 week and declines thereafter. Serum IL-10 increases reaching a peak at 4 weeks and also declining thereafter. PB: pre-BMT, W: weeks, M: months.

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 T_3, T_4 and TSH levels between the patients with and without TBI except for serum T_4 levels at post-BMT 3 weeks. Serum TSH levels in the patients with TBI tended to be lower than those without TBI during the entire observation period, but without statistical significance (Fig. 3A). Patients from both groups did not display any differences in serum FT_4 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 T_3 (nmol/L)	0.33	-0.28	-0.48*	0.01	-0.02	0.26
	serum T_4 (nmol/L)	0.27	0.11	0.08	0.08	-0.41	0.49
	serum TSH (mU/L)	-0.04	-0.24	-0.08	-0.07	-0.54	-0.26
	serum FT_4 (pmol/L)	0.03	0.15	-0.07	0.27	-0.10	-0.83*
IL-10 (pg/mL)	serum T_3 (nmol/L)	-0.16	-0.45*	-0.30	-0.30	-0.29	-0.10
	serum T_4 (nmol/L)	-0.23	-0.10	-0.28	-0.18	-0.57	-0.10
	serum TSH (mU/L)	0.28	-0.16	0.1	0.10	-0.02	-0.67
	serum FT_4 (pmol/L)	-0.21	-0.10	-0.24	-0.39	-0.31	0.21

*p <0.05

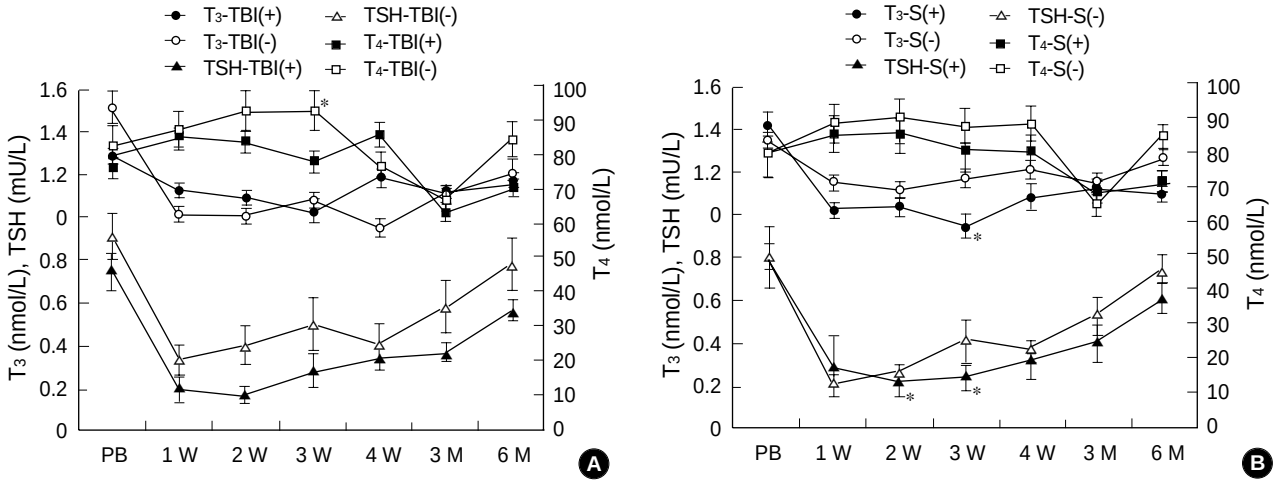

Fig. 3. The effects of TBI (A) and high dose steoid therapy (B) on thyroid function after BMT. Data are given as mean values (±SEM). *p<0.05 between TBI (+) and TBI (-) or S (+) and S (-). TBI (+): patients with TBI; TBI (-): patients without TBI. S (+): patients with high-dose steroid therapy; S (-): patients without high-dose steroid therapy. PB: pre-BMT, W: weeks, M: months.

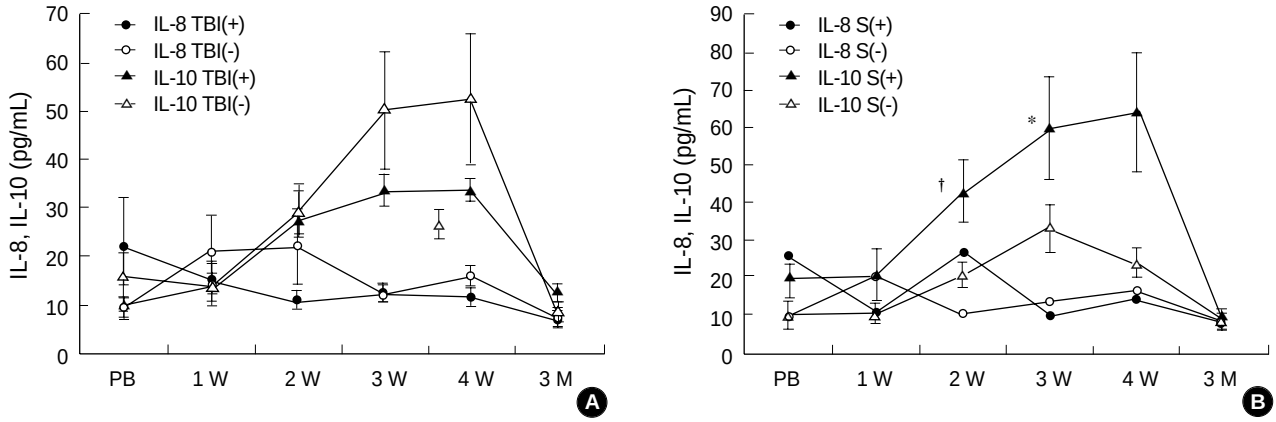

Fig. 4. The effects of TBI (A) and high dose steoid therapy (B) on IL-8 and IL-10 levels after BMT. Data are given as mean values (±SEM). *p<0.05 and †p<0.01 between TBI (+) and TBI (-) or S (+) and S (-). TBI (+): patients with TBI; TBI (-): patients without TBI. S (+): patients with high-dose steroid therapy; S (-): patients without high-dose steroid therapy. PB: pre-BMT, W: weeks, M: months.

Patients with high dose steroid represented lower levels of T_3 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 T_3, T_4 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 FT_4 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 T_3 levels decreased significantly at the first months after BMT compared to basal values, but serum T_4 levels declined in less degree and more slowly than serum T_3 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 T_3 and T_4 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 T_3 syndrome was found in 58.8% patients and low T_3, T_4 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 (T_3, T_4, 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 autoimmunity. 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 administered 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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