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CASE REPORT

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Case reports of hyperthyroidism after kidney transplantation: a review of literature

Alparslan Ersoy[1], Canan Ersoy[2]

[1]*Department of Internal Medicine, Division of Nephrology, Uludag University Medical School, Bursa, Turkey*
[2]*Department of Internal Medicine, Division of Endocrinology and Metabolism, Uludag University Medical School, Bursa Turkey*

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Abstract
Different disturbances of thyroid hormones in the absence of concurrent thyroid disease have been reported in patients on maintenance hemodialysis. After a successful kidney transplant, thyroid hormone metabolism normalizes. Although increased frequency of goiter and thyroid adenomas have been observed, hyperthyroidism is very rare. Herein, we report two kidney transplant recipients under immunosuppressive therapy that presents with hyperthyroidism.

Keywords: Kidney transplant, hyperthyroidism, toxic multinodular goiter

Introduction

Patients with end-stage renal disase (ESRD) may present a numerous disturbances of thyroid hormones such as elevated thyroid stimulating hormone (TSH) levels, reduced TSH responses to thyroid-releasing hormone, and reduced total and free triiodothyronine (T3) and thyroxin (T4) serum values in the absence of primary thyroid disease [1,2]. Although the majority of uremic patients are clinically euthyroid, goiter and thyroid dysfunction in uremic patients are more common than the general population [1]. Dialysis does not significantly normalize thyroid hormone metabolism, but these abnormalities usually normalizes after a successful kidney transplantation [2]. We report two rare cases with hyperthyroidism diagnosed in the early period following kidney transplantation.

Case report

Case 1. A 33-year old male patient, who started hemodialysis therapy in December 2002 due to ESRD of unknown etiology, underwent a deceased donor kidney transplant in our center in December 2004. Post-transplant immunosuppressive treatment consisted of prednisolone, tacrolimus, mycophenolate sodium and antithymocyte globulin. Following the need for hemodialysis during the first week, the graft function improved. His serum creatinine level was 1.3 mg/dL. He had hypertension and received amlodipine 20 mg/day, carvedilol 25 mg/day, indapamide 2.5 mg/day. In the follow-ups, he admitted with complaints of palpitation and excessive perspiration in February 2005. On physical examination, his blood pressure was 130/90 mmHg and heart rate was 104/min and rhytmic. He had staring, bilateral exophtalmus and lid lag. Thyroid examination revealed a nodule sized approximately 2 cm in the left lobe. His serum thyroid hormone levels were as follows; free T3: 5.55 pg/ml (normal range-NR: 1.71-3.71); free T4: 2.55 ng/dl (NR: 0.7-1.48); TSH: <0.005 mIU/ml (NR: 0.35-4.94). Anti-thyroglobuline (Tg Ab) and anti-thyroid peroxidase autoantibodies (TPO Ab) were negative. Thyroid ultrasonography revealed multinodular thyroid gland with heterogenous parenchyma echogenity. Dominant nodules sized 8.5x5 mm in the right and 24x16 mm in the left lobe. Scintigraphy demonstrated an enlarged thyroid gland and a autonomous nodule sized 29x32 mm at the superior part of the left lobe. Also another nodule with a lesser activity was seen beneath the dominant nodule. Remainder of thyroid gland was clearly suppressed. He was diagnosed as having toxic multinodular goiter (TMNG). Propylthiourasil (PTU) 300 mg/day and propranolol 40 mg/day were started as the initial treatment. The patient became euthyroid in April 2005. All the symptoms of hyperthyroidism were dissappeared. The dose of PTU was decreased to maintenance dose of 100 mg/day and a fine needle aspiration biopsy was performed in euthyroid condition. Cytological examination demonstrated benign thyroid cells. A radioactive iodine therapy (131-I) was given at a dose of 10 mCi and later PTU was continued at a dose of 50 mg/day. At the sixth month of the ablation therapy, cessation of antithyroid treatment was attempted. After one month, 50 mg/day PTU was restarted because of subclinical hyperthyroidism (TSH: 0.07 mIU/ml) and continued till 1 year post-ablation. PTU was stopped after

***Corresponding Author:** Alparslan Ersoy, Department of Internal Medicine, Division of Nephrology, Uludag University Medical School, Bursa,Turkey
E-mail: alpersoy@uludag.edu.tr

he became euthyroid. The patient is still followed up with a normal graft function (serum creatinine 0.99 mg/dL). He is still at euthyroid status (TSH: 1.018 µlU/mL, free T4: 1.01 ng/dL free T3: 3.63 pg/mL) without any antithyroid medication.

Case 2. A 47-year old female patient with a history of goiter for 10 years without any treatment showed a diffuse growth in her thyroid gland and an approximately 2 cm nodule was palpated in the left lobe in her examination in the pretransplant period. Her serum free T3 was 2.65 pg/ml, free T4 1.45 ng/dl, TSH 0.01 mlU/ml, TPO Ab 10.6 IU/ml (NR: 0-5.6) and Tg Ab 1.8 IU/ml. Thyroid US revealed iso- and hypoechoic solitary multiple nodules including cystic degenerations, among which the largest one sized 23x25 mm located in the left lobe. In her scintigraphy, both thyroid lobes were larger than normal with heterogenous activity. She was diagnosed as subclinical hyperthyroidism with nodular goitre, and not started any antithyroid treatment since she was asymptomatic. After a successful live donor KT from a relative in November 2006, she had an immunosuppressive treatment consisted of prednisolon, tacrolimus and mycophenolate mofetil. After a month, TSH level decreased to 0.001 mIU/ml but free T3 and free T4 were within normal ranges. After two and a half month, although she had no complaint except palpitation and no eye sign or symptom, free T4 (2.21 ng/dl) and free T3 (4.58 pg/ml) were higher than normal values. TSH was supressed (0.002 mIU/ml) and thyroid antibodies were normal. US and scintigraphy indicated similar findings with her previous imagings. PTU 300 mg/day and metaprolol 50 mg/day were started. A radioactive iodine therapy (131-I, 10 mCi) to ablate hyperthyroidism was given in 2010 and later PTU was continued at a dose of 50 mg/day. FNAB was performed to the patient who had subclinical hyperthyroidism due to hypoactive and hyperactive nodules, and it was reported as benign. She goes on her follow-ups with a serum creatinine of 0.75 mg/dL. She is still at euthyroid status (TSH: 0.470 µlU/mL, free T4: 1.00 ng/dL free T3: 3.16 pg/mL) without any antithyroid medication.

Discussion

Toxic adenoma and TMNG are the results of focal hyperplasias of thyroid follicular cells with functional activities uncontrolled by TSH. Activating somatic mutations of the genes of TSH receptors have been identified in both situations [3], which is quite uncertain in cases of TMNGs. A recent study evaluated types and incidence of thyroid biochemical disorders in kidney transplant patients [4]. They found subclinical hyperthyroidism in 1 patient (2.5%), clinical hypothyroidism in 2 patients (5%), low T4 syndrome in 3 patients (7.5%), low T3 syndrome in 5 patients (12.5%) and subclinical hypothyroidism in 7 patients (17.5%). To our knowledge one case of transient hyperthyroidism with subacute thyroiditis [5], 1 TMNG [6] and 1 Graves' disease [7] in kidney transplant recipients were described in the English literature until today. In our country where iodine deficiency is common, a study investigated the prevalence of goiter and thyroid dysfunction in 87 patients on hemodialysis and 169 healthy individuals as controls [8]. Euthyroid nodular goiter (36.8% vs 17.1%), hypothyroidism (3.4% vs 0.6%) and alteration of thyroid functions compared to healthy controls were common in patients on hemodialysis, but the incidence of hyperthyroidism was similar in both groups (1.14% vs. 1.1%) [8].

It is known that patients after kidney transplantation have an increased frequency of goiter and thyroid nodules. Patients with ESRD had elevated concentrations of TSH and reverse T3 (rT3) and decreased concentrations of T3 and free T3. These hormones normalize except TSH after transplantation, although episodes of acute rejection or delayed graft function may disturb this process [1]. T3 concentration diminished till 6th day, and thereafter started to rise with regression of goiter during early period after transplantation. Also rT3 increased till 3rd day and later decreased [9]. Furthermore, the risk of developing de novo tumors including thyroid cancers after kidney transplantation is generally increased. Immunosuppressive drugs such as cyclosporine and steroids may contribute to the development of these thyroid diseases [1]. Czyzyk and Jakóbisiak [10] examined the influence of cyclosporine on thyroid gland function by assessing serum concentration of T4 during development of experimental autoimmune thyroiditis in mice. They reported that a high dose cyclosporine (360 mg/kg) prevented the development of thyroid deficiency whereas a small dose (25-60 mg/kg) potentiated the decrease of T4 serum level. But, there is no observation about the effect of calcineurin inhibitors on development of hyperthyroidism in the literature. Besides our patients were receiving tacrolimus, mycophenolate and prednisolone, but not cyclosporine. Gungor et al. [11] observed a high prevalence of hyperthyroidism (10 subclinical thyrotoxicosis) in 122 kidney transplant patients. The occurrence of hyperthyroidism in recipients receiving immunosuppressive therapy is extremely rare [6,7]. The higher prevalence of thyrotoxicosis in this study was explained by steroid therapy to some extend. In our cases, the prednisolone dosage was tapered (after 1 mo, 30 mg/d; after 2 mo, 20 mg/d; after 3 mo, 5-10 mg/d) in time as scheduled. They had no acute rejection, and were not treated with pulse therapy.

Infectious thyroiditis due to viruses, bacteria or fungi may be another reason for thyrotoxicosis in kidney transplant recipients. Infectious thyroiditis due to aspergillosis should be suspected in kidney transplant recipients who are immune supressed and had painful thyroid, clinical and biochemical hyperthyroidism features [12]. Our patients had no clinical and laboratory finding concerning infectious thyroiditis.

The diagnosis of hyperthyroidism may be difficult because of similar signs and symptoms seen in uremia. The differentiation of clinical hyperthyroidism from abnormal thyroid function tests in an euthyroid patient has been a challenge in the dialysis population. Our cases did not suffer from the clinical features of hyperthyroidism in their dialysis treatment periods before kidney transplantation. Hyperthyroidism should be suspected in ESRD patients with unexplained symptoms and signs like weight loss, atrial fibrillation, hypotension on hemodialysis, sinus tachycardia, congestive heart failure or psychiatric symptoms. Uremia may also be a protective factor for the development of thyrotoxicosis. Peces et al [6] diagnosed TMNG in a kidney transplant recipient who had euthyroid goiter for 10 years and developed an episode of atrial fibrillation 5 months after kidney transplantation who responded well to a five-week of methimazole treatment. Concerning our cases, among two kidney transplant recipients with TMNG, the appearance of the first case's complaints in the very early period after a successful kidney transplantation suggested the probability of a previous TMNG, but it might be undiagnosed. Probably due to the euthyroid state, the second case having a long lasting history of goitre did not receive any therapy including thyroidectomy for thyroid diseases before transplantation. Then, both cases showed an exacerbation in thyroid function tests (more depressed TSH and elevated free T3 and T4) after kidney transplantation, in concordance with the physiological expectations. Unlike Graves' disease, toxic nodules and TMNG do not resolve spontaneously with prolonged thionamide therapy. The goal of thionamide therapy in these patients is to attain an euthyroid state before therapy with radioiodine or surgery. Surgery is preferred in patients with very large goiters (>80 g), symptoms or signs of compression and/or obstruction, the need for rapid return to euthyroidism, and coexisting thyroid cancer [13]. Veroux et al. [14] reported that 10 recipients underwent surgery to treat thyroid disease (8 with MNG, 1 with micropapillary carcinoma and 1 with follicular adenoma) among 184 transplant recipients. Radioiodine is a widely used approach for the treatment of hyperthyroid patients. It induces extensive tissue damage, resulting in destruction of the autonomous foci within 6 to 18 weeks, which may last upto 6 months. In follow-ups of our both cases, relapse and hypothyroidism did not occur after radioiodine therapy.

ESRD patients with decreased serum free T3 concentration before kidney transplant are at greater risk of subsequent graft failure [15]. A cross-sectional study demonstrated that decreased serum free T3 level were associated with poor outcomes of renal grafts, electrolyte disorders, high body mass index and anemia in long-term kidney transplant recipients [16]. Pretransplant positivity for TPO Ab in kidney recipients may affect long-term graft survival, but it is not associated with the occurrence of acute rejection and chronic allograft nephropathy [17]. Our patients had good graft function throughout all transplantation period.

As a conclusion, the development of hyperthyroidism in transplant recipients is extremely rare. If there is a history of nodular goiter in euthyroidic candidates before kidney transplantation, posttransplant thyroid function tests should be monitored for the nadir possibility of hyperthyroidism. Our experience suggested no possible explanation for the development of hyperthyroidism in our cases and indicated that hyperthyroidism was a co-morbid disorder. However, the effects of kidney transplantation or immunosuppression on somatic mutations in late period, especially in recipients with euthyroid goiter are unclear and require further investigations.

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