CASE REPORT

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Acute Kidney Injury after Thyroid Hormone Withdrawal in an Adolescent with Papillary Thyroid Carcinoma

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ABSTRACT

We report a patient with papillary thyroid carcinoma (PTC) who developed acute kidney injury (AKI) and elevated creatine kinase (CK) after thyroid hormone withdrawal (THW) prior to radioiodine therapy. A 12-year-old female patient who had undergone total thyroidectomy for PTC one year previously, presented with leg pain for the past two days. Following THW three weeks earlier, she had received 70 mCi radioiodine treatment six days before this presentation. Serum creatinine [1.53 mg/dL, normal range (NR): 0.3-1.1], aspartate aminotransferase (102 IU/L, NR: 0-40) and CK (3451 IU/L, NR: 26-174) levels were elevated. Thyrotropin level was elevated (μIU/mL, NR: 0.51-4.3), and free T4 level was decreased (0.05 ng/dL, NR: 0.98-1.63). Serum creatinine and CK levels decreased after intravenous hydration and levothyroxine treatment. In PTC cases with thyroidectomy, kidney function and CK elevation should be assessed after THW and dehydration should be prevented.

Keywords: Papillary thyroid carcinoma, thyroid hormone withdrawal, rhabdomyolysis, acute kidney injury, radioactive iodine therapy

What is already known on this topic?

Differentiated thyroid cancer is the most common thyroid cancer in children. The standard treatment is total thyroidectomy. Radioactive iodine (RAI) therapy is indicated for patients with pulmonary metastases or small-volume, unresectable residual cervical disease. During RAI therapy, having a thyrotropin above 30 μIU/mL facilitates ^{131}I uptake, which may usually be achieved by thyroid hormone withdrawal (THW) for ≥14 days in children.

What this study adds?

Patients who have undergone thyroidectomy may experience creatine kinase (CK) elevation and acute kidney injury may occur as a result of THW prior to RAI treatment. Kidney function tests and CK levels should be assessed in cases with THW and dehydration should be prevented.

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Introduction

Differentiated thyroid cancer (DTC) is the most common thyroid cancer in children. A previous history of radiotherapy used in treatment regimens for other malignancies is a risk factor for the development of thyroid cancer (1). However, less than 2% of all thyroid cancers develop in childhood and adolescence most commonly in female adolescents aged 15–19 years (1,2). Papillary thyroid carcinoma (PTC), a subtype of DTC, accounts for 90% of pediatric cases. At the time of diagnosis, approximately 50% of children with PTC have cervical lymph node metastasis (1).

Total thyroidectomy is the standard surgical approach for pediatric DTC due to the higher frequency of bilateral or multifocal involvement in children compared to adults (3). In cases with central cervical lymph node involvement, central lymph node dissection should be performed along with total thyroidectomy (2). Radioactive iodine (RAI) therapy is indicated for patients with pulmonary metastases or small-volume, unresectable residual cervical disease (2,3). During RAI therapy, having thyrotropin (TSH) levels above 30 μIU/mL facilitates ^{131}I uptake and this can usually be achieved by thyroid hormone withdrawal (THW) for ≥14 days in children (3).

In patients with DTC, short-term hypothyroidism during THW causes an increase in serum creatinine levels of approximately 30% (4). Thyroid hormones have direct and indirect effects on the cardiovascular system and hemodynamic conditions in the kidney. The decrease in cardiac output and increase in peripheral resistance seen in hypothyroidism may decrease renal blood flow. Decreased renal perfusion and glomerular filtration rate (GFR) will lead to decreased water excretion and increased creatinine levels.

Hypothyroidism may also precipitate rhabdomyolysis. The diagnosis of rhabdomyolysis is based on medical history and laboratory findings. For the diagnosis of rhabdomyolysis, the serum creatine kinase (CK) level should be greater than five times the upper limit of normal or greater than 1000 IU/L when the serum myoglobin >150 ng/mL. Acute kidney injury (AKI) is a common and serious complication of rhabdomyolysis. It has been reported that 13-46% of patients with rhabdomyolysis develop AKI. Rhabdomyolysis causes kidney damage due to fluid sequestration in injured skeletal muscle, activation of the renin-angiotensin system and sympathetic nervous system, antidiuretic hormone release, and renal vasoconstriction. AKI is thought to be the result of salt and water retention and tubular damage due to myoglobin-induced oxidative damage (5).

In this case report, we describe a patient with PTC who developed AKI and elevated CK after planned THW prior to RAI therapy.

Case Report

A 12-year-old female patient who had undergone total thyroidectomy and cervical lymph node dissection for PTC one year previously presented with leg pain of two days duration. She had received L-thyroxine and cholecalciferol treatment for iatrogenic hypoparathyroidism after the operation. Following THW for three weeks, she had received 70 mCi radioiodine treatment six days before the current presentation. No infections, metabolic disorders, or recent medication use were noted in her medical history. Physical examination revealed tenderness in the thigh muscles without other symptoms. The urine output was 3.15 mL/kg/h. Previous examinations showed normal complete blood count and serum creatinine value [0.44 mg/dL, normal range (NR): 0.3-1.1]. However, on admission, laboratory tests revealed increased levels of serum creatinine (1.53 mg/dL, NR: 0.3-1.1) and the estimated GFR was 52 mL/min/1.73m^2. Uric acid (7.3 mg/dL, NR: 2-5.5) and aspartate aminotransferase (AST) 102 IU/L (NR: 0-40) levels were elevated, while CK levels were significantly elevated at 3451 IU/L (NR: 26-174), 19.8 times the upper limit of normal. Electrolyte levels, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) levels were normal. TSH level was elevated (>100 μIU/mL, NR: 0.51-4.3), and free T4 level was low (0.05 ng/dL, NR: 0.98-1.63). The urinalysis showed low urine specific gravity (1005, NR: 1010-1030), with no blood and no protein on dipstick. Urine microalbumin/creatinine ratio (0.015 mg/g, NR: <30 mg/g) and urine β2-microglobulin level (0.16 mg/L, NR: 0.02-0.25 mg/L) were within the NR. Thyroid ultrasonography did not show any signs of disease relapse. She received an intravenous infusion of normal saline (0.9% NaCl) at a rate of 2000 mL/m^2/day for five days and oral L-thyroxine at 100 μg/day was initiated. Serum creatinine (0.47 mg/dL, NR: 0.3-1.1) and CK (136 IU/L, NR: 26-174) levels decreased after hydration and L-thyroxine treatment (Figure 1).

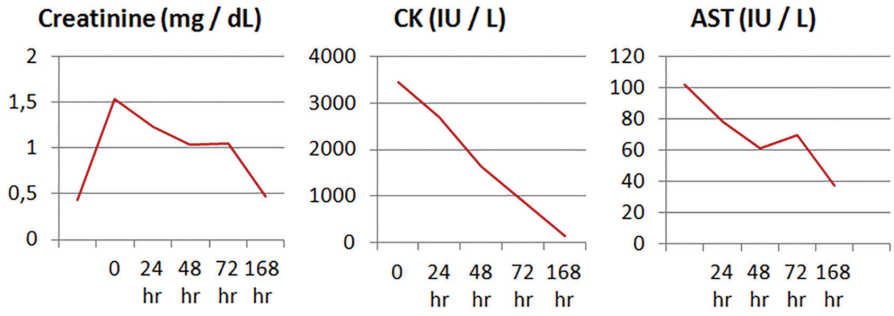

Figure 1. Serum creatinine, CK and AST levels of the patient
CK: creatine kinase, AST: aspartate aminotransferase, hr: hour

Discussion

In patients with PTC who undergo thyroidectomy, temporary hypothyroidism-induced rhabdomyolysis may occur after THW. Although AKI from rhabdomyolysis is a rare complication in children and adolescents, the severity of the side-effect may be variable. The management varies depending on the patient and severity. We report our experience with a patient diagnosed with PTC who developed rhabdomyolysis and AKI associated with THW prior to RAI therapy.

Causes of rhabdomyolysis include excessive muscle activity, trauma or injury, inherited muscle enzyme disorders, infections, drugs and toxins, as well as metabolic and endocrine disorders (5). The severity of rhabdomyolysis due to hypothyroidism ranges from minimal CK elevation to acute renal failure (6,7). In patients with Graves' disease and PTC, CK elevation and rhabdomyolysis have been reported following THW before RAI therapy (8,9). During THW for RAI therapy, serum lipid, creatinine, CK, AST, ALT, GGT, and LDH levels increase (4).

AKI resulting from hypothyroidism-associated rhabdomyolysis is rarely reported in children and adolescents. Saroufim et al. (7) reported a 16-year-old male adolescent with AKI attributed to rhabdomyolysis secondary to acquired hypothyroidism. In another case, a 10-year-old girl with hypothyroidism secondary to autoimmune thyroiditis was reported by Galli-Tsinopoulou et al. (10). She presented with rhabdomyolysis, pericardial effusion, renal failure, and acquired von Willebrand disease. Both of these cases were successfully treated with thyroid replacement therapy and hydration (7,10). In addition, Comak et al. (11) reported the administration of 24 sessions of hemodialysis in a 13-year-old girl with acute renal failure due to hypothyroidism secondary to thyroid hypoplasia. Hemodialysis and thyroid replacement therapy resulted in the recovery of kidney function (11). In our case, a three-fold increase in serum creatinine from baseline was defined as stage 3 AKI according to the KDIGO criteria (12). CK had increased to 20-fold the normal level, AST level was slightly elevated but GGT, ALT, and LDH levels were normal. After one week of hydration and L-thyroxine treatment, serum creatinine and CK levels decreased in our patient.

In hypothyroidism, reduced cardiac output leads to reduced renal blood flow and prerenal AKI (3). When muscle cells break down, they release myoglobin into the bloodstream and in cases of significant muscle damage, the increased load of myoglobin may lead to impaired kidney function. High concentrations of myoglobin in the kidneys can lead to acute tubular necrosis because of the combination of the direct toxic effects of myoglobin and the obstruction of renal tubules (5). However, kidney function is important for iodine excretion (3). Adequate hydration is required to increase ^{131}I clearance which can be hazardous for the renal tubules if clearance is decreased. Therefore, if necessary, additional supportive care with stool softeners, laxatives, and antiemetics may be considered to increase ^{131}I clearance (3). In addition, the effect of ^{131}I on the renal tubules has been associated with early complications of RAI therapy. These include radiation thyroiditis, xerostomia, ocular dryness, taste changes, sialadenitis, nausea, and vomiting which may increase the degree of dehydration (1,3). We speculate that AKI may be due to tubular damage associated with rhabdomyolysis as a result of THW and possible ^{131}I toxicity due to dehydration (9,13).

The main goal in the management of rhabdomyolysis is the preservation of kidney function and prevention of AKI. Early recognition is important to prevent AKI, and treatment consists of aggressive intravenous fluid resuscitation with correction of electrolyte abnormalities. Adjunctive therapies, including the urinary alkalization of urine, diuretics, and continuous renal replacement therapy, have been discussed but the benefits of these treatment modalities are controversial (5). Increased serum creatinine and CK levels can be reversed simultaneously with thyroid replacement therapy and intravenous fluid resuscitation (9).

Data on the use of recombinant human thyrotropin (rhTSH) in children are limited. It is reported that rhTSH is clinically safe and

provides adequate TSH stimulation in children and adolescents with DTC (14). However, its use is recommended in adults with endogenous hypothyroidism who are at risk of comorbidity (congestive heart failure, coronary artery disease, or psychiatric disorders) or in whom THW does not provide an adequate TSH response (TSH deficiency) (3). While THW for the preparation of RAI therapy causes a significant transient decrease in kidney function by reducing GFR, rhTSH injection is recommended for the preparation of RAI therapy without risking kidney function in patients at risk (15). Therefore, rhTSH could be considered as an alternative to THW in children who are going to receive RAI therapy (9).

Conclusion

Complications of short-term THW include cognitive, cardiovascular, affective, renal clearance, and lipid abnormalities. A significant complication of hypothyroidism is rhabdomyolysis and associated AKI. Kidney function and CK level should be assessed in cases with THW and dehydration should be prevented. Recombinant human TSH can be used in selected patients instead of THW, despite insufficient evidence for its use in the pediatric and adolescent population.

Ethics

Informed Consent: Informed consent was obtained from the parents of the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Yavuz Özer, Rüveyda Gülmez, Oya Ercan, Concept: Yavuz Özer, Oya Ercan, Design: Yavuz Özer, Oya Ercan, Data Collection or Processing: Yavuz Özer, Rüveyda Gülmez, Hande Turan, Gürkan Tarçın, Dilek Bingöl Aydın, Olcay Evliyaoğlu, Oya Ercan, Analysis or Interpretation: Yavuz Özer, Oya Ercan, Literature Search: Yavuz Özer, Rüveyda Gülmez, Oya Ercan, Writing: Yavuz Özer, Rüveyda Gülmez, Oya Ercan.

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