DOI: 10.4274/jcrpe.galenos.2024.2023-11-10

Case Report

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

Short Title: Thyroid Carcinoma and Acute Kidney Injury

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What is already known on this topic?
Differentiated thyroid cancer is the most common type of thyroid cancer in children. The standard surgical 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 TSH above 30 µIU/mL facilitates 131I uptake. It can 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.

Abstract
Objectives: 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.
Case presentation: A 12-year-old female patient who had undergone total thyroidectomy for PTC one year ago presented with leg pain for the past 2 days. Following THW 3 weeks ago, the case had received 70 mCI radioiodine treatment 6 days ago. 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 (>100 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.
Conclusion: 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

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24.11.2023
02.02.2024

Published: 20.02.2024

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). Less than 2% of thyroid cancers develop in childhood (2). Thyroid cancer is most common in females aged between 15 and 19 years in the pediatric and adolescent population (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. It 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%. Thyroid hormones have direct and indirect effects on the cardiovascular system and the hemodynamic conditions in the kidney. The decrease in cardiac output and increase in peripheral resistance seen in hypothyroidism decreased renal blood flow. Decreased renal perfusion and glomerular filtration rate (GFR) lead to decreased water excretion and increased creatinine levels (4).
Hypothyroidism may lead to 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 5 times the upper limit of normal or greater than 1000 U/L and 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. Acute kidney injury is thought to be the result of salt and water retention and tubular damage due to myoglobin-induced oxidative damage (5).
We report a patient with PTC who developed AKI and elevated CK after 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 ago presented with leg pain for the past 2 days. She had received L-thyroxine and cholecalciferol treatment for iatrogenic hypoparathyroidism after the operation. Following THW for 3 weeks, she received 70 mCI radioiodine treatment 6 days ago. 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 cc/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), aspartate aminotransferase (AST) 102 IU/L (NR: 0-40) levels were elevated, while CK levels were significantly high at 3451 IU/L (NR: 26-174). Electrolyte levels, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) levels were normal. Thyrotropin 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 reaction. Urine microalbumin/creatinine ratio (0.015 mg/g, NR: 30-300 mg/g) and urine β2-microglobulin level (0.16 mg/L, NR: 0.02-0.25 mg/L) were within the normal range. Thyroid ultrasonography did not show any signs of disease relapse. She received intravenous infusion of saline solution (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 (Fig. 1).

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 disease can be variable. The management of the condition varies depending on the patient. We report our experience with a patient diagnosed with PTC who developed rhabdomyolysis and AKI associated with after 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).

Acute kidney injury resulting from hypothyroidism-associated rhabdomyolysis is rarely reported in children and adolescents. Saroufim et al reported a 16-year-old male adolescent with AKI attributed to rhabdomyolysis secondary to acquired hypothyroidism (7). In another case, a 10-year-old girl with hypothyroidism secondary to autoimmune thyroiditis was reported by Galli-Tsinopoulou et al. She presented with rhabdomyolysis, pericardial effusion, renal failure, and acquired von Willebrand disease (10). Both cases were successfully treated with thyroid replacement therapy and hydration (7,10). In addition, Comak et al 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). Creatine kinase level 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 kidneys may struggle to handle the increased load of myoglobin. High concentrations of myoglobin in the kidneys can lead to acute tubular necrosis the combination of the direct toxic effects of myoglobin and the obstruction of renal tubules (5). On the other hand, 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 together 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 transient kidney function by reducing GFR, rhTSH injection is recommended for the preparation of RAI therapy without reducing 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

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

Financial Disclosure: The authors declared that this study received no financial support.

Conflict of Interest: The authors have no conflicts of interest to declare.

References

1. Prasad PK, Mahajan P, Hawkins DS, Mostoufi-Moab S, Venkatramani R. Management of pediatric differentiated thyroid cancer: An overview for the pediatric oncologist. Pediatr Blood Cancer. 2020 Jun;67(6):e28141.
2. Christison-Lagay ER, Baertschiger RM, Dinauer C, Francis GL, Malek MM, Lautz TB, et al. Pediatric differentiated thyroid carcinoma: An update from the APSA Cancer Committee. J Pediatr Surg. 2020 Nov;55(11):2273-2283.
3. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;25(7):716–59.
4. Papadakis G, Kalaitzidou S, Triantafillou E, Drosou A, Kakava K, Dogkas N, et al. Biochemical Effects of Levothyroxine Withdrawal in Patients with Differentiated Thyroid Cancer. Anticancer Res. 2015;35(12):6933–40.

5. Lim YS, Cho H, Lee ST, Lee Y. Acute kidney injury in pediatric patients with rhabdomyolysis. Korean J Pediatr. 2018;61(3):95–100.
6. Gunther DF, Chiu HK, Numrych TE, Kletter GB. Onset of acquired autoimmune hypothyroidism in infancy: A presentation of delayed gross-motor development and rhabdomyolysis. Eur J Pediatr. 2006;165(5):320–2.
7. Saroufim R, Alkotob S, Eugster EA. Rhabdomyolysis: A Rare Presentation of Hashimoto Thyroiditis in an Adolescent Boy and Review of the Literature. Horm Res Paediatr. 2023;96(5):538-541.
8. Benavides V, Rivkees S. Myopathy Associated with Acute Hypothyroidism following Radioiodine Therapy for Graves Disease in an Adolescent. Int J Pediatr Endocrinol. 2010;2010(1):717303.
9. Espiritu RP, Stan MN. Rhabdomyolysis after withdrawal of thyroid hormone in a patient with papillary thyroid cancer. Endocr Pract. 2008;14(8):1023–6.
10. Galli-Tsinopoulou A, Stylianou C, Kokka P, Panagopoulou P, Nousia-Arvanitakis S. Rhabdomyolysis, renal failure, pericardial effusion, and acquired von Willebrand disease resulting from hypothyroidism in a 10-year-old girl. Thyroid. 2008 Mar;18(3):373–5.
11. Çomak E, Koyun M, Kiliçarslan-Akkaya B, Bircan I, Akman S. Severe rhabdomyolysis and acute renal failure in an adolescent with hypothyroidism. Turk J Pediatr. 2011;53(5):586–9.
12. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013 Feb;17(1):204.
13. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-84.
14. Luster M, Handkiewicz-Junak D, Grossi A, Zacharin M, Taïeb D, Cruz O, et al. Recombinant thyrotropin use in children and adolescents with differentiated thyroid cancer: A multicenter retrospective study. J Clin Endocrinol Metab. 2009;94(10):3948–53.
15. Cho YY, Kim SK, Jung JH, Hahm JR, Kim TH, Chung JH, et al. Long-term outcomes of renal function after radioactive iodine therapy for thyroid cancer according to preparation method: thyroid hormone withdrawal vs. recombinant human thyrotropin. Endocrine. 2019;64(2):293–8.

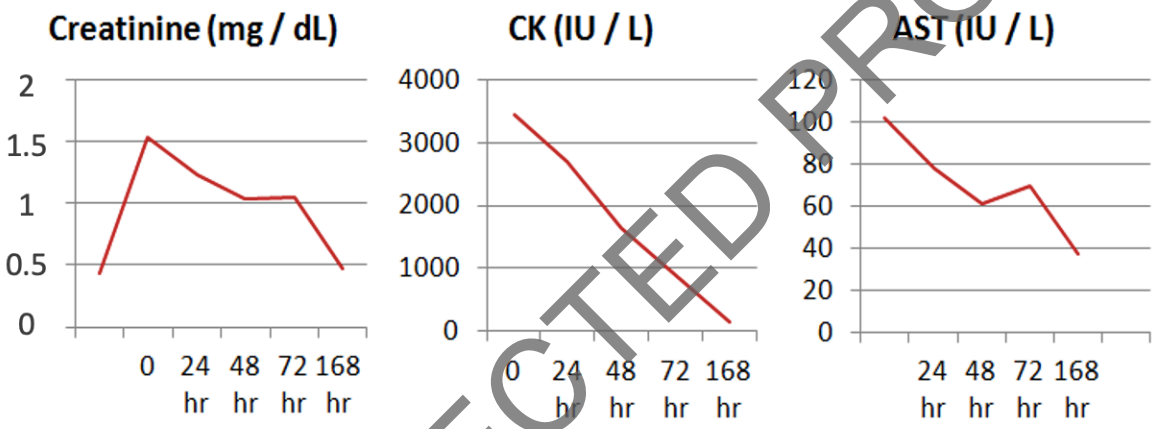

Figure 1. Serum creatinine, CK and AST levels of the patient decreased dramatically after thyroid hormone and intravenous fluid replacements
(*CK: Creatine kinase, AST: Aspartate aminotransferase, hr: hour)*