An Interesting Case of Hypothyroidism Associated Acute Kidney Injury

Abstract

Muscle involvement is common in hypothyroidism. However, hypothyroidism as a causal factor for severe rhabdomyolysis and acute kidney injury (AKI) is rarely reported. We report a case of a 56-year-old Arab male who presented with unexplained acute worsening of chronic kidney disease. The patient was detected to have hypothyroidism and rhabdomyolysis on laboratory investigations. However, thyroxine replacement led to partial recovery of renal function. CPK also improved with vigorous hydration and thyroxine replacement. Although this is a rare association, in the absence of other causes of rhabdomyolysis, hypothyroidism should be suspected in patients presenting with AKI and high creatinine phospho-kinase.

Keywords: *Acute kidney injury, acute tubular injury, hypothyroidism, rhabdomyolysis*

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Introduction

Hypothyroidism causing acute kidney injury (AKI) is a rarely reported phenomenon. While hypothyroidism is a definite cause of rhabdomyolysis, cases of AKI due to hypothyroidism-induced rhabdomyolysis are isolated. Hypothyroidism is an uncommon, non-traumatic cause of rhabdomyolysis, the exact mechanism of which remains unclear.[1] Electrolyte abnormalities such as hyponatremia are well known to occur with hypothyroidism; however, association with renal impairment in the absence of any other clear underlying cause is rare. We report a case of acute worsening of chronic kidney disease (CKD) in which thyroxine replacement led to partial recovery of renal function.

Case Report

A 56-year-old Arab male presented to the hospital with pain in the right chest wall and right shoulder for 5 days. There was no reported shortness of breath, vomiting, diarrhea, or urinary symptoms. There was no history of trauma, lifting heavy objects, or any vigorous exercise. His medical history included CKD stage 3 secondary to hypertensive renal disease (baseline serum creatinine: 1.6 mg/dL, eGFR: 47 mL/min, urea: 44 mg/dL, proteinuria: 500 mg/day, and normal-sized kidneys) and coronary artery disease that required percutaneous intervention and stenting in March 2020. Family history for renal and endocrine disorders was negative. Medications included aspirin, clopidogrel, bisoprolol, and rosuvastatin 40 mg nightly.

Physical examination revealed stable vital parameters (pulse: 64/mt, BP: 104/65 mm Hg), and system examination was unremarkable. The skin was normal, with no presence of edema, and speech was also normal. Thyroid size was also normal. Laboratory investigations are given in Table 1. He was diagnosed to have rhabdomyolysis with acute worsening of CKD stage 3. His ECG showed T-wave inversions, and serial cardiac markers showed no significant increase. Rosuvastatin was continued as it was deemed essential in the setting of recent percutaneous cardiac intervention.

Upon further investigations, he was found to be severely hypothyroid (TSH of >100 uIU/mL) and a free T4 of 5.3 though clinically there was no sign of hypothyroidism. An endocrinologist was consulted, and further investigations were requested. Thyroglobulin antibody was 2689.0 IU/mL, and thyroid peroxidase antibody value was 254 IU/mL. A diagnosis of autoimmune thyroiditis was made. The patient was commenced on vigorous hydration with gradual thyroxine replacement. He was started on a low dose of thyroxine 25 mcg daily with a

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gradual increase every 2 weeks by 25 mcg, which resulted in significant improvement of his symptoms, correction of his thyroid function tests, and a gradual improvement in his renal function [Table 2 and Figures 1 and 2]. There was partial recovery of renal function after treatment of rhabdomyolysis and hypothyroidism. TSH returned to normal values within a period of 4 months from the commencement of thyroxine replacement [Table 2].

Table 1: First hospitalization investigations

Laboratory investigation	Value
Hb	12 g/dL
WBC	7.4×10^3/cc
Platelets	201×10^3/cc
Total bilirubin	0.5 mg/dL
Alkaline phosphatase	56 IU/L
ALT	28 IU/L
Creatinine	4.4 mg/dL
Urea	137 mg/dL
Sodium	133 mmol/L
Potassium	3.5 mmol/L
Bicarbonate	22 mmol/L
Urine routine analysis	Color: hazy
	Protein: 1+
	WBC: 0-5/hpf
	RBC: 0-2/hpf
	Casts: Nil
CPK	4640 IU/L
Urine myoglobin	80++ (Normal: <20)
Troponin T	44 ng/L (Normal: <14)
CKMB	57
CKMB/CPK ratio	1%
Covid RT-PCR swab	Negative
TSH	>100 uIU/L
Free T4	5.3 pmol/L (Normal: 12-22)
Free T3	2 pmol/L (Normal: 3.1-6.8)
Thyroglobulin Antibody	2689 IU/mL
Thyroid peroxidase antibody	254 IU/mL
HbA1C	6.1%
Cholesterol	106 mg/dL
Triglycerides	128 mg/dL
HDL	55 mg/dL
LDL	25 mg/dL

He was lost to follow up for the next 9 months and presented with a history of having defaulted on his thyroxine, having been admitted to another hospital in Yemen with AKI, and receiving four sessions of hemodialysis. Further details of his hospital stay there were unavailable. On presentation to our hospital, vital parameters were within normal limits. Investigations are described in Table 3. TSH was highly elevated. The cause for the acute deterioration in renal function was not clear. From the laboratory investigations, AKI due to acute interstitial nephritis was a possibility in view of sterile pyuria. He was initiated on hemodialysis and we performed a renal biopsy. Thirty-one glomeruli were sampled. Two glomeruli were globally sclerotic. The remaining glomeruli were normo-cellular with patent capillary lumina. Tubules displayed diffuse acute tubular injury. There was moderate tubular atrophy and interstitial fibrosis with patchy chronic inflammation. We assume that he had an intercurrent severe infection (while in Yemen) that precipitated acute tubular injury in the background of hypoperfusion caused by severe hypothyroidism. Renal functions partially recovered after three sessions of hemodialysis and thyroxine replacement. He was discharged on 125 mcg/day of thyroxine. The trend of renal functions is outlined in Table 4.

Discussion

We report a patient with hypothyroidism and acute on CKD stage-3 due to rhabdomyolysis with no additional

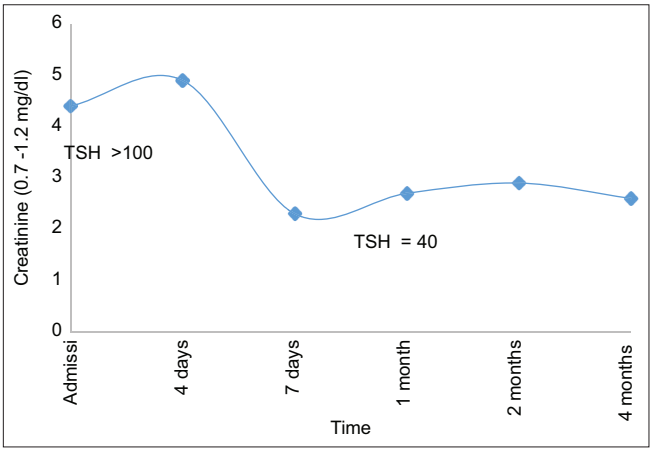

Figure 1: Correlation between serum creatinine and TSH following thyroxine replacement

Table 2: Trend of blood results

	Admission	4 days	Discharge (9 days)	1 month	2 months	4 months
Sodium (135-145 mmol/L)	134	133	139	137	138	141
Potassium (3.6-5.3 mmol/L)	3	3.1	3.8	4.5	4.4	5.2
Urea (12-40 mg/dL)	149	149	98	74	92	87
Creatinine (0.7-1.2 mg/dL)	4.4	4.9	2.3	2.7	2.9	2.6
TSH 0.4-5.0 mU/L	>100			40		2.8
T4 12.0-23.0 pmol/L	5.3			13.9		21
CPK 0-170 IU/L	4054	4952	780			

precipitating factor. The diagnosis of rhabdomyolysis was established based on laboratory investigations. The initial laboratory parameters showed raised creatinine of 4.4 mg/dL (his baseline Cr was 1.6 mg/dL). He also had markedly raised CPK level (4054 IU/L), with a high level of TSH (>100 uIU/mL) and very low levels of T4 (5.3).

The patient was started on vigorous hydration with gradual thyroxine replacement therapy. Despite a remarkably short hospital stay and five days of thyroid replacement therapy, this patient began to show a significant decline in his CPK level, which dropped to 780 IU/mL. In addition, partial recovery of his renal injury was achieved as his creatinine came down to 2.3 mg/dL from a value of 4.4 mg/dL at the time of admission [Figures 1 and 2]. There was a gradual increase in his thyroxine replacement therapy with a 25-mg increase every 1–2 weeks. The patient was discharged on thyroxine 50 mcg/day. His TSH returned to normal values (2.8 mU/L) within 4 months from the commencement of thyroxine replacement.

Table 3: Second hospitalization investigations

Laboratory investigation	Value
Hb	9 g/dL
WBC	7.3×10^3/cc
Platelets	315×10^3/cc
Serum albumin	3.4 g/dL
ALT	47 IU/L
Creatinine	13.9 mg/dL
Urea	137 mg/dL
Sodium	142 mmol/L
Potassium	5.0 mmol/L
Bicarbonate	20.6 mmol/L
Urine routine analysis	Color: hazy
	Protein: 1+WBC: numerous/hpf
	RBC: 3-5/hpf
	Casts: Nil
Urine culture	No growth
Urine protein/creatinine ratio	510 mg/g
CPK	188
Calcium	8.7 mg/dL
Phosphate	7.7 mg/dL
CRP	14.6
TSH	>100 uIU/L
Free T4	6.8 pmol/L (Normal: 12-22)
Complements	Normal
HIV Ag/ab	Negative
Hepatitis B surface antigen	Negative
HCV antibody	Negative

The second hospitalization was also complicated by AKI and severe hypothyroidism. A renal biopsy performed after hemodialysis revealed acute tubular injury in addition to chronic tubular atrophy and interstitial fibrosis. In investigating a patient with abnormal renal function tests, thyroid function should be assessed, especially in patients with unexpected deterioration of renal function, including those with underlying CKD.[2]

Elevated creatinine levels can be observed within a short time of less than two weeks from the detection of severe hypothyroidism. Rapid improvement of kidney function tests from the commencement of appropriate treatment of hypothyroidism is noted frequently, but patients can sometimes have a slower response or incomplete renal recovery due to severe or prolonged hypothyroidism. The abrupt increase in creatinine level that can manifest even after a short period of hypothyroidism is usually followed by a rapid response to replacement of thyroxine.

Regarding full recovery, the normalization in creatinine kinase and TSH levels can be seen within weeks to months, depending on the severity and duration of hypothyroidism,

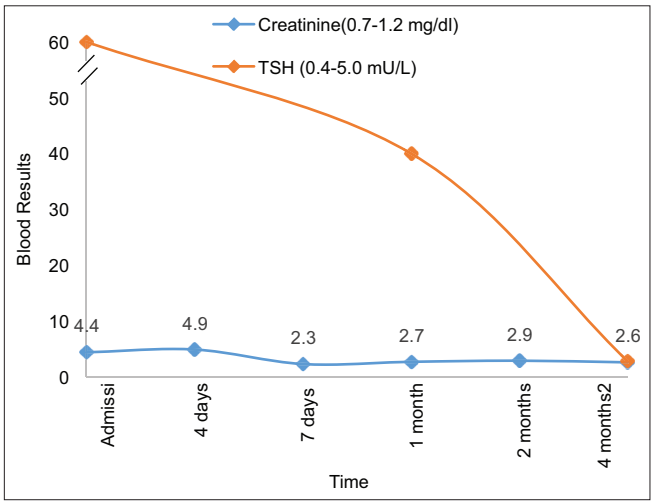

Figure 2: Improvement in serum creatinine following Thyroxine replacement

Table 4: Trend of blood results – second hospitalization

	Admission	4 days	Discharge	1 month	2 months
Sodium (135-145 mmol/L)	142	137	136	136	139
Potassium (3.6-5.3 mmol/L)	5.0	4.6	5.4	5.5	4.7
Urea (12-40 mg/dL)	137	83	180	114	104
Creatinine (0.7-1.2 mg/dL)	13.9	7.1	5.9	3.5	3.7
TSH 0.4-5.0 mU/L	>100		18.6	1.2	1.2
T4 12.0-23.0 pmol/L	6.8		19.1	22.8	23.1

and most importantly, the initiation of thyroxine replacement therapy. It has also been documented that some factors, such as advanced age, presence of diabetes and hypertension, and worse renal function at presentation, are associated with poorer renal recovery on follow-up.[3] However, initial recovery after commencement of therapy can be detected very early in some cases, as observed in our case, wherein it required only five days of therapeutic intervention for the onset of recovery of renal function. Therefore, it is evident that prompt early diagnosis and treatment can lead to patients responding favorably, subsequently leading to better outcomes and prognosis.

During the first hospitalization, improvement of the patient's renal function with no intervention other than thyroxine supplementation and vigorous hydration strengthens the fact that his hypothyroidism-associated rhabdomyolysis appeared to be the only contributor to his acute on top of CKD. Rosuvastatin was a likely contributory factor to the rhabdomyolysis in addition to hypothyroidism. This well-established reversibility of renal failure after the onset of thyroxine replacement remains the most consistent method of demonstrating a possible cause-and-effect relationship between hypothyroidism and renal failure. However, it should also be noted that higher degrees of renal impairment on presentation lead to diminishing recoverability of renal function.[3] During his second hospitalization, acute deterioration of renal function was due to biopsy-proven acute tubular injury, possibly contributed to by severe hypothyroidism. Partial recovery of renal function was noted after correction of hypothyroidism. Counselling hypothyroid patients about the importance of maintaining compliance to medications and the need for regular follow-up with a physician is imperative to preventing drug default.[3]

There are varying reports of reversibility of renal impairment after correction of hypothyroidism. Nakahama *et al*.[4] reported only partial recovery of renal function following initiation of thyroxine replacement and correction of hypothyroidism. However, Kreisman and Henessey reported full reversibility of renal function after 2 weeks of thyroxine replacement.[5] The complete but gradual recovery of renal functions after thyroxine replacement has also been reported by Joshi *et al*.[6]

Among the muscle disorders noted with hypothyroidism, rhabdomyolysis is the most serious disorder.[7,8] Rhabdomyolysis associated with hypothyroidism has been described as early as 1979.[9] There have been earlier case reports regarding rhabdomyolysis as the initial presentation of hypothyroidism.[7,10,11] Two among these cases were precipitated by alcohol and strenuous physical activity.[10,11] The exact cause of rhabdomyolysis in hypothyroidism remains unclear. Usually, an aggravating factor such as the use of lipid-lowering drugs, alcohol, exercise, or CKD has been identified. Thyroid hormone replacement improves thyroid and renal function and reverses rhabdomyolysis. Myolysis in hypothyroidism is caused by changes in muscle fibers from fast-twitching type II to slow-twitching type I fibers, deposition of glycosaminoglycan, poor contractility of actin-myosin units, low myosin ATPase activity, and low ATP turnover in skeletal muscles.[12] In addition, there is an inhibition of mitochondrial activity in muscle cells as well as dysregulation of many metabolic pathways such as Kerb's cycle, fatty acid catabolism, and glycolytic energy production.[13] These metabolic abnormalities may trigger patients with hypothyroidism to develop rhabdomyolysis, especially in the presence of other precipitating factors.

It is necessary to be cognizant of the fact that hypothyroidism is not only the cause of a new AKI and that it can also precipitate deterioration of renal function in patients with stable CKD, like in the case of our patient. There have been previous reports of similar improvement in renal failure following treatment of hypothyroidism.[4] Clinicians must also keep in mind that pre-dialysis patients with advanced CKD (CKD stages 4 and 5) may have an increased risk of hypothyroidism compared to the general population. This is often subclinical and is, therefore, more important to be detected, especially in the elderly, as the condition is easily treatable.[6]

Conclusion

Hypothyroidism-induced renal injury, with or without rhabdomyolysis, is reversible partially to completely, over weeks to months of appropriate thyroxine replacement therapy. Our case highlights the importance of performing thyroid function tests in the evaluation of unexplained renal failure, even in the presence of underlying chronic kidney disease, with or without a clinical presentation of hypothyroidism.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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