Rhambdomyolysis induced by Hypothyroidism in A Patient with Hypopharyngeal Cancer: A Case Report and Review of the Literature

Hao-Wen Lin

Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Yun-Lin branch

Abstract

Though neuromuscular involvement is common in hypothyroid patients, rhambdomyolysis is only seen in case reports and usually with precipitating factors such as strenuous exercise or statin. Here we reported a rare case of rhambdomyolysis induced by post treatment hypothyroidism in a patient with hypopharyngeal cancer. A 41 year-old male with left oral cancer and left hypopharyngeal cancer suffered from myagia about one year after he underwent total laryngopharyngectomy and concurrent radiochemotherapy. There was no major trauma, no local necrosis and he did not take medications which may induce rhambdomyolysis. Recent magnetic resonance imaging revealed no evidence of local recurrence. Lab data revealed high creatine phosphokinase (CPK) of 13034 IU/L (38-160 IU/L), hypocalcemia with calcium of 7.1mg/dl (8.3-10.5mg/dl) and deteriorated renal function. Hydration and urinary alkalization were given. Further investigation revealed overt hypothyroidism and hypoparathyroidism. The free thyroxin was <0.4 ng/dL (0.7-1.48ng/dL) and the thyrotropin was 171μIU/mL (0.35-1.94μIU/mL). The thyroid peroxidase antibody was 0.4 IU/mL (0-5.61 IU/mL). After supplement of levothyroxin and calcium carbonate, the patient achieved euthyroid, his myalgia improved, the CPK level decreased to normal limit and the creatinine decreased to baseline. Hypothyroidism should be kept in mind and treat properly with patients suffering from unexplained rhambdomyolysis. (J Intern Med Taiwan 2013; 24: 418-423)

Key Words: Rhambdomyolysis, Hypothyroidism, Hypopharyngeal cancer

Introduction

Hypothyroidism stands a rare cause of rhambdomyolysis[1]. Though muscle involvement is common in hypothyroid patients[2-5], rhambdomyolysis caused by hypothyroidism is rare, seen in case reports, and usually with a precipitating factor[6-16]. Here we reported a rare case of rhambdomyolysis induced by post treatment hypothyroidism in a patient with hypopharyngeal cancer.

Case Presentation

We reported a 41-year-old male who suffered from myalgia of shoulder and legs for months. He had history of left oral cancer and left hypopharyngeal cancer. The initial presentation of left oral squamous

Reprint requests and correspondence：Dr. Hao-Wen Lin
Address：Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Yun-Lin branch, No.579, Sec. 2, Yunlin Rd., Douliu City, Yunlin County 640, Taiwan

cell carcinoma was intermittent sorethroat in 2010. He underwent wide excision of tumor and left selective neck lymph node dissection on 2010/03/16. The pathological staging was pT2N0M0, stage II.

During follow up, left hypopharyngeal tumor was noted. Neck magnetic resonance imaging (MRI) on 2010/08/17 revealed an irregular enhancing lesion about 1.8cm at the left tongue base and oropharynx, suspected recurrent oropharyngeal tumor and an irregular mass involving the left pyriform sinus and bilateral posterior hypopharyngeal wall with greatest dimension about 3.9 cm, suspected hypopharyngeal cancer. Biopsy of hypopharyngeal tumor revealed squamous cell carcinoma. The staging was cT4aN0M0, stage IVA.

Due to direct tumor invasion of thyroid cartilage, he underwent total laryngopharyngectomy, right selective neck dissection level II-IV, left modified radical neck dissection type I and tracheostmy on 2010/9/8

He underwent concurrent chemoradiotherapy with weekly cisplatin from 2010/10 to 2010/12. Radiotherapy consisted of 66Gy in 33 fractions at 2Gy per fraction was delivered to hypopharyngeal tumor bed and bilateral upper neck, 60Gy was delivered to bilateral lower neck, and 54Gy was delivered to bilateral supraclavicular fossa.

He had follow up at our oncology and otolaryngology clinic. Neck MRI on 2011/8/23 revealed no evidence of local recurrence.

However, he suffered from myalgia over bilateral shoulders and legs since 2011/9. Lab data revealed high creatine phosphokinase (CPK) of 11341 IU/l (38-160 IU/l) and elevated lactate dehydrogenase (LDH) of 1968 IU/L (260-450 IU/L) on 2011/10/6. Admission was suggested however he refused. Oral sodium bicarbonate and hydration were given. Followed lab data showed persistent elevated CPK and abnormal renal function compared to his baseline creatinine 1.2mg/dl (Table 1.) He was admitted on 2011/10/14 for rhambdomyolysis.

Among admission, his consciousness was clear with the Glasgow coma scale E4VTM6. His body weight was 70.2 kg and he was 176 cm in height. The blood temperature was 36.2°C, the pulse rate was 60 beats per minute, and the respiratory rate was 18/min. His blood pressure was 108/75 mmHg. The neck was supple with tracheotomy tube. The chest expanded symmetrically and the breath sounds were clear. The heartbeats were regular without audible murmur. His abdomen was soft and flat without tenderness and the bowel sounds were normoactive. The extremities were freely movable without pitting edema. There was no obvious local necrosis at otolaryngology field.

Laboratory data was listed in Table 1. Hypocalcemia, hyperphosphatemia and elevation of uric acid were noted. The urinary analysis revaled pH 6.0, RBC 0-2/HPF, and negative occult blood. The CPK and Creatine Phosphokinase-MB (CK-MB)

Table 1. Lab data on 2011/10/14

WBC	3680/μl	Na(136-146)	138mmol/l
Hb	9.3 g/dl	K(3.5-5)	3.7mmol/l
Platelet	182k/μl	Ca(8.3-10.5)	7.1mg/dl
AC Glucose	82mg/dl	P(2.3-4.5)	7.1mg/dl
Alb(3.8-5.1)	4.5g/dl	Uric acid(2.4-7.6)	8.3 mg/dl
Cr(0.7-1.5)	2mg/dl	CPK(38-160)	13034 IU/L
Total bilirubin(0.2-1.2)	0.77mg/dl	CKMB(0-16)	211.9 U/L
ALT(4-44)	33 IU/L	LDH(260-450)	1968 IU/L

both elevated. Test of urine myoglobin level was unable to be performed at our hospital.

Hydration and urinary alkalization were given. However, the CPK decreased suboptimally. Further survey for rhambdomyolysis was performed. There was no evidence of trauma and local compression. There was no obvious local necrosis at otolaryngology field. Reviewing back his history, he did not take alcohol, medications such as statin or colchicine that could cause rhambdomyolysis. There was no evidence of infection. Blood culture was done but the result was negative and the C-reactive protein was not elevated.

Metabolic factors were surveyed and revealed hypothyroidism. On 2011/10/24, the free thyroxin (free T4) was <0.4 ng/dL (0.7-1.48ng/dL) and the thyrotropin (TSH) was 171μIU/mL (0.35-1.94μIU/mL). The thyroid peroxidase antibody (Anti-TPO) was 0.4 IU/mL (0-5.61 IU/mL). Lab data also revealed hypoparathyroidism with intact parathyroid hormone(iPTH) <3 pg/mL (12-72pg/mL). Levothyroxin was applied and titrated to 100mcg per day gradually. Intravenous and oral calcium supplement were applied for severe hypocalcemia. The CPK level decreased gradually to 3688 IU/L on 2011/11/03 and serum calcium level raised to 9.8mg/dl under calcium carbonate 3g per day. His myalgia improved gradually. Hydration and urine alkalization were tapered gradually and he was discharged with oral calcium carbonate and levothyroxin. Euthyroid status achieved under levothyroxin 150mcg per day with free T4 1.29ng/dL, TSH 0.659 uIU/mL on 2012/01/18. The CPK level decreased gradually while he achieved euthyroid status (Table 2).

Discussion

Hypothyroidism induced rhambdomyolysis

Rhambdomyolysis may be induced by trauma, exertion, muscle hypoxia, genetic defects, infections, body temperature changes, metabolic and electrolyte disorders, drug and toxins, or idiopathic causes[1]. Common nontraumatic causes include exogenous agents toxic to muscles, especially alcohol, illicit drugs and lipid lowering agents[1]. Hypothyroidism stands a rare cause of rhambdomyolysis.

In patients with hypothyroidism, muscle involvement is common. Duyff RF et al reported that 79% of hypothyroid patients had neuromuscular complaints such as weakness, cramping, myalgia, even carpal tunnel syndrome[2]. Elevation of CPK is also common in hypothyroid patients[2-4]. The serum CPK level did not correlate with weakness[2]. Hekimsoy Z et al. reported a positive correlation between CPK and TSH and a negative correlation between CPK and free T3 and between CPK and free T4[4]. Thus, hypothyroidism should be kept in mind in patients with an unexplained increase of serum CPK.

CPK elevations in hypothyroid patients were usually lower than ten times up the reference level[5-6]. And despite common CPK elevation, rhambdomyolysis caused by hypothyroidism is rare, seen in case reports, and usually with a precipitating factor like intensive exercise, using drug such as lipid lowering agents, trauma, underlying infection, and toxins (Table 3,[6-16]). Our patients represents a rare case of hypothyroidism induced rhambdomyolysis. Hypocalcemia may be a result of rhambdomyolysis however hypocalcemia itself might proceed rhambdomyolysis[1]. In our patient, the low iPTH

Table 2. Change of thyroid function Ca, and CPK level

	Ca mg/dl	CPK IU/L	FT4 ng/dL	TSH μIU/mL
2011/10/14		13034	<4	171.2
2011/10/15	7.1	9835		
2011/10/27	8.9	4936		
2011/10/31	8.3	3946		
2011/11/03	9.8	3688		
2011/11/30	7.6	381	1.15	15.68
2012/01/18	8.6	127	1.29	0.659

Table 3. Hypothyroidism induced rhambdomyolysis*

Author	Nation	Age	Sex	Etiology of hypothyroidism	CPK (IU/L)	TSH (μIU/mL)	Precipitating factor	Renal function impairment
Nobuo S, 1993	Japan	61	F	Hashimoto thyroiditis	8437	110.4	Strenuous exercise	Y
Barahona MJ, 2002	Spain	49	M	Hashimoto thyroiditis	9332	147.7	No	N
Kisakol G, 2003	Turkey	19	M	Hashimoto thyroiditis	10210	>75	No	N
Mustafa A, 2005	Turkey	31	M	Hashimoto thyroiditis	2291	>100	No	Y
Chowta MuktaN, 2008	India	39	M	not mentioned	972	>100	Alcohol	Y
Kus HT, 2010	Taiwan	75	F	s/p I131 and subtotal thyroidectomy	6020	142.03	Renal function impairment	Y(CKD)
Nikolaidou C, 2010	Greece	41	F	Hashimoto thyroiditis	3239U/L	75	No	Y
Moeller RF, 2011	USA	15	F	Hashimoto thyroiditis	34724	77.2	Strenuous exercise	N
Hurtado1 JJD, 2011	Guatemala	5	M	Unknown	4615	299	Cardiac temponate	N
Muir P, 2012	New Zealand	22	M	Hashimoto thyroiditis	>25000	>100	Adrenal insufficiency Hyponatremia	Y
Ying C, 2013 (5 patients)	China	37 to 62	4M 1F	1: Hashimoto thyroiditis 1: amiodarone related 3: unknown	1297 to 3573	87.25 to >100	Not mentioned	Y

*Reference 6-16.

level suggested his hypocalcemia is a result of hypoparathyroidism. Treatment with levothyroxin and calcium supplement lead to a successful recovery of renal function and symptoms.

Hypothyroidism after treatment of head and neck cancer

Hypothyroidism is common in patients treated for head and neck malignancies. The incidence varies from 23-53%[17-19]. Mostly it has been observed after radiation, however sometimes after surgery and combined-modality therapies[18]. Onset of hypothyroidism varies from 4 weeks to late as 5 or 10 years after completion of therapy[18]. Studies suggested thyroid function should be tested on a regular basis following radial therapy to the low-neck region[17-19]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommended thyroid function tests should be repeated at 6–12 month intervals after radiotherapy[20].

Our patient suffered from symptoms of rhambdomyolysis about 9 months after completion of radial therapy. Early screen of thyroid function test and early supplement might help this patient from his illness.

Mechanism of radiotherapy induced hypothyroidism includes direct microvascular and macrovascular damage in and around thyroid tissue, direct damage to follicular epithelium, and radiation-induced autoimmune thyroiditis[18]. It may also be a result of radiation-induced damage to the hypothalamic-pituitary axis, which results in central hypothyroidism[18].

Though the actuarial risk of developing hypothyroidism is significantly higher when the thyroid gland is included in the target radiation volume, it

was not possible to define a clear dose–volume effect and threshold doses are not well elucidated[18-19]. Studies reported increased probability of developing primary hypothyroidism when the mean radiology dose on thyroid gland increased beyond 45Gy to 65Gy[18]. The dose delivered to our patient (66Gy) might increase the probability of hypothyroidism.

Conclusion

Hypothyroidism should be kept in mind and treat properly with patients suffering from unexplained rhambdomyolysis. And thyroid function should be checked periodically in patients with laryngeal or hypolaryngeal cancer whom underwent total laryngectomy and radiotherapy.

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下咽癌治療後甲狀腺低下引起之橫紋肌溶解症

林皓雯

台大醫院雲林分院內科部　內分泌新陳代謝科

摘　要

雖然甲狀腺低下的病人常有神經肌肉的症狀，甲狀腺低下造成的橫紋肌溶解症卻很少見，僅見於案例報告，並且通常合併有其他的加重因子：如劇烈運動或使用降血脂藥物等。本案例報告為一下咽癌病人在接受手術和放射線治療後產生甲狀腺低下並造成橫紋肌溶解症。此為一位41歲男性病患，本身有左側口腔癌和左側下咽癌。在接受全喉切除術、化療及放射線治療後約一年開始有肌肉疼痛的症狀。病人沒有受過嚴重肢體創傷、口腔咽喉處沒有局部壞死、也沒有服用可能造成橫紋肌溶解症的藥物。最近一次的核磁共振顯示腫瘤沒有局部復發的情形。實驗室檢查顯示肌酸磷酸激酶(CPK)升高至13034 IU/L (38-160 IU/L)，同時有低血鈣(calcium 7.1mg/dl) (8.3-10.5mg/dl)和肌肝酸上升。進一步的檢查顯示甲狀腺低下及副甲狀腺低下，抗甲狀腺過氧化抗體為0.4 IU/mL (0-5.61 IU/mL)。補充甲狀腺素和鈣後，病人甲狀腺機能回復正常，肌肉疼痛改善，CPK值和肌肝酸亦回復至基礎值。若病人出現原因不明的橫紋肌溶解症，應想到是否有甲狀腺低下，仔細診斷並適當治療。