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

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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 myalgia 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. Though muscle involvement is common in hypothyroid patients, rhambdomyolysis caused by hypothyroidism is rare, seen in case reports, and usually with a precipitating factor. 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...
cell carcinoma was intermittent sore throat 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 1.8 cm 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 tracheostomy 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 rhabdomyolysis.

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 revealed pH 6.0, RBC 0-2/HPF, and negative occult blood. The CPK and Creatine Phosphokinase-MB (CK-MB)
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 rhabdomyolysis 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 rhabdomyolysis. 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 rhabdomyolysis**

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

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. Elevation of CPK is also common in hypothyroid patients. The serum CPK level did not correlate with weakness. 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. 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. And despite common CPK elevation, rhabdomyolysis 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). Our patients represents a rare case of hypothyroidism induced rhabdomyolysis. Hypocalcemia may be a result of rhabdomyolysis however hypocalcemia itself might proceed rhabdomyolysis. In our patient, the low iPTH

<table>
<thead>
<tr>
<th>Ca</th>
<th>CPK</th>
<th>FT4</th>
<th>TSH</th>
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<tr>
<td>mg/dL</td>
<td>IU/L</td>
<td>ng/dL</td>
<td>μIU/mL</td>
</tr>
<tr>
<td>2011/10/14</td>
<td>13034</td>
<td>&lt;4</td>
<td>171.2</td>
</tr>
<tr>
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<td>7.1</td>
<td>9835</td>
<td></td>
</tr>
<tr>
<td>2011/10/27</td>
<td>8.9</td>
<td>4936</td>
<td></td>
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<tr>
<td>2011/10/31</td>
<td>8.3</td>
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<td>2011/11/03</td>
<td>9.8</td>
<td>3688</td>
<td></td>
</tr>
<tr>
<td>2011/11/30</td>
<td>7.6</td>
<td>381</td>
<td>1.15</td>
</tr>
<tr>
<td>2012/01/18</td>
<td>8.6</td>
<td>127</td>
<td>1.29</td>
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Table 3. Hypothyroidism induced rhambdomyolysis*

<table>
<thead>
<tr>
<th>Author</th>
<th>Nation</th>
<th>Age</th>
<th>Sex</th>
<th>Etiology of hypothyroidism</th>
<th>CPK (IU/L)</th>
<th>TSH (μIU/mL)</th>
<th>Precipitating factor</th>
<th>Renal function impairment</th>
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<td>9332</td>
<td>147.7</td>
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<td>10210</td>
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<td>Mustafa A, 2005</td>
<td>Turkey</td>
<td>31</td>
<td>M</td>
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<td>2291</td>
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<td>M</td>
<td>not mentioned</td>
<td>972</td>
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<td>Kus HT, 2010</td>
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<td>75</td>
<td>F</td>
<td>s/p 131 and subtotal thyroidectomy</td>
<td>6020</td>
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<td>3239U/L</td>
<td>75</td>
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<td>F</td>
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<td>34724</td>
<td>77.2</td>
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<td>Guatemala</td>
<td>5</td>
<td>M</td>
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<td>Muir P, 2012</td>
<td>New Zealand</td>
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<td>M</td>
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<td>&gt;100</td>
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<td>1F</td>
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<td>3573</td>
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<td></td>
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<td></td>
<td></td>
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<td>3: unknown</td>
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*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 therapies18. Onset of hypothyroidism varies from 4 weeks to late as 5 or 10 years after completion of therapy18. Studies suggested thyroid function should be tested on a regular basis following radial therapy to the low-neck region17-19. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommended thyroid function tests should be repeated at 6–12 month intervals after radiotherapy20.

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 thyroiditis18. It may also be a result of radiation-induced damage to the hypothalamic-pituitary axis, which results in central hypothyroidism18.

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 elucidated18-19. Studies reported increased probability of developing primary hypothyroidism when the mean radiology dose on thyroid gland increased beyond 45Gy to 65Gy18. 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 rhabdomyolysis. And thyroid function should be checked periodically in patients with laryngeal or hypolaryngeal cancer whom underwent total laryngectomy and radiotherapy.

References

下咽癌治療後甲狀腺低下引起之橫紋肌溶解症

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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，口腔喉頭處沒有局部壞死、也沒有服用可能造成橫紋肌溶解的藥物。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)，同時有多低血鈣 (calcium 7.1mg/dl) (8.3-10.5mg/dl) 和肌肝素上升。進一步的檢查顯示甲狀腺低下及副甲狀腺低下，抗甲狀腺過氧化物酶為0.4 IU/mL (0-5.61 IU/mL)。補充甲狀腺素和鈣後，病人甲狀腺機能恢復正常，肌肉疼痛改善，CPK 值和肌肝素亦回復至基礎值。若病人出現原因不明的横紋肌溶解症，應想到是否有甲狀腺低下，仔細診斷並適當治療。