

Case Report

Elevation of Serum Creatine Kinase Induced by Anti-Thyroid Drugs: Two Cases Report and a Literature Review

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Abstract

Anti-thyroid drugs (ATDs), such as methimazole (MMI) and propylthiouracil (PTU), are the most common treatment options for hyperthyroidism. Although effective, well-known adverse effects include agranulocytosis, toxic hepatitis, vasculitis, and arthralgias. Myalgia and elevation of serum creatine kinase (CK) are relatively rare, with an unclear mechanism. Rapid decrease in the thyroid hormone level may be associated with ATDs-related myopathy; however, the direct effects of the drug on muscle tissue cannot be excluded. Here we report on two Chinese patients with myalgia and an elevated CK due to ATDs. Early recognition of this rare medication-induced adverse effect and close monitoring of the CK level are particularly important. Physicians and pharmacists should inform the patients about the earliest symptoms of adverse effects for patients to know when to discontinue the drug. If adverse events occur, different treatment strategies such as ATD dose reduction and switching to alternative ATDs can be applied depending on the case.

Keywords: Myalgia; Creatine kinase; Anti-thyroid drugs; Hyperthyroidism; Adverse effect

Introduction

Anti-Thyroid Drugs (ATDs) are the most common treatment options for hyperthyroidism [1]. These agents exert anti-thyroid action by inhibiting the oxidation and organic binding of thyroid iodide and by affecting the immune system of patients with Grave's disease [1,2]. They are generally prescribed for patients because of their potency and infrequent side effects, which are usually mild. More serious well-known adverse effects of ATDs include agranulocytosis and toxic hepatitis. Musculoskeletal complaints are relatively rare and mainly characterized by arthralgia, myalgia, muscle spasms, elevated Creatinine Kinase (CK) levels, and myoglobinuria [1]. Moreover, severe cases may be complicated with secondary Acute Renal Failure (ARF). To date, the exact cause for this complication remains uncertain. Several researchers suggested that this phenomenon may result from a rapid decrease in thyroid hormone [3,4]; however, the effects of the drug on muscle tissue cannot be excluded. In this case report, we report on two Chinese patients with myalgia and an elevated CK level undergoing treatment for hyperthyroidism with ATDs and discuss the potential underlying mechanism.

Case Presentation

Case 1

A 22-year-old female patient presented to the clinic with a 1-month history of heat intolerance, excessive sweating, and weight loss on August 3, 2019. She had no past medical or family history. On initial physical examination, her heart rate was 103 beats per minute, and a grade goiter was noted. Her blood work showed low levels of thyroid-stimulating hormone (TSH, <0.01 mIU/L, normal 0.56-5.91 mIU/L) and high levels of free triiodothyronine (FT₃, >46.08 pmol/L, normal 3.80-6.47 pmol/L) and free thyroxine (FT₄, 69.49 pmol/L, normal 7.90-14.40 pmol/L). Serum antithyrotropin receptor antibody was significantly elevated (TR-Ab, 34.86 U/l, normal <1.75 U/l), whereas the thyroid peroxidase and thyroglobulin antibodies tested negative. Ultrasonography of her neck demonstrated diffuse swelling of the thyroid gland. Based on her clinical symptoms and laboratory findings, Grave's disease was diagnosed, and she was started on methimazole (methimazole [MMI], 10 mg/d) added onto a β -blocker (propranolol), inosine, compound vitamin B, and Yingqining tablet (traditional Chinese medicinal agent with anti-thyroid properties). The dose of MMI was gradually increased to 25 mg/d over 3 months. Subsequently, blood tests showed FT₃ and FT₄ levels were within the normal range (FT₃ 6.56 pmol/L, FT₄ 9.91 pmol/L), whereas the serum TSH level was still undetectable (TSH, <0.05 mIU/L). However, the patient complained of a left upper limb twitch, and the serum CK level (CK, 328 U/l, normal 40-200 U/l) was slightly elevated. However, serum levels of Parathyroid Hormone (PTH), calcitonin, and electrolytes (including serum calcium) were within the normal range. The treatment regimen remained unchanged. After approximately 1 month of treatment, her limb twitch improved. As the potential induction of muscular damage by MMI could not be excluded, the treatment was switched from MMI to propylthiouracil (PTU, 300 mg/d) with continuation of other medications. However, serum CK was dramatically elevated to 872 U/l a month later. Following this, the

Citation: Yuqi S, Fenli S, Zhisen P, Haoxiang W, Chuangpeng S. Elevation of Serum Creatine Kinase Induced by Anti-Thyroid Drugs: Two Cases Report and a Literature Review. *Ann Short Rep Clin Image*. 2022; 3(2): 1027.

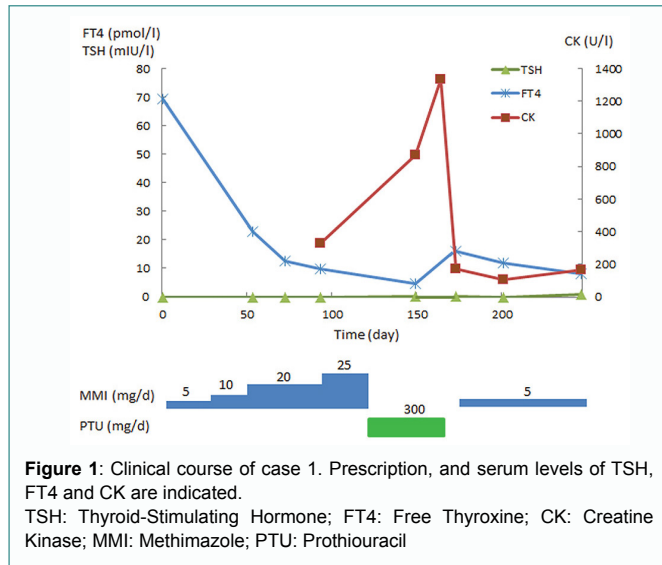
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Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 07th, 2022

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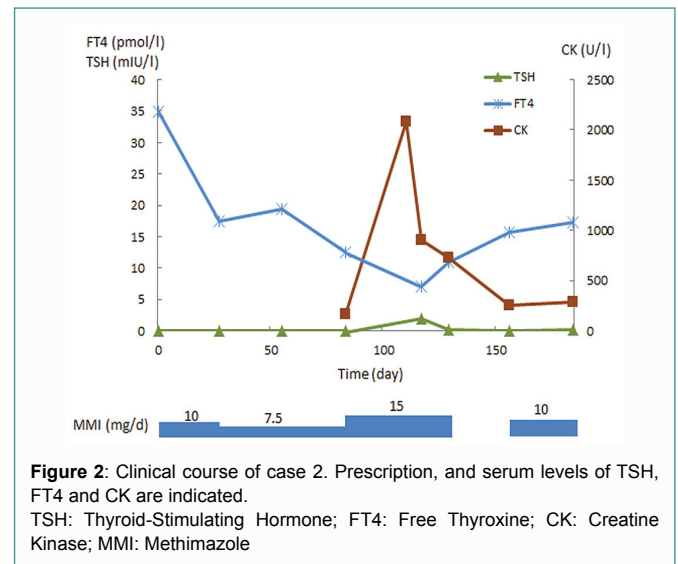
other medications were discontinued. Only 2 weeks later, the serum CK increased to 1332 U/l. These were in accordance with the normal level of serum CK (174 U/l), while the thyroid function tests also suggested a relapse of hyperthyroidism (FT_3 10.61 pmol/l, FT_4 15.99 pmol/l, TSH < 0.01 mIU/l) following termination of PTU for 9 days. As the patient had no obvious myalgia, MMI was re-administered at 5mg/d. At the 3-month follow-up, the patient remained clinically stable on 5 mg/d of MMI. Blood tests showed that thyroid function (FT_3 5.43 pmol/l, FT_4 8.03 pmol/l, TSH 0.852 mIU/l) and CK level (CK 164 U/l) were within the normal range on April 4, 2020 (Figure 1). The patient has since been on MMI (5 mg/d) treatment without recurrence of myalgia or elevation of serum CK.



Case 2

A 39-year-old male patient presented to the clinic with a 2-year history of heat intolerance, excessive sweating, and weight loss on July 14, 2019; he also complained these symptoms had worsened in the last six months. He had a history of hepatitis B and was taking telbivudine, an anti-hepatitis B drug. He had no specific family history or food and drug allergies. On physical examination, his heart rate was 96 beats per minute, and no goiter was noted. Her blood work showed low levels of TSH (0.013 mIU/l, normal 0.56-5.91 mIU/l) and high levels of FT_3 (14.52 pmol/l, normal 3.80-6.47 pmol/l) and FT_4 (34.97 pmol/l, normal 7.90-14.40 pmol/l). Serum thyroid peroxidase antibody (anti-TPO), thyroglobulin antibody (anti-Tg), and antithyrotropin receptor antibody (TR-Ab) levels were 279.24 IU/ml (normal 0-5.60 IU/ml), 11.56 IU/ml (normal 0-4.10 IU/ml), and 6.98 U/l (normal < 1.75 U/l), respectively. Liver enzymes were slightly elevated (ALT 46 U/l, normal 0-41 U/l, GGT 95 U/l, normal 10-60 U/l). Ultrasonography of his neck performed at another hospital indicated Hashimoto thyroiditis combined with hyperthyroidism. Based on his clinical symptoms and laboratory findings, Hashitoxicosis was diagnosed and he was started on MMI (10 mg/d) added onto inosine, compound vitamin B, and Yingqing tablets. In addition, gluconolactone was administered to improve liver function. After approximately 1 month of treatment, the patient felt improvements in most of the aforementioned symptoms. Thyroid hormone levels nearly normalized (TSH < 0.005 mIU/l, FT_3 7.2 pmol/l, FT_4 17.48 pmol/l), and liver enzyme values returned to normal. The MMI dosage was then decreased to 7.5 mg/d. After 2 months of treatment, FT_3 and FT_4 levels were within the normal range, and the serum TSH level was still undetectable. However, the

patient complained of myalgia, while the serum CK level was normal (CK, 171U/l). Considering that the TSH level was still abnormal, the dose of MMI was increased to 15 mg/d. After 3 weeks of treatment, the myalgia increased in severity and CK significantly increased to 2087 U/l when tested in another hospital; however, the patient continued to receive MMI at 15 mg/d for 1 week. Subsequently, all drugs were discontinued except telbivudine and serum CK gradually decreased to 256 U/l (normal 50-310 U/l) when tested at another hospital, and the patient's myalgia completely resolved after 6 weeks. Other test results including complete a blood count and liver enzyme assessment were within the normal range. The antinuclear antibodies tested negative. Thus, the patient was re-administered with MMI (10 mg/d) added onto inosine, compound vitamin B, and a Yingqing tablet. At the 1-month follow-up, the patient remained clinically stable on 10 mg/d of MMI without recurrence of myalgia. Blood tests showed that thyroid function (FT_3 5.29 pmol/l, FT_4 17.3 pmol/l, TSH 0.147 mIU/l) and CK level (CK 283 U/l, normal 50-310 U/l) on January 14, 2020 (Figure 2).



Discussion

CK is a muscle specific kinase, and the elevation of which may indicate the occurrence of muscle damage. Muscle complaints are frequent in patients with thyroid disease, including hyperthyroidism and hypothyroidism, as skeletal muscle is a target tissue for thyroid hormones [5,6]. Hypothyroid-induced myopathy often presents with myalgia and raised serum level of CK, while hyperthyroid-induced usually presents as a gradual onset of weakness and fatigue without myalgia, along with a normal or even decreased CK level [5,6]. CK elevation may occur as a complication of thyroid storm, which is precipitated by dehydration and electrolyte imbalance [7,8]. Thyrotoxic periodic paralysis is another relatively common complication that is usually seen in Asian men. However, it is painless and the CK level is usually normal [9]. In this case report, CK was not detected on the initial diagnosis of hyperthyroidism in two patients, and myalgia did not occur in the patients. Instead, symptoms of myalgia and muscle convulsion with increased CK level occurred during MMI treatment. Therefore, in contrast to the above, the increase in CK level was not related to high thyroid hormone level, but related to the treatment process. In recent years, several case reports [10-15] demonstrating elevations in serum CK

level during medical treatment for hyperthyroidism in adults and children have been published. We reviewed the previous 12 cases of hyperthyroidism that were associated with an elevation of CK level (Table 1). The commonly shared aspect of most of these cases was that there was an onset of myalgia with a concurrent rise of the CK level within 2 to 4 weeks of initiation of MMI treatment. The underlying reason for this phenomenon may be the rapid reduction of thyroid hormone (or relative hypothyroidism) by anti-thyroid treatments. Lu et al. [4] reported a case of a patient with high CK level and muscular symptoms after ATD treatment for 7 weeks and radioactive iodine (¹³¹I) treatment for 1 months. They observed elevated CK level with rapid normalization of thyroid hormone levels that supports the idea that “relative hypothyroidism” can induce myopathy during the treatment of hyperthyroidism. However, in our cases, myalgia and elevation of CK level occurred 3 months after ATDs therapy, and the decline in thyroid hormone levels was relatively mild. In addition, we found that many patients with drug-induced hypothyroidism due to ATD overdose also rarely experience elevated CK level and myalgia in a clinical setting. Therefore, the direct toxic effect of ATDs on myocytes and immune-related responses secondary to ATDs cannot be ignored. Although both our patients were treated with MMI, the complications persisted despite switching from MMI to PTU in case 2. Thus, these complications do not appear to be specific to either for MMI or PTU. The mechanisms underlying the elevation of CK level and the development of myalgia during treatment for hyperthyroidism with ATDs should be further investigated. The relationship between elevated CK level and the dose of ATDs is unclear. In the present cases, the dose of MMI was 15-25 mg/d for both patients with elevated CK,

and there was no consistency between the CK level and the dose of MMI. However, the myalgia symptoms were relieved after ATDs were discontinued. Both patients were eventually treated with low-dose (5-10 mg/d) MMI without recurrence of myalgia and CK elevation. These findings suggest that low-dose ATDs are relatively safe and less likely to cause muscle complications. It has been reported that the use of selective β -blockers may also cause an elevation of CK level [16], but this rarely occurs with non-selective blockers like propranolol [17], which is related to having only partial sympathetic activity. Setoguchi et al. [18] suggested that propranolol could also increase the risk of myopathy. As shown in Table 1, six patients [10,11,13,15] received β -blockers, four of whom [10,11,13] received propranolol. The physicians did not discontinue or reduce the dose of propranolol during the treatment, and the CK level still returned to normal [10,11]. In our report, the CK level continued to elevate after propranolol was discontinued in Case 1. This indicates that there is no correlation between the elevation of CK and the use of propranolol. Various treatment methods for myopathy have been used due to various mechanisms by which the myopathy resulting from treatment of hyperthyroidism could be caused as shown in Table 1. The symptoms of most patients were soon alleviated, and CK returned to normal after dose reduction of ATDs, switching to alternative ATDs, with or without supplementation of thyroid hormone.

Conclusion

Myalgia and elevation of serum CK are relatively rare complications of ATDs, and can occasionally develop over the first few weeks or even months in patients starting ATD therapy. Predicting the incidence in individual patients is difficult, and it is therefore recommended

Table 1: Comparison of cases increased serum CK levels during methimazole treatment in Graves' disease between previous studies and our case.

Study	Age(yrs)/ gender	Diagnosis	Dose of ATD	Drug combination	Time before symptom onset	Treatment
Fang [10]	20/female	Graves' disease	MMI, 30 mg/d	propranolol	3 wks	Change MMI to PTU (100mg/d)
	30/female	Graves' disease	MMI, 30 mg/d	propranolol	4 wks	Reduction of MMI dose (15 mg/d)
Tsang [11]	28/female	Graves' disease	CMZ, 30 mg/d	propranolol	2 wks	Discontinuation of CMZ; maintenance propranolol; subsequently treated with PTU
Cheng [12]	25/female	Graves' disease	MMI, 30 mg/d		not clear (after treatment with MMI)	Change MMI to PTU (100 mg/d); coenzyme Q ₁₀ and L-thyroxine addition
	34/female	Hyperthyroidism	MMI, 20 mg/d, tapered to 10 mg/d	L-thyroxine	3 mths	Change MMI to PTU (150 mg/d); recurred after switch to MMI, finally lost to follow-up
	25/male	Hyperthyroidism	MMI, 30 mg/d, tapered to 20 mg/d		2 mths	Reduction of MMI dose (10 mg/d); coenzyme Q ₁₀ addition
Khalil [13]	29/male	Graves' disease	MMI, 20 mg/d	propranolol	2 wks	Discontinuation of MMI; maintenance propranolol; and propranolol; subsequently treated with ¹³¹ I
Andia Melero [14]	34/female	Hyperthyroidism	MMI 15 mg/d, tapered to 10 mg/d		2.5 mths	Discontinuation of MMI; recurred after switch to PTU; finally, L-thyroxine addition after thyroidectomy
Mizuno [15]	12/female	Graves' disease	MMI, 30 mg/d	β -blocker	1 mth	Reduction of MMI dose (7.5mg/d); discontinuation of β -blocker
	14/female	Graves' disease	MMI, 30 mg/d		1 mth	Change MMI to PTU; L-thyroxine addition
Case1	22/female	Hyperthyroidism	MMI, 5 mg/d, increased to 25 mg/d	propranolol, inosine, compound vitamin B and Yingqining tablet	3 mths	Change MMI to PTU (300 mg/d); discontinuation of other medications; finally, change PTU to MMI (5mg/d)
Case 2	39/male	Hashitoxicosis	MMI, 10 mg/d, tapered to 7.5 mg/d, then increased to 15 mg/d	tibivudine, glucuro lactone, inosine, compound vitamin B, Yingqining tablet	3 mths	Discontinuation of MMI; subsequently treated with MMI (10mg/d)

that physicians and pharmacists should be aware of this potential side effect when initiating treatment for hyperthyroidism. Myalgia must be monitored closely in the initial state of ATD treatment. CK measurement may serve as a good tool when patients present with myalgia. However, it is not necessary to routinely screen the serum CK level of every patient, given the rarity of the complication.

Funding

National Natural Science Foundation of China (No.81873265).

Authors' Contributions

Shen Chuangpeng conceived the presented idea. The manuscript was written through contributions of all authors. Si Yuqi and Su Fenli provided final approval of the version to be published. All authors have read and approved the final manuscript for publication.

Patient Consent for Publication

The patient provided written informed consent for the publication of any associated data and accompanying images.

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