Anti-Thyroid Drugs-Related Myopathy: Is Carbimazole the Real Culprit?

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1. Introduction

Thyroid dysfunction can lead to musculoskeletal symptoms, as thyroid hormones are essential to the growth, development and continued optimal function of most tissues and organs including skeletal muscle (1). The Anti-thyroid drugs (ATDs), carbimazole (CMZ) and propylthiouracil (PTU) are widely used as first-line medical therapy for treatment of hyperthyroidism due to Graves’ disease. These drugs are generally safe and effective, though patients can develop side effects (2). In literature, ATDs-related myopathy has been reported (3-10). It is characterized by clinical evidence of proximal muscle weakness, raised creatine kinase (CK) after recent commencement of ATDs and rapid resolution of symptoms after stopping or reducing the drugs, with or without addition of thyroid hormone supplement.

2. Case Presentation

A 28-year old Chinese female was treated with carbimazole (CMZ) for Graves’ disease with hyperthyroidism. Two weeks later, she developed myalgia and proximal muscle weakness. Investigations showed evidence of myopathy. CMZ was stopped and rapid improvement of clinical condition and biochemical parameters ensued.

Conclusions: Rapid decrement of thyroid hormone level is recognized as an important association for anti-thyroid drugs (ATDs)-related myopathy; however, the drug effects on muscle tissue cannot be excluded. Further elucidation of pathophysiology and identification of risk factors are needed. After commencing ATDs, early recognition of this rare condition and close monitoring are the essence of management. Different treatment strategies: dose reduction of ATDs, switching to alternative ATDs, with or without addition of thyroid hormone supplement can be applied depending on clinical situation.

Keywords: Muscular Disease; Myositis; Carbimazole; Graves’ disease; Hyperthyroidism; Creatine Kinase

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2. Case Presentation

A 28-year old woman presented to outpatient clinic with two months history of goiter, hand tremor, sweating, palpitation, heat intolerance and weight loss. She enjoyed a good past health and did not smoke nor drink. She denied recent intake of drugs or herbs. Clinically she was negative for feverishness and skin rash. Clinically there was proximal muscle weakness of upper and lower limbs with power grade 4/5. CK and LDH were found elevated with level 2.614 U/L and 219 U/L respectively. Other blood investigations showed ALP 294 U/L, ALT 20 U/L, calcium 2.18 mmol/L (normal range < 100) and anti-thyroglobulin titer 400 (normal range < 100) and anti-thyroid microsomal titer 102400 (normal range < 100). Graves’ hyperthyroidism was diagnosed. CMZ 10 mg thrice daily and propranolol 5 mg twice daily were given. About two weeks later, she developed myalgia especially at proximal parts of limbs. Two weeks after appearance of muscle symptoms, the patient was admitted to hospital for investigation. Patient reported no recent trauma, strenuous exercise or intramuscular injection. There was absence of feverishness and skin rash. Clinically there was proximal muscle weakness of upper and lower limbs with power grade 4/5. CK and LDH were found elevated with level 2.614 U/L and 219 U/L respectively. Other blood investigations showed ALP 294 U/L, ALT 20 U/L, calcium 2.22 mmol/L, phosphate 0.93 mmol/L (normal range 0.82-1.40), sodium 138 mmol/L (normal range 134-145), potassium 3.9 mmol/L (normal range 3.5-5.1), creatinine 43 µmol/L (normal range 44-80), white cell count 5.3 × 10⁹/L (normal range 3.6-9.9) with normal differential, hemoglobin 10.8 g/dL (normal range 11.1-15.1), platelet count 166 × 10⁹/L (normal range 150-400) and urine for myoglobin was negative. CMZ was stopped but propranolol was continued upon admission. Thyroid function was rechecked FT4 0.54 ng/dL, thyrotropin stimulating hormone (TSH) < 0.02 mIU/L (normal range 0.27-4.20). Erythrocyte sedimen-
tation rate, C-reactive protein and Troponin T were normal. Electromyography (EMG) revealed low motor unit action potential (MUAP) amplitudes, early recruitment and scantly polyphasia and no increase in spontaneous activity, which was suggestive of myopathy. Muscle biopsy was not performed. The CK peaked at 12,413 U/L; LDH peaked at 402 U/L, and then gradually declined. This was in line with patient’s clinical improvement. No renal complication was observed. Anti-nuclear antibody titre was 80, anti-DNA was < 50 U/mL and anti-extranuclear antibodies (Sm, RNP, La, Ro, Jo-1, Sc1-70) were negative. The diagnosis of carbimazole related myopathy was made. CK returned to normal three weeks later. PTU was commenced for anti-thyroid treatment. EMG was repeated and the result was normal. There was neither recurrence of muscle symptom nor elevation of muscle enzymes then. The thyroid hormones and muscle enzymes levels over time are summarized in Table 1. This case was reported to adverse drug reaction monitoring unit of Department of Health, Hong Kong SAR.

### 3. Discussion

Four forms of muscle disorders associated with thyroid disease have been described (3, 11). Hypothyroidism-related myopathy presents as myalgia, cramps, stiffness and proximal muscle weakness. Serum muscle enzymes including CK, LDH and myoglobin are frequently elevated. Though the elevation is usually mild, reports of a polymyositis-like illness or rhabdomyolysis with dramatic elevations in muscle enzymes do exist (12). The clinical manifestations of hypothyroid myopathy may precede the biochemical detection of hypothyroidism, so repeated tests of thyroid function are warranted in patients with idiopathic hypothyroid myopathy. The thyroid hormones and muscle enzymes levels over time are summarized in Table 1. This case was reported to adverse drug reaction monitoring unit of Department of Health, Hong Kong SAR.

| Time | FT4 (0.9-1.7) | CK (32-180) | LDH (87-213) |
|------|--------------|-------------|--------------|
| 0 d  | > 7.8        | 49          | 174          |
| 30 d | 0.5          | 2614        | 219          |
| 32   | FT4 not measured, so result not available | 12413 | 402 |
| 33   | FT4 not measured, so result not available | 7036 | 283 |
| 38   | FT4 not measured, so result not available | 632 | 212 |
| 50   | 4.1          | 67          | 159          |
| 170  | 3.8          | 42          | 167          |

**Abbreviation:** FT4, free thyroxine level; TSH, thyrotropin stimulating hormone; CK, creatine kinase; LDH, lactate dehydrogenase.

**Notes:**
- TSH (0.27-4.20) for all of them is < 0.02
- Days after first presentation.
- Treated with Carbimazole.
- Treated with Propylthiouracil.

### Table 1. Summary of Thyroid Function, Muscle Enzymes Level and Use of ATDs Over Time

A recent review of these 14 reported cases suggested a possible genetic susceptibility in Asian and female preponderance (5). Our patient falls in this category. Nearly all cases were diagnosed Graves’ disease with hyperthyroidism and treated with MMZ or its pro-drug CMZ. The onset of muscle symptoms was within three months of commencing the medications. Common features of ATDs-related myopathy are summarized in Table 2. Management of myopathy varied among reported cases. Dose reduction of MMZ or CMZ (4, 6, 9), cessation of MMZ or CMZ and switching to PTU (3, 5, 9), or addition of levothyroxine (4, 6-8) had led to resolution of myopathy. The exact pathophysiology of the myopathy is unclear. Various mechanisms including direct effect of antithyroid drugs on myocytes, immune-related responses secondary to ATDs and rapid decrements in thyroid hormone has been proposed (5, 6). The former two mechanisms rationalize the effectiveness of reducing or stopping current ATDs. On the other hand, one case successfully managed by continuing same dose of methimazole with addition of levothyroxine points more to the harmful effect of rapid decrements in thyroid hormone (6). This can explain the development of myopathy in the early course of hyperthyroidism, which often involves substantial decrease in thyroid hormone level after treatment.
Reports of myopathy occurred after radioactive iodine therapy (7, 17) or thyroidectomy (8) is also supportive to this mechanism. Shaheen and Kim postulated this relative hypothyroidism could lead to deficiency in the transport and/or production of local triiodothyronine in skeletal muscle, and contributing to myositis (8). One may reasonably postulate that the myopathy remits itself as the thyroid hormone level stabilized after appropriate diagnosis and adjustment of ATDs. Though addition of levothyroxine seems to be beneficial in treating myopathy, whether it can hasten the remission of myopathy is unclear, and no obvious effect is observed in these case reports. If rapid decrement of thyroid hormone were the sole explanation, though ATDs-related myopathy may be underreported (8), it would be expected to be more common. Should we treat patients with Graves’ disease in a more gradual manner to prevent the myopathy? We cannot answer confidently before further elucidating the pathophysiology and identifying the risk factors of this condition.

Although the ATDs-related myopathy is rare, early recognition of this condition is important in management. Putting high index of suspicion in recognizing muscle symptoms and signs after starting ATDs followed by appropriate investigations including muscle enzymes, EMG and muscle biopsy help early diagnosis. In terms of management, switching to alternative ATDs, as in our case may terminate the possible drug effect on muscle tissue. The rapid decrement of thyroid hormone level after commencing ATDs can contribute to development of myopathy. Maintaining a stable thyroid hormone level, with or without adding thyroid hormone supplement is believed to be essential.

This case report illustrated a rare side effect of ATDs myopathy that may cause patients significant morbidity. Early recognition of this condition and close monitoring are the essence of management. Dose reduction of ATDs, switching to alternative ATDs, with or without addition of thyroid hormone supplement can be applied depending on clinical situation.

Authors’ Contributions

Dr. Chiu Chi Tsang worked on conception and design, acquisition of data, analysis and interpretation of data, drafting manuscript, administrative support. Dr. Wai Shan Hui, Dr. Kwun Man Lo and Dr. Jonas Hon Ming Yeung worked on analysis and interpretation of data, critical revision of the manuscript, Dr. Yuk Lun Cheng worked on analysis and interpretation of data, critical revision of the manuscript, study supervision.

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Table 2. Common Features of ATDs-Related Myopathy

| Features                                      |
|----------------------------------------------|
| Asian ethnic                                 |
| Graves’ disease with hyperthyroidism         |
| Young to middle-aged lady                    |
| Onset of muscle weakness within three months of methimazole or carbimazole |
| Proximal muscle weakness                     |
| Elevated muscle enzymes                      |
| Suppressed or normal TSH                      |
| TSH-thyrotropin stimulating hormone          |

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