When polymyositis meets Graves' disease: A rare case report

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SUMMARY

Polymyositis is rarely associated with Graves' disease. A 22-year-old woman was admitted for progressively worsening proximal muscle weakness of both upper and lower extremities. One month prior to admission, she was diagnosed with thyrotoxicosis and prescribed carbimazole 10mg twice daily. Neurological examination confirmed proximal myopathy and blood investigations revealed marked elevation of muscle enzymes, particularly creatine kinase. Electromyography demonstrated myopathic changes while right quadriceps muscle biopsy showed only traces of inflammatory myopathy. She was treated with pulsed intravenous methylprednisolone followed by tapering doses of oral prednisolone, which was eventually down-titrated to 5mg daily during subsequent clinic visits. The initial clinical improvement that she exhibited did not persist despite being rendered euthyroid. She was re-admitted approximately one year later with the same complaint. A second course of intravenous methylprednisolone brought about clinical improvement as well as reduction of creatine kinase levels. A diagnosis of polymyositis was then made, for which she was managed with oral prednisolone 20mg daily in combination with gradual up-titration of azathioprine. She continued to show clinical and biochemical improvements during follow-ups. Polymyositis should be considered in the diagnostic workup of proximal myopathy in a patient with Graves' disease, especially in the setting of markedly raised muscle enzymes.

INTRODUCTION

Muscle involvement is common in hyperthyroidism and has been reported in about 80% of thyrotoxic patients.[1] However, polymyositis has rarely been described as the aetiology of proximal muscle weakness in a patient with Graves' disease.[2-5] We report a young lady who presented with proximal myopathy at diagnosis of Graves' disease which was eventually attributable to polymyositis.

CASE REPORT

A 22-year-old woman was admitted in March 2020 at Hospital Sultanah Aminah, Johor, Malaysia for further investigation and management of proximal muscle weakness. She experienced progressively worsening bilateral lower limb weakness since the end of January 2020, which hampered her ability to rise from a sitting or squatting position. This was associated with palpitations and hand tremors. She denied heat intolerance, weight loss or menstrual irregularity. There was no family history of thyroid disorder. A diagnosis of thyrotoxicosis was made at a primary care clinic based on her presentations, supported by a biochemical picture in keeping with hyperthyroidism (Table I). She was prescribed with carbimazole 10mg twice daily and subsequently referred for tertiary care in our centre.

Physical examination revealed a calm and thin (Body mass index, BMI 16.5 kg/m^2) woman who had exophthalmos, a diffuse goitre and bilateral hand fine tremors. Blood pressure was 117/72mmHg and pulse rate was 124 beats per minute. There was no evidence of heliotrope rash, shawl sign or Gottron's papules. Neurological examination showed a predominantly proximal muscle weakness: Medical Research Council (MRC) scale 3 for bilateral shoulder abduction and adduction as well as hip flexion and extension; scale 4 for muscle power over bilateral elbows, wrists, fingers, knees and ankles. Neck flexion and extension were MRC scale 3 and 5 respectively. There were no muscle wasting and fasciculations. Other systemic examinations were unremarkable.

Relevant investigations during this admission were detailed in Table I. Of note, free thyroxine (T4) was subnormal while thyroid-stimulating antibody (TSH) remained suppressed after one month of carbimazole treatment. Significant elevation of both thyroid autoantibodies indicated the diagnosis of Graves' disease. There was only mild hypokalaemia. Muscle enzymes, in particular creatine kinase (CK), were markedly elevated. Autoimmune markers including anti-nuclear antibody (ANA), extractable nuclear antigen (ENA) and rheumatoid factor (RF) were negative. Complement factors C3 was low while C4 was low normal. Inflammatory myopathy panel was not sent.

In view of raised muscle enzymes, she was treated with three days of pulsed intravenous methylprednisolone after right quadriceps muscle biopsy. Physiotherapy was also commenced. Slight improvement of upper limb proximal muscle power was observed following treatment and this was accompanied by a gradual decrease in CK levels (Figure 1). She was subsequently discharged with tapering doses of oral prednisolone. Carbimazole was withheld throughout admission due to very low free T4 level but resumed one month later when a repeat free T4 rose above normal range.

During a follow-up visit in neurology clinic three months after discharge, our patient demonstrated clinical improvement as evidenced by her ability to rise from a sitting

This article was accepted: 19 September 2021
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Table I: Blood investigations at initial presentation and on first hospital admission

Blood tests	Reference range	Initial Presentation	Admission
TSH (mIU/L)	0.27-4.20	<0.01	<0.005
Free T4 (pmol/L)	12.0-22.0	50.2	6.75
Free T3 (pmol/L)	3.1-6.8	17.9	
TPOAB (IU/ml)			1395.33
ATGAB (IU/ml)			1002.65
Hb (g/L)	120-150		100
WBC (10^9/L)	4.0-10.0		2.8
Platelet (10^9/L)	150-410		436
Sodium (mmol/L)	136-145		133
Potassium (mmol/L)	3.50-5.10		3.47
Urea (mmol/L)	2.8-8.1		1.5
Creatinine (µmol/L)	44-80		29
Albumin (g/L)	35-52		32
ALT (U/L)	5.0-33.0		68
ALP (U/L)	35.0-104.0		43
CK (U/L)	26-132		2514
AST (U/L)	5.0-32.0		193
LDH (U/L)	135-214		834
ESR (mm/hr)	0-20		57
CRP (mg/L)	<5		<0.3
RF (IU/ml)	<14		<10
C3 (g/L)	0.9-1.8		0.784
C4 (g/L)	0.1-0.4		0.109
Anti-Nuclear Antibody IF Test			
Anti-Nuclear Antibody			Negative
Anti-Double-Stranded DNA			Negative
Extractable Nuclear Antigen			
ENA			Negative
Anti-Smith			Negative
Anti-RNP			Negative
Anti-Sjogren's Syndrome A/Ro			Negative
Anti-Sjogren's Syndrome B/La			Negative
Anti-SCL-70			Negative
Anti-JO-1			Negative

TSH thyroid-stimulating hormone, T4 thyroxine, T3 triiodothyronine, TPOAB Thyroid Peroxidase Antibody, ATGAB Anti-thyroglobulin Antibody, Hb haemoglobin, WBC white blood cell, ALT alanine transaminase, ALP alkaline phosphatase, CK creatine kinase, AST aspartate aminotransferase, LDH lactate dehydrogenase, ESR erythrocyte sedimentation rate, CRP C-reactive protein, RF rheumatoid factor, C3 complement factor 3, C4 complement factor 4, IF immunofluorescence, ENA extractable nuclear antigen, Anti-RNP anti-ribonucleoprotein, Anti-SCL-70 anti-topoisomerase I, Anti-JO-1 anti-histidyl-transfer RNA (tRNA) synthetase

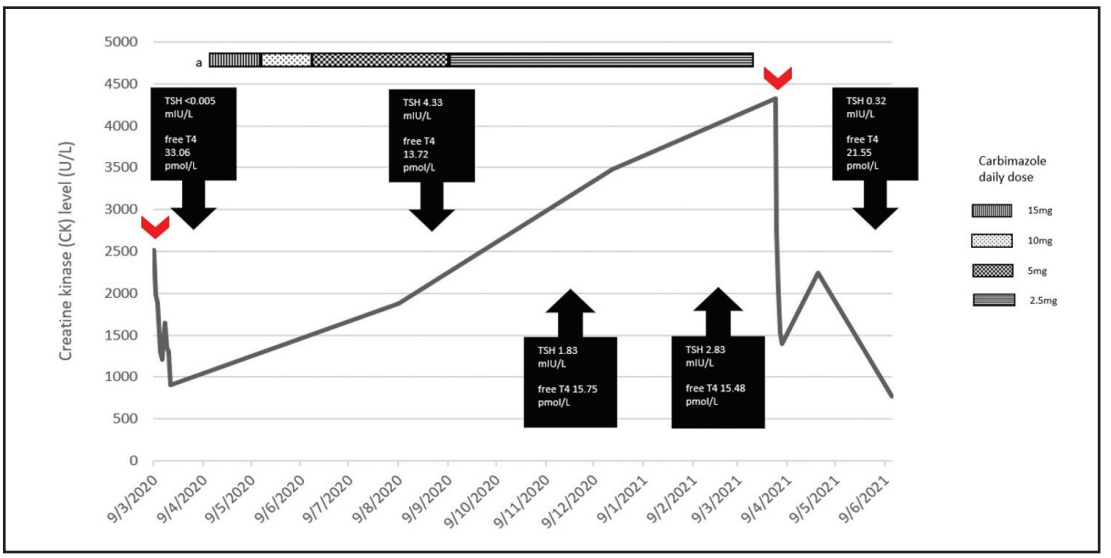

Fig. 1: Creatine kinase (CK) trend with corresponding thyroid function tests from first hospital admission till last clinic review. Arrow heads represent the timepoints of pulsed intravenous methylprednisolone.
[a]Doses of carbimazole at respective time intervals

position and gradual normalisation of proximal muscle power (MSC scale 4 in proximal muscle groups and scale 5 in distal muscle groups). Electromyography (EMG) showed motor unit potentials (MUPs) of small amplitude with short-duration waveforms and early recruitment pattern, which were in line with myopathic changes. Right quadriceps muscle biopsy was also reported as showing myopathic changes with marked variation in fibre size, few pyknotic nuclei, scattered atrophic fibres, and few necrotic and regenerating fibres. No lymphocytic infiltrate was seen. Her prednisolone dose was then down-titrated to 5mg daily in light of good clinical response.

Meanwhile, she attained euthyroid state while taking carbimazole. Approximately one year after her initial presentation, she was able to come off carbimazole and remained in remission of Graves' disease (Figure 1). However, this had not been the case for her proximal muscle weakness. Despite initial clinical improvement, complete recovery was not observed. She was readmitted in April 2021 due to worsening lower limb weakness, which again limited her movement from a chair. There was concurrent rise in her CK levels. A three-day course of pulsed intravenous methylprednisolone led to both clinical and biochemical improvements (Figure 1). She was discharged with oral prednisolone 20mg daily. Azathioprine was added during subsequent clinic visits.

DISCUSSION

Our patient presented with proximal muscle weakness at the onset of hyperthyroid symptoms. Differential diagnoses for such presentation include thyrotoxic periodic paralysis, thyrotoxic myopathy or co-existing polymyositis. The absence of profound hypokalaemia and protracted course of illness excluded thyrotoxic periodic paralysis.

Manifestation of thyrotoxic myopathy at the onset of thyrotoxic symptoms is, in fact, a rare occurrence. Commonly reported symptoms encompass predominantly proximal muscle weakness and wasting, although distal muscle involvement has also been described. The mechanism which underlies thyrotoxic myopathy likely involves upregulation of metabolic activity, which then accelerates catabolism of muscle cells. Muscle enzymes, including CK, are invariably normal while EMG generally exhibits a myopathic pattern. Muscle biopsy is frequently normal. Attainment of euthyroid state resolves thyrotoxic myopathy.[1]

Our patient's proximal myopathy was accompanied by marked elevation of CK levels, which responded to pulsed intravenous methylprednisolone followed by tapering doses of oral prednisolone. Despite initial improvement in her muscle symptoms, full regain of muscle power appeared to be delayed. To make matters worse, she had another episode of worsening proximal muscle weakness, which necessitated second hospital admission for pulsed intravenous methylprednisolone, approximately one year after her first hospitalisation. It is important to note that this recurrence of worsening muscle symptoms happened while she was euthyroid. In other words, restoration of euthyroid state did not seem to ameliorate her proximal muscle weakness. Hence, these findings clearly argue against the diagnosis of thyrotoxic myopathy.

All treatment modalities of hyperthyroidism, including antithyroid medications, radioactive iodine or total thyroidectomy, have been reported to cause abnormal increase in CK levels. Rapid reduction of thyroid hormone levels induced by these treatments has been implicated in creating a relative hypothyroid state which leads to muscular damage and thence release of muscle enzymes. In most reported cases where antithyroid drugs were used, muscle symptoms and elevated CK concentrations resolved with either dose reduction or discontinuation of antithyroid drugs, with or without addition of levothyroxine.[6] Our patient did have a rapid drop of free T4 from 50.2pmol/L at diagnosis of Graves' disease to 6.75pmol/L one month after carbimazole therapy. However, she did not have a baseline CK before initiation of carbimazole. Hence, it is unclear whether her CK levels were already elevated before or rose only after taking carbimazole. Additionally, her CK level was 19 times above upper limit of reference range during her first hospital admission. This degree of CK rise is in stark contrast to that reported by a Chinese group whereby majority of their patients, who were found to have increased CK concentrations while taking antithyroid drugs, had only mildly elevated CK levels (less than twice upper limit of normal range).[7] Moreover, dose reduction and eventually discontinuation of carbimazole did not result in a drop in our patient's CK concentrations. On the contrary, her CK continued to rise alongside worsening proximal muscle weakness, so much so that she needed to be hospitalised again, despite discontinuation of carbimazole one month prior (Figure 1). Therefore, we believe that carbimazole treatment is unlikely the aetiology which underlies her clinical symptoms and markedly high CK concentrations. Similarly, even though positive correlation between TSH and CK levels has been described,[7,8] we are of the opinion that the slightly raised TSH level in our patient four months after re-initiation of carbimazole could not have contributed to the increasing CK concentrations as subsequent normalisation of TSH did not abate CK rise (Figure 1).

Even though myopathic changes were demonstrated in our patient's EMG, these findings are actually non-specific and can be seen in both thyrotoxic and inflammatory myopathies. On the other hand, histopathological examination of our patient's right quadriceps muscle biopsy showed marked fibre size variability as well as few necrotic and regenerating fibres, which constitute some of the main features of polymyositis.[9] Lymphocytic infiltrate, another characteristic finding, was nonetheless absent in this muscle biopsy sample. All in all, putting clinical presentation and subsequent course of illness, muscle enzyme elevation, myopathic EMG pattern as well as presence of inflammatory features in muscle biopsy all together, a diagnosis of polymyositis co-existing with Graves' disease was made. She was treated with both oral prednisolone and azathioprine, and continued to experience improvement in her muscle symptoms and reduction in CK levels thereafter.

Coexistence of Graves' disease and polymyositis is rare.[2-5] A review of literature by Wang H et al. summarised the findings of seven cases of polymyositis with hyperthyroidism (five of which had positive thyroid autoantibodies). All patients were females, aged between 16 and 52 years, and were diagnosed with polymyositis and hyperthyroidism at mean age of 35.3 years and 32.7 years respectively. Hyperthyroidism was

frequently diagnosed before polymyositis. The most common complaint of polymyositis was proximal muscle weakness. Muscle enzymes were almost always elevated. Electromyography results were available in four cases and generally showed myopathic changes. Muscle biopsy in four patients demonstrated inflammatory infiltrate, variation of fibre size, fibre atrophy as well as fibre necrosis. All were treated with antithyroid therapy, out of which six received corticosteroid with or without additional immunosuppressive agents for polymyositis. Complete recovery of muscle dysfunction, as defined by clinical remission and/or normalisation of muscle enzymes, were seen in all but one. One patient experienced partial recovery, as indicated by clinical improvement short of a complete clinical response.[10] Our case is similar to those reported in the aforementioned review. Long term follow-up is imperative to monitor her progress, both clinically and biochemically.

The pathogenetic links between these two autoimmune conditions have yet to be discerned. Some of the proposed mechanisms include common environmental triggers of both conditions in genetically susceptible individuals, cross-reactivity between thyroid autoantibodies with antigens on other tissues or organs or vice versa, immunomodulatory effects of autoantibodies, cytokine imbalance, and possible genetic link between thyroid autoimmunity and predisposition to other autoimmune diseases.[10] More research in this area would be beneficial in providing a clearer picture on the pathogenesis behind the rare coexistence of Graves' disease and polymyositis.

In summary, polymyositis should be considered in the diagnostic workup of proximal muscle weakness in conjunction with markedly raised muscle enzymes in a patient with Graves' disease, despite the rare association. Muscle biopsy remains the gold standard to confirm the diagnosis. Timely management diminishes or eliminates inflammation, restores muscle function and thence accelerates recovery.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia for the permission to publish this case report.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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