An Unusual Presenting Symptom of Graves' Disease: Myalgia

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What Is Known about This Topic?

- Hyperthyroidism has a profound effect on skeletal muscles and often leads to myopathy, with muscular weakness being the commonest sign [1].
- The prevalence of myopathic features in hyperthyroidism is reported to be between 60 and 80% [2, 3].
- Thyrotoxic myopathy usually resolves after the restoration of euthyroidism [4, 5].

What Does This Case Report Add?

- It highlights that myalgia can rarely be the presenting symptom of thyrotoxicosis and resolves rapidly after euthyroidism is restored.
- Awareness of this very rare manifestation of thyrotoxicosis may obviate the need to seek alternative diagnoses.

Key Words

Graves' disease • Thyrotoxicosis • Myalgia

Abstract

A 50-year-old female patient presented with severe myalgia involving her proximal muscles for 3–4 weeks. She also reported mild thyrotoxic symptoms over the same time period. Examination revealed mild thyrotoxicosis, a moderate diffuse goiter and no eye signs. The clinical picture was dominated by muscle pain and tenderness involving mainly her proximal arms and legs, her calves and her fingers, requiring opiate analgesia. Muscle power and tendon reflexes were normal. Laboratory evaluation revealed undetectable serum

thyroid stimulating hormone (TSH) with raised FT4, FT3 and positive TSH receptor antibodies. Treatment with carbimazole was started. Additional laboratory investigations were negative (inflammatory markers, creatine kinase and antibodies to antinuclear antibodies, gastric parietal cell, smooth muscle, mitochondrial, dsDNA, centromere, extractable nuclear antigen (ENA) ribonucleoprotein, ENA Sm, ENA Ro, ENA Anti-La, ENA Scl70, ENA Jo-1, anti-CCP and rheumatoid factor). Further assessment in the rheumatology clinic confirmed there was no small joint tenderness or loss of range of movement of her limbs, but widespread and profound muscle tenderness of the common extensors of the forearms, biceps, trapezius, calves and thighs. She was treated symptomatically with analgesic medication and continued

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on carbimazole. A month later she was euthyroid and her myalgia had resolved. Hyperthyroidism has a profound effect on skeletal muscle and often leads to myopathy. Severe myalgia in association with Graves' disease is rare and resolves with the restoration of euthyroidism.

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Introduction

Graves' disease is the commonest cause of thyrotoxicosis [6]. It is an autoimmune disorder in which circulating immunoglobulin G autoantibodies bind to and activate G-protein-coupled thyrotropin receptors, causing increased hormone production. Symptoms and signs of Graves' disease result either from the effect of hyperthyroidism or autoimmune processes. The latter include orbitopathy, goiter and thyroid dermopathy. Musculoskeletal complaints are common in patients with thyroid dysfunction. Patients suffering from Graves' disease usually experience weakness in their proximal muscles [1]. Muscle weakness may rarely be due to thyrotoxic periodic paralysis, a potentially fatal complication of thyrotoxicosis [7]. In addition, Graves' disease has been associated with autoimmune disorders of muscles such as polymyositis and myasthenia gravis [8, 9]. We describe a 50-year-old patient with Graves' disease, whose dominant presenting symptom was myalgia.

Case Presentation

A 50-year-old female patient presented to an endocrinology outpatient clinic for further management. For 3–4 weeks, she had been experiencing severe muscle aches in her arms and thighs and pain in her fingers, shoulders and calves, resulting in sleep disturbance. Over the same period of time she reported an increase in her appetite, a small rise in her weight and excessive thirst. The myalgia tended to be more intense in the mornings and was associated with stiffness lasting up to 2 h. She had experienced no previous episodes similar to this and there was no history suggestive of viral infection. Her past medical history included osteoarthritis of her knee and cervical spine and a right frozen shoulder, for which she had undergone a hydrodilatation with significant benefit. She had a previous history of recurrent urinary tract infections, for which cefalexin was prescribed as long-term prophylaxis. The patient was also taking propranolol, trazodone and tramadol.

Upon physical examination, she was mildly thyrotoxic with no features of Graves' orbitopathy. A moderate diffuse goiter was observed. Her proximal muscles were significantly tender. Muscle power and tendon reflexes were within the normal range. Laboratory evaluation showed a suppressed serum thyroid stimulating hormone (TSH; <0.05 mU/l, normal range 0.3–4.7), whereas FT4 (54.1 pmol/l, normal range 9.5–21.5 pmol/l) and FT3 (22.7 pmol/l,

Table 1. Laboratory investigations for myalgia

Double-stranded DNA antibody	negative
Rheumatoid factor	negative
Centromere antibody	negative
ENA RNP antibody	negative
ENA Sm antibody	negative
ENA Ro antibody	negative
ENA Anti-La antibody	negative
ENA Anti-Scl70 antibody	negative
ENA Jo-1 antibody	negative
Anti-CCP antibody	negative
ESR	6
C-reactive protein	<5 mg/l (0–5)
Creatine kinase	36 U/l (10–160)
Serum potassium	4.4 mmol/l (3.5–5.3)
Total vitamin D	53 nmol/l (>50 indicate sufficiency)
Serum parathyroid hormone	24 ng/l (10–60)
Serum alkaline phosphatase	57 U/l (35–120)
Serum alanine transaminase	105 U/l (0–40)

Ranges are in parentheses. ENA = Extractable nuclear antigen; ESR = erythrocyte sedimentation rate; RNP = ribonucleoprotein.

normal range 3.5–6.5) were increased (measured using electrochemiluminescence technology Modular E170; Roche Diagnostics, 2-site sandwich assays for TSH and competitive assays for free thyroid hormones) with positive TSH receptor antibodies (5 IU/l, upper limit of normal 1.5 IU/l, measured by an RIA-coated tube kit (RSR Ltd., Pentwyn, Cardiff) and negative thyroid peroxidase antibodies (7 IU/ml, normal range 0–34, Roche Diagnostics). She was prescribed carbimazole (20 mg) to be taken orally twice a day. The patient was referred to a rheumatology clinic for further investigation of the myalgia. Detailed musculoskeletal examination revealed widespread and profound muscle tenderness of the common extensors of the forearms, biceps, trapezius, calves and thighs, but no small joint tenderness or loss of range of limb movement. A musculoskeletal ultrasound was performed with no evidence of hand synovitis or tenosynovitis. Additional laboratory investigations were negative (table 1). The serum alanine transaminase was elevated at 105 U/l but without concurrent elevation of creatine kinase. Within 1 month of commencing treatment with carbimazole, the patient's myalgia had almost completely resolved. One month later she was clinically and biochemically euthyroid and levothyroxine was added to her treatment.

Discussion

Muscular weakness is a common sign in hyperthyroidism. Symptoms are primarily those associated with chronic proximal myopathy [1]. Rarely, bulbar muscles may also be involved [10, 11]. Thyrotoxic myopathy usu-

ally resolves following the restoration of euthyroidism [4, 5]. However, musculoskeletal symptoms including myalgia have been described as an adverse effect of treatment with antithyroid drugs [12, 13]. Thyrotoxic periodic paralysis is a rare life-threatening complication of Graves' disease. It is characterized by transient, recurrent episodes of flaccid muscle paralysis, affecting proximal muscles more severely than distal muscles. Both hypokalemia and elevated levels of thyroid hormones are important features during the acute episode for establishing the diagnosis [14]. The coexistence of Graves' disease and myasthenia gravis is rare but well recognized [9, 15]. Polymyositis has also been associated with Graves' disease [8, 16]. On the other hand, increasing evidence indicates that vitamin D plays an essential role in skeletal muscles. Vitamin D deficiency can be an etiological factor of nonspecific musculoskeletal pain. Up to 93% of individuals reporting nonspecific musculoskeletal pain are deficient in vitamin D (serum 25-hydroxyvitamin D [25(OH)D] <20 ng/ml [50 nmol/l]), suggesting that insufficient levels of this secosteroid may contribute to the etiology of musculoskeletal pain [17].

The absence of muscle fatigue and other features of myasthenia gravis ruled out this diagnosis in our case. Likewise, the clinical picture and normal serum potas-

sium were inconsistent with periodic paralysis. Negative autoantibody screen, normal serum creatine kinase, normal inflammatory markers and the absence of muscle weakness excluded the diagnosis of polymyositis, and the normal serum vitamin D, calcium and parathyroid hormone levels excluded vitamin D deficiency as a cause of her symptoms. The improvement of our patient's myalgia in parallel with the restoration of euthyroidism is highly suggestive of thyrotoxicosis being the cause of the myalgia. To the best of our knowledge, this is a very rare manifestation of Graves' disease, with one other case having been reported previously [18].

Conclusion

Myalgia can rarely be the presenting symptom of thyrotoxicosis and may resolve rapidly after the restoration of euthyroidism.

Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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