



A Case of Proximal Myopathy Resulting from Multiple Causes

Parathyroidectomy was unsuccessful in presence of co-existing inclusion body myositis

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ABSTRACT

We describe here a 73 year old woman who was referred to the endocrine clinic with hypercalcaemia and worsening proximal myopathy of the lower limbs. She was diagnosed with hypercalcaemia secondary to mild primary hyperparathyroidism four years previously. She was taking levothyroxine for hypothyroidism. She was referred to neurology as well. Her blood results also suggested vitamin D deficiency. She underwent muscle biopsy which was diagnostic of Inclusion body myositis. Thus she had multiple causes contributing to proximal myopathy, i.e. Inclusion body myositis, hyperparathyroidism, vitamin D deficiency and long standing hypothyroidism. She was treated with methotrexate with no improvement of her myopathy. As hypercalcaemia with excess Parathyroid hormone can worsen myositis, after repletion of vitamin D, she underwent parathyroidectomy. When she last visited the clinic her serum calcium and vitamin D were normal but there had been no improvement in her myopathy. This was owing to her co-existent Inclusion body myositis.

Key words: Hyperparathyroidism, Hypercalcaemia, Vitamin D deficiency, Inclusion body myositis, proximal myopathy.

Birçok Neden Kaynaklı Bir Proksimal Miyopati Olgusu

Eşlik eden inklüzyon cisimciği miyoziti varlığında paratiroidektomi başarısızdı.

Burada 73 yaşında, hiperkalsemi ve alt ekstremitte proksimal miyopati kötüleşmesi ile endokrin polikliniğine sevk edilen bir kadın hasta sunuldu. Hastaya 4 yıl önce hafif primer hiperparatiroidizme sekonder hiperkalsemi tanısı konmuştu. Hasta hipotiroidizm nedeniyle levotiroksin kullanmaktaydı. Aynı zamanda nöroloji kliniğine de gönderilmişti. Hastanın kan bulguları aynı zamanda vitamin D eksikliğini düşündürmekteydi. Hastaya kas biyopsisi yapıldı ve sonuç inklüzyon cisim miyoziti tanısı olarak geldi. Bu bulgulara göre hasta proksimal miyopatiye neden olacak inklüzyon cisim miyoziti,

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hiperparatiroidizm, vitamin D eksikliği, uzun süreli hipotiroidizm gibi birçok patolojiye sahipti. Hasta metotreksat ile tedavi edildi ve fayda görmedi. Artmış paratiroid hormonu ile birlikte hiperkalsemi miyoziti kötüleştirebileceğinden, hastaya vitamin D replasmanı sonrası paratiroidektomi yapıldı. Hasta son klinik vizitine geldiğinde vitamin D ve serum kalsiyum düzeyleri normaldi ancak miyopatisinde düzelme olmamıştı. Bunun hastanın eşlik eden inklüzyon cisim miyozitine bağlı olduğu düşünüldü.

Anahtar kelimeler: *Hiperparatiroidizm, hiperkalsemi, vitamin D eksikliği, inklüzyon cisim miyoziti, proksimal miyopati*

INTRODUCTION

Hyperparathyroidism is amongst the few established endocrine causes of proximal myopathy. Correction of hypercalcaemia and lowering of parathyroid hormone level can mitigate the problems with myopathy. However despite undergoing parathyroidectomy there was no alleviation of our patient's symptoms. Once an established cause is found, the other rare causes tend to be overlooked. However in this patient, a muscle biopsy was undertaken which confirmed Inclusion body myositis. Though the net outcome of management was not beneficial, the diagnosis of Inclusion body myositis was important from the patient's psychological perspective; she was informed about the prognosis of her condition (1-4).

CASE

A 73 year old woman came to the clinic with weakness of the proximal muscles of her legs, which began about four years back, and hypercalcaemia. Her background history included hyperparathyroidism, decompression laminectomy 1 year previously for large postero-lateral disc extrusion compressing L5 nerve root, hypertension and hypothyroidism. Her medications included indapamide, lacidipine, valsartan, atenolol, Arthrotec (diclofenac and misoprostol) and levothyroxine. She had wasting of her thigh muscles with no fasciculation, tone was normal, knee and ankle jerks were normal and planter was flexor. At this presentation her adjusted serum calcium (adjusted for albumin) was 2.92 mmol/l (normal: 2.15- 2.60) , phosphate was 0.78 mmol/l (normal: 0.84-1.45 mmol/l), creatinine phosphokinase was 220

IU/l (normal: 60-170) and alkaline phosphatase and thyroid function were normal. She was diagnosed with mild hypercalcaemia four years ago when her serum calcium was 2.76 mmol/l with a parathyroid hormone level of 59 pg/ml (normal: 12-81).

Further investigations undertaken showed: an urinary calcium of 2.05 mmol/24 hours (normal: 2.5- 7.5) and a creatinine clearance of 51.4 ml/min (normal: 85-125). An abdominal radiograph showed no renal stone. To ensure that she did not have benign hypocalciuric hypercalcaemia, a repeat urine calcium was done which showed a calcium excretion of 3.40 mmol/24 hours. Her serum calcium repeated was 2.73 mmol/l with an ionised calcium of 1.40 mmol/l (normal: 1.05-1.30). Her parathyroid hormone was inappropriately high at 6.58 pmol/l (normal: 1.1-6.9; however in presence of hypercalcaemia a level > 2.7 suggests hyperparathyroidism). Her calcium : creatine excretion ratio was 0.013 (<0.01 suggests benign hypocalciuric hypercalcaemia) and 25(OH) D3 was 8.5 ng/ml (normal: 10-60 in summer when the test was done) . Her DEXA (dual energy x-ray absorptiometry) scan showed: SXA Forearm bone mass- Ultra (integral) was normal but in the lower quartile of the range and Distal (cortical): T score of -2.10 (osteopenic) ; DXA L1-L4 spine BMD (bone mineral density) was normal but in the lower quartile of the range; Total left hip BMD was normal. Hypercalcaemia with excess Parathyroid hormone can precipitate or aggravate myopathy; the patient was referred for parathyroidectomy. Following a 10 day course of 1.25 mg of ergocalciferol with careful monitoring of her serum calcium and proper imaging of the neck, the patient underwent parathyroidectomy The two lower parathyroids were removed (right one was 0.68 g with diffuse enlargement with parenchymal cells mainly chief cells and the left one was 0.61 g with abnormal nodules of parenchymal cells exhibiting a mixture of chief cells and oxyphil cells).

From the neurology department she had an EMG (electromyogram) which was inconclusive. Thus a biopsy of right tibialis anterior muscle was done which suggested Inclusion body myositis with the findings of inflammatory infiltrate of non- vacuolated fibres, muscle-fibre degeneration, cytoplasmic vacuolation, and filamentous inclusions. The patient was treated with weekly methotrexate with no consequence. She was also commenced on risedronate. The patient's latest blood results were normal: Adjusted serum calcium- 2.38 mmol/l, ionised calcium- 1.24 mmol/l, parathyroid hormone -5.5

pmol/l, 25(OH)D3- 14 ng/ml, phosphate- 1.04 mmol/l and alkaline phosphatase- 108 IU/l (normal: 35-105). Her thyroid function had remained normal throughout on 125 mcg of levothyroxine. However despite the correction of high serum calcium and excess parathyroid hormone level, the impact on her myopathy was not encouraging. This was presumably because of the rare co-existent Inclusion body myositis.

DISCUSSION

The patient was referred with hyperparathyroidism and proximal myopathy. She fulfilled two other NIH (National Institute of Health, USA) criteria for referral for parathyroid surgery (1,2). At the time of presentation on this occasion her serum calcium was 2.92 mmol/l and hence > 0.25 mmol/l above the upper limit of normal and her creatinine clearance was lower than 30% of normal. Hyperparathyroidism with hypercalcaemia can cause proximal myopathy (3,4). In the presence of hypercalcaemia influx of calcium into the muscle fibres can worsen myositis. In 1949, a myopathic syndrome associated with hypercalcaemia was first described by Vicale (5) and studied in 1974, in more detail by Patten and colleagues in both primary (6) and secondary (Mallette et al. 1975) hyperparathyroidism 25 years later (7). The syndrome improves with treatment of hyperparathyroidism. The similarities in the neuromuscular syndrome caused by primary (in which calcium is high) and secondary hyperparathyroidism (in which calcium is normal or low) may suggest a central role for parathyroid hormone (PTH) itself. There have been case reports of proximal myopathy improving after removing of parathyroid adenoma (8). The pathophysiology is possibly due to oversecretion of hormone, frequently from a parathyroid adenoma. Myopathy related to parathyroid dysfunction therefore appears to result from altered parathyroid hormone (PTH) level and impaired action of vitamin D.

After extensive review of the literature, we found mention of two case reports of hyperparathyroidism with polymyositis (9,10). The relationship was uncertain. We report the first case where hyperparathyroidism was associated with an infrequent entity, Inclusion body myositis. Hyperparathyroidism with hypercalcaemia, vitamin D deficiency and Inclusion body myositis all contributed to her myopathy. Long standing hypothyroidism (though her TFTs were normal with levothyroxine) could possibly

have been a contributing factor as well. The low and low-normal urinary calcium in the presence of hyperparathyroidism was possibly due to the effect of indapamide. Vitamin D deficiency can occur with primary hyperparathyroidism (11,12). Parathyroid surgery in the presence of vitamin D deficiency can lead to profound hypocalcaemia or "hungry bone syndrome" (13). Hence it was necessary to replete vitamin D before parathyroidectomy. There have been reports of proximal myopathy and respiratory muscle weakness improving following parathyroidectomy in secondary hyperparathyroidism secondary to chronic renal impairment (14).

Inclusion body myositis (IBM) is a form of inflammatory myopathy characterized by chronic muscle inflammation accompanied by muscle weakness (15,16). The onset of muscle weakness in IBM is generally gradual (over months or years) and can affect both proximal and distal muscles (usually proximal muscles). For some individuals, the disorder begins with weakness in the wrists and fingers that causes difficulty with pinching, buttoning, and gripping objects. There may be weakness of the wrist and finger muscles and atrophy of the forearm muscles and quadriceps in the legs. Dysphagia occurs in 50% of cases. Symptoms of the disease usually begin after the age of 50, although can occur earlier. IBM occurs more frequently in men than in women. IBM is generally resistant to all therapies. Histologically, the features include: inflammatory infiltrate, cytoplasmic vacuolation and characteristic tubo-filamentous inclusions within the cytoplasm and nuclei of muscle cells. EMG shows both myopathic and neurogenic changes. It occurs in both sporadic and inherited forms (s-IBM and i-IBM respectively). I-IBM has autosomal recessive and dominant variants. Genetic susceptibility factors are thought to influence who develops s-IBM but this is poorly understood currently. Familial and sporadic types share the same clinical, biological, MRI and histological features. The aetiology of IBM is largely unknown. Theories have proposed it as an autoimmune or viral-induced disorder or a degenerative muscle disorder with deposition of substances in the muscles similar to those found in Alzheimer's disease, for example, amyloid precursor protein. Corticosteroids and immunosuppressive drugs are not very helpful. Intravenous immunoglobulin may have a doubtful beneficial effect in a small number of cases. Physiotherapy may be helpful in maintaining mobility.

In conclusion, there may be multiple causes of proxi-

mal myopathy in a patient. Even if endocrine causes are present, it is imperative to search for different causes of myopathy. EMG may not be conclusive. Hence, a muscle biopsy is necessary. Vitamin D deficiency (usually causing hypocalcaemia) may co-exist with primary hyperparathyroidism (causing hypercalcaemia) and hence should always be looked for. Parathyroidectomy should be advised whenever necessary. Correction of hypercalcaemia and lowering of PTH level may prove to be beneficial in the presence of myopathy. However, in this case the myopathy did not improve because there were multiple causes, including co-existent Inclusion body myositis (diagnosed only by muscle biopsy) contributing to it.

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