Regression of calcinosis associated with adult dermatomyositis following diltiazem therapy

Str, Widespread ectopic tissue calcification is an important complication of dermatomyositis, sometimes causing severe disability, even after remission of underlying myositis. Its pathogenesis is poorly understood and hence treatments have been largely empirical with inconsistent success. We report an adult patient with dermatomyositis, who, despite aggressive immunosuppressive therapy and remission of underlying myositis, has suffered increasing calcification. After commencing diltiazem, however, he showed an objective reduction in his calcification as judged by serial dual energy X-ray absorptiometry (DXA) scans, and improvement in his clinical condition and function as assessed by health assessment questionnaires (HAQ).

A 15-yr-old patient presented with a violaceous rash affecting the face and the extensor surfaces of his limbs, generalized muscle tenderness and proximal muscle weakness (MRC grade 3–4). Small areas of calcification were noted in the right biceps and left hamstring muscles. His creatine phosphokinase (CPK) was 2528 U/l (normal range 30–250 U/l), his erythrocyte sedimentation rate (ESR) was 102 mm in the first hour (normal range 1–20) and he was antinuclear antibody (ANA) positive. An electromyogram and muscle biopsy (left quadriceps muscle) confirmed active myositis—dermatomyositis was diagnosed.

Prednisolone 40 mg daily was commenced but he proved refractory to therapy and, over the next 6 yr received courses of azathioprine and cyclosporin orally and intravenous pulsed methylprednisolone. He was also given 11 courses of intravenous immunoglobulin and underwent plasmapheresis on two occasions. This led to remission of his myositis.

Although the disease was complicated by calcification at an early stage, this only became significant 5 yr after presentation when its severity led to encasement of muscles and restriction and contractures of joints. This was so disabling that he became wheelchair bound despite physiotherapy and hydrotherapy. Despite worsening calcification his myositis remained in remission with normal CPK values allowing the reduction of his oral prednisolone to 12.5 mg once daily.

Following case reports of its successful use in calcinosis complicating systemic sclerosis [1, 2], diltiazem 60 mg daily was commenced. The dose was increased over the next 17 months to 360 mg daily during which time he underwent whole body DXA scanning including regional analysis of his bone mineral density in the areas most affected by calcification (arms, thighs and trunk). As the maximal dose of diltiazem was reached, a fall in the mineral content of the regions predominantly affected by calcification was recorded whilst his function and HAQ scores improved (Fig. 1).

Current treatment is cyclosporin 200 mg and diltiazem 360 mg daily together with alternate day prednisolone 5 mg/7.5 mg. He is no longer wheelchair bound, has a part-time job and can even play football.

Calcinosis associated with connective tissue disorders is thought to be due to localized processes rather than a systemic disturbance in calcium homeostasis. A possible mechanism in dermatomyositis is release of mitochondrial calcium from cells within damaged muscles which then forms the focus for dystrophic calcification [3].

We report a young man with severe calcification complicating dermatomyositis which has shown marked improvement following diltiazem treatment over 2.5 yr. This has resulted in functional improvement and a sustained reduction of calcification (monitored by DXA) following optimal diltiazem dose. Although his myositis was in remission when improvement occurred, we feel it unlikely that this alone could explain the regression of calcinosis, as such spontaneous improvement is rare even in remission. Moreover, although his myositis was suppressed during the year prior to starting diltiazem, the extent of his calcification had worsened, and only started to improve as diltiazem therapy reached the optimal dose of 360 mg daily.

Previous drug treatments used in ectopic calcification have included bisphosphonates [4], probenecid [5], aluminium hydroxide [6], warfarin [7] and the local injection of glucocorticosteroids [8]. Unfortunately none have shown more than anecdotal success. Several reports from the recent literature suggest that diltiazem may offer more consistent therapeutic benefit [1, 2, 9, 10]. The original use of diltiazem was based on modification of calcium physiology where a normally large gradient in calcium concentration exists between extracellular space (calcium concentration 10^{-3} M) and cytosol (concentration 10^{-7} M). Palmieri et al. postulated that if such a gradient was disrupted and cellular calcium was to increase, this could promote the dystrophic process whereby calcium is laid down. As diltiazem has an inhibitory effect on cell membrane calcium channels, they suggested it could prevent a build up in calcium, and have therapeutic potential in treating calcinosis [2].

First tested on an animal model of Duchenne’s muscular dystrophy (a disease also characterized by increased muscle calcium content) diltiazem caused a reduction in calcium content and improvement in muscle function. Diltiazem is thought to work by preventing the laying down of new calcium, but this cannot explain the additional re-absorption of existing calcium. This re-absorption may be due to the scavenging actions of macrophages which are more able to clear existing deposits once new accumulation has ceased [2].

Following successful animal studies, diltiazem has now been shown to reduce muscle calcium content in patients with Duchenne’s. Further reports have con-
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reduce ectopic soft tissue calcification in adult patients with dermatomyositis.

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Accepted 20 September 1999
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I read with interest the paper by Harms et al. [1]. They have attempted to characterize spinal manipulative forces in an ingenious and scientific manner. However, I am concerned about the method of mobilization used on the lumbar spine. Specifically, direct postero-anterior pressure on any spinous process can be painful, especially in thin subjects, and pain may account for some of the spread of force data in grade III and IV mobilizations.

I would like to point out that Harms et al. have looked at one aspect of manipulation, namely mobilization. High-velocity manipulative thrust is also used by professional manual therapists [2, 3] (but rarely in the...). Often during such procedures, one hears an audible click which is generally attributed to distraction of facet joints, and movement of related soft tissues. Remembering the law of conservation of energy, one... products of manipulation (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia), systemic sclerosis, and childhood dermatomyositis [1, 2, 9, 10]. Based on our observations, we suggest that diltiazem may also...