**Case Report**

**Severe Dystrophic Calcinosis Cutis: The Need for Early Intervention and Optimal Treatment of Juvenile Dermatomyositis**

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**Abstract**

Dystrophic calcinosis cutis (DCC) is a severe, debilitating sequelae of juvenile dermatomyositis (DM) that can have significant morbidity. Treatment of extensive DCC can be very challenging with inconsistent results and limited evidence to guide best therapy. We present a case of a particularly severe form of DCC presenting in an adult, which highlights the necessity of early optimisation of juvenile DM treatment to help prevent this occurring.

**ABBREVIATIONS**

JDM: Juvenile Dermatomyositis; DCC: Dystrophic Calcinosis Cutis

**INTRODUCTION**

Dystrophic calcinosis cutis (DCC) is a severe debilitating entity secondary to juvenile dermatomyositis (DM) that can have significant morbidity later in life. DCC is characterised by the abnormal deposition of calcium salts within skin, subcutaneous tissue, muscles, and tendons in the setting of normal serum calcium and phosphate levels. Juvenile DM and DCC progressing into adulthood is an uncommon occurrence. We present a rare case of a patient with juvenile DM who presents with DCC after a prolonged period of being lost to follow-up.

**CASE PRESENTATION**

A 49-year-old Caucasian woman was referred to a tertiary centre for assessment of painful large nodules located over her bilateral posterior thighs, elbows, flexor arms and posterior torso that had been gradually worsening over 10-years with initial nodules noticed in her twenties. This was associated with joint contractures that limited her physical mobility resulting in deconditioning and psychological stress including anxiety and depression. The patient had been diagnosed with juvenile DM aged 12 whilst living in regional Australia. She had been treated with oral prednisolone initiated by her general practitioner and subsequently was lost to follow-up without any regular rheumatology care. In her teenage years, she began to develop calcific deposits that caused contractures of her bilateral achilles tendons which required tendon lengthening. Her comorbidities include hypertension and hyperandrogenism secondary to ovarian enlargement for which she underwent a bilateral salpingo-oophrectomy.

Clinical examination revealed multiple irregular protuberant painful masses in the bilateral posterior thighs and torso (Figure 1) that cause the patient significant discomfort and limited her range of movement including the ability to sit down for prolonged periods. She displayed generalised muscle atrophy of the upper and lower limbs however had 4+/5 power symmetrical bilaterally. Violaceous papules (Gottron’s papules) were identified over dorsal hands overlying the metacarpophalangeal and proximal interphalangeal joints and bilateral elbows. She had a fixed flexion deformity (less than 10 degrees) of her right

**Figure 1** Protuberant and indurated masses in the bilateral posterior thighs and torso.
Serology tests revealed a positive Antinuclear Antibody (ANA) with a Homogenous Titre of 640. Extractable Nuclear Antigen (ENA) testing were negative, specifically negative Anti-Ro and Anti-La antigens. Creatine kinase (CK) was 100 [Reference Interval (RI): 30-170 IU/L], CRP 17 [RI: <5 mg/L], ESR 19 [RI: 2-12 mm in 1 hr] and a mild leucocytosis was present (WCC 11.3 x 10^9/L) [RI: 140-400 x 10^9/L]. Her corrected calcium represented the upper range of normal at 2.57 mmol/L [RI: 2.1 - 2.6 mmol/L] with a normal serum phosphate level of 0.96 mmol/L [RI: 0.75-1.5 mmol/L]. Parathyroid hormone (PTH) testing revealed a normal level of 6.7 pmol/L [RI: 1.7-7.5 pmol/L].

A bone mineral density (BMD) scan revealed a femoral Z score of -0.3 and a lumbar spine T = + 1.1 which is in normal range. Computed tomography of her thighs revealed predominantly intramuscular calcification with large intramuscularly calcified soft tissue masses in the posterior thigh compartment bilaterally (Figure 2). The largest lesion in the hamstrings measuring 85 x 75 x 290 mm on the left and 43 x 46 x 250 mm on the right.

The patient was diagnosed with extensive dystrophic calcinosis cutis (DCC) and concomitant inflammatory joint and cutaneous symptoms secondary to her inadequately treated juvenile DM that has likely progressed into adulthood.

Management required a multidisciplinary approach that was co-ordinated by dermatology with input from rheumatology, plastics and reconstructive surgery, pain medicine and endocrinology. Diltiazem extended-release 360mg daily, prednisolone 7.5mg daily and probenecid 500mg twice-daily were commenced initially. The patient declined plastics and reconstructive surgical intervention given the extensive undertaking required to excise the intramuscular calcification. Pain was managed with pregabalin (75mg twice-daily) under the care of a pain specialist and she continues to have regular follow-up with her psychiatrist for management of depression and anxiety. Furthermore, use of photo-protective measures and non-pharmacologic interventions involving physical therapy to assist with stretches, prevention of worsening contractures and building muscle strength were encouraged.

On review 3 months later, the patient’s inflammatory joint and cutaneous rash had resolved. Despite this, she did not notice any meaningful improvement in her pain or reduction in the dystrophic calcification. Bisphosphonates were considered however given the limited evidence demonstrating its efficacy and the patient’s normal BMD, its use was deemed currently premature.

The patient’s DCC continues to persist causing significant debilitating effects that have a negative impact on her quality of life. DCC is a well-known sequel of juvenile dermatomyositis and can be a very challenging disease entity to treat especially when extensive. This case highlights extensive complicating DCC manifesting into adulthood after a chronic period of inadequately treated JDM. It raises the valid point questioning whether earlier adequate treatment of her JDM, would have prevented such severe DCC that has now manifested into her adult life.

DISCUSSION

Calcinosis cutis can be sub-classified into four categories: dystrophic (due to localised tissue damage), metastatic (due to abnormal calcium or phosphate metabolism), iatrogenic (eg. parenteral calcium or phosphate administration) or idiopathic. Calcinosis cutis affects up to 40% of patients with juvenile DM [1]. Juvenile DM and DCC progressing into adulthood are uncommon occurrences, which at times can also have unpredictable clinical patterns.

The presence of myositis specific auto-antibodies can provide strong evidence for the diagnosis of DM. Myositis specific antibodies may also aid the possibility of predicting clinical patterns. The presence of anti-p155 myositis associated antibody (MAA) can also predict worse cutaneous involvement and p140 can predict calcinosis, severity of disease course and persistent disease activity [2,3]. Although these antibodies were not measured in our patient’s case, perhaps there may have been a role in assisting with predicting clinical disease course earlier. Despite this, muscle enzymes are not always elevated at the diagnosis of juvenile DM and are poorly responsive to changing disease activity. This is also complicated also by the incompletely understood pathogenesis of DCC.

One postulation involves tissue necrosis caused by tissue injury that may result in alkaline phosphatase release by damaged lysosomes [4]. This subsequently may cause inhibition of calcium phosphate crystallisation and elevated intracellular calcium levels and deposition [5]. Calcium homeostasis may also be disturbed by ectopic sources and this would be important to exclude as part of the work up. Lobo et al., (2008) have suggested the manifestation of DCC may be a localised process rather an imbalance of calcium homeostasis [6]. This could be possible...
Central given our patient had normal phosphate levels and a corrected calcium level within the upper range of normal.

Another theory relates to possible activation of macrophages which are typically found, along with pro-inflammatory cytokines, in calcium rich fluid [7]. This may explain the use of intravenous immunoglobulin (IVIG) where effector macrophages can be suppressed [7] that may contribute to its anti-inflammatory properties. Despite this, the mechanism by which IVIG eradicates DCC remains uncertain and conflicting efficacy data exists.

Complications of DCC include infection, ulceration, pain, disfigurement and restricted range of movement in limbs. Overall, it can also have a significant negative impact on quality of life, as our patient’s experience demonstrates.

Treatment of DCC is currently based on limited evidence with inconsistent therapeutic success. Evidence based therapeutic options for DCC are summarised in Table (1). Our priorities in managing this patient included controlling any residual DM activity to minimise any progression of calcification, targeted treatment of the DCC and alleviating the sequelae of pain, functional limitations and any possible associated psychological distress.

In consultation with Rheumatology, it was felt our patient’s normal CK level and the absence of cutaneous or myopathic symptoms of DM did not warrant aggressive immune suppressive therapy. Following case reports [8] and a retrospective study [9] demonstrating the successful use of diltiazem for calcinosis cutis in patients with autoimmune connective tissue disease, this was commenced. Probenecid 500mg twice-daily was added based on the anti-inflammatory properties, although evidence on its use is controversial [10].

Bisphosphonates have value in its ability to reduce calcium turnover resulting in reduced calcium deposition within soft tissue with success reported in children [7]. In consultation with Endocrinology, bisphosphonates were considered not appropriate at this point in time given the patient’s normal BMD, although may be considered in the near future.

Table 1: Summary of management options for dystrophic calcinosis cutis and levels of evidence.

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>LEVEL OF EVIDENCE</th>
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<tr>
<td><strong>Oral Therapies</strong></td>
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<tr>
<td>Colchicine</td>
<td>Level IIIc Retrospective study evaluating 78 patients with calcinosis cutis and autoimmune connective tissue disease</td>
</tr>
<tr>
<td>• MOA: Inhibits inflammation by concentrating in leukocytes and interfering with lysosomal degranulation</td>
<td>Mixed results</td>
</tr>
<tr>
<td>• Dose: 1 mg daily</td>
<td></td>
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<tr>
<td>Minocycline</td>
<td>Level IIIc Retrospective study evaluating 78 patients with calcinosis cutis and autoimmune connective tissue disease</td>
</tr>
<tr>
<td>• MOA: Antibiotic with anti-inflammatory properties</td>
<td>Mixed results</td>
</tr>
<tr>
<td>• Dose: 200mg daily</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Level IIIc Retrospective study evaluating 78 patients with calcinosis cutis and autoimmune connective tissue disease</td>
</tr>
<tr>
<td>• MOA: Inhibits intracellular calcium influx within macrophages</td>
<td>Mixed results</td>
</tr>
<tr>
<td>• Dose: 2-4mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Probenecid</td>
<td>Level IV Case report</td>
</tr>
<tr>
<td>• MOA: Increases renal phosphate clearance &amp; anti-inflammatory actions</td>
<td>19-year-old male showed reduced pain and improvement in calcification at 3-5 months.</td>
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<tr>
<td>• Dose: 500mg twice-daily</td>
<td></td>
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<tr>
<td>Warfarin</td>
<td>Level IV Case report</td>
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<td>• MOA: Vitamin K has a role in calcium binding within bones and also calcium deposition within soft tissues</td>
<td>Reduction in the amount of subcutaneous calcium and mobility improvement in a 27-year-old male with DM and calcinosiaversalis.</td>
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<tr>
<td>• Dose: 1 mg daily</td>
<td></td>
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<tr>
<td><strong>Intravenous Therapies</strong></td>
<td></td>
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<tr>
<td>Bisphosphonates</td>
<td>Level IV Case series</td>
</tr>
<tr>
<td>• MOA: Inhibits macrophage pro-inflammatory cytokine production (IL1, IL6 and TNF alpha)</td>
<td>3 patients with juvenile DM received pamidronate at 1mg/kg/day for 3 consecutive days, repeated every month. Complete resolution of calcinosis in 1 case and satisfactory response in others.</td>
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<td>• Dose: variable depending on type bisphosphonate</td>
<td>[Marco et al, 2010] [12]</td>
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The literature describes a wide array of different treatment options for DCC, however data on efficacy is limited and often conflicting therefore making consensus on the most appropriate treatment regimen difficult. Furthermore, the required duration of therapy to address DCC is also uncertain, though a case report demonstrating marked improvement in calcinosis cutis after 2-3 years of diltiazem use has been reported [8]. Surgical resection is also usually considered last line due to the chance of surgical trauma possibly inducing further calcification, not to mention the complexity of excising calcification that crosses multiple tissue planes and likely poor healing post-operatively.

This case highlights the severe effects of DCC that has progressed into adulthood following inadequately treated JDM. It supports the notion that early and aggressive therapy may prevent or stabilise organ damage and disease sequelae such as calcinosis [18], a condition that is associated with significant morbidity due to pain and infection. Our patient is currently able to ambulate independently however have significant difficulties with activities of daily living. The patient remains on diltiazem and probenecid. Regular photo-protective measures are employed with activities of daily living. The patient remains on diltiazem and probenecid.

The pathogenesis of DCC is poorly understood and a more thorough understanding of the underlying disease mechanism is critical in finding new novel treatments. Higher order evidence guiding treatment regimens for DCC is limited and currently there is uncertainty about which management option(s) is best. Multimodal therapies should be considered. Early initiation of optimal treatment for juvenile DM is likely necessary to help prevent the sequelae of extensive DCC. It is imperative patients with adult and juvenile DM are followed up on a regular basis by Rheumatology and Dermatology to be able to identify and treat inflammatory symptoms of DM and possible DCC early.

REFERENCES
Poon et al. (2017) 

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