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The Presentation, Assessment, Pathogenesis, and Treatment of Calcinosis in Juvenile Dermatomyositis

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Abstract Calcinosis is one of the hallmark sequelae of juvenile dermatomyositis (JDM), and despite recent progress in the therapy of JDM, dystrophic calcification still occurs in approximately one third of patients. This review discusses our current, albeit limited, understanding of risk factors for the development of calcinosis in JDM, as well as approaches to assessment, and current views on its pathogenesis. Anecdotal approaches to treating calcinosis associated with JDM, including both anti-inflammatory therapies and agents aimed at inhibiting the deposition of calcium hydroxyapatite, are reviewed. An improved understanding of the pathogenesis of calcinosis, the establishment of standardized measurement tools to assess calcinosis, and randomized controlled trials employing more sensitive outcome measures are needed to develop efficacious therapies for this often disabling complication.

Keywords Juvenile dermatomyositis · Calcinosis · Dystrophic calcification · Treatment · Pathogenesis

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Introduction

Juvenile dermatomyositis (JDM) is a rare childhood systemic autoimmune disease characterized by proximal muscle weakness and rashes due to chronic muscle and skin inflammation of unknown etiology [1]. Two rashes, Gottron's papules and the heliotrope rash, are pathognomonic and assist in confirming the diagnosis. Evidence of myositis by muscle biopsy or electromyography (EMG) is also necessary to definitively establish the diagnosis [2]. The disease has a number of protean manifestations, but calcinosis, the abnormal deposition of insoluble calcium salts within the skin, subcutaneous tissue, myofascia, or muscle, is the sequela that is perhaps most characteristic for this illness, most troublesome, and least understood. This article updates a prior extensive review of calcinosis in JDM with current concepts on prevalence, risk factors, differential diagnosis, pathogenesis, and treatment [3].

Calcinosis occurs in up to 40 % of patients with JDM, although current prevalence ranges from 10 to 70 % [4–10, 11•, 12–14]. This wide variation of the prevalence of calcinosis in JDM cohorts may depend on the length of follow-up and the treatment approaches utilized, among other factors, but there may be differences regionally and internationally in the frequency of calcinosis [8]. The calcification is dystrophic, which by definition occurs at sites of an injured tissue with simultaneously generally normal serum calcium and

phosphorous levels [15]. The sites most frequently affected are the elbows, knees, trunk, hands, feet, buttocks, and head, although it may occur virtually anywhere over the body [16••]. The onset of calcinosis is most often 1–3 years after illness onset but has been reported to occur from the time of illness onset to as long as 20 years later [7, 17, 18]. Compared to JDM, calcinosis in adult-onset dermatomyositis (DM) tends to occur later (7.8 vs. 2.9 years), less frequently (20 %), and with lesions occurring primarily on the extremities [16••]. Prior to therapy with corticosteroids, when mortality exceeded 50 %, the development of calcinosis was considered a good prognostic sign. Today, however, as our understanding of calcinosis associated with JDM evolves, it is instead deemed a marker of disease morbidity and possibly inadequate treatment.

Calcinosis Phenotypes

Calcinosis is pleomorphic and may present in multiple ways, including superficial plaques or nodules known as calcinosis circumscripta; larger nodular deposits that may extend to deeper tissue layers including muscle known as tumoral calcinosis or calcinosis universalis; collections along fascial planes of tendons or muscles; or an exoskeleton of calcium, an extensive hard calcium deposition over all surface areas which can lead to significant joint contractures and immobility. These four main phenotypes have been described, although there may be overlap and multiple subtypes may occur in individual patients [19]. In a prior series of children with JDM and calcinosis, 33 % developed calcinosis circumscripta, 20 % developed tumoral calcinosis, 16 % developed calcinosis along fascial planes, 10 % developed exoskeletal calcinosis, and 22 % had a mixture of calcinosis subtypes [19]. Calcinosis is often painless but may present with deep-seated pain and tenderness to palpation, with panniculitis on biopsy, or even with ulcerations [16••]. These areas may be raised or erythematous, warm and tender, and can be confused for cellulitis. When calcium deposits breach the surface of the skin, these deposits may become a nidus for true infection, most commonly with staphylococcal and streptococcal organisms but including mycobacteria and other species [20–22]. Areas of calcinosis may expand over time, spontaneously regress, or change subtype. Improvement may be more likely in patients with inactive disease and more superficial deposits.

Risk Factors for Calcinosis

Risk factors for calcinosis in patients with JDM are not well understood and information has been largely limited to retrospective series of patients, from which associations can be found but causality cannot be inferred. Calcinosis has had a long-standing association with delay to diagnosis and initiation of therapy and also occurs in chronic, severe disease [7, 23]. Patients with a chronic or polycyclic course, and therefore with longer duration of active disease, may be more likely to develop calcinosis despite adequate therapy [7, 8, 24]. The presence of cardiac involvement and the use of one or more immunosuppressive therapies (other than oral corticosteroids) have been associated with the development of calcinosis [25].

Calcinosis in myositis patients has been associated with anti-MJ autoantibodies that recognize the nuclear protein NXP-2/MORC3, and anti-MJ autoantibodies are present in up to 25 % of children with JDM. In JDM patients with anti-MJ autoantibodies, calcinosis may be present in up to 54 % [26•, 27, 28, 29•, 30]. Calcinosis has also been associated with the presence of PM-Scl autoantibodies [31]. Tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and other pro-inflammatory cytokines have been found in the milk of calcium fluid examined from subjects [32•]. Pro-inflammatory polymorphisms of the TNF-α-308A allele have been associated with increased risk of calcinosis in two separate cohorts, and IL-1α-889T is a protective allele [33, 34]. Higher initial levels of serum creatine kinase and prolonged elevation of muscle enzymes have been associated with calcinosis as well [5, 35]. An association with lipodystrophy and panniculitis may be seen due to the fact that these complications are also associated with severe and prolonged disease [8, 9, 36]. A large international multicenter study found that calcinosis in JDM is associated with earlier year of onset, older age at onset, chronic polycyclic or chronic continuous illness course, and increased disease duration [8]. Analysis of a Danish cohort, including long-term follow-up, confirmed disease duration greater than 4 years to be a risk factor for calcinosis [9]. Another multicenter registry has described an association of calcinosis with African American race, even after adjustment for duration of disease and time to rheumatologic care [37]. Similarly, it was reported that African children with JDM have increased vasculitic disease and a high frequency of calcinosis, even with lower serum muscle enzyme levels [38•]. In a JDM cohort from the UK, calcinosis was associated with younger age of disease onset [29•].

Assessment/Diagnostics

Conventional radiographs are generally sufficient for identifying calcinosis in the pediatric population and have been recommended as the initial imaging study of choice when there is clinical suspicion for calcinosis (Fig. 1) [39•]. In a case series of 37 patients with autoimmune connective tissue disease and suspected calcinosis, including 17 cases of DM, of whom 7 were children, radiographs were able to detect calcinosis in all patients. The same series identified nodular lesions as the most common (84 %), followed by sheet-like (32 %),

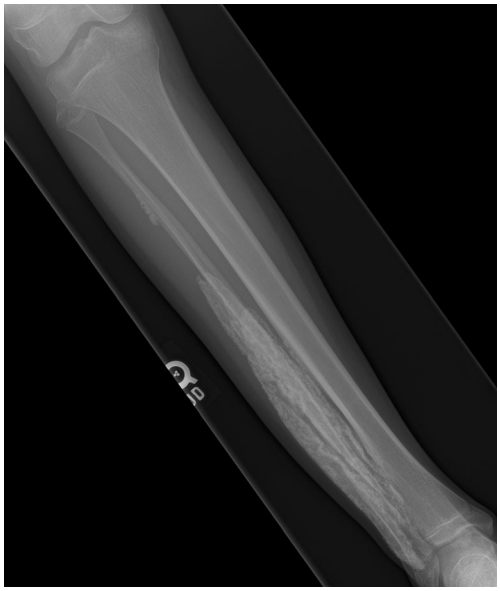

Fig. 1 Plain radiograph demonstrating sheet-like calcification in the lower leg of a 13-year-old girl with JDM

reticular (22 %), amorphous (14 %), and linear (5 %) deposits. The presence of a reticular pattern has been suggested as predicting a more severe and chronic disease course in JDM patients [19].

In addition to plain radiography, other imaging modalities have been successfully utilized in assessing calcinosis in pediatric patients. Scintigraphy has identified soft-tissue calcinosis missed on radiographs but may not be able to detect all lesions [40]. Thin-section computed tomography (CT) appears to be more sensitive for identifying early calcinosis lesions because of the sensitive bone-water interface [41] but is limited in utility due to associated radiation. Magnetic resonance imaging (MRI) can demonstrate calcified lesions as well as subcutaneous edema, which was found to be a precursor for radiographic calcinosis in one case series [42]. When lesions are superficial and without large echo shadows, ultrasound may be useful to monitor the surrounding edema and change in size of calcific deposits (Oberle, personal communication). However, this method cannot assess the depth of these lesions or the presence of larger or deeper lesions.

Calcinosis is frequently one of many factors used in the assessment of myositis disease damage [43]. However, no standardized guidelines exist to grade or assess calcinosis. The development of sensitive assessment tools for calcinosis is required in order to assess the efficacy of therapeutic agents, as well as to identify those patients at greatest risk of poor functional outcomes. Such a tool should include clinical symptoms (pain scale), physical exam findings (location and size of lesions, associated erythema or other color change), imaging features (depth of lesions, effect on surrounding structures), and patient reported indicators (quality of life).

Differential Diagnosis

Calcinosis cutis can be associated with a number of conditions, including autoimmune connective tissue disorders, inherited disorders, cutaneous neoplasms, and following venipuncture (iatrogenic) or blunt trauma (Table 1). Aside from DM, scleroderma is the most common autoimmune disorder to present with calcinosis, with involvement reported in 25–40 % of patients with limited cutaneous systemic scleroderma [16••, 45, 46]. Calcinosis may develop at any time during the disease course and may predate the diagnosis of scleroderma [16••] but typically occurs at least 10 years following diagnosis [15]. Lesions occur on the hands and feet, with a high predilection for fingertips and areas of microtrauma [16••]. Raynaud's and digital ulcers are risk factors for calcinosis in scleroderma, suggesting a role for vascular ischemia [46].

Calcinosis rarely occurs with systemic lupus erythematosus. The onset is generally after long-standing disease [16••].

Table 1 Differential diagnosis for calcinosis cutis

Autoimmune connective tissue disorders	Dermatomyositis
	Systemic scleroderma
	Limited scleroderma, CREST syndrome
	Systemic lupus erythematosus
	Lupus panniculitis
	Mixed connective tissue disease
	Overlap connective tissue disease
	Sjogren's syndrome
	Rheumatoid arthritis
	Polymyositis
Pancreatic panniculitis	
Porphyria cutanea tarda	
Inherited disorders	Familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome
	Ehlers-Danlos syndrome
	Pseudoxanthoma elasticum
	Werner syndrome
	Fibrodysplasia ossificans progressiva
Hypercalcemia	Chronic renal disease
	Hypervitaminosis
	Hyperparathyroidism
	Milk alkali syndrome
	Post-liver transplant
Neoplastic	Basal cell carcinoma
	Pilomatricoma
	Trichilemmal cyst
Iatrogenic	Vaccination
	Venipuncture
	Calcium infusion
Trauma	Myositis ossificans circumscripta
Idiopathic	

The presentation can vary greatly; however, patients generally are asymptomatic, with the calcifications incidentally found on radiographic studies [47]. Calcinosis may occur on the extremities, particularly around the joints, as well as the buttocks, and deep to active cutaneous lupus lesions [44]. The occurrence of calcinosis in other rheumatologic conditions has been reported but is uncommon.

Familial tumoral calcinosis (FTC) is a rare autosomal recessive metabolic disorder characterized by the deposition of periarticular calcific masses either within the muscular or subcutaneous tissue in areas of repeated trauma. The hips, shoulders, elbows, and knees are most often involved [15]. Lesions vary in size and may enlarge, resulting in impairment of joint function. Lesions have been reported in young children but tend to occur in healthy adolescents. Several genetic mutations related to the regulation of renal reabsorption of phosphate resulting in serum hyperphosphatemia have been identified in affected families; however, normal serum phosphate levels can occur in individuals with FTC [48].

Fibrodysplasia ossificans progressiva is a rare and severely debilitating, autosomal dominant disorder, resulting from mutations in activin receptor IA/activin-like kinase-2 (ACVRI/ALK2), which encodes a bone morphogenetic protein type I receptor, leading to progressive heterotopic ossification of skeletal muscle and soft connective tissues. Individuals appear normal at birth, aside from a characteristic malformation of the great toes, and over the first decade of life develop calcific deposits, initially in the proximal and cranial regions of the body followed by the appendicular and caudal areas. Affected regions become immobile with most individuals becoming wheelchair bound by the third decade of life. The median age of survival is approximately 45 years [49].

Myositis ossificans circumscripta is a reactive process resulting in heterotopic ossification of muscle after an injury or repeated minor injuries [50]. The most common locations are the muscles of the thigh, buttocks, and upper arm. Lesions typically reach 4 to 10 cm in diameter. There can be resorption of the calcification over years, but these masses rarely resolve completely.

Pathogenesis

Local tissue trauma, active inflammation, and dysregulation of the proteins involved in calcium metabolism have all been suggested to play a role in the formation of calcinosis in patients with JDM [3]. Tissue-nonspecific alkaline phosphatase (TNAP) and hydrolytic product inorganic pyrophosphate (PPi), a potent inhibitor of calcium hydroxyapatite formation, and other targets in this metabolic pathway, have been demonstrated to be important to several genetic disorders associated with vascular calcification, but a role for this pathway in JDM-associated calcinosis has not yet been determined [51].

Dystrophic calcification in JDM and other rheumatic diseases tends to occur at sites of repetitive use, localized trauma, or chronic mechanical stress [52]. Anecdotally, JDM patients with tissue injuries following minor trauma appear to develop calcinosis at the injured sites, particularly when the underlying myositis is still active. Examples include a JDM patient who developed calcinosis in the medial thigh with repetitive horseback riding, as well as along the humerus after being pulled when walking a dog, and a patient who developed a hematoma following a surgical muscle biopsy procedure and subsequent calcinosis at the same site [3]. Tissue injury and hematoma formation have been associated with other dystrophic calcification processes [15].

The calcinosis itself is also associated with inflammation. Several reports describe macrophages and pro-inflammatory cytokines, including IL-6, IL-1, TNF-α, soluble TNF receptors, neopterin, and IL-18, present in the milk of calcium fluid examined from patients with JDM [33, 53, 54]. Calcinosis has also been more frequently associated with the TNF-α-308A promoter polymorphism, which is associated with increased TNF-α production by peripheral blood mononuclear cells [34], and additional genetic and developmental risk factors are likely to be involved [36, 55]. Also, new-onset calcinosis has been associated with subcutaneous edema in the same location, which is presumed to be inflammation, on a prior short tau inversion recovery (STIR) MRI exam [41].

The histopathology of surgically removed specimens, often of long-standing duration, demonstrates chronic inflammatory cells encapsulating the mineral consisting apparently of a variety of cell types, including macrophages, giant cells, lymphocytes, and eosinophils [33, 56–58]. The calcium mineral itself may be a chemoattractant for macrophages and monocytes [59].

The mineral is calcium hydroxyapatite or carbonate apatite, from X-ray diffraction, infrared spectroscopy, and X-ray microcomputed tomography studies [60, 61]. The properties of the mineral in the calcinosis lesions are closest to that of enamel, and the mineral clearly differs from bone. The mineral appears to be deposited in fragments and becomes solid over time [61].

Several reports have demonstrated connective tissue and mineral-associated proteins in calcinosis lesions and JDM muscle tissue. Immunohistochemistry reveals a number of small integrin-binding ligand, N-linked glycoprotein (SIBLING) proteins, including osteocalcin, osteopontin (OPN), osteonectin, bone sialoprotein, and matrix-Gla protein (MGP), that promote and inhibit mineralization within the lesions, and osteoclasts at the periphery of the lesions that are secondarily infiltrating in an attempt to resolve the calcification [62]. The deposited calcium appears to be nucleated around collagen and elastic fibers [62]. MGP, a calcification inhibitor, is expressed at sites of muscle damage and by infiltrating macrophages in the muscle tissue of JDM patients, whereas only phosphorylated MGP is elevated in biopsies of JDM patients who developed calcinosis [63]. These proteins,

likely upregulated in expression by tissue macrophages, cytokines and tissue injury, and may serve as a nidus for nucleation of the mineralized calcium that would then promote crystal growth [64, 65]. Some of these proteins may initiate or promote mineralization, including dentin matrix protein 1, and matrix extracellular phosphoglycoprotein (MEPE), whereas others, including osteopontin, decorin, albumin, and fetuin-A, apparently inhibit hydroxyapatite crystal growth [55, 66]. Osteopontin apparently not only inhibits mineral deposition but also actively promotes its dissolution by inducing expression of carbonic anhydrase in monocytes and promoting acidification of the extracellular environment [67]. A balance of pro-mineralizing matrix proteins would favor growth of existing lesions and further deposition of new lesions.

Figure 1 provides a hypothesis of the pathogenesis of calcinosis in JDM, based on these limited data, providing a central role in the cascade for the associated inflammatory process [3].

Treatment

Multiple treatment strategies have been attempted to target calcinosis in JDM and other autoimmune diseases, including anti-inflammatory drugs, drugs that affect calcium metabolism, and mechanical modalities (Table 2). However, no therapy has proven to be reproducibly efficacious, and evidence in the literature is limited to open-label case studies and case series [43, 46, 68].

Anti-inflammatories

IVIG Intravenous immunoglobulin (IVIG) has been used in rheumatology for a variety of anti-inflammatory indications, including the treatment of DM [69]. The potential mechanism in reducing calcinosis is uncertain but may include the inhibition of activated macrophages [70]. Several case reports describe improvement in calcinosis in adults with DM and limited systemic scleroderma who had failed multiple other therapies, including warfarin, diltiazem, and extracorporeal shock wave lithotripsy [70–72]. The only case involving a child was a 10-year-old male with JDM who developed calcinosis universalis and had failed pamidronate, probenecid, cyclosporine, diltiazem, and alendronate. After 4 monthly infusions (2 g/kg/dose), he reported improved myalgias and muscle fatigue. Radiographs before and after treatment showed no new calcifications. Knee flexion contractures and limp resolved. At a 7-year follow-up, sustained efficacy of IVIG was reported [73]. Conversely, Kalajian et al. reported two adult patients with DM who showed no response to IVIG at the same dose and interval [74].

Infliximab Given that TNF-α has been isolated from calcinosis lesions and the development of calcinosis has been associated with the TNF-α-308A promoter polymorphism, blockade of TNF-α may be of therapeutic benefit in treating calcinosis. This is supported by a series of 5 patients with JDM who had improvement in their manifestations of JDM including calcinosis after receiving infliximab at a dose of 3 mg/kg at 0, 2, and 6 weeks followed by every 8 weeks [75]. All 5 patients had improvement with joint contractures, calcinosis, and muscle weakness between 8 and 30 months of starting infliximab. In 4 patients, calcinosis was still present, but lesions were softer, painless, and less extensive [75]. A preliminary report in 30 JDM patients suggests improvement in calcinosis in 46 % treated with infliximab [76].

Abatacept A recent report describes the improvement of ulcerative skin lesions and calcinosis in a 14-year-old girl with JDM treated with abatacept, a monoclonal T cell activation inhibitor (10 mg/kg at weeks 0 and 2, and then monthly), and sodium thiosulfate IV and topical (10 g IV sodium thiosulfate administered three times weekly for 2 weeks, then 15 g twice weekly for the next 3 months; topical 3 % increased to 10 %). The patient's calcinosis had previously failed to respond to tacrolimus, IVIG, cyclophosphamide, infliximab, colchicine, and alendronate. At 6 weeks, analgesic use was decreased, and at 3 months, pulse methylprednisolone was stopped and oral prednisone dosage was decreased by 30 %. At 6 months, she had significant improvement in muscle strength and function, and her cutaneous ulcerations largely healed. Plain X-rays of her upper extremities confirmed lack of progression of calcinosis. However, concomitant use of both drugs makes it impossible to determine the role of abatacept in improvement of the patient's calcinosis [77•].

Thalidomide Thalidomide inhibits the expression of TNF-α and IL-6 mRNA in monocytes; however, its use is often limited by toxicity concerns. Miyamae et al. reported improvement in the inflammatory calcinosis of a 14-year-old girl with JDM treated with 1.3 mg/kg/day (50 mg), increased to 75 mg/day after 4 weeks. Her calcinosis had not progressed at 18-month follow-up, and a whole body PET-CT at 15 months post-treatment showed fewer hot spots around the subcutaneous lesions [54].

Rituximab Rituximab, the anti-CD20 monoclonal antibody that eliminates peripheral B cells, has mixed results reported in adults with calcinosis associated with systemic scleroderma [78•, 79, 80]. A 53-year-old woman with CREST and diffuse calcinosis affecting the knee, elbow, and thumb prone to frequent ulcerations and pain, was treated with rituximab. At follow-up, 5 months later, lesions had not ulcerated, their sizes were stable, and no new lesions had developed. At 1-year follow-up, knee and elbow lesions had significantly

Table 2 Published treatment options for calcinosis complicating juvenile dermatomyositis

Medication	Dosing	Route	Mechanism of action	JDM publications
Anti-inflammatory				
IVIG	2 g/kg every 4 wks	IV	Uncertain: inhibits macrophages	Touimy et al. 2013 [73]
Infliximab	3 mg/kg at 0, 2, and 6 wks, then every 8 wks	IV	Inhibits TNF-α	Riley et al. 2008 [75]
Abatacept	10 mg/kg at 0, 2, and 4 wks, then every 4 wks	IV, SQ	Binds CD80/CD86 inhibiting T cell costimulatory signal	Arabshahi et al. 2012 [77]
Depo-Medrone, intra-lesional	80 mg once	Local injection	Uncertain: facilitates dissolving and resorption of calcified materials	Al-Mayouf et al. 2010 [82]
Thalidomide	50 mg/d (1.3 mg/kg/d)× 4 wks, then increased to 75 mg/d	PO	Inhibits TNF-α and IL-6, anti-angiogenesis	Miyamae et al. 2010 [54]
Rituximab	750–1000 mg/m^2/wk×2 wks	IV	Binds CD20 on B cells	
Calcium and phosphate modulators				
Diltiazem	4–6 mg/kg/d	PO	Calcium channel blocker	Oliveri et al. 1996 [87]
Pamidronate	1 mg/kg/d×3 d; repeated every 3 mos	IV	Bisphosphonate: reduces bone resorption via reduced osteoclast activity, inhibits macrophages, and deregulates expression of genes involved in phosphate homeostasis and mineralization	Slimani et al. 2010 [96]
	2 mg/kg/yr	IV		Marco Puche et al. 2010 [97]
Alendronate	0.4 mg/kg/d	PO	Bisphosphonate	Ambler et al. 2005 [98]
Sodium thiosulfate	10–25 % cream, daily	Topical	Uncertain: dissolves calcium deposits and chelates-free calcium	Pagnini et al. 2014 [108]
	10 g, 3 wks×2 wks, then 15 g, 2 wks×3 mos	IV		Arabshahi et al. 2012 [77]
Aluminum hydroxide	1.8–2.4 g/d	PO	Decreases intestinal absorption of phosphate	Aihara et al. 1994 [109] Nakagawa et al. 1993 [110] Wang et al. 1988 [111]
Probenecid	500 mg/d titrated up to 1000–1250 mg/d	PO	Uncertain: increases renal excretion of phosphate and decreases extracelullar ATP levels with resultant decrease in PPi	Nakamura et al. 2006 [112] Harel et al. 2001 [113]
Colchicine	1–1.8 mg/d	PO	Uncertain: inhibits microtubule polymerization and inhibits IL-1β and inflammasome activation	Taborn et al. 1978 [84]
Surgical excision	N/A	Surgical	Direct removal of calcium deposits	Al-Mayouf et al. 2010 [82] Vitale et al. 2009 [115] Wu et al. 2008 [116]

IVIG intravenous immunoglobulin, *g* gram, *kg* kilogram, *mg* milligram, *d* day, *wk* week, *mos* months, *yr* year, *IV* intravenous, *SQ* subcutaneous, *PO* by mouth, *TNF-α*, tumor necrosis factor-alpha, *IL* interleukin

improved, and pain no longer required analgesics. She was given a second course of rituximab in the hopes to further improve her condition. Six months after the second course, knee and elbow calcinosis lesions were significantly improved, the thumb lesion was unchanged, and there was no reported pain. At the most recent follow-up, no new calcinosis had developed and her condition was stable [78•]. To date, there are no reports regarding the impact of rituximab on calcinosis in DM or JDM. Our clinical experience is that of progression of calcinosis with rituximab therapy (Rider, unpublished observation) [81].

Intra-lesional Steroids A 10-year-old boy with JDM had resolution of calcinosis at his olecranon bursa with a local injection of 80 mg of Depo-Medrone. The calcinosis had not recurred at 2-year follow-up. He had previously failed pamidronate and colchicine [82].

Colchicine Hydroxyapatite crystals invoke an inflammatory response in joints and soft tissue, making colchicine a consideration when trying to treat calcinosis, particularly in light of its inhibition of IL-1β and the inflammasome [83]. Taborn et al. reported two JDM patients with a good response. A 14-year-old girl in the midst of a disease flare with fever and acute calcinosis was started on 0.6 mg twice daily and, within days, became afebrile and showed improved local inflammation. At 1-year follow-up, she was stable. A 13-year-old male also presented with disease flare and had fever and generalized

calcinosis universalis. He was treated with 0.65 mg three times daily and was afebrile within 4 days. At 1-year follow-up, he was clinically stable. These cases illustrate improvement with colchicine in the systemic inflammatory response attributed to hydroxyapatite [84]. Fuchs et al. also had positive results in a patient with progressive systemic sclerosis (SSc) and a second with adult DM. There was significant regression in local inflammation and healing of skin ulcers within 2 months of treatment with 1 mg daily [85]. However, colchicine failures have been reported as well [86].

Treatments with minocycline, ceftriaxone, and salicylates have been tried with varying success [46, 68].

Drugs That Affect Calcium or Phosphorous Metabolism

Calcium Channel Blockers Diltiazem is the most widely studied calcium channel blocker used as medical therapy for calcinosis. It is hypothesized that by decreasing the intracellular calcium levels and decreasing the influx of calcium into the cells, the ability for calcinosis to form and for calcium to crystallize is reduced. An 8-year-old girl with JDM was treated with oral diltiazem (5 mg/kg/day) and oral pamidronate (4 mg/kg/day) with calcium and vitamin D supplementation. After 21 months on treatment, she had dramatic regression of calcinosis, both clinically and radiographically [87]. A second case of a 3-year-old girl with JDM and multiple subcutaneous lesions and severe intraphalangeal calcinosis showed near resolution radiographically and clinically after 12 months of diltiazem (30 mg/day) [39•]. A larger case series of adult patients with SSc-associated calcinosis showed only 3 of 12 SSc patients with improvement radiographically [88].

Bisphosphonates This class of drugs is showing promising results in the treatment of calcinosis. Bisphosphonates are being used as therapy for disorders including vascular calcification, hypercalcemia, and calcification disorders, such as osteogenesis imperfecta and Paget's disease [89–91]. Bisphosphonates are known to inhibit calcium turnover and remodeling, but they also have effects on macrophages and inflammatory cytokines localized to calcinosis lesions [92–94] and also deregulate the expression of genes that are involved in phosphate homeostasis and mineralization [95]. A 14-year-old girl with JDM and associated calcinosis universalis who failed colchicine had complete resolution of calcinosis after treatment with pamidronate (15 mg every 3 months for 1 year followed by 30 mg every 3 months for a second year), with no new calcifications at 5-year follow-up [96]. Another report describes significant improvement in three patients with JDM-associated calcinosis with pamidronate, one having resolution, using the protocol established for osteogenesis imperfecta (1 mg/kg/day for 3 consecutive days each month) [97]. Alendronate therapy has also shown positive results with complete resolution of calcinosis in a 6-year-old boy with JDM who was unresponsive to diltiazem and probenecid [98]. The results for pamidronate and alendronate are better than those for etidronate, which have been largely negative [99, 100]. Interestingly, two cases of DM (without calcinosis) have been reported in adults after administration of zoledronic acid [101, 102]. The structural differences among these drugs may explain the difference in efficacy.

Sodium Thiosulfate Among the effects of sodium thiosulfate are the ability to dissolve calcium deposits and chelate-free calcium. There are numerous reports of the successful use of sodium thiosulfate in both topical and intravenous forms to treat various diseases of abnormal calcium deposition, including calcific uremic arteriopathy [103–107]. Only two reports describe the successful use of sodium thiosulfate to significantly improve calcinosis associated with JDM. The previously mentioned report used IV sodium thiosulfate in addition to abatacept in a 14-year-old girl [77•]. Most recently, a 4-year-old boy with JDM was reported to have improvement in calcinosis and cutaneous ulcerations using topical sodium thiosulfate (3 %, followed by 10 %) under occlusive dressings over 9 months [108].

Aluminum Hydroxide Aluminum hydroxide is thought to decrease intestinal absorption of phosphate, which would potentially result in a reduction of calcium-phosphorus product in the serum, with a resultant decrease in calcium deposition in the tissue. Several case reports describe significant improvement in JDM-associated calcinosis with oral aluminum hydroxide therapy. One patient had complete resolution after 8 months of therapy, while two others showed significant improvement [109–111].

Probenecid Probenecid is a known treatment for gout and has shown some efficacy in the treatment of calcinosis in two patients with JDM [112, 113]. The mechanism is uncertain but may be related to decreasing extracellular ATP levels with a resultant decrease in PPi, as well as increased renal excretion of phosphorus along with lowered systemic levels of phosphorus [114]. An important secondary effect to consider is the resultant decreased renal tubular secretion of methotrexate and non-steroidal anti-inflammatory drugs, which are commonly used to treat patients with JDM. An 11-year-old boy with refractory calcinosis from JDM had reduction in the size of lesions after 17 months of therapy [112]. A 9-year-old girl with JDM and extensive calcifications had resolution of calcification after 18 months of treatment [113].

Mechanical Therapy

Surgical Resection Despite concerns about recurrence of lesion due to mechanical trauma at the operative site, surgical resection has been effective in treating calcinosis. Several successful surgical resections of calcinosis are reported in JDM with no

or minimal recurrence of the lesions, although some reports have suggested the possibility for recurrence when underlying JDM disease activity is not well controlled [91, 113, 115, 116]. Surgery is generally reserved for discrete lesions with problems of recurrent infection, severe pain, or functional impact.

Treatment with extracorporeal shock wave lithotripsy and carbon dioxide laser therapy have shown promise in a few cases and need further study (reviewed in [46, 68]).

Conclusion

In summary, dystrophic calcification as a sequela of JDM is associated with prolonged or inadequately treated JDM disease activity and has the potential to possibly be prevented through early, aggressive immunosuppressive therapy for JDM. Calcinosis is also frequently associated with not only active JDM but also a pro-inflammatory process surrounding the lesions. Early intervention with immunosuppressive agents, as well as drugs that alter calcium or phosphate metabolism, may be helpful in prevention of further deposition based on anecdotal reports. The development of new assessment tools and outcome measures and studies involving randomized controlled trials are needed to develop evidence-based therapies for this complication. A better understanding of the pathogenesis of calcinosis should aid in improving its treatment.

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Compliance with Ethics Guidelines

Conflict of Interest Mark F. Hoeltzel, Edward J. Oberle, Angela Byun Robinson, Arunima Agarwal, and Lisa G. Rider declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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