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Treatment Outcome of Calcinosis Cutis in Autoimmune Connective Tissue Disorders: A Series from a Tertiary Care Centre

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Abstract

Background: Several pharmacological options are available currently in the management of calcinosis cutis (CC) associated with autoimmune connective tissue disorders (ACTD). However, standard recommendations for the same are lacking. We tried to study the clinical characteristics as well as the treatment response of CC among patients with ACTD to the various pharmacological options utilized at our institution

Methods: The institutional medical records were screened for patients with the diagnosis of CC / calcinosis from August 2014 to April 2017 using Electronic Records System. Clinical data of those patients with ACTD, who have received treatment for CC and completed at least 3 months of follow up in our department, were studied. Summary statistics were used for reporting the demographic and clinical characteristics.

Results: Fourteen patients (female: male = 13:1) with underlying ACTD and satisfying the inclusion criteria were included in this study. Dermatomyositis contributed to the majority of patients [78.6% (11)] with CC. Combination of diltiazem [mean dose 188.6 (131.3) mg/day] and pamidronate (mean dose 60mg/month) was used to treat calcinosis in 85.7% (12) patients. All patients completed a median (IQR) duration of 17.5 (12-41.25) months on follow up. Two patients had complete resolution of the lesions. Subjective clinical improvement and no new calcinotic lesions were documented during the follow up visits amongst the other patients. All four patients with CC associated ulcerations had documented resolution of ulcers on follow up.

Conclusion: Combination of calcium channel blockers and bisphosphonates served as an effective treatment option among our patients of CC with underlying connective tissue disorder.

Introduction

Calcinosis Cutis denotes a rare morbidity characterized by deposition of calcium salts in the skin and subcutaneous tissue (1). Four types of calcinosis cutis (CC) have been described based on the underlying etiology namely: dystrophic (with normal calcium and phosphorus), metastatic (with elevated calcium or phosphorus), iatrogenic (calcium and phosphorus levels dependent on etiology) and idiopathic (with normal calcium and phosphorus) (2).

Autoimmune connective tissue diseases (ACTD) have been commonly associated with dystrophic calcinosis (3). CC has been frequently associated with dermatomyositis [44-70% of juvenile onset (JDM); 25% of adult onset (aDM)](1), followed by systemic sclerosis (SSc) [25-40%] (4). It has been reported uncommonly in systemic lupus erythematosus and rarely in other ACTDs like mixed connective tissue disorder, rheumatoid arthritis, primary sjogren's syndrome and polymyositis. (1). The clinical presentation of CC varies broadly from being incidentally detected during clinical/radiological evaluation to overt symptoms of pain, limitation of joint movement and cutaneous ulceration.

Various non-pharmacological and pharmacological treatment options have been tried, but no standard therapy has been established. Current level of evidence for these therapeutic options range from 2b to 4. Balin et al (5), in their retrospective study of 78 patients seen over 14 years at the Mayo clinic, did not find any particular treatment to be uniformly effective. They found that surgical excision of symptomatic lesions and medical treatment with diltiazem provided benefit for some patients.

In this study, we tried to study the clinical characteristics of CC among patients with ACTD under our care as well as the treatment response to the various pharmacological options utilized.

Methods

All outpatient and inpatient records under the department of Rheumatology at Christian Medical College (CMC), Vellore, India were screened using the institutional Electronic Records System (ERS). Patients with the diagnosis of CC / calcinosis from August 2014 to April 2017 were screened. Out of the patients screened, those with underlying ACTD were included in the study. Clinical data of those patients who have received treatment for CC and completed at least 3 months of follow up in our department were studied.

Patient demographics, disease duration, symptoms at presentation, clinical as well as imaging characteristics of CC were noted from the ERS. Details of the treatment offered for CC, according to the treating physician's discretion, were also recorded. Subjective and /or objective evidence of improvement in the calcinotic lesions, as documented in the records during the last patient follow up, was analyzed.

Summary statistics were used for reporting the demographic and clinical characteristics. Data was expressed as mean and standard deviation (SD) for normally distributed data while median and interquartile range (IQR) was used for unevenly distributed data.

Results

Baseline patient characteristics and underlying ACTD

On screening the ERS, 18 patients were found to have Calcinosis Cutis during the study period. Out of these, 14 patients (female: male = 13:1) were found to have underlying ACTD and satisfied the inclusion criteria. Mean (SD) age of patients was 37 ± 12.9 years and mean (SD) age at onset of symptoms was 29.4 ± 11.6 years.

The median (IQR) duration of the symptoms prior to diagnosis of ACTD was 16.5 (8.25-34) months. Majority of patients [78.6% (11/14)] had underlying dermatomysotis (DM). aDM was diagnosed in 50% (7/14) and JDM in 14.3% (2/14), satisfying the Bohan and Peter criteria. On looking at the antibody profile among these patients with aDM, two patients were positive for Mi 2, one patient each with PL12 and Ku positivity. Three patients with aDM and both the patients with JDM did not have any positive result for the myositis antibodies tested at our institution.

Others ACTDs contributed to 7.1% (1) each as mentioned in Table 1, all satisfying their respective classification criteria. All patients had normal calcium and phosphate levels at baseline. Osteoporosis was documented in 57.1% (8) and avascular necrosis/ bone infarcts in 14.3% (2) of the patients at baseline.

Table 1: Characteristics of underlying ACTD and treatment received (N=14)

ACTD	No. of patients (%)	Age at symptoms onset (years)	Treatment received $				Steroid dose at onset (mg/kg)	Baseline Calcium (mg/dl)	Baseline Phosph-orus (mg/dl)
			MPA	Cyclo	Aza	MTX			
aDM	7 (50%)	30.7 (8.5)*	6 (42.9%)	2 (14.3%)	4 (28.6%)	2 (14.3%)	1*	9 (0.56)*	4.01(0.4)*
JDM	2 (15%)	12.5 (0.7)*	1 (7.1%)	0	0	2 (14.3%)	1*	9.2(0.28)*	3.7(0.14)*
AmDM	1 (7%)	20	1	0	1	0	0.5	8.7	4.1
ATS	1 (7%)	34	1	1	0	0	0.5	8.5	3.9
SSc	1 (7%)	39	0	0	1	0	0.25	8.7	4.8
OCTD	1 (7%)	27	1	0	0	0	0.5	8.1	3.1
UCTD	1 (7%)	52	1	0	0	0	0.5	9.2	3.5

* Depicts mean (SD) value
$ Patients may have received various medications in order to achieve disease control
AmDM – Amyopathic dermatomyositis, ATS – Antisynthetase syndrome, Aza – Azthioprine,
Cyclo – Cyclophosphamide, aDM – Adult onset dermatomyositis, JDM – Juvenile onset dermatomyositis,
MPA – Mycophenolate (Mofetil and Sodium), MTX – Methotrexate, OCTD – Overlap connective tissue disorder,
SSc – Systemic sclerosis UCTD - Undifferentiated connective tissue disorder

Calcinosis- Frequencies and Distribution

Calcinosis was documented in 50% (7) of patients at the time of diagnosis of the underlying ACTD. They included 21.4% (3) patients with aDM and one patient each with JDM, AmDM, UCTD and OCTD. Rest of the patients (4 patients with aDM, 1 patient each with JDM, ATS and SSc) had calcinosis documented following the ACTD diagnosis, after a median (IQR) duration of 13 (12.5-31) months.

Out of eleven patients with IIM, the onset of calcinosis was documented in 54.5% (6/11) patients after a median (IQR) duration of 13 (12.75-25.75) months following the index visit. Among the seven patients with aDM, 57.1% (4/7) patients reported CC symptoms 21.5 (12.5-34.5) months following the diagnosis. The rest 42.9% (3/7) patients, who had calcinosis at the time of index visit, had a median (IQR) duration of symptoms of 6 (6-9) months prior to diagnosis. Calcinosis was documented among the 2 patients with JDM, 9 months after and 12 months before the diagnosis respectively.

Pain [64.3% (9/14)] and ulceration [(28.6% (4/14)] were the predominant symptom attributed to CC documented in all these patients. All the patients with ulceration had concomitant pain as well.

Table 2: Symptom and Anatomical Distribution of Calcinosis Cutis (N=14)

	Incidentally detected calcinosis n(%)	Symptom attributed to Calcinosis		Location of Calcinosis (n)					
		Pain n(%)	Ulceration n(%)	Buttock	Upper Extremity*	Lower Extremity*	Trunk#	Hands	Face
aDM (n=7)	3 (42.9%)	4 (57.1%)	2 (28.6%)	7	3	5	3	2	1
JDM (n=2)	2 (100%)	-	-	1	1	0	1	1	0
AmDM (n=1)	-	1(100%)	-	1	1	1	1	1	1
ATS (n=1)	-	1(100%)	1(100%)	1	0	0	0	0	0
SSc (n=1)	-	1(100%)	-	1	0	1	0	0	0
OCTD (n=1)	-	1(100%)	1(100%)	1	0	1	0	0	0
UCTD (n=1)	-	1(100%)	-	0	0	0	0	1	0

#Trunk – included abdominal wall and axilla

*Extremity – included upper and lower limbs excluding the hands and feet

Calcinosis Treatment administered

Diltiazem [85.7% (12)] followed by pamidronate [64.3% (9)] were the most frequently used treatment options as shown in Table 3. Other treatment options used were alendronate [35.7% (5)], warfarin [14.3 % (2)] and sodium thiosulphate [14.3 % (2)]. Majority of these patients [85.7% (12)] were treated with a combination of diltiazem along with either oral or parenteral bisphosphonate, irrespective of their clinical / radiological presentation. Mean (SD) dose of diltiazem used was 188.6 (131.3) mg/day. Warfarin was used in 21.4% (3) patients. Out of these, one patient received warfarin indicated as an oral anticoagulant.

Table 3: Details of treatment offered for ACTD associated Calcinosis Cutis (N=14)

	Ditiazem			Alendronate			Pamidronate			Warfarin		
	n (%)	Dose (mg) mean (SD)	Duration in months mean (SD)	n (%)	Dose (mg) mean (SD)	Duration in months mean (SD)	n (%)	Dose (mg) mean (SD)	Duration in months mean (SD)	n (%)	Dose (mg) mean (SD)	Duration in months mean (SD)
aDM (n=7)	7	231.4 (114.5)	18 (15.5)	1	70	48	6	60	12 (10.1)	2*	3.5 (3.53)	21.5 (21.9)
JDM (n=2)	2	195 (148.5)	12	0	0	0	2	60	15 (4.2)	1	1	12
AmDM (n=1)	1	360	60	0	0	0	1	60	60	0	0	0
ATS (n=1)	0	0	0	1	70	5	0	0	0	0	0	0
SSc (n=1)	1	180	32	1	70	28	0	0	0	0	0	0
OCTD (n=1)	0	0	0	1	70	24	0	0	0	0	0	0
UCTD (n=1)	1	90	6	1	70	6	0	0	0	0	0	0

*One patient was given warfarin for anticoagulation in view of documented pulmonary embolism at a dose of 6mg. The other patient received warfarin at a dose of 1mg.

Treatment response on follow up

These patients had completed a median (IQR) duration of 17.5 (12-41.25) months on follow up. No mortality was documented during this period.

Two of these patients had clinical resolution of the CC on follow up. One patient was a gentleman with aDM who had completed 14 months of follow up. He was treated with diltiazem (90mg) for 11 months as well as pamidronate (60mg monthly) for 4 months and then discontinued. The other was a lady with JDM who had completed 80 months of follow up and was also treated with diltiazem (90mg) as well as pamidronate (60mg).

This patient was continued on lower dose of diltiazem (60mg) and was on 3 monthly pamidronate in view of the documented osteoporosis and avascular necrosis during the course of her treatment. Overall, 2 out of 3 patients receiving pamidronate alongwith diltiazem had shown resolution of calcinosis cutis.

Amongst the other patients on treatment, no new calcinotic lesions were documented during any of the follow up visits. Subjective clinical improvement was documented in all patients, despite the persistence of calcinosis. All four patients with CC associated ulcerations had documented resolution of ulcers.

Discussion

Dystrophic calcinosis usually occurs in the dermis as a result of chronic tissue damage or defective collagen synthesis in the setting of normal serum calcium and phosphate levels (3). These calcium salts form insoluble hydroxyapatite crystals in the tissues, presenting variably from localized nodules to those involving large areas of the body.

Interestingly, the time to onset and location of CC has been found to differ depending on the underlying connective tissue disease. In DM, calcinosis has been shown to occur 2.9 years and 7.8 years after the diagnosis of JDM and adult onset DM, respectively (1,5). Our patients with DM had calcinosis documented earlier as compared to that described in literature. Also, our patient of SSc had calcinosis documented 32 months following her diagnosis. Balin et al (5) reported CC in SSc appearing around 7.5 years post-diagnosis. However the location of the calcinotic lesions in all our patients, are concurrent with the findings of Balin et al and other investigators (1,5).

Several pharmacological options have been used in the treatment of calcinosis. CCBs, in particular diltiazem, has been widely used in the treatment of CC and recommended as the first line by several groups (6,7). Although the exact mechanism of action is not clear, it has been proposed to correct the ab normal intracellular calcium imbalance by decreasing the influx of calcium ions into cells (8). Recently Dima et al reviewed all the pharmacological treatment for CC in ACTDs and found diltiazem to be beneficial, independent of the underlying pathology (7). Treatment response also seem to be maintained during follow up and maximum duration of such response is reported to be 12 years (9).

Use of bisphosphonates was considered logical, as these autoimmune conditions were associated with increased bone resorption providing calcium for soft tissue deposition. Its anti-inflammatory effect on macrophages and local cytokine production have been proven to reduce ectopic calcification (10). Intravenous pamidronate has been found to be efficacious in several case reports, particularly in JDM as well as in those patients who failed on other treatment options. Although, anti-calcification potency has been established to be the same for alendronate and pamidronate, only patients receiving pamidronate showed complete resolution of CC in our series.

Warfarin was thought to be a viable treatment option through inhibition of Y-carboxyglutamic acid generation, a vitamin K dependent calcium-binding amino acid. One study that highlights the role of warfarin was the double- blind placebo controlled study of four patients with calcinosis universalis by Berger et al (12). They found two thirds of the patients receiving 1 mg/day of warfarin had decrease in extra-skeletal nuclear tracer uptake after 18 months, compared with none of the four patients receiving placebo. However, several other studies have shown the contrary and thus evidence has remained divided regarding warfarin. Discrepancy in these outcomes led to the hypothesis that warfarin might be more efficacious in early-onset and localized disease.

The common pharmacological options used in our patients were calcium channel blockers (CCBs), bisphosphonates and warfarin. None of our patients had documented worsening of calcinosis and most of the patients were treated with more than one medication. The most frequently used regime was CCB along with a bisphosphonate, which was in accord to the practice worldwide.

Limitations of the study included small number of patients, retrospective nature and lack of appropriate radiological documentation of status of CC on follow up.

Conclusion

Combination of calcium channel blockers and bisphosphonates served as an effective treatment option among our patients of calcinosis cutis with underlying connective tissue disorder.

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