

## Clinico-Histopathological Study of Calcinosis Cutis among Iraqi Patients

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### Abstract:

**Background:** Cutaneous calcification results from deposition of insoluble calcium phosphorous salts in the cutaneous tissues. There are wide clinical presentations of calcinosis cutis and it's a rare dermatological problem. However serious implication may arise due to delayed diagnosis.

**Objective:** To highlight and elaborate different clinical types of calcinosis cutis among Iraqi patients.

**Patients and Methods:** This observational, descriptive, clinical and histopathological study was done in Department of Dermatology- Baghdad Hospital-Medical City, Baghdad, Iraq during the period from January 1997-December 2012. History, examination and complete investigations if needed were done for each patient including all demographic points related to the disease. Excisional or incisional biopsies from each patient for histopathological evaluation were done.

**Results:** A total of 72 patients were included. They were 46 (63.01%) females and 27(38%) males. Their ages ranged from 3.5– 65(24.74±15.9) years. They were classified into 2 groups: **Group A** the dystrophic type with 65(89.04%) patients and was subdivided into **calcinosis cutis universalis** which constituted from 6(8.2%) cases. The 2<sup>nd</sup> subtype is **calcinosis cutis circumscriptum** which consist of 58(79.7%) cases. **Group B:** 8 (11.11%) patients with idiopathic type, 1 (12.5%) with idiopathic scrotal calcinosis and 2(25%) with subepidermal calcified nodule.

**Conclusion:** Calcinosis cutis is a rare medical problem with multiple etiological factors in which we see calcified deposits mainly in the skin. This is the first report appeared from Iraq.

**Keywords:** Calcinosis cutis, pilomatricoma, pseudoxanthoma elasticum, Iraqi patients.

### Introduction

Calcinosis cutis is the deposition of insoluble calcium salts in skin. The deposition can be in the dermis, subcutaneous tissue, or vascular endothelium when the local calcium concentration exceeds its solubility in the tissue.<sup>(1)</sup>

According to etiology, calcinosis cutis is divided into four major categories:<sup>(2,3)</sup>

#### **1-Dystrophic:**

The most common type and occurs as a result of local tissue injury. Although calcium and phosphate metabolism and serum levels are normal, local tissue abnormalities, such as alterations in collagen, elastin, or subcutaneous fat may trigger calcification. The internal organs usually remain unaffected.<sup>(1)</sup> Theoretically, dystrophic calcification occurs because the underlying disease process damages cell membranes, allowing calcium influx and subsequent intracellular crystallization. This dystrophic type is further classified clinically into **calcinosis circumscripta and calcinosis universalis**.

This dystrophic type frequently occurs in connective tissue disease like CREST syndrome, systemic sclerosis, in juvenile (50-70%) rather than adult-onset(20%) dermatomyositis ,nephrogenic systemic fibrosis and other different types of lupus erythematosus.<sup>(3,4)</sup> Inherited disorders as pseudoxanthoma elasticum, Ehlers-Danlos syndrome, porphyria cutanea tarda, Werner and Rothmund-Thomson syndromes are among other conditions associated with the dystrophic type.<sup>(1, 5)</sup> Dystrophic calcinosis cutis also occurred in cutaneous neoplasms such as pilar cyst, basal cell carcinoma, intradermal nevi, desmoplastic malignant melanoma, pyogenic

granuloma, hemangioma, trichoepithelioma, and seborrheic keratosis and mixed tumors (chondroid syringomas).<sup>(1)</sup>

**Other type of calcinosis Circumscripta is so called Pilomatricomas (calcifying epithelioma of Malherbe)** are hamartomas of the hair matrix and the most common cutaneous neoplasms that manifest calcification. Females are more commonly affected than males. It's relatively common benign tumor seen in children and young persons, sometimes in older adults with bimodal age distribution in the 1<sup>st</sup> and 6<sup>th</sup> decades. The lesions present as solitary, skin-colored, or pigmented cystic or firm nodules on the head, neck and upper extremities.

Also calcinosis cutis in burns, trauma, surgery, and keloids were well described.<sup>(1)</sup>

**Pseudoxanthoma elasticum** is an inherited disorder characterized by generalized fragmentation and progressive calcification of elastic tissue in the dermis, blood vessels and Bruch's membrane of the eye.<sup>(6)</sup> Mutations in the *ABCC6* gene on the short arm of chromosome16 had been reported. The skin changes generally present as small, circumscribed yellow to cream- colored papules on sides of the neck and flexures, giving the skin a "plucked chicken skin" appearance. Lax, redundant folds of skin, nuchal comedones and milia en plaque may also be seen. Characteristic exaggerated nasolabial folds and mental creases are common.<sup>(7)</sup> Ischemic heart diseases and recurrent mucosal hemorrhages may result. The changes in Bruch's membrane give rise to angioid streaks, and rupture of the retinal vessels to hemorrhages and choroiditis<sup>(6)</sup>. PXE can be demonstrated in more than half of patients with

angioid streaks, and 85% of PXE patients will have retinal findings. Histologically, elastic fibers are fragmented and mineralized with calcium. They stain gray-blue with Hematoxylin and Eosin (H&E), and are twisted, curled, and broken, suggesting "raveled wool."<sup>(7)</sup>

### **2-Metastatic:**

Chronic renal failure is the most common metabolic disease which takes the form of either benign nodular calcification often periarticular, calcifying panniculitis or calciphylaxis.<sup>(1, 8)</sup> Hypervitaminosis D, milk-alkali syndrome, excessive ingestion of calcium containing foods or antacids had also been associated.<sup>(1,5)</sup>

### **3-Idiopathic:**

The condition had followed intravenous calcium therapy extravasations, electroencephalography, heparin interferon injection neonatal heel sticks and post liver transplantation.<sup>(5,9)</sup>

### **4-Idiopathic:**

It includes idiopathic calcification of the scrotum<sup>(10)</sup>, sub-epidermal calcified nodules exposed areas of the head and the extremities<sup>(1)</sup> and milia-like idiopathic calcinosis cutis on the dorsa of hands and forearms of patients with syringoma and Down's syndrome<sup>(11)</sup>. Tumoral calcinosis as intramuscular or subcutaneous calcific masses around major joints in otherwise healthy adolescent in sporadic or familial cases had also been described.<sup>(5)</sup>

### **Diagnosis of calcinosis cutis:**

can be aided with the use of plain x-ray, CT-scan (the most sensitive), RN bone scan and sometimes MRI<sup>(12)</sup> and skin biopsy showed calcium deposits stains deep blue with H&E, red with alizarin red, and brown with aldehyde fuchsin and fluoresces with pentahydroxyl flavanol and black with Von Kossa stain for calcium phosphate in dermis and subcutis. With large deposits foreign body reaction, giant cells, an inflammatory infiltrate and fibrosis may be present around them.<sup>(1,3,13)</sup>

Calcinosis cutis has not been reported in Iraqi medical literature, accordingly the aim of present work is to report and evaluate these conditions in Iraqi patients regarding its clinical and histopathological aspects.

### **Patients and Methods:**

This observational, descriptive, clinical and histopathological study was carried out in Department of Dermatology and Venereology- Baghdad Hospital - Medical City, Baghdad, Iraq during the period from January 1997-December 2012.

Formal consent was taken from each patient or their parents before starting the study. Full explanation about the nature of the disease, course, and the options of treatment, follow up, prognosis, complications and the need for pre and post treatment photographs were

discussed. Also, the ethical approval was given by the scientific committee of the Scientific Council of Dermatology & Venereology-Iraqi Board for Medical Specializations.

History was taken regarding: gender, age, age of onset, duration of disease, recurrence rate, associated signs and symptoms, past history of the condition and all points related to the disease.

Full physical and dermatological examinations were carried out including the following points: clinical appearance of the lesion, site of the lesions, edges, size, number, systemic involvement. Medical or surgical consultations if needed were done for each patient to assess any systemic association according to the type of the disease.

Excisional or incisional biopsy from each patient and stained by H&E stain for histopathological study was done. Complete hematological, biochemical, X-Ray for bones, ultrasound, MRI and CT scan were performed depending on the type of the disease.

All patients were photographed by a digital camera (Sony: Cyber shoot with resolution 12 mega pixels) in the same place with fixed illumination and distance.

Descriptive statistics done by mean and standard deviation, frequency and percent.

### **Results:**

A total of 72 patients with calcinosis cutis were included in this work. 45 (62.5%) females and 27(37.5%) males with a female to male ratio: 1.6:1. Their ages ranged from 3.5– 64years with a mean  $24.771 \pm 16.0103$  years.

All the patients had no family history of similar lesions or diseases. The frequency and the clinical presentations of calcinosis cutis in the patients were as follow (Table- 1).

**1-Dystrophic Calcinosis Cutis:** Sixty four (88.9%) patients out of 72 cases .They consisted of 40 (62.5%) females and 24(37.5%) males with a female to male ratio of 1.6:1. Their ages ranged from 3.5– 64years with a mean  $\pm$  SD of  $25.586 \pm 15.6354$  years. Depending to their clinical aspects, they were subdivided into the following subtypes:

**A- Calcinosis universalis subtype:** They were 6(9.3%) cases. All of them were associated with severe well established childhood **dermatomyositis** that proved by all features and investigations. They were 3(50%) males and 3(50%) females with a male to female ratio of 1:1. Their ages ranged from 4– 12years with a mean  $\pm$  SD of  $8 \pm 2.768$  years. The disease duration ranged from 1-60 months with a mean  $\pm$  SD of  $28.16 \pm 21.32$  months. All had multiple to numerous lesions involving scalp, ears, elbows, knees, fingers, chest and abdomen. They showed features of growth retardation. The lesions consisted of wide, multiple plaques and nodules, atrophic skin,

extruded white chalky material from multiple orifices. They were located on trunk, elbows, knees and buttocks (Figure .1).

**B- Calcinosis circumscripta subtype:** were consisted of the following types;

**I-Pilometricoma:** was the most frequent dystrophic type with 21 (32.81%) patients. They were 14 (66.6%) females and 7 (33.3%) males with a female to male ratio 2:1. Their ages ranged from 5-45years with a mean ± SD of 18.800±9.7365 years. The disease duration ranged from 4-24 months with a mean ± SD of 10.30±5.202 months. All of the patients had solitary lesion. The sites of **pilometricoma** lesions were as follow: ten (47.61%) patients on arm; 4 (19.04 %) patients on leg; 2(9.52 %) patients on thigh; 1 (4.76%) patient on face; 1 (4.76%) patient on neck; 1 (4.76%) patient on shoulder; 1(4.76%) patient on forearm; 1(4.76%) patient on back (Figure -2).

**II -Pseudoxanthoma Elasticum (PXE):** constituted the 2<sup>nd</sup> frequent dystrophic type with 12 (18.75%) patients. They were 10 (83.3%) females and 2(16.7%) males with a female to male ratio 5:1. Their ages ranged from 3.5– 45years with a mean ± SD of 24.125 ±11.6621 years. The disease duration ranged from 1-20 years with a mean ± SD of 10.58±5.946 years. 10 (83.3%) patients had angioid streaks. Two (16.66 %) male

patients had eruptive pseudoxanthoma elasticum with no associated angioid streaks or systemic involvements and their ages were 3.5 and 5 years.

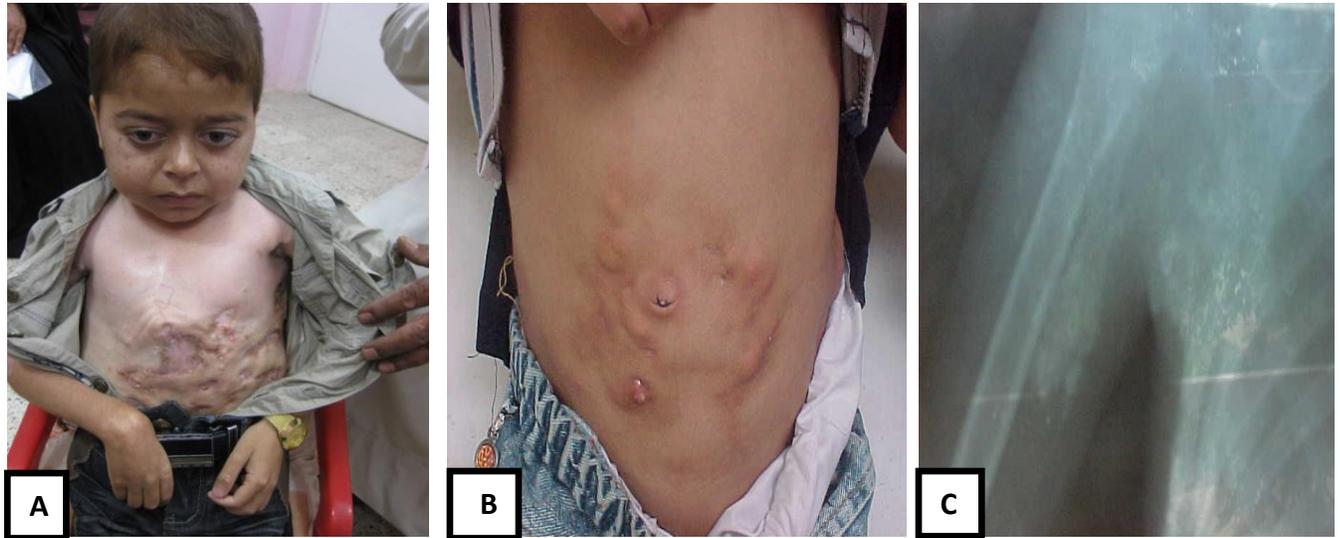
The sites of PXE lesions were as follow: 10 (83.3%) patients had lesions involving neck, axillae and groin whereas the 2(16.7%) patients with the eruptive type had lesions on the neck and trunk.

**2-Idiopathic Calcinosis Cutis:** Eight (11.11%) patients out of 72cases.They were 5(62.5%) females and 3(37.5%) males with a female to male ratio 1.6:1. Their ages ranged from 4– 50 years with a mean ± SD of 18.250 ±18.5761years. the disease duration ranged from 6-60 months with a mean ± SD of 16.75 ±17.726.Two (25%) patients their lesions distributed on the fingers only; 1 (12.5%) had multiple subepidermal calcified nodules (molluscum- like) on face; 1 (12.5%) had multiple lesions on forehead, arms and forearms; 1 (12.5%) had multiple lesions on fingers, elbows and knees; 1 (12.5%) had multiple lesions on arms and thighs; 1 (12.5%) had solitary lesion on back only; 1 (12.5%) had idiopathic scrotal calcinosis (Figure -3).

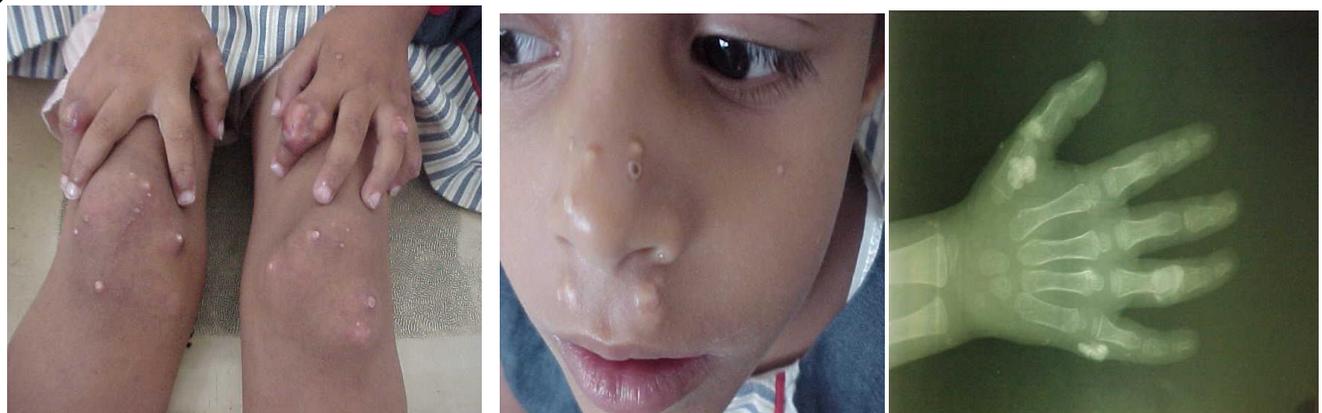
Histopathological findings of all types of calcinosis cutis were included the presence of well demarcated amorphous basophilic dermal masses or granules or subcutaneous masses. While the radiological features were calcified deposits around the joints in dystrophic calcinosis cutis universalis and idiopathic type (Figure .4)

**Table 1.** The frequency and the clinical presentations of calcinosis cutis in all patients.

Type	Subtypes	Diagnosis	No.	%
DYSTROPHIC	<i>Universalis</i>	Dermatomyositis	6	8.3
		Pilomatricoma	21	29.2
	<i>Circumscripta</i>	Pseudoxanthoma Elasticum	12	16.7
		Pilar cyst	10	13.88
		Lipoma	3	4.2
		Cystic acne	3	4.2
		Dermoid cyst	1	1.4
		Trichelemmal cyst	1	1.4
		Angiolipoma	1	1.4
		Tendon trauma	1	1.4
		Haemangioma	1	1.4
		Prurigo nodularis	1	1.4
		Burn scar	1	1.4
		Surgery	1	1.4
		Squamous cell carcinoma	1	1.4
<i>Total</i>	64	88.88		
IDIOPATHIC	Idiopathic	6	8.3	
	Subepidermal calcified nodule	1	1.4	
	Idiopathic scrotal calcinosis	1	1.4	
	<i>Total</i>	8	11.1	
<b>Total</b>		72	100.0	



**Figure .1:** (A) Eleven years old age male patient with severe dermatomyositis.  
 (B) The same patient with calcified nodules on the abdomen.  
 (C) The same patient showing calcifications around shoulder.

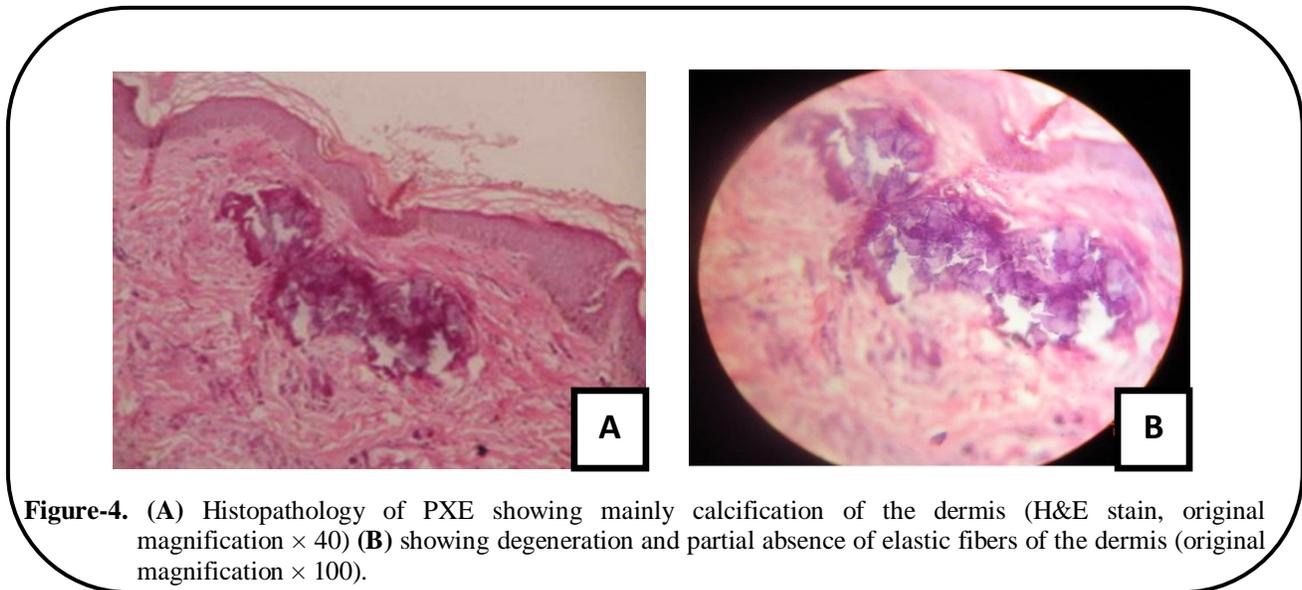


(A) Calcified nodules of fingers & knees      (B) Calcified nodules on face      (C) The same patient showing calcifications around phalanges.

**Figure.3** Five years old female patient. Idiopathic calcified nodules of the fingers.



**Figure 2.** Twenty two years old male with solitary pilomatricoma on the left arm.



**Figure-4.** (A) Histopathology of PXE showing mainly calcification of the dermis (H&E stain, original magnification  $\times 40$ ) (B) showing degeneration and partial absence of elastic fibers of the dermis (original magnification  $\times 100$ ).

#### Discussion:

Calcinosis cutis although is a rare a condition<sup>(4)</sup> but when dermatologist faces such cases get difficulty in reaching final diagnosis and is often neglected in the teaching curriculum of training trainees in dermatology.

In Iraq similar to any country calcinosis cutis seems to be a rare problem as only 72 cases reported during 15 years period. When these cases compared with what had been reported in the world many variations had been noted.<sup>(1,3,5)</sup>

There is wide range in the age presentation with a mean  $\pm$  SD of  $24.771 \pm 16.0103$  years.

Dystrophic calcinosis cutis is the most common type and pilomatricoma is the most frequent dystrophic type. While in other countries, scleroderma is the most common cause.<sup>(5)</sup>

Pilomatricoma may be reported with syndromes, but in the present study no syndrome or underlying disease were noted.<sup>(1,3,5)</sup>

Pseudoxanthoma elasticum was the second frequent dystrophic type, although it is mostly genetically predisposed disease,<sup>(6)</sup> but no familial cases were reported in the present study although there is a high rate of relative marriages.<sup>(14)</sup> Marked female predominance raise controversy with the slight female predominance which had been reported.<sup>(3)</sup>

Calcinosis cutis in dermatomyositis in the present work was only noticed among children and no adult cases. In all cases there was a delay in diagnosis and all of them had retardation of growth, crippled and the main presenting features were catastrophic calcinosis cutis.

Calcinosis cutis of scrotal epidermal cyst was noticed in one case, although scrotal epidermal cyst is a common presentation in patients.

Although nodulocystic acne is a common dermatological problem among youth population that encountered in clinical practice but only two cases had seen in the present study and this is comparable with other studies.<sup>(5)</sup>

The most common cause of metastatic calcinosis cutis is renal failure<sup>(1,3,5,6)</sup> but fortunately in the Iraqi patients is rare as no cases recorded during the course of this study. It is difficult to explain the causes behind that but we can speculate that these patients with bad health condition do not consult or are not well investigated.

To the best of our knowledge is the first medical report recorded this cutaneous problem in Iraqi population.

In conclusion, calcinosis cutis although is a rare disease but deserves an attention as many cases passed undiagnosed and should be included in the syllabus of the teaching curriculum.

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