Case Presentation

Milia-like idiopathic calcinosis cutis in a child with Down syndrome

Piyush Kumar¹, Sushil S Savant², Esther Nimisha³, Anupam Das⁴, Panchami Debbaman⁵

Dermatology Online Journal 22 (5): 9

¹ Dermatology, Katihar Medical college, Katihar
² Dermatology, Katihar Medical College, Bihar
³ Consultant Dermatologist
⁴ Dermatology, KPC Medical College and Hospital, Kolkata
⁵ Consultant Dermatology

Correspondence:

Piyush Kumar
docpiyush@gmail.com

Abstract

Idiopathic calcinosis cutis refers to progressive deposition of crystals of calcium phosphate in the skin and other areas of the body, in the absence of any inciting factor. Idiopathic calcinosis cutis may sometimes take the form of small, milia-like lesions. Most commonly, such milia like lesions are seen in the setting of Down syndrome. Herein, we report a 5-year-old girl with multiple asymptomatic discrete milia-like firm papules distributed over the face and extremities. A diagnosis of milia-like idiopathic calcinosis cutis associated with Down Syndrome was provisionally made and was confirmed by histopathology and karyotyping.

Keywords: Down syndrome, calcinosis cutis, milia

Introduction

Calcification represents the deposition of amorphous, insoluble calcium salts and when it occurs in cutaneous tissue it is termed “calcinosis cutis” [1, 2, 3]. Milia-like idiopathic calcinosis cutis (MICC), first described by Sano et al in 1978 [4] and named by Smith in 1989 [5], usually appears in children with Down syndrome, but some rare cases of MICC without any association with Down syndrome are also known [6]. Similar but perforating lesions have been reported by Maroon et al [7] and by Kanzaki and Nakajima [8]. These authors have described palpebral and perilesional syringomas in association with the calcinosis [9]. We report a case of a 5-year-old girl with multiple asymptomatic discrete milia-like papules distributed over the face and extremities from the age of one and a half years. The histopathology showed a well-defined amorphous basophilic deposition in the papillary dermis, consistent with calcinosis cutis. There were clinical findings suggestive of Down syndrome, which was later confirmed by karyotyping.

Case synopsis

A 5-year-old girl was brought with multiple, asymptomatic, discrete, white, firm papules distributed over the face, and extremities. The mother first noticed a few tiny white lesions over the face and dorsa of hands when the girl was one and a half year old. The
lesions gradually increase in size and number over a few months, with their distribution extending from face to neck and from distally to proximally over the extremities. These lesions used to subside spontaneously within 2-3 months, without any scarring or pigmentedary changes. However, during spontaneous healing transient erythema was appreciable. New lesions kept appearing and followed the same course. Parents denied any history of trauma, joint pain, bony swellings/deformity, muscle weakness, abnormal posture of the child, allergic drug reaction, dysphagia, dyspnoea, vomiting, seizures, joint hyperextensibility, and increased skin fragility. Symptoms associated with photosensitivity and Raynaud phenomenon were absent. Past medical history, surgical history, and family history (including elder sibling) were unremarkable.

The child, the second issue of a non-consanguineous marriage, was born full term by normal vaginal delivery. Ante-natal and post-natal periods were uneventful. The girl had received all scheduled immunizations as per her age. Of note, all her developmental milestones were delayed. Face was notable for epicanthic fold and upward slanting of eyes. There was a wide gap between first and second toes of both feet (Figure 1).

![Figure 1. Both feet showing wide 1st web space](image)

On mucocutaneous examination, there were multiple, small, discrete, firm, smooth-surfaced, white papules of 1 to 5 millimeters in diameter on face and extremities. The lesions on close examination looked like milia and many of the small papules were surrounded by macular erythema (Figures 2a, 2b and 2c).
Figure 2a. Multiple white papules on lower extremities. Note macular erythematous lesions on upper thigh. **Figure 2b.** Multiple white papules on dorsum of hands. Some of the lesions (arrow) show a central core, covered by white chalky material. **Figure 2c.** Multiple white papules on upper extremity. Some of the lesions (arrow) show erythematous halo.

A few faint erythematous macules were noted distributed randomly over extremities. On puncturing one of the lesions with a 26 gauge needle, a chalky white material, harder in consistency, could be expressed out. Levels of lactate dehydrogenase, creatine phosphokinase, serum uric acid, and alkaline phosphatase were normal. The parathyroid hormone assay also showed a normal value. Of note, she had normal levels of serum calcium (9.2 mg/dl, normal: 8.5–10.3 mg/dl), serum phosphorus (4.4 mg/dl, normal: 3.0–6.0 mg/dl), serum 25-hydroxy vitamin D (49 ng/dl, normal: 17–54 ng/dl), and parathyroid hormone. The 24-hour urinary calcium and phosphorus excretion were reported normal. Serology for antinuclear antibody test, anti-DNA, ANCA, rheumatoid arthritis (RA) test, and serum complement levels were within normal limits. Mantoux test was negative. Radiological examination did not reveal any joint or bone abnormality, but showed widespread extensive amorphous calcifications in the periarticular soft tissues. A punch biopsy from a papule over dorsum of the left hand was done. Histology showed orthokeratosis, acanthosis, and a well defined condensation of homogenous amorphous basophilic material (suggestive of the calcium deposition) in the superficial papillary dermis, surrounded by dense collagen. There was no associated inflammatory infiltrate in the dermis (Figure 3).
Figure 3. Upper dermis showing a well-defined homogenous amorphous basophilic material (suggestive of the calcium deposition). Epidermis and rest of dermis are unremarkable. (H&E x 100)

There was no evidence of transepidermal elimination of calcium deposits or any presence of epidermal cyst. Karyotyping revealed 47 chromosomes with trisomy 21 in all cells, thus establishing the diagnosis of Down syndrome. After considering the clinical features with the biochemical tests, histopathological findings, and karyotyping data, the final diagnosis was made as ‘milia-like idiopathic calcinosis cutis with Down syndrome’.

**Discussion**

Calcium regulates major functions in the skin including epidermal keratinocyte proliferation, differentiation, and cell–cell adhesion [1]. When factors that regulate calcium in the skin are disrupted, either by local or systemic events, the result can be cutaneous calcification or ossification as well as acantholysis and dyskeratosis [2]. Ionic calcium concentration in serum is primarily controlled by three regulatory hormones [1]: Parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D3 (Cholecalciferol). A coordinated regulation of all three hormones in coalition is necessary for a normal calcium homeostasis of blood (9-11mg/100ml).

Calcinosis cutis is an uncommon disorder, which is characterized by the progressive deposition of crystals of calcium phosphate (hydroxyapatite) in the skin. Depending on the etiology the cutaneous calcifying disorders are divided into four broad categories: dystrophic, metastatic, idiopathic, and iatrogenic [1, 2, 3]. Dystrophic calcification occurs in the presence of an underlying disease process, which causes localized tissue damage, resulting in cell membrane disruption followed by influx of calcium and intracellular crystallization. There are no associated systemic/metabolic abnormalities in calcium/phosphorous regulation and the serum calcium and phosphorous levels are essentially normal. Metastatic calcification occurs in the normal tissue owing to precipitation of calcium salts because of an underlying calcium/phosphorous metabolism dysfunction. The calcification may be widespread involvement of the skin, blood vessels, kidneys, lungs, and gastric mucosa. The serum calcium and phosphorous levels are typically raised. Idiopathic calcification occurs without any tissue damage and in the absence of abnormal calcium/phosphorous metabolism. Consistent with our case, there is no local or systemic identifiable cause and serum calcium and phosphorous levels are normal. When the lesions are generalized they are termed as calcinosis universalis, but when they are localized they may manifest as a subepidermal calcified nodule, localized idiopathic dermal calcinosis, tumoral calcinosis, and scrotal calcinosis. Iatrogenic calcification may occur secondary to any medical or surgical intervention. It occurs owing to rapid precipitation of calcium salts within the skin. When the tissue concentration of calcium rises and exceeds the solubility product, calcium precipitates within the tissue, resulting in firm nodules in the dermis and/or subcutaneous tissue. A secondary
inflammatory response is elicited and, over a period of weeks to months, the calcium is either absorbed or transepidermally eliminated, depending on the depth of the deposit [1,3]. Disorders associated with calcinosis cutis have been tabulated in Table 1.

Idiopathic calcinosis cutis is a rare phenomenon [10] and is divided into six main clinical types [3]: Calcinosis universalis, subepidermal calcified nodule, localized idiopathic dermal calcinosis, tumoral calcinosis, scrotal calcinosis, and Milia-like Idiopathic Calcinosis Cutis (MICC). MICC is a rare condition manifesting as multiple, smooth, firm skin colored to whitish papules resembling milia. There may be an associated perilesional erythematous halo in a few lesions. Some of the papules may have a central crust representing transepidermal elimination of calcinosis and resemble lesions of perforating dermatosis. It primarily affects the upper and lower limbs. The face may rarely be affected. Lesions have a waxing and waning course and they usually heal without any scarring. There is a tendency to decreased frequency of recurrence with increasing age and lesions completely disappear by adulthood. Two-thirds of cases have been reported with Down syndrome and up to one-third of patients with coexisting palpebral or perilesional syringomas [3, 11, 12, 13, 14, 15]. The mean age of the patients reported is 10.4 years [16].

The pathogenesis of idiopathic calcification is not clearly understood and the underlying mechanism is not known. It has been postulated that there may be some abnormality in the metabolism of gamma carboxy-glutamic acid (GCGA), a unique amino acid, which is normally found in bones and tissues. It has calcium and phospholipid binding properties. Probably GCGA gets deposited in the skin owing to some aberration in its metabolism, leading to deposition of calcium phosphate in the skin [10, 17]. Cultured fibroblasts from a patient with Down syndrome showed higher levels of calcium. However, its clinical significance is unknown [18]. Eccrine sweat ducts too are suspected to play a role and may cause calcium deposition through increased sweat calcium concentrations or low excretion [7, 19]. Calcified sweat ducts have been described occasionally in some patients [7, 14]. However, there is no histopathological evidence of sweat duct involvement in MICC, since most of the lesions do not appear to be closely related to sweat glands [16]. Some authors believe that these lesions might represent microepidermal cysts [20] that secondarily generate a chronic inflammatory reaction and calcium deposition [21].

Down syndrome is a multisystem disorder caused by an extra chromosome 21 [22, 23]. Table 2 enlists the different phenotypic and cutaneous manifestations associated with Down syndrome [23, 24]. The first case of MICC associated with Down syndrome was reported by Smith and Golitz in 1989 [5].

Histopathology examination of calcinosis cutis shows a focus of calcium in the papillary dermis surrounded occasionally by a lymphocytic infiltrate and giant cells. Perforation may or may not be present. In cases associated with syringomas, orthokeratosis and acanthosis is present. A small nodular foci of calcium is present in the papillary dermis, along with proliferation of eccrine ducts forming small syringomas. Serial sections of a crusted lesion may occasionally show transepidermal elimination of the papillary dermal calcium deposits in both the forms. Owing to the concomitant presence of phosphate and carbonate, the deposit stains black with the Von Kossa stain [3].

Because the differential diagnosis of MICC includes common conditions like milia, epidermal cysts, warts, perforating dermatoses, and molluscum contagiosum, it is important for the clinicians to be aware of this condition.

The pharmacological treatment of calcinosis cutis is difficult and includes bisphosphonates, intralesional corticosteroids, aluminum hydroxide, warfarin, diltiazem, minocycline, ceftriaxone, intravenous immunoglobulin/EDTA, probenecid, and colchicine [25, 26, 27, 28, 29]. Topical therapy with sodium thiosulfate 100% powder mixed in ratio 1:4 (25%) in zinc oxide applied under occlusion with elastic wraps is another option. Local excision is the current existing therapeutic option but recurrence is common [30, 31]. Introduction of low calcium diet, and use of cellulose phosphate/sodium sulphate has been proposed by some authors but without much benefit [10, 32]. Surgical intervention is indicated when lesions are painful or in the situation of recurrent infection, ulceration, and functional impairment [10]. Because the surgical trauma might act as a stimulus for further calcification and result in scarring, it is worth giving a trial of exciting a single lesion as a test initially over a cosmetically hidden area before aggressively excising larger lesions [10]. Cryotherapy with liquid nitrogen, extracorporeal shock wave lithotripsy, and carbon dioxide laser are other surgical options that can be tried.

Our case was diagnosed as milia-like idiopathic calcinosis cutis with Down Syndrome after a detailed coalition of history, clinical examination and investigations. Parents were reassured and counseled. Topical sodium thiosulfate compounded in zinc oxide was applied to a few lesions, but emergence of newer lesions did not stop.

Acknowledgement

The authors would like to thank Dr Sanjay Khare for his valuable help in preparing manuscript.
References


