CASE REPORT

Sanjad-Sakati Syndrome with calcinosis cutis

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INTRODUCTION

Sanjad-Sakati syndrome is a recently described genetic disease confined to children of Arab populations (Bedouin origin) in the Middle-East countries,[1] predominantly of consanguineous parents.[2] The syndrome consists of congenital hypoparathyroidism, severe growth retardation, intellectual deficit, seizures, and typical dysmorphic features.[3,4]

All Children affected with this condition are universally born IUGR (intrauterine growth retardation) and present with hypocalcaemic tetany or seizures due to hypoparathyroidism at an early stage in their lives. Intravenous calcium infusion is often offered to these children.[5] On the other hand, cutaneous manifestations including calcium deposition in the skin (calcinosis cutis) have never been reported in this syndrome. In this issue, we describe the first case, to our knowledge, of Sanjad-Sakati syndrome with calcinosis cutis.

CASE

A 2 year- old Kuwaiti male baby admitted several times in pediatric ward in Jahra hospital for recurrent convulsions, hypocalcaemia and respiratory distress treated by repeated calcium infusions. Medical history included; low birth weight (2.4 Kg), delayed milestones and, a previous attack of cardiac arrest managed by resuscitation. The patient was referred to Dermatologists for an ulcer on the head and multiple nodules on the extremities, developed since two weeks. Clinical examination demonstrated a large, about 7X5 cm, irregular ulcer with thick erythematous border on the left temporal side of the scalp. The floor of the

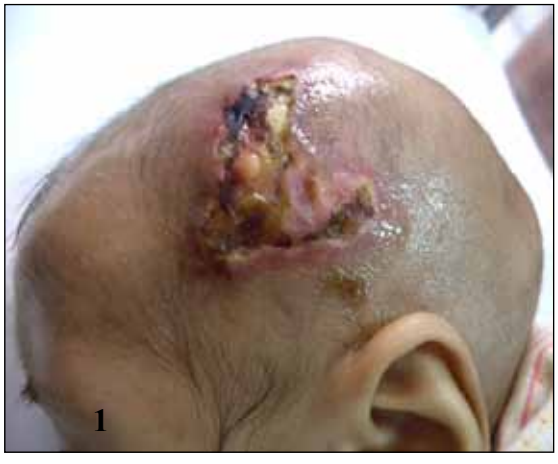

Fig. 1 Irregular ulcer with thick erythematous border on the left temporal side of the scalp.

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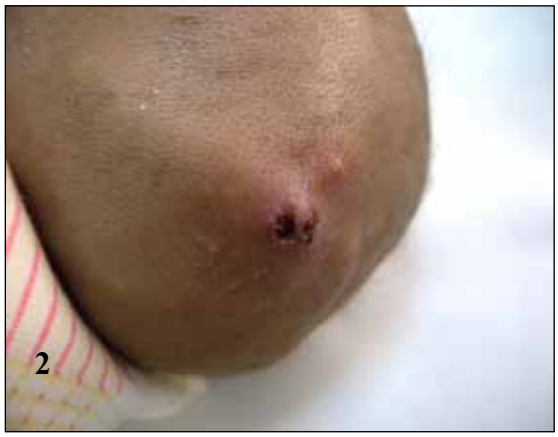

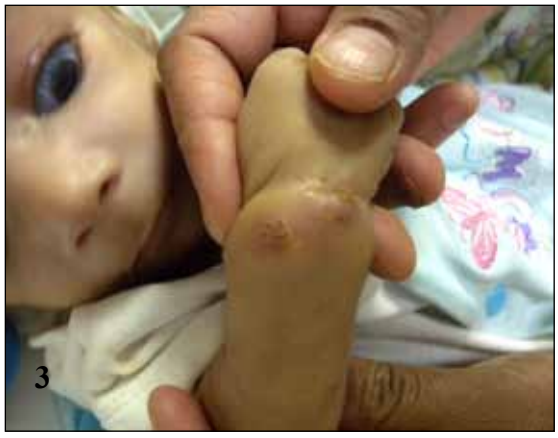

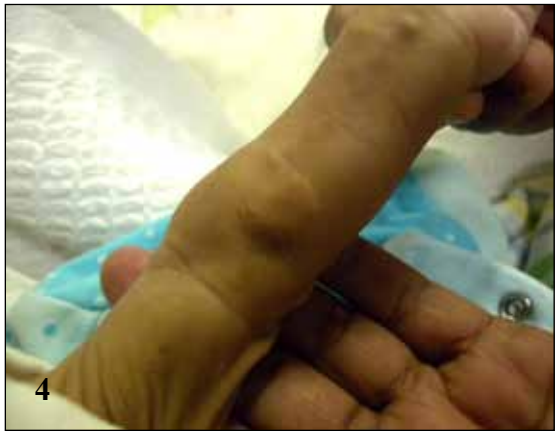

Fig. 2, 3, 4 Multiple hard nodules of different sizes, on the scalp and the extensor surfaces of both upper and lower limbs.

ulcer was indurated with oozing, crustation, and white chalky material (Fig.1). There were also multiple hard nodules of different sizes, 0.5 - 3 cm, on the scalp and the extensor surfaces of both upper and lower limbs (Fig. 2,3,4). Most of the nodules were non - ulcerated and skin colored. Few of them were inflamed, tender, erythematous with or without superficial erosions. The baby had characteristic facies with typical long narrow face, deep set small eyes, micrognathia, and microchephaly. Mucous membranes, hair and nails were free. Family history was negative for similar cases.

Laboratory investigations showed mild leuckocytosis, anemia, and low level of parathyroid hormone. Elevated liver enzymes (ALP, ALT, and GGT), direct bilirubin, LD, CK. Serum calcium and corrected calcium levels, at time of examination, were 2.99 mmol/L and 3.0 mmol/L, respectively. Previous serum calcium and corrected calcium levels, before last infusions, were 1.45 mmol/L and 1.63 mmol/L respectively (Reference Range 2.225 - 2.73 mmol/L).

Chest X-ray revealed uniform opacity on the right side (lung consolidation). Two biopsies were taken; one from one of the nodules on the left forearm and the other from the ulcer on the scalp. Histological examination of the two biopsies revealed epidermal acanthosis and hyperkeratosis. The dermis showed uniform calcification of the entire dermis along with the adnexal structure (Fig. 5). Von Kossa stain was strongly positive showing large irregular calcium deposits (Fig. 6).

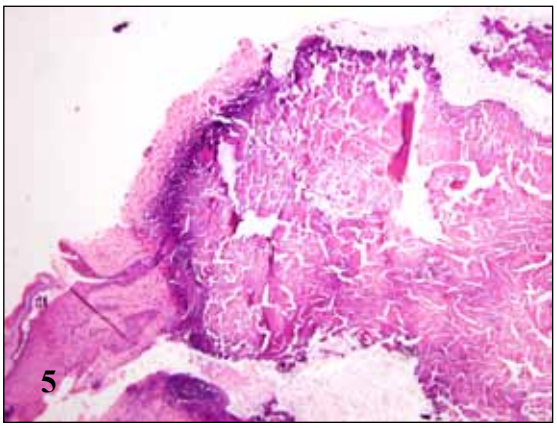

Fig. 5 Epidermis showed acanthosis, hyperkeratosis and dermis showed uniform calcification of the entire dermis along with the adnexal structure.

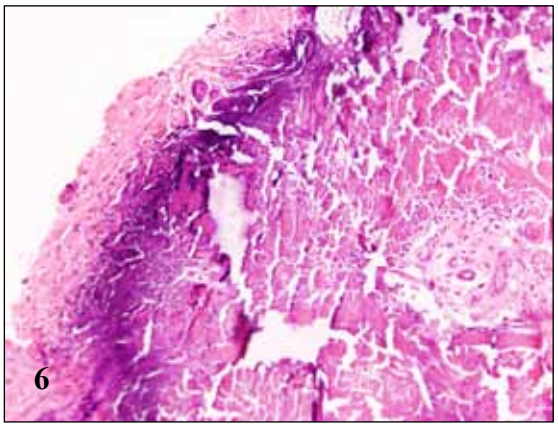

Fig. 6 Von Kossa stain was strongly positive showing large irregular calcium deposits.

DISCUSSION

Middle Eastern cultures are tribal and heavily consanguineous. Marriage between cousins has been part of the culture for millennia leading to "founder" effect and a large number of autosomal recessive diseases.[6] Sanjad-Sakati Syndrome is transmitted in an autosomal recessive manner, with equal distribution in both sexes, reported exclusively from the Arabian Peninsula. Reported patients have been Saudi, Qatari, Israeli Arabs, Kuwaiti and Omani.[5,7,8]

Sanjad-Sakati Syndrome has distinct clinical, biochemical, and genetic abnormalities.[4] The initial report of Sanjad et al[9] in 1988 and their definitive report in 1991[10] clearly established this as a distinct disorder comprising of congenital hypoparathyroidism, hypocalcaemia, hyperphosphataemia, severe intrauterine and postnatal growth failure, respiratory infection susceptibility, dwarfism, mild to moderate mental retardation, seizures and, abnormal dentition.[1,11] They also have, typical craniofacial dysmorphic features namely: microcephaly with prominent forehead, long narrow face, deep set small eyes, depressed nasal bridge with beaked nose, large floppy ears, long filtrum, thin upper lip, micrognathia / retromicrognathia and small hands and feet.[1,5] Our patient showed most of the cardinal features described previously. Other reported associations include: GH insufficiency with low serum IGF-I concentrations and several of the males have clinical features suggestive of hypogonadotropic hypogonadism.[3] Table 1 summarizes the signs associated with the Sanjad-Sakati syndrome.

Neuroimaging studies demonstrated reduced white matter mass with delayed myelination, hypoplastic anterior pituitary, and hypoplasia of the corpus callosum. MRI features could contribute to the varying degrees of developmental delay reported in this syndrome. Pituitary function has additionally demonstrated hypocortisolemia with blunted cortisol responses to glucagon stimulation

Table 1 List of signs associated with the Sanjad-Sakati syndrome:[4,7]

Signs	Frequency
Autosomal recessive (AR)	100%
IUGR	100%
Short stature	100%
Deepset eyes/ enophthalmos	100%
Depressed nasal bridge	100%
Difficulties for feeding in infancy	100%
Hypoparathyroidism	100%
Long philtrum	100%
MR	100%
Microcephaly	100%
Micrognathia/ retrognatia	100%
Ph/ Ca metabolism abnormalities	100%
Seizures	100%
Small feet	100%
Small hand	100%
Thin lips	100%
Teeth anomalies	frequent sign
Thick ear lobe	frequent sign
Cellular immune deficits	occasional sign

and standard synacthen test.[4]

The disorder has been listed by McKusick in OMIM as "hypoparathyroidism - retardation - dysmorphism syndrome; HRD as entry 241410. Recently, Parvariet al[3] reported the assignment of the gene for this disorder to chromosome 1 at 1q42-43[7] and caused by homozygous mutation in the tubulin cofactor E (TBCE) gene.[5,12] leading to loss of four amino acids (c.155-166 del 12) in the TBCE protein.[4,13]

Hypoparathyroidism and growth failure are universally present in all of the affected children with subsequent development of fatal hypocalcaemia, hypomagnesemia and hyperphosphataemia. These metabolic derangements are responsible for nephrocalcinosis, medullary stenosis of long bones and convulsions. Multiple pathological fractures of long bones is uncommon.[14] Supportive treatment in the form of vitamin D, calcium infusion and growth hormone is often offered to these children.[5]

The phenomenon of calcium deposition in the skin (calcinosis cutis) has not been reported in association with Sanjad-Sakati syndrome so far. In addition, no other skin manifestations have been described with this syndrome. Hence it is not familiar to dermatologists. Calcinosis cutis is classified into 4 major types according to etiology: dystrophic, metastatic, iatrogenic, and idiopathic.[15]

Metabolic and physical factors are pivotal in the development of most cases of calcinosis. In metastatic calcinosis, ectopic calcification can occur in the setting of hypercalcemia and/or hyperphosphatemia when the calcium-phosphate product exceeds 70 mg /dL,[2] without preceding tissue damage. Alternatively, damaged tissue may allow an influx of calcium ions leading to an elevated intracellular calcium level and subsequent crystalline precipitation (dystrophic). Iatrogenic calcinosis cutis arises secondary to a treatment or procedure like parenteral administration of calcium or phosphate, repeated heel sticks in the newborn, and prolonged use of calcium-containing electrode paste.[16]

Our case is suffering from hypocalcemia and hyperphosphatemia, which is highly suggestive of metastatic calcinosis. This suggestion, is supported by the presence of calcinosis in distant locations away from infusion sites. On the other hand, the occurrence of calcinosis cutis at sites of calcium infusion may support that it is an iatrogenic calcinosis due calcium extravasation. Another explanation for the iatrogenic reason is that the calcium level in the serum of the patient has been increased by frequent calcium infusions with subsequent development of iatrogenic hypercalceamia and calcinosis cutis. Combination of both metastatic and iatrogenic calcinosis is possible.

Medical therapy of calcinosis cutis is limited and of variable benefit. The first step is to identify and treat the underlying cause. Some cases may require surgical removal of the lesion but often this can result in a recurrence of symptoms. For our case, cessation of calcium infusion, low calcium diet, and daily dressings of the ulcers were quiet

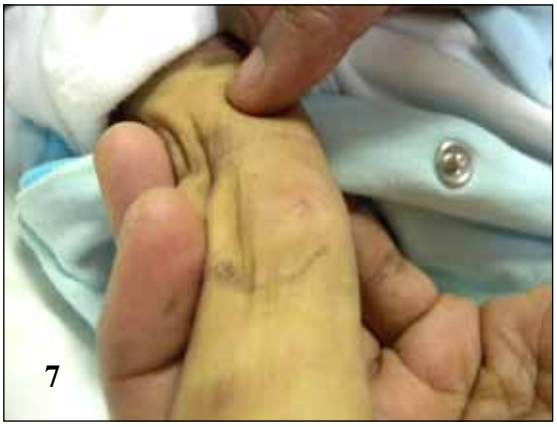

Fig. 7 Disappearance of lesions after 3 months of treatment.

enough to clarify all lesions by 3 months (Fig. 7). The differential diagnoses of Sanjad-Sakati syndrome include DiGeorge syndrome, Kenny Caffey syndrome, HDR (Hypoparathyroidism, Deafness, Retardation) syndrome, retinoic acid embryopathy and X- Linked isolated hypoparathyroidism.[8] Although some of the features resemble DiGeorge syndrome, Kenny-Caffey syndrome and familial hypoparathyroidism, absence of association with cardiac lesions, lymphopenia or skeletal abnormalities makes it a distinct entity.[5] However, some authors consider that Sanjad-Sakati syndrome and type 1 Kenny-Caffey syndrome are at least allelic disorders if not the same condition. Both disorders are caused by mutations in TBCE and share the locus 1q42-43 and many clinical signs like growth retardation, craniofacial anomalies, hypocalcaemia and hypoparathyroidism.

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