Epidermal Nevus Syndrome with Hypophosphatemic Rickets

Sir,

Epidermal nevus syndrome (ENS) is a rare multisystemic disorder characterized by the presence of congenital epidermal nevi and abnormalities involving skeletal, ocular, neurological, cardiovascular, or genitourinary system. Hypophosphatemic rickets in patients with ENS results from the production of phosphaturic factor-fibroblast growth factor-23 (FGF-23) by the epidermal nevi. However, this has only been reported through a handful of cases in the literature.[1-14]

An 8-year-old boy presented with progressive bony deformities, proximal muscle weakness, and growth retardation since the age of 3 years. At 4 years of age, he sustained a fragility fracture in the right forearm which was managed conservatively. He was born of a nonconsanguineous marriage with uneventful birth history. He had delayed permanent tooth eruption; however, there was no history to suggest premature tooth fall, tooth abscess, or hearing difficulties. There was no history of seizures or vision problems. The child attained developmental milestones at a normal age. Family history was noncontributory. He had been given multiple courses of calcium and vitamin D (cholecalciferol) supplementation elsewhere without any significant improvement. Clinical examination found a young prepubertal child with severe short stature (height<-3 standard deviation score), features of rickets (wrist widening and rachitic rosary), severe bony deformities of all four limbs, kyphoscoliotic deformity of the dorsal spine, proximal muscle weakness involving upper and lower limbs, and multiple linear hyperpigmented verrucous nevus over right half of the body (at the back of scalp, hand, forearm and arm, chest and inner aspect of thigh) [Figure 1].

On investigation, the child had normal renal and liver function tests. Serum calcium was normal at 2.3 mmol/L (normal range 2.1–2.6 mmol/L), serum inorganic phosphorus was low at 0.32–0.58 mmol/L (normal range for age 1.19–1.74 mmol/L), and serum alkaline phosphatase was elevated at 2666 IU/L (normal range for age 240–840 IU/L). Serum bicarbonate, 25-hydroxyvitamin D, parathyroid hormone, thyroxine, and thyroid-stimulating hormone levels were normal. Renal tubular maximum reabsorption rate of phosphate corrected for glomerular filtration rate (TmP/GFR) was also low at 0.40–0.72 mmol/L (normal range for age 1.22–1.60 mmol/L), suggestive of renal tubular phosphate wasting. Skeletal survey revealed features of active rickets, severe osteopenia, deformities involving appendicular, and axial skeleton and pseudoarthrosis [Figure 2]. Bone scintigraphy showed findings of metabolic bone disease [Figure 3]. A clinical diagnosis of epidermal nevus was confirmed on skin biopsy. Considering the presence of multiple linear epidermal nevi with hypophosphatemic rickets and renal

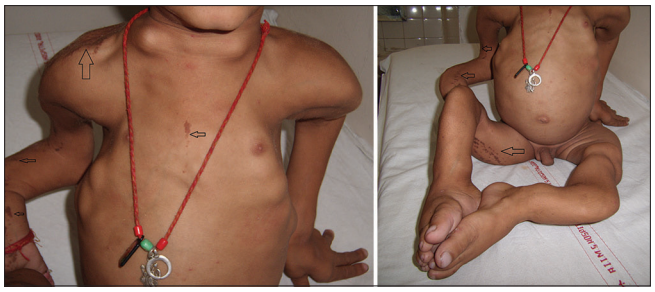

Figure 1: Multiple linear epidermal nevi (arrows) noted on clinical examination

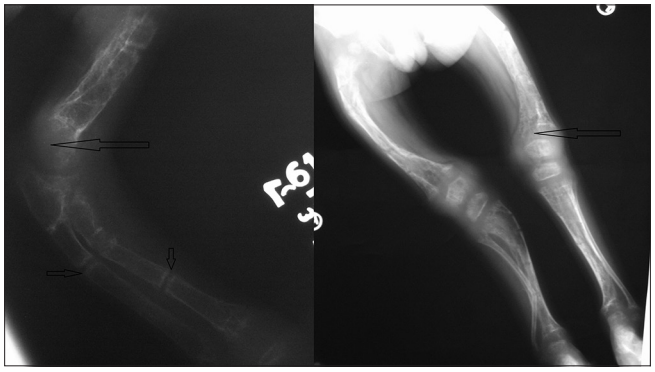

Figure 2: Radiographs of elbow and knee showing severe osteopenia, features of active rickets (long arrows), bony deformities, and pseudoarthrosis (short arrows)

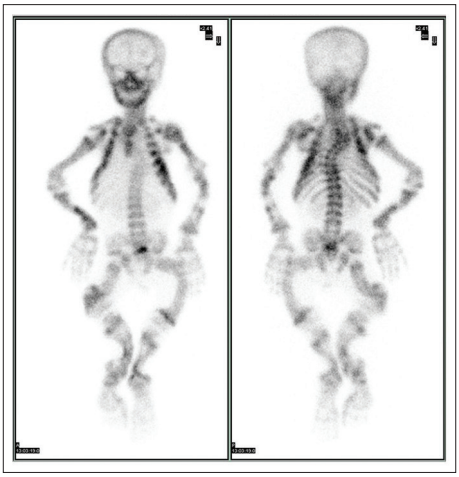

Figure 3: 99mTc-methylene diphosphonate (MDP) bone scan showing features of metabolic bone disease- increased uptake in the mandible, sternum, costochondral junctions, deformed appendicular skeleton, and kyphoscoliotic dorsal spine with mild diffusely increased tracer uptake and faintly visualized kidneys

phosphate wasting, the patient was diagnosed with ENS. Due to the extensive distribution of nevi, surgical excision of skin lesions was deemed inappropriate and the patient was initiated on medical management with neutral phosphate solution and calcitriol.

ENS is characterized by the presence of several cutaneous and extracutaneous features. The epidermal nevus lesion in ENS is extensive, unilateral, and usually follows the Blaschko lines. Skeletal manifestations have been reported in about 50% of patients with ENS and include kyphoscoliosis, bone cysts, joint deformities, and vitamin D-resistant hypophosphatemic rickets. Neurological manifestations have been reported in 50–70% of patients and include seizures, hemiparesis, developmental delay, mental retardation, abnormal cerebral gyri, underdeveloped temporal lobe, cortical blindness, and sensorineural hearing loss.[15,16] Central nervous system manifestations are more likely to be associated with the presence of epidermal nevus on the head, with anatomical lesion ipsilateral to the side of skin lesion.[17] About one-third of the patients may have ocular abnormalities. These include involvement of eyelid or conjunctiva by the nevus, conjunctival dermolipoma, strabismus, nystagmus, coloboma, ophthalmoplegia, ptosis, and corneal clouding. Precocious puberty, cardiovascular defect (aortic coarctation), and renal anomalies have also been described rarely.[3]

Our case illustrates the rare association of hypophosphatemic rickets with ENS; only a handful of such cases have been reported in the literature.[1-14] A casual association between skin lesions in ENS and hypophosphatemic rickets was first demonstrated by Aschinberg *et al.*[2] The authors demonstrated biochemical improvement and radiological healing following excision of skin lesions in a child with ENS and rickets. Moreover, injection of a portion of excised tissue into a 6-week-old puppy induced phosphaturia, suggestive of production of a rachitogenic phosphaturic substance by the skin lesions. Subsequently, a few more cases replicating similar findings have been reported in the literature.[3,4] Elevated FGF-23 levels have also been reported in ENS associated hypophosphatemic rickets.[17] Our patient presented with features of vitamin D-resistant hypophosphatemic rickets secondary to renal phosphate wasting, likely related to FGF-23 excess. We could not measure the FGF-23 level in our patient. In patients with ENS and hypophosphatemic rickets, surgical excision of skin lesions should be tried in an attempt to remove the source of FGF-23 excess, analogous to patients with tumor-induced osteomalacia. However, in patients with extensive skin lesions, surgical excision may not be possible and medical treatment with phosphate and calcitriol should be considered. Patients initiated on medical management should be closely followed for improvement of musculoskeletal symptoms, bony deformities, and growth parameters. A close watch should also be kept on possible adverse effects of long-term medical therapy, such as secondary hyperparathyroidism, hypercalcemia, hypercalciuria, and nephrocalcinosis.[18]

To conclude, we have described a rare case of ENS and hypophosphatemic rickets, which was brought to clinical attention with symptoms of multiple bony deformities, proximal muscle weakness, and growth retardation. The presence of hypophosphatemia with renal phosphate wasting and multiple linear epidermal nevi lead us to a diagnosis of ENS in this patient. Although surgical excision of skin lesions could not be done due to their extensive distribution, it remains a worthwhile treatment option in patients with limited extent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's guardian has given the consent for the use of images and other clinical information to be reported in the journal. The child's guardian understands that the name of the child will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 02-Jan-2020 **Accepted:** 03-Jan-2020
Published: 30-Apr-2020

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_3_20

How to cite this article: Goyal A, Damle N, Kandasamy D, Khadgawat R. Epidermal nevus syndrome with hypophosphatemic rickets. Indian J Endocr Metab 2020;24:227-9.