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Epidermal Nevus Syndrome Presenting as Hypophosphatemic Rickets

A Case Report of an Uncommon Association

Oranee Sanmaneechai, MD, Wanee Wisuthsarewong, MD,† and Pairunyar Sawathiparnich, MD‡*

Abstract: The epidermal nevus syndrome is a multisystem defect that includes epidermal nevi and cerebral and musculoskeletal abnormalities. We report the case of a 7-year-old Thai boy with hypophosphatemic rickets in a rare association with the epidermal nevus syndrome. The patient presented with growth retardation, bone pain, and generalized muscle weakness.

Key Words: epidermal nevus syndrome, hypophosphatemic rickets, phosphorus

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Learning Objectives

- Recall the physical and laboratory abnormalities presented by this young boy – 1 of only 16 patients to be reported with a combination of epidermal nevus syndrome (ENS) and hypophosphatemic rickets.
- Compare the treatment response of ENS and rickets in the present patient with the results achieved in the 15 other, previously reported patients having both of these disorders.
- Appraise competing explanations of the origin of hypophosphatemic rickets in patients diagnosed as having ENS.

*Clinical Instructor, Division of Pediatric Endocrinology; †Associate Professor, Division of Pediatric Dermatology and Department of Pediatrics, and ‡Assistant Professor, Division of Pediatric Endocrinology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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Reprints: Pairunyar Sawathiparnich, MD, Assistant Professor, Division of Pediatric Endocrinology, HRH Princess Mahachakri Building, 9th Floor, Department of Pediatrics, Siriraj Hospital, 2 Prannok Road, Bangkoknoi, Bangkok 10700, Thailand. E-mail: sipry@mahidol.ac.th.

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Schimmelpenning-Feuerstein-Mims syndrome (SFM) is characterized by congenital epidermal nevi and abnormalities of the neuroectodermal organs, which include the cerebrum, musculoskeletal system, ocular, cardiovascular, and urogenital systems.[1,2] It was first described by Schimmelpenning in 1957[3] and then by Feuerstein and Mims in 1962.[4] It is known as the SFM syndrome, the epidermal nevus syndrome (ENS), the linear sebaceous nevus syndrome, Jadassohn syndrome, organoid nevus syndrome, and Solomon syndrome.[5] To our knowledge, only 15 cases of hypophosphatemic rickets have been reported in association with epidermal nevus syndrome in the world literature. We report an additional case of this rare association of ENS and hypophosphatemic rickets.

CASE REPORT

A 7-year-old Thai boy presented to the Department of Pediatrics, Siriraj Hospital, Mahidol University, Bangkok, Thailand, with a history of growth retardation, bone pain, and generalized muscle weakness.

The patient was the first child born to healthy, nonconsanguineous parents without any family history of bone or skin disease. His mother had a normal pregnancy and delivery. His birth weight and length were 2500 g and 49 cm, respectively. At birth, he had alopecia and multiple, small, yellowish plaques on the right side of his face and neck. At 2 months of age, brownish plaques on his scalp, face, and neck became more extensive. A linear epidermal nevus on his left arm developed and cafe au lait spots on his back and buttocks appeared. At 1 year of age, the clinical diagnosis of epidermal nevus was confirmed by skin biopsy. Laser dermabrasion was repeated 8 times with some improvement of the skin lesions. At 7 years of age, he developed leg pain and generalized muscle weakness.

Clinical Findings

The height and weight were 93 cm and 10 kg, respectively, both of which were less than the third percentile. His upper:lower body segment ratio was 1.1:1 and his arm span

was 94 cm. Multiple dental caries were noted. Cutaneous abnormalities included multiple brownish verrucous plaques over the temporoparietal area, face, and ears extending to the nose and lips (Fig. 1); linear verrucous lesions on the left arm (Fig. 2); and multiple, flat, raised melanocytic nevi and cafe au lait spots on his back and buttocks. Musculoskeletal abnormalities were muscle wasting, generalized muscle weakness, thoracolumbar kyphoscoliosis, lumbar lordosis, genu valgus; rachitic rosary, pectus carinatum; and widening of the wrists, knee, and ankle joints. Neurologic and eye examination were normal.

Laboratory Results

Serum calcium was 2.22 mmol/L (normal, 2.2–2.7 mmol/L), ionized calcium was 2.15 mmol/L (normal, 2.40–2.46 mmol/L), and serum phosphorus was 0.77 mmol/L (normal, 1.19–1.80 mmol/L). Serum alkaline phosphatase was 630 U/L (normal, 145–420 U/L). Serum parathyroid hormone (PTH) was 8.38 pmol/L (normal, 0.95–6.84 pmol/L).

An analysis of concomitant blood and 2-hourly urine samples collected for phosphorus and creatinine revealed a 64% tubular reabsorption of phosphate (TRP). There was no glucosuria or aminoaciduria. Serum electrolytes, liver function tests, and a thyroid function test were within normal limits.

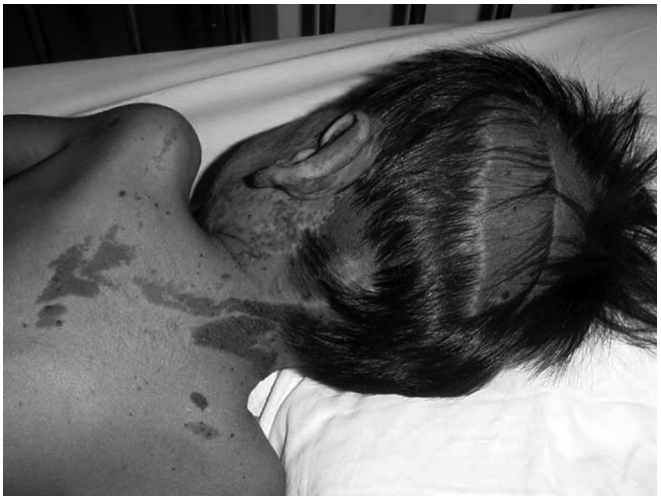

FIGURE 1. Multiple brownish verrucous plaques over the temporoparietal area of the scalp extend to the neck.

FIGURE 2. Linear verrucous lesions on the left arm.

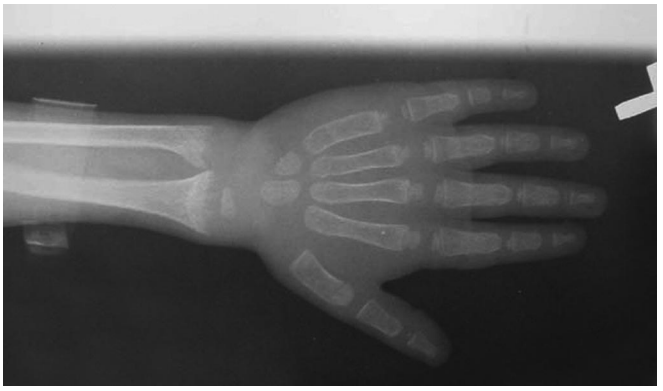

FIGURE 3. Anteroposterior radiograph of the wrists showing severe generalized osteopenia, fraying, flaring, and cupping of the metaphysis and widening of the joint spaces.

Radiologic Findings

Skeletal x-rays revealed severe generalized osteopenia, fraying, flaring, and cupping of the metaphysis, widening of the joint spaces, thoracolumbar scoliosis, and multiple fractures of the ribs and left femur (Fig. 3). The diagnosis of epidermal nevus syndrome with hypophosphatemic rickets was made.

Diagnosis

Other investigation:

- IQ test = 73 (borderline mental retardation)
- Brain MRI: An arachnoid cyst was present at the right cerebral hemisphere

Treatment and Clinical Progression

Phosphorus supplement with acidic phosphate and 1,25-dihydroxycholecalciferol (calcitriol) was initiated (Table 1). The dosage of acidic phosphate and calcitriol was increased gradually. Despite persistently low serum phosphorus and elevated serum alkaline phosphatase at 4 weeks of treatment, the patient's bone pain markedly decreased. At 8 weeks, he was able to walk and the radiographic findings at the end of his long bones showed healing (Fig. 4). Excision of the skin lesions on the scalp and electrocautery of the skin lesions on his left arm were performed after 21/2 and 31/2 months of therapy, respectively. After 4 months of treatment, the serum phosphorus was normal and the serum alkaline phosphatase was reduced but not yet normal.

DISCUSSION

Clinical and histologic findings in our patient are compatible with ENS or SFM syndrome characterized by exten-

TABLE 1. Serial Clinical and Biochemical Data, Including Medical and Surgical Treatment in This Patient

Duration of Treatment (weeks)	Serum Calcium (mmol/L)	Serum Phosphorus (mmol/L)	Serum Alkaline Phosphatase (U/L)	Urine Ca/Cr	Serum Parathyroid Hormone (pmol/L)	Phosphorus Supplement (mg)	Calcitriol Dosages (μg)	Remarks
0	2.22	0.77	630	0.02	8.38	500	0.5	
3	—	1.13	984	0.06	—	—	—	↓ Bone pain
4	2.40	0.90	—	—	6.99	800	—	
8	2.45	1.26	—	0.1	—	—	↑ 0.75	Able to walk. X-ray showed a healing of rickets
9	2.48	0.90	775	0.1	4.39	↑ 1000	—	
10	—	—	—	—	—	—		Excision of skin lesions at the scalp
11	2.23	0.87	—	0.1	6.52	—	↑ 1	
14	2.28	1.80	—	0.2	8.81	800	—	Abrasion and electrocautery of skin lesions on the left arm
16	2.25	1.45	405	0.1	5.38	—	—	

sive epidermal nevus, skeletal deformities (kyphoscoliosis), borderline mental retardation, and growth retardation.

The clinical manifestation of ENS consists of epidermal nevus and multiorgan involvement, particularly the skeletal and central nervous system.[2] The epidermal nevus lesion is often extensive, systematized, and unilateral, and usually follows the Blaschko lines. Skeletal abnormalities have been reported in 67% of the patients,[6] including kyphosis, scoliosis, and deformities of the feet, ankles, fingers, toes, and craniofacial bones.[1] Fifty percent of the patients had neurologic involvement, including mental retardation, seizures, hydrocephalus, hemiparesis, and cortical blindness.[1,7]

Other organ involvement such as ocular (coloboma, lipodermoid of conjunctiva, choristoma, ophthalmoplegia, and cornea clouding), cardiovascular (aortic coarctation), and renal abnormalities have also been reported.[7,8] Our patient had none of these. Interestingly, he had an arachnoid cyst at the cerebral hemisphere, which had not been previously described among central nervous system abnormalities associated with ENS.

A diagnosis of hypophosphatemic rickets was made in our patient. It was characterized by low serum phosphorus, normal serum calcium, elevated serum alkaline phosphatase, normal or mildly elevated PTH, low TRP, and typical radiologic findings of rickets. Hypophosphatemic rickets is rarely associated with ENS. Only 15 cases of this association have been reported.[9–22] The cause of rickets in ENS remains unknown. In 1974, Aschinberg postulated that hypophosphatemic rickets associated with ENS was caused by a phosphaturic substance extracted from the skin lesions of ENS, because surgical removal of the skin lesions seemed to improve the rickets both clinically and biochemically in this patient.[11] Hypophosphatemic rickets associated with small, benign hemangiopericytomas and ossifying mesenchymal tumors is well described.[23,24] This type of rickets is called oncogenic hypophosphatemic osteomalacia (OHO). OHO is refractory to medical therapy but is usually cured by tumor removal. Cultured tumor cells from patients with OHO release a factor with in vitro inorganic phosphate transport inhibitory activity. Hypophosphatemic rickets associated with ENS might be a variant of OHO.

The onset of rickets in the 15 previously reported cases and in our patient developed in early childhood ranging from 5 to 13 years of age (Table 2). All cases presented with growth retardation, generalized muscle weakness, bone pain, recurrent fractures, and bone deformities resulting in painful ambulation.[21] The biochemical changes showed low serum phosphorus, normal serum calcium, and elevated serum alkaline phosphatase. All cases but one had low TRP.[18] All patients were treated with phosphorus supplement and 1, 25-dihydroxycholecalciferol (calcitriol). Nine of 13 previously reported cases had improved clinical, biologic, and radiologic findings between 3 months and 2 years of treatment. Two of the 4 patients who failed medical therapy had

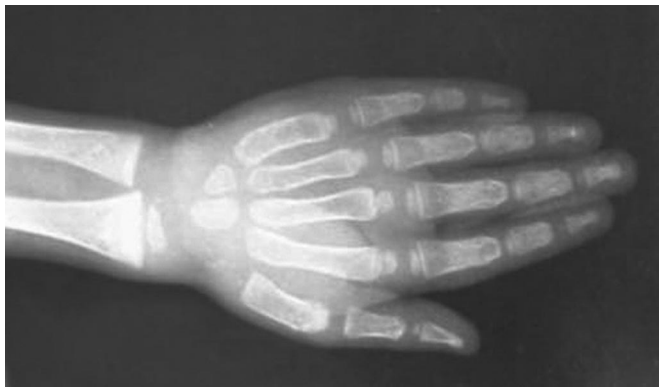

FIGURE 4. At 8 weeks of treatment with phosphorus supplement and calcitriol, radiographic findings showed healing of rickets at the end of the long bones.

TABLE 2. Clinical, Biochemical Data and Treatment Outcome of Hypophosphatemic Rickets Associated with ENS in 16 Reported Cases, Including This Patient

Data	1 Sugarman[9]	2 Moorjani[10]	3 Aschinberg[11]	4 Carey[12]	5 Carey[12]	6 Skovby[13]	7 Fritz[14]
Year	1969	1976	1977	1986	1986	1987	1988
Age	12 yr	9 mo	12 yr	7 yr	23 yr	14 mo	10 yr
Sex	Female	Female	Male	Male	Female	Male	Male
Onset of skin lesions	At birth	At birth	After birth	At birth	At birth	At birth	At birth
Onset of rickets	12 yr	N/A	5 yr	2 yr	13 yr	14 mo	N/A
Central nervous system involvement	Mental retardation, seizure, ventriculomegaly	Mental retardation, seizure, hypotonia, microcephaly	No	No	Mental retardation, seizure	Mental retardation, ventriculomegaly	No
Other organ involvement	Dermoid of right eye, aminoaciduria	Strabismus, coloboma of iris and fundus	Scoliosis, high arch palate	N/A	N/A	Esotropia	Intraosseous hemangioma
Height, weight	147 cm (P25), 25 kg (<P3)	N/A	Severe growth retardation	Severe growth retardation	N/A	Growth retardation	N/A
Serum calcium (mmol/L)	2.23 (2.2–2.7)	2.38	2.4	2.5	2.38	Normal	Normal
Serum phosphorus (mmol/L)	0.81 (0.97–1.78)	0.81	0.42 (0.95–1.75)	0.68 (1.25–2.1)	0.71 (0.95–1.75)	0.54 (1.24–1.84)	Low
Tubular reabsorption of phosphate (%)	Decreased	N/A	35%	Decreased	Decreased	37%	N/A
Serum alkaline phosphatase (U/L)	210 (30–130)	350	313 (20–124)	450 (145–420)	210 (30–130)	1472 (250–1000)	N/A
Serum parathyroid hormone	N/A	N/A	55 (29-71)	Normal	Normal	Normal	Elevated
25-hydroxycholecalciferol (nmol/L)	N/A	N/A	N/A	Normal	Normal	N/A	N/A
1, 25-dihydroxycholecalciferol (pmol/L)	N/A	N/A	N/A	Decreased	Decreased	91 (24–158)	N/A
Treatment with phosphorus and calcitriol	Not improved	Not improved	Not improved	Improved	Improved	Improved	N/A
Excision of skin lesions	—	—	Rickets improved	—	—	—	N/A

N/A indicates not available.

clinical and biochemical improvement of rickets after the excision of the skin lesion (one with cutaneous fibroangioma and the others with nevus).

Treatment of hypophosphatemic rickets includes phosphorus supplement and calcitriol. Phosphorus supplement and calcitriol can improve the clinical symptoms of bone pain, normalize serum phosphorus, and improve radiologic findings by increasing bone mineralization. However, they were not always effective in patients with ENS.[18] Apart from cosmetic reasons, removal of skin lesions is another therapeutic option for hypophosphatemic rickets. Our patient did not show a significant improvement of biochemical changes in rickets during the first 8 weeks of medical treatment. Excision of skin lesions improved his serum phosphorus and serum alkaline phosphatase markedly. One other case report has shown that excision of skin lesions could markedly improve hypophosphatemic rickets in a patient with ENS.[20] However, surgery is not always effective in the treatment of hypophosphatemic rickets associated with ENS.

CONCLUSION

Our study emphasizes the rare association of hypophosphatemic rickets with ENS. We again suggest that a phosphaturic substance secreted from the skin lesions might be the cause of rickets in patients with ENS. Early recognition and appropriate treatment of hypophosphatemic rickets in children with ENS is strongly encouraged to prevent, or at least alleviate, severe bone changes, bone deformities, and growth retardation. Serum calcium, phosphorus, and alkaline phosphatase should be analyzed early in the course of ENS and monitored periodically. If treatment with phosphorus supplement and active vitamin D fails to improve rickets in these patients, excision of the skin lesions might be an alternative therapy.

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TABLE 2. (*Continued*)

8 O'Neill[15]	9 Goldblum[16]	10 Stosiek[17]	11 Oranje[18]	12 Tokatli[19]	13 Ivker[20]	14 Olivares[21]	15 Zutt[22]	16 (Our Case) Oranee
1993	1993	1994	1994	1997	1997	1999	2003	2004
3 yr	35 yr	20 yr	12 yr	5 yr	12 mo	15 yr	52 yr	7 yr
Female	Male	Male	Male	Male	Female	Female	Female	Male
At birth	At birth	At birth	At birth	At birth	N/A	At birth	At birth	At birth
3 yr	15 mo	9 yr	4 yr	N/A	N/A	2.5 yr	5 yr	7 yr
No	No	No	Developmental delay, ventriculomegaly	No	Developmental delay, ptosis, brain anomaly	Brain anomaly	N/A	Mental retardation, arachnoid cyst
Pulmonary angiomatous malformation	Kyphoscoliosis, bone cyst, basal cell carcinoma of right pinna	Intraosseous hemangioma	Ptosis of right eye, asymmetric face	N/A	Precocious puberty	Kyphoscoliosis, pelvic asymmetry	Precocious puberty, exotropia, corneal clouding, basal cell carcinoma	Thoracolumbar scoliosis
N/A	N/A	N/A	Growth retardation	N/A	Growth retardation	Growth retardation	Growth retardation	Growth retardation
2.1	N/A	2.3	2.44	2.65	Normal	2.3 (2.2–2.7)	Normal	2.22 (2.2–2.7)
1.1 (1.25–2.1)	N/A	0.77	0.7 (1–1.8)	0.55	0.87 (1.54–2.62)	0.45 (0.9–1.75)	Low	0.77 (1.2–1.8)
N/A	N/A	Decreased	86%	N/A	68.5%	42%	Decreased	64%
600 (145–420)	N/A	304	453 (80–225)	25	420 (50–136)	350 (70–230)	Increased	630 (145–420)
N/A	N/A	Normal	Normal	N/A	Decreased	N/A	N/A	Elevated
N/A	N/A	Normal	Normal	N/A	Normal	70 (37–200)	N/A	N/A
N/A	N/A	Decreased	Normal	N/A	Low normal	21.6 (35–105)	N/A	N/A
Improved	Improved	Improved	Improved	N/A	Not improved	Improved	Improved	Improved
—	Rickets improved	—	Rickets improved	N/A	Rickets improved	Not improved	N/A	—

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