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RESEARCH ARTICLE

HYPOPHOSPHATEMIC RICKETS, EPIDERMAL NEVUS SYNDROME WITH SKELETAL CHANGES: A CASE REPORT.

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Abstract

Epidermal nevus syndrome is a rare, sporadic, congenital disorder, characterized by epidermal nevi, associated with multiple organ anomalies and skeletal changes. However, hypophosphatemic rickets-associated ENS is rarely reported. Thus, we report an 11-year-old girl with hypophosphatemic rickets and extensive linear nevi associated with a large checkerboard-speckled lentiginous nevus. Skeletal changes were characterized with severe osteoporosis, multiple recurrent low-trauma fractures, cystic lesions along the right femur, limbs discrepancies with deformities, short middle finger, and hemiatrophy.

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Introduction:-

Epidermal nevi are hamartomatous lesions derived from epidermal components, which originate from pluripotential cell mutations during early embryonic stages. They have variable locations and extensions that follow Blaschko's lines and reflect the embryonic migration patterns on the skin. The incidence of epidermal nevi is reported in 1 per 1000 live newborns (Cruz et al. 2004; Rogers 2000).

Schimmelpenning was the first to describe an association of epidermal nevi with neurologic disorders in 1957, in which Feuerstein and Mims reported the same issue in 1962. In 1975, Solomon and Esterly extensively reviewed all the associations with epidermal nevi, and grouped all variants into one category, which they defined as epidermal nevus syndrome (ENS) (Cruz et al. 2004). ENS is a rare, sporadic, congenital disorder with no established hereditary pattern of transmission.

ENS consists of a group of anomalies, including skin anomalies resulting in the appearance of a verrucous linear lesion, as well as central nervous system disorders, renal anomalies, ocular malformations, and somatic asymmetry. Typically, ENS has complex and highly variable phenotypes that cause focal or generalized skeletal disease. The skeletal changes include bone cysts, kyphoscoliosis, joint, vitamin-D-resistant rickets, cranial deformities (Heike et al. 2005; Aschinberg et al. 1977). Hypophosphatemic rickets is considered a rare presentation of ENS. In previous literature, there have been reports of only 26 patients with ENS associated with hypophosphatemic rickets, which usually develops in children the age of 5 (Cruz et al. 2004; Sukkhojaiwaratkul, Mahachoklertwattana, and Poomthavorn 2014). We report the first case of ENS with hypophosphatemic rickets in a Pakistani girl in Saudi Arabia.

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Case Report:-

An 11-year-old Pakistani girl, living in Saudi Arabia, was born at term gestation by first-degree healthy Pakistani cousins with no family history of ENS. However, the girl has developed extensive congenital linear epidermal nevi, skeletal deformities, hypophosphatemic rickets, osteoporosis with low trauma recurrent fractures, bone deformities, growth retardation, and right side hemiatrophy with limb discrepancies. Since birth, she has suffered from extensive congenital linear nevi distributed on the right side of her body following the lines of Blaschko associated with a large checkerboard speckled lentiginous nevus. (**Figure-1), (Figure-2)**. These features were associated with facial asymmetry and right side hemiatrophy. The histopathology of the skin lesions was compatible with epidermal nevi and nevus sebaceous.

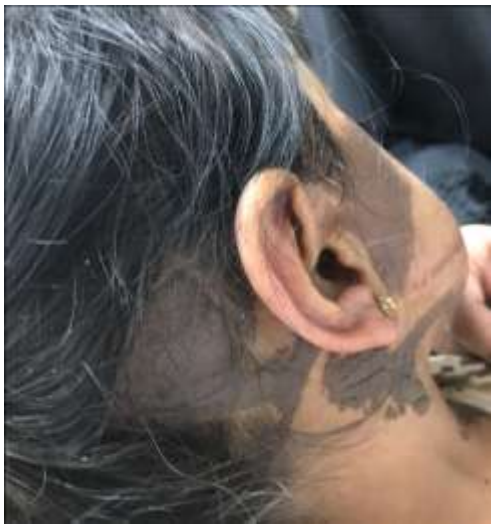

Figure-1:- Congenital linear nevus present on the face and scalp, and it caused alopecia that extended to the neck, back, and peripheral right upper limb.

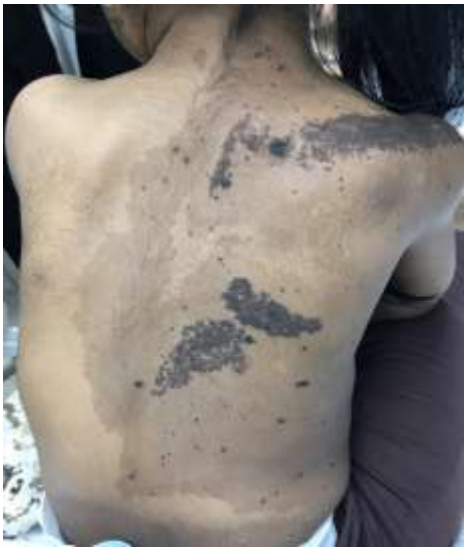

Figure-2:- Checkerboard speckled lentiginous nevus involving the abdomen, back, buttocks, and peripheral right lower limb without a sharp midline separation.

However, the patient's growth was normal up to the age of 6. Since then, she had generalized growth retardation. Her height upon presentation was (- 6.75 standard deviation) and weight was (- 3.37 standard deviation). At the age of 2, her family noticed discrepancies in her upper limbs lengths with misalignment in the right upper limb. The upper limb lengths differed by 6 cm, the lower limbs differed by 5 cm, and her foot sizes differed by 2.5 cm. She has a short middle finger in both hands. (**Figure-3), (Figure-4).**

Figure-3:- Discrepancies in her lower limbs lengths and foot size.

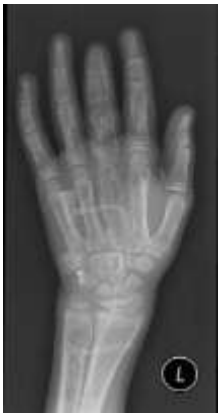

Figure 4:- Left wrist X-ray showed short middle finger.

The patient had multiple fractures in the right femur that started at the age of 6, and followed by two fractures in the right leg. These fractures resulted from low trauma and healed with residual deformities that led to an abnormal gait.

A skeletal survey showed multiple healed fractures in the vertebrae, ribs, pelvis, and femur, as well as in mild lumbar scoliosis. (**Figure-5).** Notably, all of the fractures and deformities happened on the same side of the epidermal lesions. Full-limb film X-ray showed a cystic lesion in the right femur. (**Figure-6: A, B)**. Cystic bony lesions in right femur was investigated, an isotope bone scan showed no evidence of scintigraphically active bone lesions in both femurs. **(Figure-7)**. Similarly, magnetic resonant imaging revealed no evidence of intrinsic or extrinsic tumor.

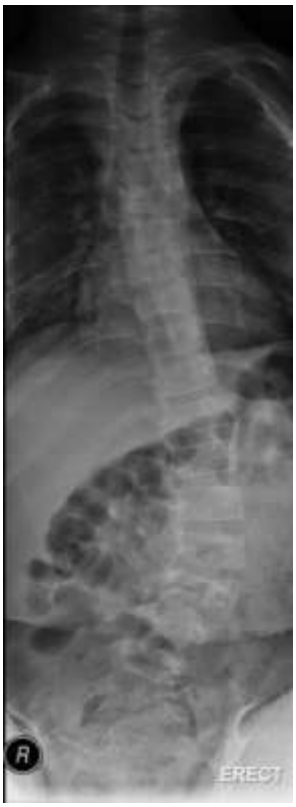

Figure5:- Spine X-ray showed compression fracture in L4 with mild lumbar scoliosis.

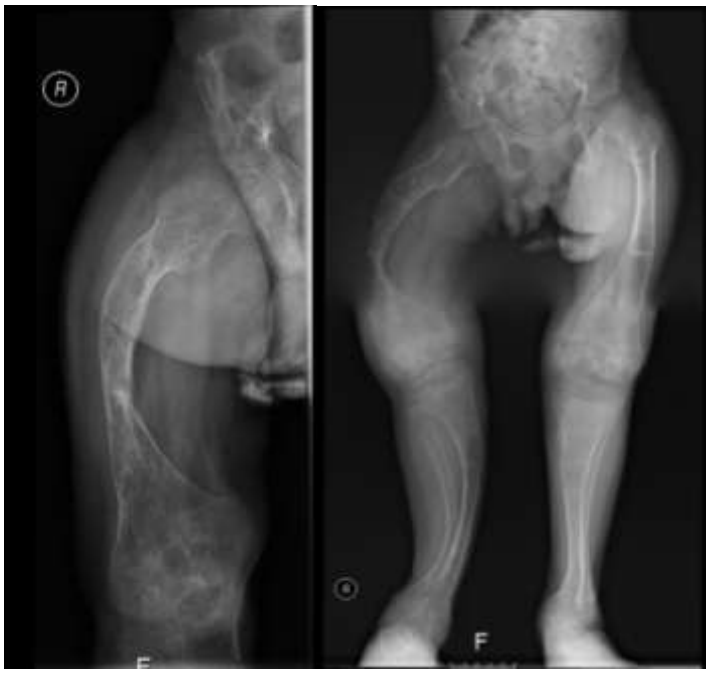

Figure-6:- A, B. Full-limb film X-ray showed a cystic lesion in the right femur.

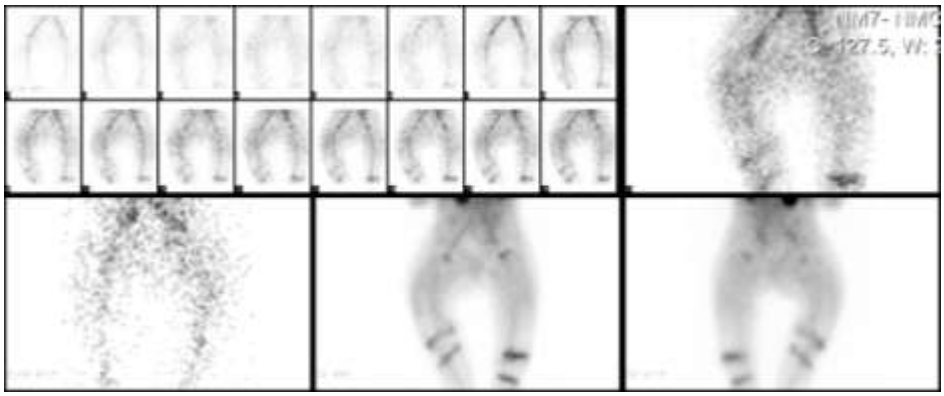

Figure-7:- Isotopes scan showed no evidence of scintigraphically active bone lesions in both femurs.

During admission, hypophosphatemic rickets was diagnosed based on laboratory investigations (**Table-1**) and severe osteoporosis was confirmed with low bone mineral densities of Z score -6.5 for the whole body and -6.3 in the lumbar vertebrae. (**Figure-8).** Afterward, the patient was put on bisphosphonate therapy, phosphate, calcium, and 1-alpha-hydroxycholecalciferol therapies.

Blood Works		
Test	**Result**	**Normal Ranges**
Calcium	2.26 mmol/L	2.12 – 2.52
Phosphate	0.58 mmol/L	0.81 – 1.58
Alkaline phosphatase	1000 U/L	140 - 460
Vitamin D	90.44 nmol/L	75 - 250
Parathyroid hormone	3.89 Pmol/L	1.18 – 8.43

Table 1. Blood chemistries diagnose hypophosphatemic rickets

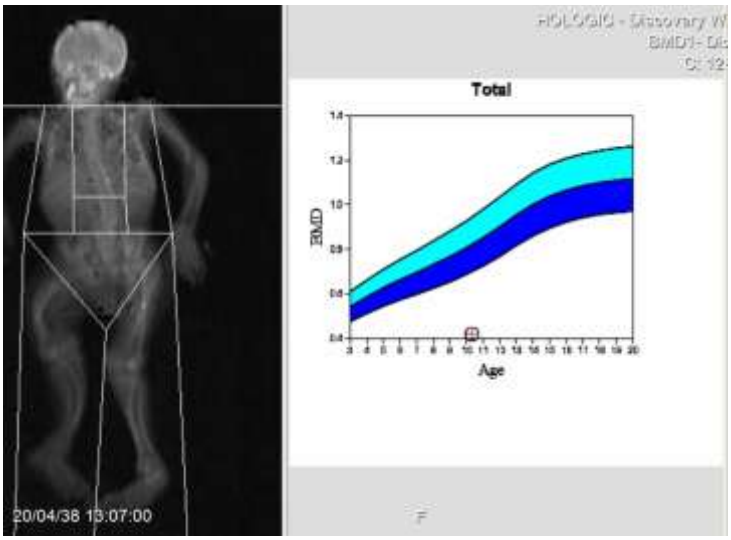

Figure 8:- BMD showed sever osteoporosis in whole body.

Discussion:-

The clinical scenario and sequence of events reported in this index case ultimately led to a diagnosis of hypophosphatemic rickets-associated ENS. The main theory associated with the mechanism of hypophosphatemic rickets is a tumor-induced etiology of oncogenic hypophosphatemic osteomalacia. The theory behind the association of hypophosphatemic rickets with ENS has been well explained in previously reported cases. One study reported a 5-year-old boy who had hypophosphatemic rickets-associated ENS and elevated serum fibroblast growth factor (FGF23) level, which is produced and released from the cutaneous nevi. The hypophosphatemia improved after the excision of skin lesions found on his face and left leg. There is also another case report of a 17-year-old boy who had the same condition, however, improved after a treatment with somatostatin agonist, octreotide, and excision of the nevus, which enhanced normalization of FGF23 and clinical improvement. Subsequent reports support this theory. The proposed pathogenesis of rickets in ENS is generally accepted to be a variant of tumor-induced osteomalacia because remission of the skeletal disease occurs after the excision of mesenchymal tumors in the bone and soft tissue associated with hypophosphatemic rickets. For technical reasons, we were not able to measure the circulating levels of FGF23. In this sense, the FGF23 level would be helpful in the workup of this type of rickets (Dermatologia et al. 2013; Sukkhojaiwaratkul, Mahachoklertwattana, and Poomthavorn 2014; Moreira et al. 2017; Hoffman et al. 2005).

The skeletal changes associated with ENS were highly addressed in a study conducted in 2005. The study gathered 27 case reports of patients with ENS in addition to different types of skeletal abnormalities, such as osteopenia, osteoporosis, osteomalacia, rickets, Cystic lesions and fractures or pseudo-fractures (Heike et al. 2005).

Growth retardation that developed at age of 6 years in the Pakistani patient revealed a similar finding in a reported case of a patient with ENS associated skeletal deformities, hypophosphatemic rickets and multiple fractures (Report 2003). Ipsilateral hemi-atrophy, found in this case, was consistent with cases published in the literature, which was the most consistent extra-cutaneous anomaly in patients who had Phacomatosis pigmentokeratotica, which was one of the ENS in case series study conducted in 1998 (Tadini et al. 1998). However, no previous reports for a patient with ENS who had short middle finger similar to this case.

The genetic base of linear nevi is thought to be a lethal gene because they survive by mosaicism. Post-zygotic mosaicism explains a highly variable expression of the disease, which can have neurological, ophthalmological, renal, and cardiac manifestations, as well as malignant changes. Specific genetic defects and the timing of mutation during embryogenesis influence the various phenotypes. To date, there have been six different types of ENS, which are differentiated from each other by their clinical features and genetic patterns. The syndromes include proteus syndrome, Schimmelpenning syndrome, nevus comedonicus syndrome, pigmented hairy ENS, congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, and phacomatosis pigmentokeratotica (Cruz et al. 2004; Dermatologia et al. 2013; Sukkhojaiwaratkul, Mahachoklertwattana, and Poomthavorn 2014).

The patient in the case was presented with extensive congenital linear epidermal nevi, skeletal deformities, hypophosphatemic rickets, and osteoporosis with low trauma recurrent fractures, bone deformities, growth retardation, and right side hemiatrophy with limb discrepancies. She did not have any manifestations in the central nervous system, such as mental deficiency, seizures, or hemiparesis. Furthermore, she did not have any sensory or motor neuropathies. Ocular examination indicated clear cornea, as well as normal irises and retinas. The results of the cardiovascular examination were normal, and renal ultrasound indicated normal kidneys. This leaves us with two syndromes that fit our patient's manifestations according to the literature: Schimmelpenning syndrome and phacomatosis pigmentokeratotica.

Schimmelpenning-Feuerstein-Mims (SFM) syndrome is a rare dermatological condition that consists of multiple neuroectodermal symptoms. The diagnosis of SFM syndrome comprises of a congenital, unilateral nevus sebaceous that follows Blaschko's lines, which might be associated with cerebral, ocular, cardiovascular, urogenital, or skeletal abnormalities. Schimmelpenning first described the condition in 1957 (Report 2003).

Phacomatosis pigmentokeratotica is a rare organoid nevus syndrome of unknown molecular etiology that was first identified in 1996. It is characterized by the occurrence of nevus sebaceous and speckled lentiginous nevus of the papular type, which is also known as nevus spilus. These are associated with extra cutaneous anomalies, which commonly include skeletal or neurological abnormalities, such as hemiatrophy, dysaesthesia, and hyperhidrosis in a segmental pattern, as well as mild mental retardation, seizures, deafness, ptosis, and strabismus (Dermatologia et al. 2013; Gamayunov, Korotkiy, and Baranova 2016; Jellinek 2003).

There are difficulties in categorizing these types of syndromes due to overlapping symptoms found in the literature. However, this patient is most likely to have phacomatosis pigmentokeratotica associated with hypophosphatemic rickets due to the presence of papular speckled lentiginous nevus, and the absence of cerebral, ocular, cardiovascular, and urogenital abnormalities that are associated with SFM syndrome. Thus, more case reports and further genetic testing are needed to identify the syndrome properly.

Conclusion:-

The presence of epidermal nevi in a child should alert pediatricians to screen for other associated anomalies, as well as skeletal changes and hypophosphatemic rickets.

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