Case 9
An 11-year-old Thai female from Nakornsawan
Chief complaint: Multiple linear skin lesions since birth

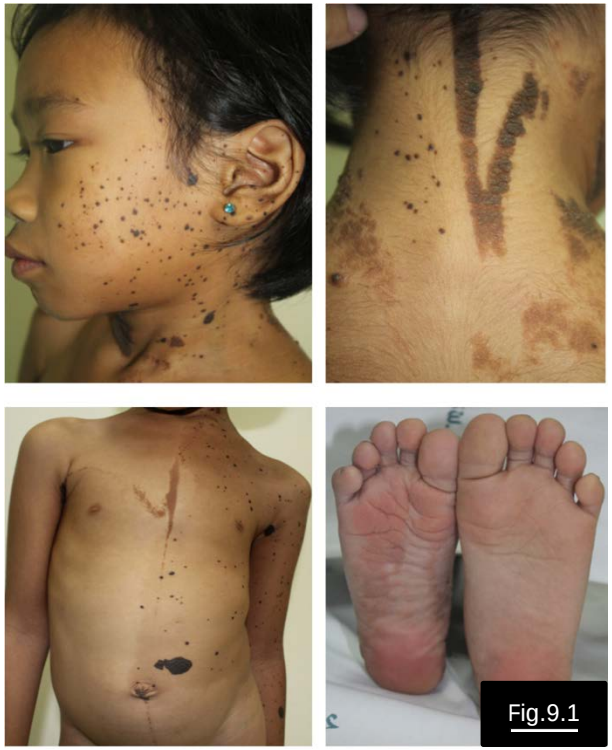
Fig.9.1

Present illness:
She had multiple linear dark brownish skin lesions on the scalp, chin, neck, chest, left arm, right leg and sole since birth. The lesions gradually increased in size and number, and occasionally caused irritation. At the age of 1, she developed walking difficulties due to right leg deformities. Her parents denied history of seizure, paresthesia or abnormal vision.
Past history:
- Born full-term to non-consanguineous parents
- Normal developmental milestones

Family history: None
Physical examination:
- HEENT: No pale conjunctivae, no icteric sclerae
- Heart: Normal S1 S2, no murmur
- Lung: Normal breath sound
- Abdomen: Soft, no hepatosplenomegaly
- Neurological system: Intact
- Musculoskeletal system: Varus deformity of right leg; limb length discrepancies (right leg shorter than left leg; 2 cm); mild scoliosis

Dermatological examination:
- Multiple linear dark brownish plaques with verrucous surfaces following Blaschko's lines on the scalp, upper back, left side of neck, medial aspect of left arm, trunk, back, right leg and foot
- Multiple dark brownish and black macules and papules scattered on a background of large, light brownish patches on the face, trunk, and extremities (Fig.9.1)

Histopathology (S14-019635, scalp):
- Epidermal papillomatosis with malformed pilosebaceous structures and proliferation of melanocytes arranged in nest at the dermoepidermal junction (Fig.9.2)

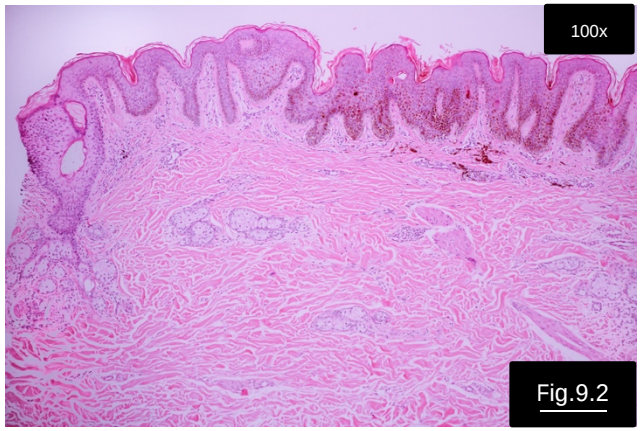

Fig.9.2

Laboratory investigations:

- Calcium 2.3 mmol/L (2.2–2.7), Phosphorus 0.6 mmol/L (1.2–1.8), PTH 12.4 mmol/L (3.7–15.9)
- 25-(OH)D 61.2 nmol/L (>50)
- ALP 2,877 U/L (169–372)
- Skeletal X-ray: Poor mineralization with rachitic changes, including flaring, cupping and fraying of metaphyses of both wrists and ankles; scattered areas of poorly defined lucency fibrous dysplasia-like lesions at right femur, tibia and fibula

Diagnosis: Phacomatosis pigmentokeratotica with hypophosphatemic rickets

Treatment:

- Phosphate solution and active vitamin D supplementation
- 0.125% tretinoin in vanishing cream applied to the right leg at bedtime
- Medications: Calcium carbonate 1,200 mg/day; multivitamin 1 tab once daily; vitamin D2 20,000U every 2 weeks; alfacalcidol 2 gm/day; phosphate solution 2 tsp 5 times daily

Presenter: Teerapong Rattananukrom, MD
Consultant: Pamela Chayavichitsilp, MD

Discussion:

Phacomatosis pigmentokeratotica (PPK) is classified as a distinct disorder in the epidermal nevus syndrome group,[1] which was first described in 1996.[2] It is characterized by a co-occurrence of sebaceous nevi and speckled lentiginous melanocytic nevi.[3]

This distinctive syndrome is believed to be caused by the "twin spot" hypothesis which demonstrates that both types of nevi are caused by a single mutation in a multipotent progenitor cell, rather than a chromosomal rearrangement affecting more than one gene.[4] Twin spotting describes the mechanism where a heterozygous cell can undergo mitotic division in such a way as to give rise to two homozygous daughter cell populations of a different phenotype as shown in this diagram (Figure1). One half of PPK is Schimmelpenning syndrome, and the other half is speckled lentiginous nevus (SLN) syndrome. Both disorders are caused by somatic mutations in *HRAS* or *KRAS.*

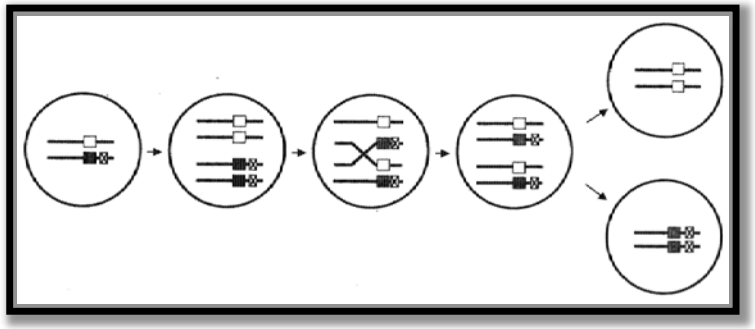

Figure1: Koopman RJ. Concept of twin spotting.
Am J Med Genet. 1999;85:355-8.

Schimmelpenning syndrome is characterized by the linear nevus sebaceous arranged along the Blaschko lines with extracutaneous manifestations affecting the CNS (e.g. hemimegalencephaly, seizures, hemiparesis, developmental delay), eye (e.g. dermoids, coloboma), and skeleton (e.g. asymmetry, abnormal skull shape, kyphoscoiosis, limb hypertrophy) as well as hypophosphatemic rickets.[1]

On the other hand, SLN syndrome consists of cafe au lait spots with multiple dark brown or black dots that represent macular or papular proliferations of superimposed melanocytes. Neurologic abnormalities associated with SLN syndrome include hyperhidrosis, muscular weakness, dysesthesia, sensory and motor neuropathy.[5]

PPK is a distinct type of epidermal nevus syndrome that occurs sporadically.[1] PPK may be limited to the skin or associated with extracutaneous abnormalities. The pattern of extracutaneous anomalies demonstrated in PPK represents variable features of Schimmelpenning syndrome or SLN syndrome. The major neurologic abnormalities in PPK are mental deficiency, seizures, hemiparesis, hyperhidrosis, cutaneous dysesthesia, muscular weakness, sensory neuropathy, and motor neuropathy. Additional extracutaneous presentations have been reported in the literature, such as ptosis,

strabismus, congenital glaucoma, esotropia, conductive hearing loss, facial dysmorphism, hemiatrophy, kyphosis, scoliosis, and hypophosphatemic rickets.

Hypophosphatemic or vitamin D-resistant rickets are caused by the overproduction of fibroblast growth factor 23 (FGF-23), which is normally secreted by osteocytes to regulate vitamin D and phosphate homeostasis. The mutation leads to a defect in phosphate reabsorption at the proximal renal tubule.[6,7]

Individuals with PPK have higher risks of developing skin and internal malignancies. These include basal cell carcinoma and malignant melanoma on the skin. Extracutaneous neoplasms include subcutaneous rhabdomyosarcoma[8] and pheochromocytoma.

Management depends on the type and extent of systemic abnormalities. Referrals to a neurologist, ophthalmologist, orthopedist, or endocrinologist may be appropriate. Treatment of cutaneous skeletal hypophosphatemic syndrome includes the administration of oral phosphate and calcitriol. The excision or ablation of the nevi is typically performed for cosmetic purposes. The use of an anti-FGF-23 antibody is under investigation.

In summary, we present a case of PPK, a rare distinct epidermal nevus syndrome with hypophophatemic rickets and extracutaneous manifestations. The patient received supplementation with phosphate, vitamin D and topical treatment with emollients and tretinoin cream. In addition, CO2 laser was performed on some areas of epidermal nevi for cosmetic purposes.

References:

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