

Epidermal Nevus in Association with Some Uncommon Manifestations

Epidermal nevus syndrome (ENS) is a rare condition characterized by congenital epidermal nevi (EN) associated abnormalities of other organs including central nervous system (CNS), skeletal system, eyes, and oral cavity (1).

ENS is divided into a group of distinct disorders, based on the associated epidermal nevus and genetic inheritance pattern. Organoid nevus could be seen in some ENS, including Schimmelpenning syndrome, phacomatosis pigmentokeratolica, nevus comedonicus syndrome, angora hair nevus syndrome, and Becker nevus syndrome (1).

The manifestations of ENS could be due to genetic mosaicism in involved cells, leading to lethal autosomal dominant genotype (2). Several genetic defects have been shown to be responsible for ENS; among them, mutations in either *FGFR3* (Fibroblast Growth Factor Receptor 3) or *PIK3CA* genes (phosphatidylinositol 3-Kinase, Catalytic, Alpha) are seen in about half of EN patients (3).

Herein, a girl with EN with various manifestations is presented, in whom several genes have been sequenced; all of them were normal

An 8-month-old girl was referred to the Children's Medical Center, Pediatrics Center of Excellence in Iran, with aplasia cutis congenita on the occipital bone and congenital hemangioma on the occipital and left parietal bone (7 cm×4 cm). Linear epidermal nevus was also evident on the right side of her face and the front of her chest, associated with a macular pigmented congenital nevus on the left scapula.

The patient was the first child to consanguine parents with no similar manifestations in the family. She had ambiguous genitalia and mislocated anus at birth; an adhesion band was detected between two labia major anteriorly. There was no male genital organ, while chromosomal analysis of peripheral lymphocytes revealed normal chromosomal pattern, 46, XX.

The occipital aplasia cutis was removed at the first admission, while the microscopic result of pathologic analysis showed flattened and thin epidermis, edema at dermis, vascular proliferation, and scattered inflammatory cells. Fatty subcutaneous tissue was also seen. No adnexal structure was identified in the center of lesion. These findings were compatible with healed lesion of aplasia cutis. The lesion had irregular, grayish, fine nodularity in the middle portion macroscopically. The adhesion band was also relieved by cystoscopy. Right cheek skin biopsy showed skin tissue with the same dysmorphic folliculosebaceous apparatus in the dermis and hypertrichosis. Organoid nevus was considered. Excisional skin biopsy of the infraclavicular pigmented lesion was indicative of congenital compound nevus.

Axial computed tomography (CT) scan of the brain without intravenous contrast media obtained at one month of age showed generalized hydrocephaly evident in the ventricular system, hypodensity in the left side of the cerebellum that was suspicious of mass lesion, and a defect in the posterior aspect of the right parietal bone with encephalocele. There was no significant pathologic finding in other organs of the brain parenchyma and skull.

At two years of age, she was referred to our institution with chief complaint of growth retardation. Laboratory tests showed normal blood electrolytes and thyroid hormones, but slightly decreased phosphorus level (2-3 mg/dL). Due to suspected hypophosphatemic rickets, additional examinations and evaluations were performed. The left leg seemed to be by about 1 cm shorter on physical examination. X-ray images showed multiple bone fractures in the humerus, femur and tibia (Fig. 1). The height and weight were under 5 percentile. Bone age was 1.5 years. Serum analysis revealed low serum P (2.1 mg/dL), Cl (93 meq/L), and PTH (5 ng/L), normal serum Ca, along with normal urine analysis.

Two years later, after resection of multiple scalp tumors, a 3.4 cm×3 cm congenital soft scalp tumor relapsed in the resection regions with a rapid growth in 2 months. The growing tumor was locally tender (in the absence of general headache), pulseless and located on the right parietal bone. There was also a skull tumor with a firm adhesion to adjacent dura. The hard tissue tumors as well as the soft tissue part were resected. Pathologic analysis diagnosed the lesion as a cavernous hemangioma penetrating the skin. Sections of the cutaneous part showed sclerosis and fibrosis in the dermis; hypodermis revealed neoplastic tissue composed of large vessels with cystically dilated lumina and thin walls. Some vessels showed thrombi, occasionally with organization noted in reticulin and trichrome stained section. Sections of bone specimen showed osteosclerosis and penetration of vascular neoplastic tissue in some areas.

Magnetic resonance imaging (MRI) scan showed cystic lesion in the upper region of the midbrain (hydrocephalus). There was a lipoma in the craniocervical region post-cordally and a lipoma in the posterior C6-C7. Axial spiral CT scan of the brain without contrast medium with 3D also revealed mild supratentorial hydrocephalus. Atrophic changes were found in



Figure 1. X-ray images showing multiple bone fractures.

the right cerebellar hemisphere. Otherwise, the brain seemed unremarkable. In bone window and reconstructed images, a left parietal bony protrusion with adjacent subcutaneous soft tissue compound was seen.

In order to identify the underlying gene mutation, DNA was extracted from blood and the FGFR3, PIK3CA, NRAS, HRAS and KRAS genes were analyzed for mutations using PCR-SnaPShot assays (4-6). No mutations were found in these genes. Table 1 depicts a list of the nucleotides that were analyzed by the assays.

EN is a neurocutaneous lesion that can vary from a single lesion to a wide spectrum of systemic presentations associated with EN. Different classifications have been proposed to describe different phenotypes of ENS (1,7), but the case presented cannot be categorized in any of the types described.

The patient suffered from a variety of common manifestations of ENS: cutaneous manifestations (reported frequency >30%) (8), including aplasia cutis congenita, hemangioma, hyperpigmented lesions and linear nevus; neurologic manifestations (reported frequency 50%-70%), including brain tumors and hydrocephalus; skeletal manifestations (reported frequency 50%-60%), including hypophosphatemic rickets and bone tumors; and ocular findings such as amblyopia (9,10). Schimmelpenning syndrome and phacomatosis pigmentokeratolica are two other diagnoses that could have been considered in this patient (1). However, some other common manifestations such as seizures (reported frequency 25%) (11) were absent in our case, but some rare conditions including genital ambiguous and mislocated anus were detected.

Table 1. Overview of all mutations analyzed (each analyzed nucleotide is indicated in bold)

Gene	Codon	Sequence
HRAS	12	GGC
	13	GGT
	61	CAG
KRAS	12	GGT
	13	GGC
	61	CAA
NRAS	12	GGT
	13	GGT
	60	GGA
	61	CAA
PIK3CA	542	GAA
	545	GAG
	1047	CAT
FGFR3	248	CGC
	249	TCC
	372	GGC
	373	AGT
	375	TAT
	382	GGG
	393	GCG
	652	AAG

We analyzed mutations that had been shown to be present in patients with ENS; however, in this patient, none of the previously described mutations was found. These findings could suggest either the presence of a mutation in an unknown gene being responsible for manifestations of this case or an undefined syndrome with manifestations resembling ENS.

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