Diffuse Epidermolytic Epidermal Nevus and Genetic Counseling: A Case Report and Brief Review of the Topic

Christa M. Tomc, DO,* Peter Malouf, DO,** Stephen Weis, DO***

*Dermatology resident, 1st year, University of North Texas Health Science Center/Texas College of Osteopathic Medicine, Fort Worth, TX
**Program director, University of North Texas Health Science Center/Texas College of Osteopathic Medicine, Fort Worth, TX
***Associate program director, University of North Texas Health Science Center/ Texas College of Osteopathic Medicine, Fort Worth, TX

Disclosures: None
Correspondence: Christa M. Tomc, DO; Christa.Tomc@unthsc.edu

Abstract
A 16-month-old female presented with an extensive epidermal nevus demonstrating epidermolytic hyperkeratosis on histologic evaluation. Individuals with this disorder are at increased risk of bearing children with epidermolytic ichthyosis. This occurs because the same mutations causing cutaneous somatic mosaicism may also affect the gonads. Genetic counseling is advised for individuals with extensive epidermolytic epidermal nevus, as the generalized epidermolytic keratinosis carries significant morbidity and mortality.

Introduction
Epidermal nevi are a class of hamartomas derived from ectoderm. They are relatively common, affecting 1 in 1,000 individuals. They may present as a single plaque or be more extensive, assuming a whorled appearance. This type of arrangement is also known as a Blaschkoid pattern, which is frequently seen in skin conditions displaying genetic mosaicism.1 Genetic mosaicism occurs when two genetically distinct cell populations proliferate in one organism. This can result in two or more phenotypically unique cutaneous lesions, as in the case of epidermal nevi.2

Keratinocytic epidermal nevi are those derived from ectoderm that goes on to differentiate into keratinocytes. There are more than 10 histologically distinct types of keratinocytic nevi. One such variant demonstrates epidermolytic hyperkeratosis and is thus known as an epidermolytic epidermal nevus. This entity is clinically indistinguishable from other subtypes within this category.3 Uniquely, this histologic finding is also seen in a generalized form, known as epidermolytic ichthyosis or bullous congenital ichthyosiform erythroderma. Generalized epidermolytic ichthyosis is an autosomal-dominantly inherited condition with significant associated morbidity and mortality, resulting from a mutation in the genes that code for keratins (K) 1 and 10. These same defects have been demonstrated in epidermolytic epidermal nevi in individuals who have born offspring with epidermolytic hyperkeratosis. This indicates that this postzygotic mutation may also result in gonadal mosaicism, especially in individuals with extensive lesions. We present a case of a patient with an extensive epidermolytic epidermal nevus to highlight the importance of genetic counseling, as these patients are at heightened risk for bearing children with epidermolytic ichthyosis.

Case Report
A 16-month-old Iraqi immigrant presented to the clinic with her parents for evaluation of a skin eruption. The lesions appeared when she was 3 weeks old and developed on her neck, arms, flanks, abdomen, and legs. The rash initially was red and scaly with no noted blisters. It was initially treated with triamcinolone acetonide 0.1% ointment, which improved the pruritus but did not alter the morphology of the lesions. Since the initial appearance of the lesions, some of the areas had become brown and scaly, others brown and warty. The mother reported an uneventful pregnancy and birth. The patient was the youngest of four sisters, none of whom had similar lesions. There was no family history of consanguinity, and the parents denied any members of the extended family with similar markings. On presentation to the clinic, the patient was being treated with isoniazid for latent tuberculosis. She was otherwise a healthy, well-developed toddler. Her parents denied a history of cognitive or developmental delays. They were concerned that the lesions were a result of a chicken pox vaccine she received in Iraq.

On physical exam, the patient was an alert 16-month-old in no acute distress. On cutaneous examination, there were whorled plaques of various morphologies in a Blaschkoid arrangement distributed on her neck, bilateral upper extremities, flanks, abdomen, and bilateral medial thighs (Figure 1). Verrucous brown papules coalesced into linear plaques on the left anterior neck, bilateral axillae, and crural folds. On the flanks were digitate erythematous plaques with white scale. A hyperpigmented plaque with large, plate-like, brown scale was located on the left lateral leg. No apparent unilateral hemihypertrophy of the limbs or dysmorphic facies was appreciated. Shave biopsies were obtained from a verrucous lesion of the left axilla and from an eczematous lesion on the left flank. These were submitted in formalin for standard pathologic evaluation.

Figure 1. Physical exam revealed various morphologies, including digitate erythematous plaques with white scale on the flank and whorled brown verrucous plaques in the axilla.
Lesions may appear macerated at birth, but tend to become more verrucous with age. ILVEN, a variant of epidermal nevi, is a verrucous and erythematous lesion that can occur at any site but is most often seen on the limbs or perineum in females.\(^7\) Characteristic of epidermal nevi is the linear or whorled arrangement, which tends to follow the lines of Blaschko. This Blaschkoid pattern is thought to be due to the clonal proliferation of two genetically distinct cell lines that arise from a postzygotic mutation during embryogenesis, referred to as genetic mosaicism.\(^2\)

A genetic mosaic is an organism composed of two or more genetically different populations of cells that originate from one genetically homogeneous zygote. There are two major categories of mosaic phenotypes: functional mosaicism, resulting from the Lyon effect of X inactivation, which can be transmitted from mother to daughter,\(^8\) and genomic mosaicism, which is caused by postzygotic autosomal mutations. This latter category is the type of mosaicism observed in epidermal nevi. The degree of clonal proliferation and the point at which the mutation occurred during embryogenesis determine the extent and distribution of an epidermal nevus, which may present as an isolated plaque or diffusely. They can involve an entire limb, half of the body in a unilateral distribution (nevus unius lateris) or both sides of the trunk, limbs, and face in a symmetric pattern with demarcation at the midline (ichthyosis hystrix).

At least 10 histologic variants of epidermal nevi have been delineated. Virtually all are characterized by hyperkeratosis, epidermal hyperplasia, acanthosis, papillomatosis, and variable parakeratosis.\(^3\) The inflammation of an inflammatory linear verrucous epidermal nevus refers to the clinical appearance of the lesion, as an inflammatory infiltrate is not typically characteristic on histologic observation.\(^{10}\) Other findings, such as epidermolytic hyperkeratosis, as in our patient, may also be seen. This is characterized by perinuclear vacuolization of keratinocytes and increased numbers of enlarged keratohyalin granules with overlying hyperkeratosis.

In patients with epidermolytic epidermal nevus, evaluation of affected tissue with epimelolysis has demonstrated mutations in KRT1 and KRT10; the genes that code for keratins 1 and 10 (K1 and K10). These abnormal keratins are found in the spinous and granular layer of the epidermis, where the epimelolysis occurs. Mutations in K1 and K10 are also seen in individuals with generalized epidermolytic hyperkeratosis. Generalized epidermolytic hyperkeratosis is usually transmitted as an autosomal-dominant trait.\(^{11}\) However, instances of individuals with extensive epidermolytic epidermal nevi carrying offspring with generalized epimelolysis have been observed.\(^{11,12}\) Studies of three unrelated persons with epidermolytic epidermal nevi demonstrated mutations in one of the two K10 alleles in keratinocytes cultured from lesional skin but not from nonlesional epidermis. Each of the patients had offspring with generalized epidermolytic hyperkeratosis, all with the same K10 mutations isolated from the parents’ epidermolytic EN.

It is crucial that persons with epidermolytic verrucous nevi who are planning pregnancy be aware of the possibility of bearing offspring with epidermolytic hyperkeratosis. Epidermolytic hyperkeratosis is also known as epidermolytic ichthyosis, bullous congenital ichthyosiform erythroderma of Brocq, or bullous ichthyosis. It presents at birth with erythroderma, erosions, and peeling, with widespread areas of denuded skin. Skin fragility and blistering decrease over time, and marked hyperkeratosis supersedes. Epidermolytic ichthyosis can be severely disfiguring and have a tremendous impact on patient quality of life. Neonates are at high risk for sepsis as well as fluid and electrolyte imbalances. Later in life, issues with secondary skin infections, in addition to postural and gait abnormalities secondary to the severe hyperkeratosis, may develop. Awareness of these issues is essential for family planning.

The risk of recurrence of epidermolytic ichthyosis in future offspring is 50% if one parent is affected with generalized EHK. It is difficult to estimate the risk of a parent with an epidermolytic epidermal nevus producing a child with the generalized form. According to the mosaic hypothesis, the risk depends on the percentage of gonadal cells that are involved, ranging from 50% if all the cells were involved to 0% if no cells were involved. A correlation between the extent of cutaneous involvement and the likelihood of gonadal mosaicism may exist.\(^{12}\) Postzygotic mutations that occur very early in embryonic development may lead to more extensive epidermal nevus and may affect organ systems other than the skin, such as the gonads.\(^4\)
time, it is not possible to accurately predict if a person with an epidermolytic epidermal nevus will have a child with generalized epidermolytic hyperkeratosis.

Prenatal diagnosis of epidermolytic ichthyosis was initially performed by ultrastructural analysis of fetal skin biopsies and amniotic fluid cells. The presence of keratin filament aggregates within these cells confirms the diagnosis. However, analysis of amniotic cells is not sufficient to exclude epidermolytic ichthyosis, as tonofilament clumping may not be uniformly present. The sensitivity of ultrastructural fetal skin analysis is improved by multiple fetal skin biopsies. Biopsies must be performed after 14 weeks gestational age, the earliest point at which K1 and K10 are expressed in the suprabasal layer. Rothnagel et al. demonstrated that direct gene sequencing of DNA from a parent with generalized epidermolytic hyperkeratosis could be performed to isolate the K1 and K10 mutations. Subsequent analysis of chorionic villus DNA sampled at 15 weeks could then be performed as a means of prenatal diagnosis. This method has also been used in prenatal testing for epidermolytic ichthyosis in parents with extensive epidermolytic epidermal nevi.

Given the extent of our patient’s lesions, she and her family were advised to seek genetic counseling were she to become pregnant in the future. Genetic sequencing of lesional skin could be performed to isolate the specific gene mutation, which could then be compared to fetal DNA. This case is presented as a reminder that cutaneous postzygotic mosaicism can have an increased risk for gonadal involvement, resulting in offspring with generalized disease. Epidermolytic ichthyosis results in significant morbidity, further emphasizing the importance of early patient education in patients with epidermolytic epidermal nevi.

Acknowledgements
We would like to thank Dr. Ryan Hick of Propath Laboratory of Dallas, TX, for reviewing and discussing the pathology in this case.

References