Phenotypic Heterogeneity in Bullous Congenital Ichthyosiform Erythroderma

Possible Somatic Mosaicism for Keratin Gene Mutation in the Mildly Affected Mother of the Proband

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Background: Bullous congenital ichthyosiform erythroderma (BCIE) shows phenotypic variability. An epidermal nevus may represent somatic mosaicism for keratin gene mutation, which produces generalized BCIE in the next generation. This fact provides evidence that a postzygotic mutation can be passed on to the next generation in BCIE. We hypothesized that the same phenomenon occurred in a family with BCIE whose phenotypes were extremely different.

Observations: We studied a 19-year-old boy with severe ichthyosiform erythroderma and prominent palmoplantar hyperkeratosis with digital contracture. In contrast, the proband’s mother exhibited only mild ichthyosiform skin, granular verrucous lesions, and less severe streaky palmoplantar hyperkeratosis. Mutation analysis in the proband showed a keratin K1 mutation (N187S, ie, an A-to-G transition at the second position of codon 187, resulting in an asparagine-to-serine substitution). In the mother, the same keratin gene mutation was recognized, but only faintly in the leukocyte DNA, indicating that the amount of the mutated allele in leukocyte DNA was very low compared with that from the proband.

Conclusions: We speculate that the mildly affected mother showed keratin 1 gene mosaicism, and that the BCIE phenotype had been transmitted in a severe form through a mechanism that passes the keratin gene mutation to the next generation. These results suggest that mild forms of BCIE may actually represent extensive epidermal nevi/keratin gene mosaicism.

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Bullous congenital ichthyosiform erythroderma (BCIE), or epidermolytic hyperkeratosis, is a rare autosomal dominant genetic skin disease (MIM No. 113800) characterized by generalized erythroderma, ichthyosiform skin, and blistering.1 In affected individuals, mutations in the keratin K1 and K10 genes have been identified as the cause of the disease.2,3 It is known that the offspring of patients with an epidermolytic-type of epidermal nevi may have generalized BCIE.4,5 Paller et al6 and Moss et al7 showed that epidermal nevus represents somatic mosaicism for a keratin 10 gene mutation, which may produce generalized BCIE in the next generation if germ line cells carry the mutation. Although theoretically a possibility, keratin 1 gene mosaicism has not yet been described as a cause of epidermal nevi. In this report, we describe a family with BCIE whose phenotypes were extremely different. The proband exhibited a very severe BCIE phenotype, but the mother was affected only mildly. Our clinical and molecular findings suggest that the mildly affected mother had somatic mosaicism for keratin gene mutation.

RESULTS

The mutation detection enhancement method demonstrated a heteroduplex DNA, in the gel only, in the gene encoding the N-terminus of the keratin K1 rod domain (data not shown). The starting PCR product containing heteroduplex DNA was subjected directly to DNA sequencing, which showed a heterozygous A-to-G transition at the second position of codon 187 (AAC→AGC). The amino acid was deduced to have changed from asparagine to serine (Figure 4). The mutation was in residue position 8 of the 1A rod domain segment. The mutation led to creation of a Ddel endonuclease restriction site. This was confirmed by the di-
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The proband, a boy, had burnlike erythema with scales over the whole body at birth (Figure 1A). As he developed, he frequently experienced blistering on his trunk and extremities. In addition, he had ichthyosiform and scaly skin. At the age of 9 years, his palms began to macerate and became hyperkeratotic (Figure 1B). Intermittent administration of oral etretinate, 1 mg/kg per day, led to a remarkable reduction in the hyperkeratosis and a gradual decrease in blistering.

Physical examination at the age of 19 years showed extensive erythroderma, ichthyosiform skin with scales, and hyperkeratosis, particularly on the nape of his neck, elbow, knee, abdomen, and face. His palms and soles were covered with thick scales, and severe hyperkeratosis and maceration of the palms with contractures of the palms and digits was observed. His height was 147 cm and his body weight, 39 kg. No other abnormality was recognized.

Histologic examination of a skin specimen showed a prominent vacuolar degeneration in the granular layer of the epidermis and gross keratohyaline bodies, indicating epidermolytic hyperkeratosis (Figure 2).

The proband’s 46-year-old mother exhibited similar but far less severe symptoms, evident from a few days after birth. She had no antecedent family history. Physical examination at the age of 46 years showed scattered, brown, verrucous, granular papules in her cubital regions (Figure 3A) and very mild blistering with subsequent erosion on her abdomen and lower back. Several “skipped areas” were seen without clear patterning along the lines of Blaschko. However, most of her body was covered with normal skin. Her palms and soles were hyperkeratotic and covered with thick, yellow, spiny scales arranged partly along the lines of Blaschko (Figure 3B), but severity was mild compared with the proband. Linear epidermal nevus was not observed. On the basis of these clinical and histologic findings, she was diagnosed as having a mild form of BCIE.

MUTATION IDENTIFICATION

To detect keratin gene mutations in the proband, we used a genomic polymerase chain reaction (PCR) to amplify the keratin K10 and K1 genes. To simplify the analysis, we focused initially on the regions encoding the N- and C-termini of the rod domains in keratin K10 and K1. The mutation detection enhancement method was used to screen for mutation fragments. The oligonucleotide primers used for amplifying the genes encoding the N-terminus of the K1 rod domain were 5’-TTTGGTGCTGGTGGTGGATTT-3’ (V1 subdomain, sense) and 5’-TGCGTGTGTTTTGACTGACCGAT-3’ (intron 1, antisense).

Figure 1. A, Generalized burnlike erythema at birth. B, Palms began to macerate and became hyperkeratotic at the age of 9 years.

Figure 2. Histologic features of epidermolytic hyperkeratosis showing spongiform appearance of upper malpighian layers with extensive vacuolization and gross keratohyaline granules.

gestion of the PCR product with DdeI, which resulted in replacement of the 497–base pair (bp) band by 2 fragments with predicted sizes of 347 and 150 bp in the proband’s unaffected father, although the proband’s DNA was heterozygous for 347-bp and digested (mutant) 103/47-bp bands (Figure 5). In contrast, the mother’s DNA was heterozygous for 347-bp and digested 103/47-bp bands, but the intensity of digested (mutant) bands appeared to be weak on the gel compared with those of the proband. We performed the digestion procedure 3 times and confirmed that the mother’s band was always fainter than that of the proband. Next, we performed a biopsy of the mother’s lesional skin and isolated the DNA directly. We sequenced and digested PCR product by the same procedure but failed to detect any mutational band in the DNA from the mother’s lesional skin.
Bullous congenital ichthyosiform erythroderma is a strikingly heterogeneous group and shows phenotypic variability in many families. It is also well known that the severity of the disease appears to decrease with age.9 However, in this case, there was considerable phenotypic variability between the proband and his mother. The proband exhibited a severe BCIE phenotype, showing generalized erythroderma and conspicuous palmoplantar hyperkeratosis with digital contractures. In contrast, the mother showed scattered verrucous lesions in her cubital region bilaterally, very mild blistering and subsequent erosion on her trunk, and less severe palmoplantar hyperkeratosis.

Several cases of parents with epidermal nevus having offspring with BCIE have been reported.4,5 Recently, Paller et al6 demonstrated the same keratin gene mutations in the lesional keratinocytes of the epidermal nevi of parents and in the DNA of their offspring with BCIE. These results provide evidence that a postzygotic mutation can be passed on to the next generation in BCIE. We hypothesized that the same phenomenon occurred between the proband and his mother, and we searched for a keratin gene mutation.

We identified a keratin K1 gene mutation (N187S) in the proband. This residue position is a highly conserved IA domain in keratin chains, and the same mutation was reported by McLean et al.10 This mutation is reported to produce a severe clinical phenotype with palmoplantar keratoderma.11 Interestingly, the mutation was present in the mother’s leukocyte DNA, but the amount of mutant allele appeared to be lower than in the proband’s leukocyte DNA. Paller et al6 observed a small amount of mutant DNA from the blood of a patient with epidermal nevi. In our experiment, it is conceivable that only a small amount of mutant allele was detected in the leukocyte DNA from the mother. Therefore, it appears that the mutation that caused the disease in the mother occurred early enough in the development of the embryo to affect both mesodermal (leukocyte) and ectodermal tissues. Unfortunately, only a small amount of skin was donated by the mother, and we were unable to detect the mutation in skin. Although the small percentage of mutational DNA from the maternal leukocytes allowed detection of mosaicism, it should be recognized that, in general, mosaicism involving the epidermis is more easily recognized from epidermal tissues than from leukocyte DNA analysis alone.

In this case, the mildly affected mother was thought to have generalized BCIE of an intermediate severity. Mutational analysis, however, provided evidence of mosaicism for the keratin gene mutation. Although lesions were not obviously linear along Blaschko lines, areas of sparing were common. In fact, review of previously described cases showed that distribution along Blaschko lines is not characteristic of patients with mosaic BCIE and extensive phenotypic involvement.6 Clearly, the mosaicism affected germine cells in that the mother was able to transmit the gene mutation to the proband as a generalized mutation. Many families with BCIE show phenotypic variability.3 We speculate that some of this phenotypic variability may be explained by somatic cell mosaicism in the first individual in the family with the disease. As such, patients with a mild form of BCIE and areas of sparing should be counseled about the likelihood of mosaicism and the risk of transmission of the severe generalized form to the next generation.

Figure 3. The proband’s mother at the age of 46 years. Scattered brown granules are present in her cubital region (A) and there is prominent plantar hyperkeratosis, covered with thick, yellow, spiny scales arranged partly along the lines of Blaschko (B).

Figure 4. DNA sequencing showing a heterozygous A aG transition (arrow) at the second position of codon 187 (AAC aAGC). The nucleotides were read complementarily.

Figure 5. Digestion of the polymerase chain reaction product with DdeI. In the proband, heterozygosity for 347-base pair (bp) and digested 103/47-bp mutant bands (arrows) were clearly recognized. In the mother, the intensity of digested 103/47-bp bands (arrows) on the gel appeared to be weak.
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REFERENCES


News and Notes

The Pacific Dermatologic Association’s 53rd Annual Meeting will be held October 3-7, 2001, at the Pointe South Mountain Resort in Phoenix, Ariz. The meeting will include the traditional clinicopathologic conference and other topics such as an update on human immunodeficiency virus (HIV) and hepatitis C, atopic dermatitis, psoriasis, eczema, nail lesions, retinoids, drug synergism, and more. For additional information, please contact Cathy Powers at the association headquarters, Pacific Dermatologic Association, 930 N Meacham Rd, Schaumburg, IL 60173; phone: (847) 330-9830; fax: (847) 330-1135; or e-mail: cpowers@aad.org.