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Article

Mosaic and Generalized Forms of Keratinopathic Ichthyoses

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Abstract: Mutations in KRT1 (keratin 1) or KRT10 (keratin 10) underlie a spectrum of diseases known as keratinopathic ichthyoses. Epidermolytic ichthyosis (EI) is caused by heterozygous missense mutations in the genes KRT1 or KRT10, mutations in the gene KRT2 (keratin 2) lead to superficial epidermolytic ichthyosis, and congenital reticular ichthyosiform erythroderma is caused by frameshift mutations in the genes KRT10 or KRT1, which lead to the phenomenon of revertant mosaicism. Epidermolytic ichthyosis is also present in a mosaic pattern known as epidermolytic (acantholytic) nevus, isolated or diffuse. In the latter case, gonadic involvement is possible, leading to a rare pedigree in which a parent with diffuse epidermolytic nevus (linear EI) gives birth to a child affected by EI. We present here an update on the phenotypic presentations of keratinopathic ichthyoses and their molecular mechanisms.

Keywords: keratin 1; keratin 2; keratin 10; epidermolytic ichthyosis; keratinopathic ichthyoses; congenital reticular ichthyosiform erythroderma; ichthyosis en confetti; revertant mosaicism; epidermolytic nevus, mosaicism

1. Introduction

Keratinopathic ichthyoses (KPI) are defined as inherited skin disorders caused by mutations in the genes for keratin 1 (KRT1), keratin 2 (KRT2) or keratin 10 (KRT10) [1]. Keratins are heteropolymeric structural proteins which form the intermediate filament; these filaments, along with actin microfilaments and microtubules, compose the cytoskeleton of epithelial cells, providing mechanical resilience and serve as scaffolds for tissue growth and stress responses [2].

KRT1 is a type II cytokeratin specifically expressed in the spinous and granular layers of the epidermis and pairs with type I family member KRT10. Mutations in these genes are responsible for most cases of epidermolytic ichthyosis (EI, OMIM #113800) but also congenital reticular ichthyosiform erythroderma (CRIE, OMIM #609165) [3,4]. KRT2 is a type II cytokeratin largely expressed in the upper spinous layer of epidermal keratinocytes and mutations in this gene have been associated with superficial epidermolytic ichthyosis.

2. Results

2.1 Epidermolytic ichthyosis (EI)

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EI, previously known as epidermolytic hyperkeratosis, is characterized by an erythematous and fine scaling pattern with superficial bullae and erosions (Figure 1).

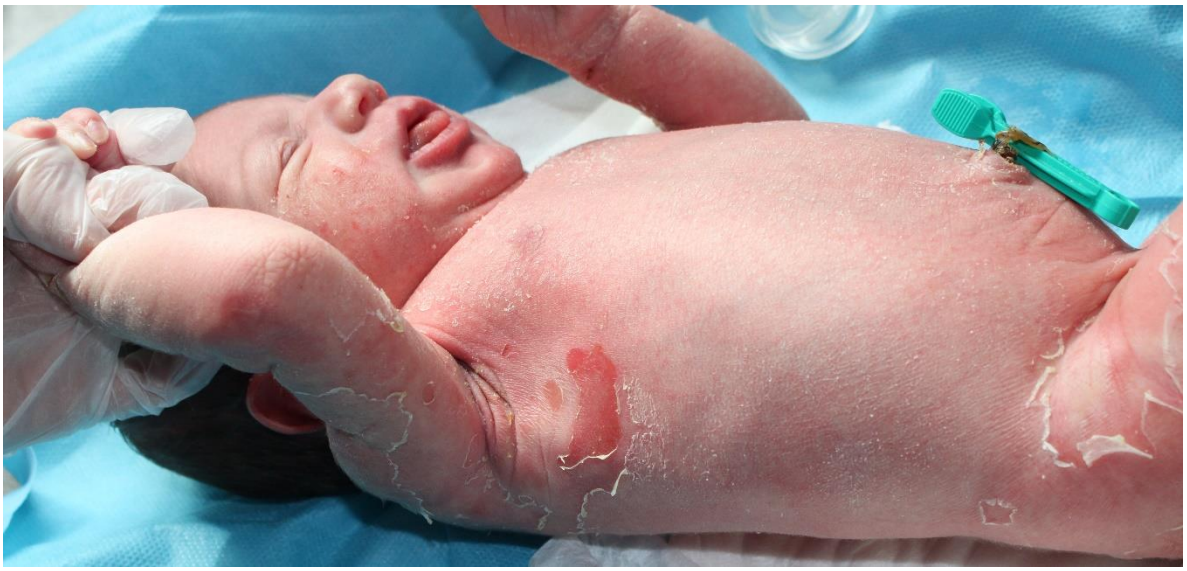

Figure 1. Collodion baby at birth, with fine scaling pattern, superficial bullae and erosions

As the years go by, the hyperkeratosis prevails, showing a peculiar pattern of enhancement of the cutaneous ridges with a particular seborrheic, yellowish aspect that is especially visible on major folds (axillary pillars and neck) (Figure 2). Patients have a characteristic acute and unpleasantly

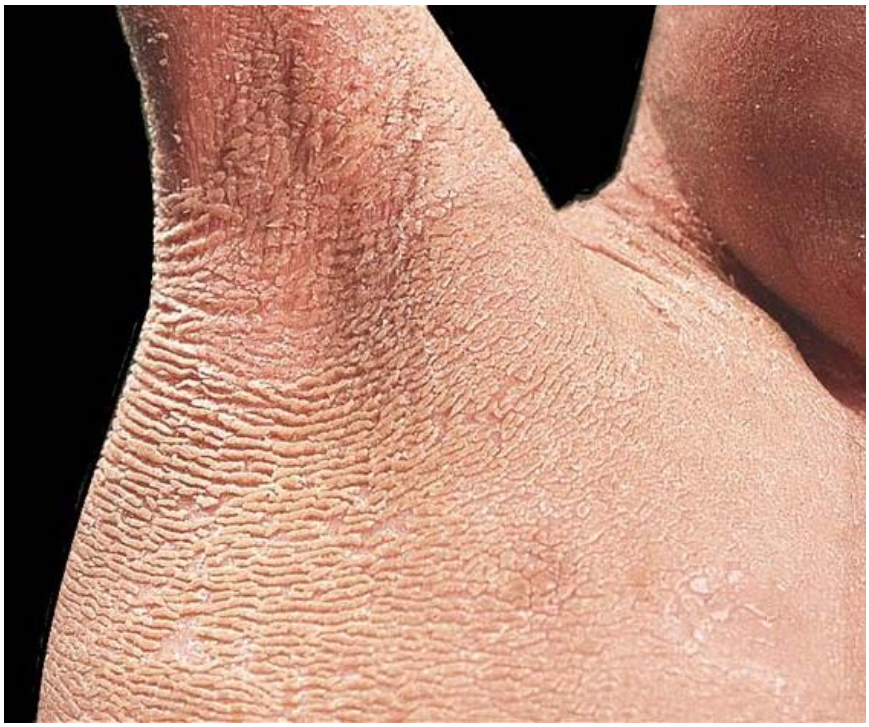

Figure 2. Diffuse hyperkeratosis with enhancement on major folds

sweetish smell due to fermentation of the bacteria in such a pabulum. In adulthood bullae are absent, whereas a polymorphic phenotype with hyperkeratosis, erosions and erythema is visible.

In some rare cases the hyperkeratosis becomes thicker, greyish and vegetant, leading to a variant previously called Curth-Macklin ichthyosis hystrix [4]. FOTO?

Due to hyperkeratosis and increased skin flaking, the thermoregulatory capabilities of patients are severely impaired, resulting in severe heat intolerance and reduced or no sweating.

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The disease is lifelong and steady, with frequent pyogenic infections, especially in the first years of life, which eventually could lead to sepsis if not treated adequally. Patients should be periodically screened for bacteriological examination with antibiograms to detect infections.

Therapy includes emollients, mild topical keratolytic agents and antibiotics to treat cutaneous infections; oral retinoids may be useful in some cases [4].

EI is due to autosomal heterozygous mutations in gene KRT1 or KRT10, occurring de novo in approximately 50% of cases [3]. Recessive familial cases of EI have also been identified in consanguineous families due to nonsense mutations in KRT10 leading to a complete absence of K10 protein [5,6].

Severe palmoplantar involvement in EI suggests KRT1 mutations, whereas KRT10 mutations in most instances give rise to phenotypes without palmoplantar involvement.

Mutated keratins are not able to polymerize and to create the ultimate keratin filaments. Keratins appear as clumps that are dynamically unable to cope with mechanical stress, leading to blister formation and erosion. In the same way, an abnormal keratin substrate does not allow the formation of a physiological stratum corneum.

In severe forms of EI, mutations are aminoacid substitutions located at the highly conserved helix boundary motifs, the helix initiation peptides, the helix termination peptides and the nonhelical H1 domain of K1 and K10 (exons 1 and 6). A milder form of the disease has been associated with mutations in the L1–2 linker of K1 or outside the helix boundary motifs [7,4].

2.2 Superficial epidermolytic ichthyosis (SEI)

SEI, previously known as ichthyosis bullosa of Siemens, is due to autosomal heterozygous mutations in KRT2 gene. Clinical phenotype is similar to those of EI, but generally milder. At birth, a collodion-like presentation is possible. (Figure 3)

A picture of superficial hyperkeratosis and erosions with rare bullae defines SEI in the first years of life, usually improving with age. The pattern of diffuse, fine scaling and the contemporaneous presence of desquamative ovalar ridges is called “mauserung phenomenon” and is typical of SEI [3,4].

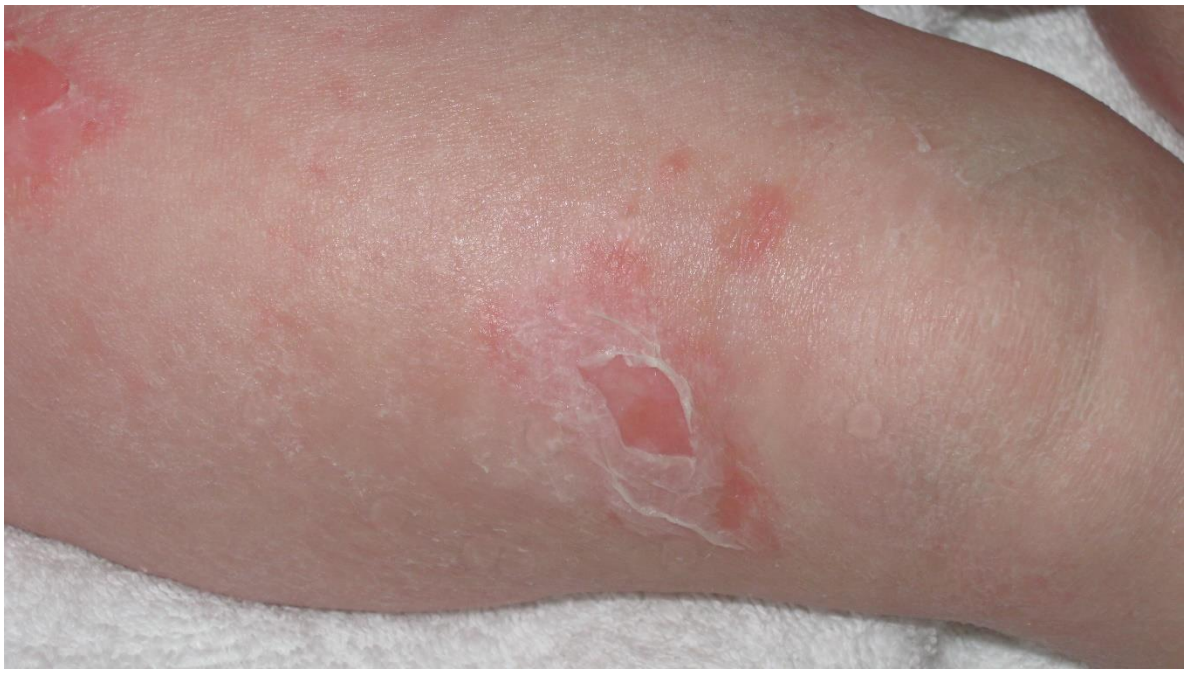

Figure 3. Mild collodion with superficial erosions.

These patients may have a discomfiting, sweetish, macerative odor, similar to EI and they could have cutaneous infections by pyogenes bacteria.

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The disease is due to mutations in the keratin 2e gene, which is expressed in the final steps of differentiation. These mutations cause instability of the keratin network and abnormalities in the subsequent formation of the corneocyte envelope [1,3,4].

2.3 Congenital reticular ichthyosiform erythroderma (CRIE)

CRIE, also called ichthyosis *en confettis* or ichthyosis variegata, is an extremely rare keratinopathic ichthyosis caused by heterozygous mutations in KRT10 or KRT1 [3,8,9].

The condition presents with a bright, erythematous, collodion baby at birth, similar to severe ARCI ichthyosis; during infancy and childhood phenotype is characterized by erythema and diffuse scaling. A peculiar phenotype at birth with hyperkeratotic presentation with thick greasy scales at birth has been described and can be a typical onset of the disease [4].

During childhood, dots of whitish, non-ichthyotic skin arise, especially on the face and upper trunk, increasing in size and number with time, reaching hundreds of whitish, slightly scaling macules intermingled in the ichthyotic erythema [Figure 4].

Later on, during the second decade, hypertrichosis appears on arms and legs, becoming a prominent feature. In some cases, hypertrichosis has already been reported during childhood.

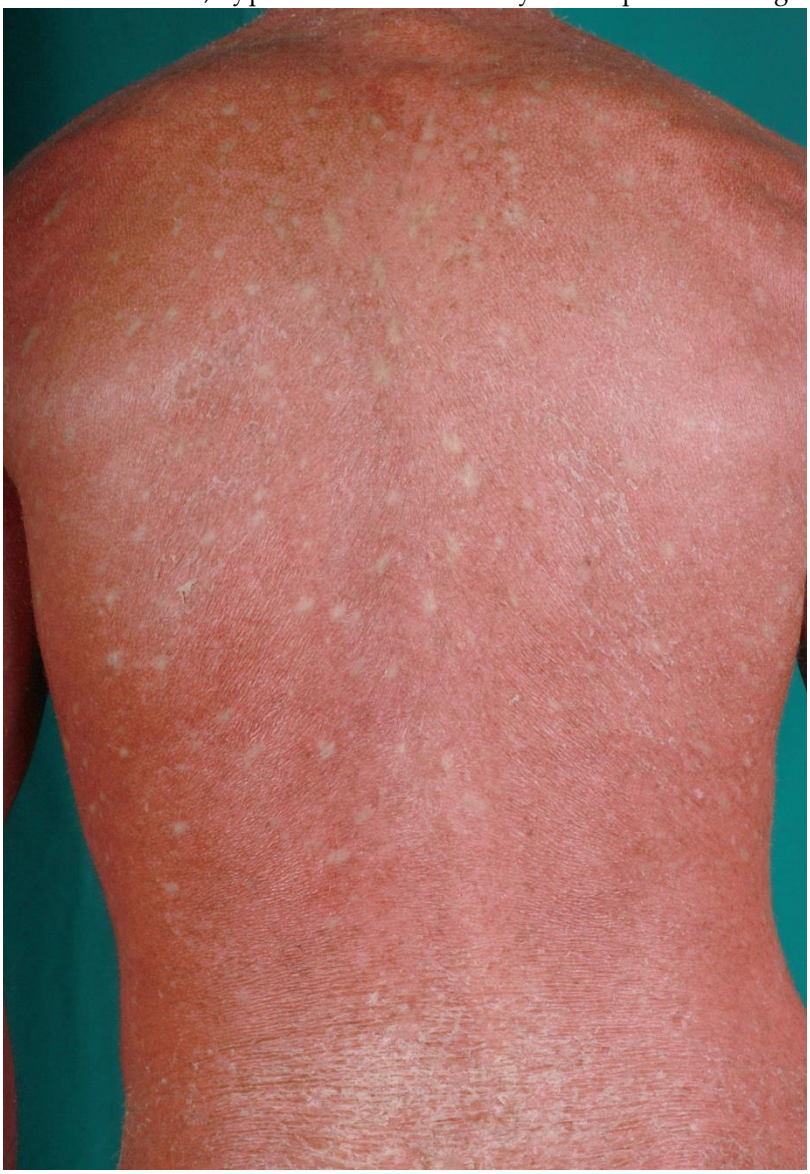

Figure 4. Whitish dots of healthy skin (confetti) appears on the trunk starting from childhood.

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Contemporaneously, brown–grayish hyperpigmented macules appear on the lower third of the legs and, less frequently, on the arms (Figure 5).

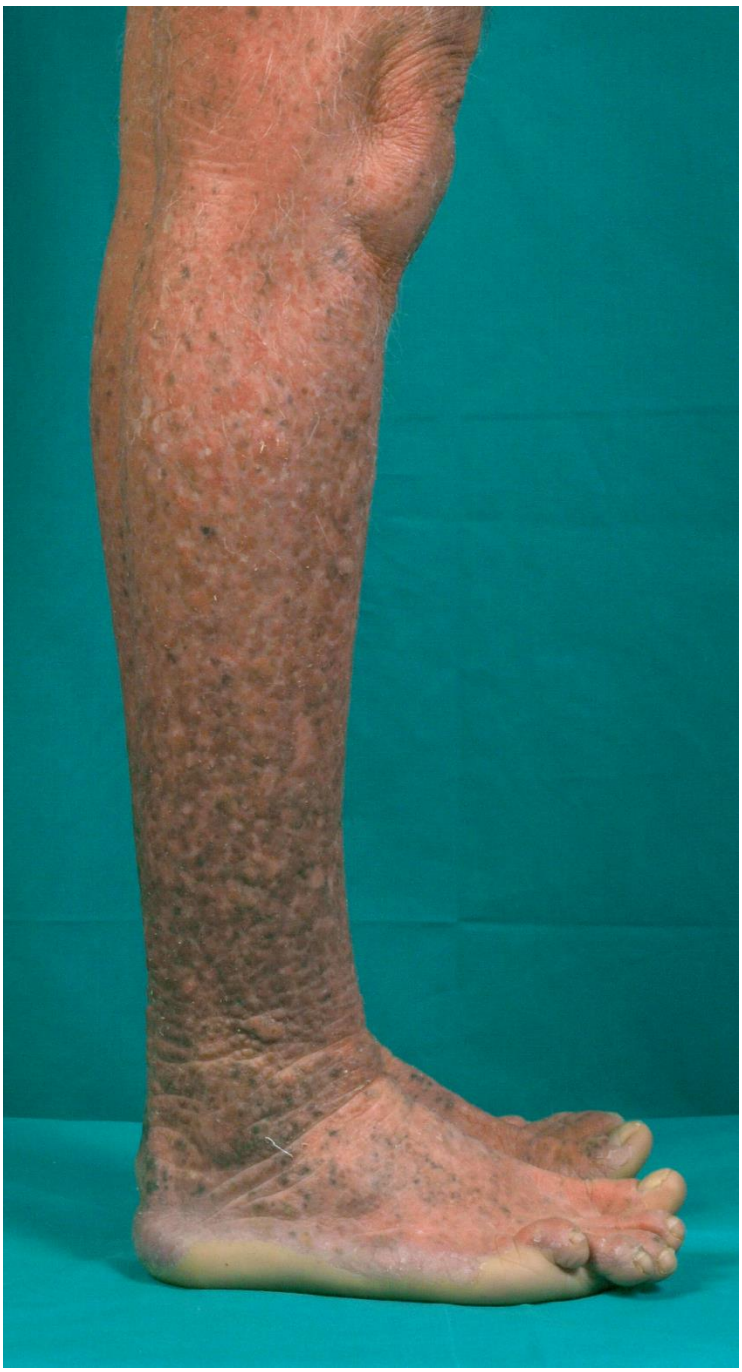

Figure 5. After 2nd-3rd decade, brown–grayish hyperpigmented macules appear on the lower third of the legs

Patients show palmoplantar hyperkeratosis with nails malformation and decreased finger length. There can be severe hyperhidrosis and pruritus.

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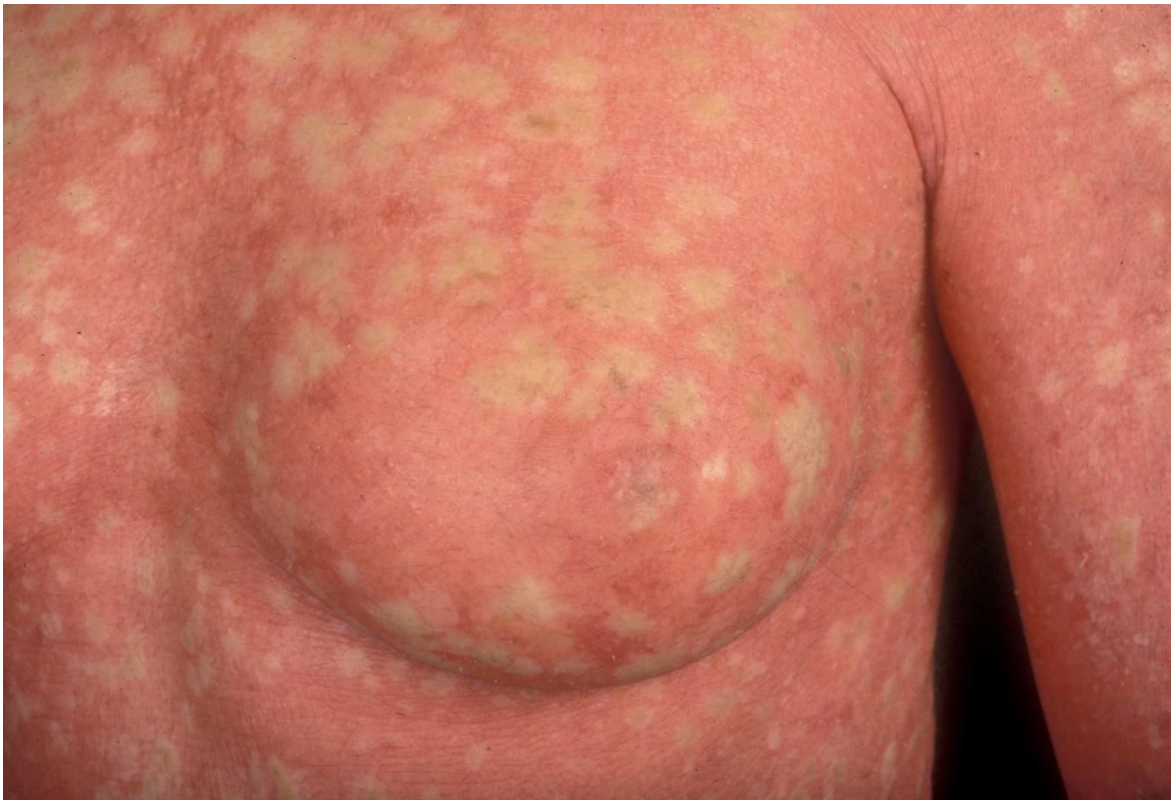
Besides cutaneous findings, this disease has several extracutaneous features such as ectropion and auricle deformities, mamillar hypoplasia (with nipples agenesia), nystagmus and growth



retardation [4,10-12] (Figure 6). Hotz and colleague studied 6 families with CRIE and found some clinical extracutaneous finding previously unreported, such as malposition of the 4th toe, spasticity, facial dysmorphisms, symblepharon and mental retardation, expanding the phenotypic spectrum of the disease [3].

Figure 6. Nipple agenesia in CRIE

Electron microscopy shows the pathognomonic feature of fine perinuclear shell-shaped storage of keratin intermediate filaments in the keratinocytes of the upper epidermal layers. Immunofluorescence staining for keratin 10 allows the visualization of the nuclear localization of keratin 10 in addition to the marked reduction of keratin 10 expression [10]. The nuclear staining for keratin 10 has been described only in CRIE and can be considered a diagnostic hallmark; for this reason, it is possible to diagnose CRIE early in infancy, especially for patients with a severe hyperkeratotic phenotype at birth, before revertant skin spots become evident, using immuno-fluorescence staining for keratin 10.

In 2010 Choate clarified the inheritance of this rare ichthyosis as an autosomal dominant trait due to heterozygous mutations on keratin 10 gene (KRT10) in ichthyotic skin only; in healthy spots the disease-causing mutation has reverted to the wild-type sequence through mitotic recombination causing copy-neutral loss of heterozygosity, which is characteristically different in each single spots, pointing out that it deals with separated events [8]. Mutations in KRT10 leading to CRIE are deletions or duplications in exon 7 or splice site mutations at the acceptor splice site of exon 6 or the donor splice site of exon 7, resulting in an arginine-rich C-terminal frameshift leading to a mislocalization of the protein to the nucleus, impairing the normal function of the keratin network [8,12]. Also, mutations in KRT1 may lead to CRIE phenotype, as shown by Choate in 2015, when he described a patient with an ichthyosis en confetti-like phenotype carrying a frameshift mutation in keratin 1 gene [9]. The patient developed his first revertant spots during the second decade of life, slightly later if compared to those caused by KRT10 mutations.

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The size of the healthy patches suggests that loss of heterozygosity occurs in the progenitor cells of an epidermal stem cell unit during early embryonic development; however, its exact mechanism and timing is unknown.

CRIE is remarkable for its high frequency of spontaneous reversion, with more than a thousand revertant clones in many subjects.

2.4 Epidermolytic nevus (EN)

Epidermolytic nevus (EN) is a rare subgroup of epidermal nevi, which arise from postzygotic mutations in keratinocytes and cells forming adnexa; this nevus is the mosaic pattern presentation of the keratinopathic ichthyosis caused by mutations in the K1 or K10 genes [4].

EN is clinically characterized by multiple verrucous papules and plaques over the trunk and limbs arranged along the lines of Blaschko, with some areas of erythema and erosions, rarely vesico-bullous lesions in early childhood, with isolated or diffuse lesions (Figure 7).

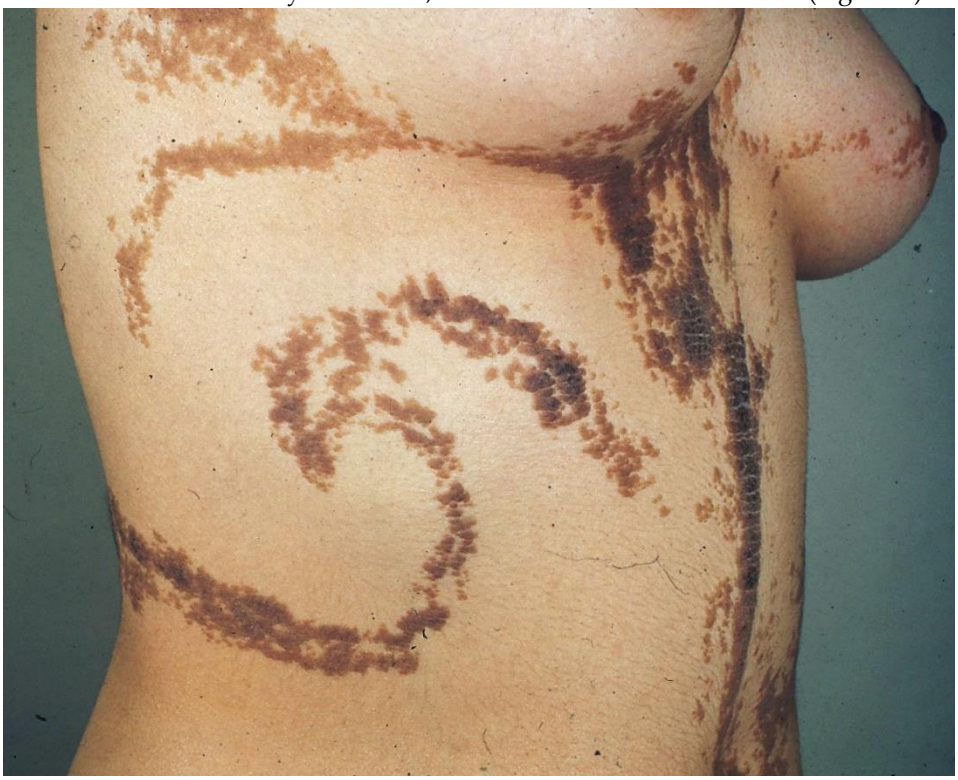

Figure 7. Multiple verrucous papules and plaques over the trunk and limbs arranged along the lines of Blaschko

The prevalence of epidermal nevi is 1:1,000 and EN is clinically indistinguishable from other types of epidermal nevi: nevertheless, it can be histopatologically differentiated from them [13].

Although this mosaic forms do not pose any major management issues, they are of important clinical relevance when the mosaicism also involves the gonadal cells. In such rare circumstances, the genetic defect can be transmitted from the parent with diffuse linear EN to the offspring who will manifest epidermolytic ichthyosis (EI) as full blown disease [13,14].

In literature, only five EI cases in which the parents have EN have been diagnosed by genetic analysis [14,15]. A group of Japanese colleagues headed by Kono M, in 2017 determined the risk of disease transmission from a father with diffuse EN to a child at future pregnancies [16]. Starting from the mutant rates in sperm, they investigated the percentage of semen with the pathogenetic KRT10 mutation from the proband's father by NGS analysis: they determined that approximately 3.9% of his sperm had the causative mutation, whereas the mutant allele frequency in his peripheral blood was 5.3% and in his affected skin 12.0% [16]. This study showed that the evaluation rates of mutant gametes in semen sample by NGS technique is effective and highly recommended, in order

to know the risk of transmitting the disease to the offspring in mosaic conditions; however, this type of examination is limited to the affected fathers.

3. Discussion

The genotype-phenotype correlations in SEI, EI and CRIE are very complex. The differential diagnosis between these diseases can be very difficult, since the phenotypes extremely ranges in severity [3]. The spectrum of keratinopathic ichthyoses also shows intrafamilial phenotypic heterogeneity, making the correct diagnosis often difficult and challenging.

Therefore, in patients born with a collodion baby presentation or in patients with suspected SEI or EI, in which no mutation in the corresponding genes can be found, analysis of other keratin genes could be useful.

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