CASE REPORT

# Epidermolytic Hyperkeratosis: a follow-up of 23 years of use of systemic retinoids *

## Hiperceratose epidermolítica: um seguimento de 23 anos de uso de retinoides orais

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**Abstract:** Epidermolytic hyperkeratosis is a form of ichthyosis normally resistant to topical treatments. Female patient monitored since 1978 diagnosed with epidermolytic hyperkeratosis. Clinical examination showed generalized hyperkeratosis and scaling. Given that no other treatments were available at the time, the patient was initially treated with keratolytic, systemic vitamin A and moisturizers, with no improvement. In 1986, with the development of oral retinoids, etretinate was introduced. In 1998 this was replaced by acitretin. The patient is receiving 25 mg/day after 23 years of using oral retinoids. Significant improvement of the condition and patient´s quality of life has been noted.
Keywords: Acitretin; Hyperkeratosis, epidermolytic; Retinoids

**Resumo:** A hiperceratose epidermolítica é uma forma de ictiose geralmente resistente a tratamentos tópicos. Relata-se um caso de paciente feminina , em acompanhamento na dermatologia desde 1978, com diagnóstico de hiperceratose epidermolítica. Foi tratada inicialmente com queratolíticos, vitamina A oral, ácido tartárico e emolientes tópicos, porém sem melhora no quadro clínico, já que não haviam disponíveis outros tratamentos na época. Em 1986, com o advento dos retinóides orais, foi introduzido o etretinato, e em 1998, foi substituído pelo acitretin, apresentando excelente resposta terapêutica. No momento a paciente está em uso de acitretin 25 mg/dia, completando 23 anos de uso de retinóides orais, com mínimos efeitos adversos e melhora significativa na qualidade de vida.
Palavras-chave: Acitretina; Hiperceratose epidermolítica; Retinóides

## INTRODUCTION

Ictiose compreende um grupo heterogêneo de doenças de pele cuja manifestação cutânea mais comum é a descamação.

É caracterizada por alteração na ceratinização, causada por uma falha na rede de queratinas [1] e/ou 10, conferindo fragilidade aos ceratinócitos, particularmente da epiderme superior.Ichthyosis consists of a heterogeneous group of skin diseases commonly manifested by cutaneous desquamation. [1] Epidermolytic hyperkeratosis (autosomal dominant transmission) has a prevalence of 1:200,000 with 50% of cases occurring as spontaneous mutations. [2]

The disorder is characterized by changes in keratinization caused by a failure in the keratin 1 and/or 10 filament network, causing fragile keratinocytes, especially of the upper epidermis. [2]

Severe forms of ichthyosis are resistant to topical treatment but oral retinoids have been shown to be an effective mode of treatment. [1]

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## CASE REPORT

48-year-old female patient, monitored by the Dermatology Unit since 1978, reported diffuse erythematous and thickened skin at birth, progressing to blisters and ulceration. Initial physical examination showed marked hyperkeratosis and thin, widespread scaling, most prominent on the knees, ankles and elbows (Figures 1A and 1B). No sign of facial involvement or palmar-plantar (*hand-foot syndrome*). Histopathology was compatible with the diagnosis of congenital bullous ichthyosiform erythroderma (Figure 2). Several treatments were undertaken at the time, such as topical salicylic acid, topical steroids, moisturizers and doses of oral vitamin A (50000U/day), with unsatisfactory results. In 1985 the treatment was changed to 5-7% tartaric acid under topical occlusion over patient´s entire body, resulting in partial improvement, but with local irritation. In 1986, with the advent of retinoids, this treatment was replaced by etretinate, with an initial dose of 50 mg/day, later reduced to 10mg/day. In 1998, etretinate was replaced by acitretin (20mg/day), with significant improvements in scaling and hyperkeratosis. Laboratory tests showed mild changes in liver function during treatment (AST 21 and ALT 26 - September 2009) and slightly elevated lipid levels (total cholesterol 195, triglycerides 193 - September 2009) which were controlled with diet. With regard to clinical side effects, the patient complained only of hair loss. To obviate the risk of pregnancy and teratogenicity, the patient used oral contraceptives continuously as a means of prevention. A bone scan performed in 2003 was normal and an x-ray of the spine in 2009 was normal. At present the patient is using 25 mg/day of acitretin. After 23 years of using oral retinoids significant improvement of her clinical symptoms and quality of life has been noted.

## DISCUSSION

A hiperceratose epidermolítica é doença genética da ceratinização e inicialmente foi descrita sob a sinonímia de eritrodermia ictiosiforme congênita bolhosa. [2] Epidermolytic hyperkeratosis is a genetic disorder of keratinized tissue, initially described as synonymous with bullous congenital ichthyosiform erythroderma. [2] It is characterized by autosomal dominant inheritance, with spontaneous mutation possibly occurring in 50% of cases. The flaw in the network of keratin 1 and/or 10 confer fragility to keratinocytes, particularly of the upper epidermis, manifested as epidermolytic hyperkeratosis. [2] The disorder usually presents at birth with blisters and erythema, progressing to hyperkeratosis with or without erythroderma. [2] The histopathology is typical, especially involving very thick stratum corneum, with vacuolar degeneration of the upper epidermis. [2]

Most types of ichthyosis that present significant scaling are not improved with moisturizing creams or keratolytic agents. [3] The quality of life of these patients is severely affected and treatment needs to be undertaken throughout life. [3] Treatment can be effected with retinoids, which control the growth and differentiation of epithelial tissue. [3,4] It is known that retinoids affect the amount of keratin in the human epidermis causing an increase of certain keratins (K4, K6, K13 and K19), while others decrease (K2e, K1 and K10) or show little or no response to treatment. [5]

Acitretin is currently the most effective systemic treatment for the majority of severe cases of ichthyosis, [3] with its side effects thoroughly discussed in the literature: mucocutaneous changes (cheilitis, xerosis, nail abnormalities, hair loss are all dose-dependent), liver toxicity (reversible elevation of transaminases and alkaline phosphatase), abnormalities of serum lipids (triglycerides and cholesterol) and the risk of teratogenicity. [3,4]

Topical retinoids may represent an alternative

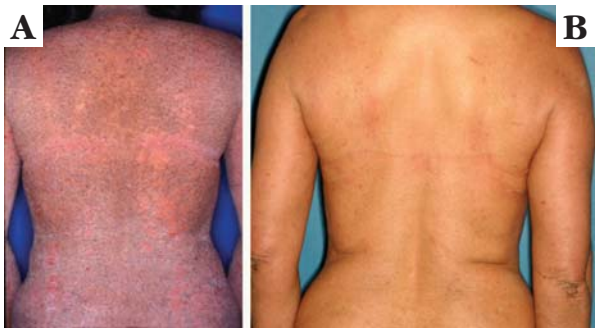


**Figure 1: A-** Left hand picture). Generalized hyperkeratosis and fine scaling, in 1985, with topical treatment. **B.** (right hand picture). Improvement in 2009 with use of oral retinoid

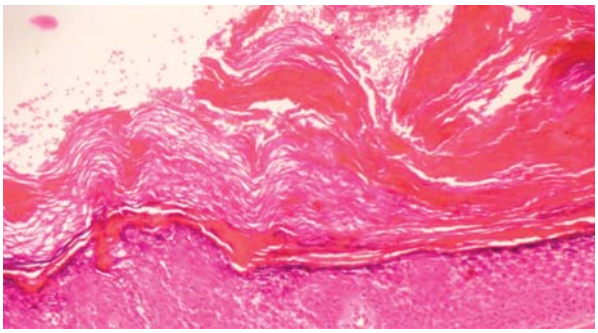

**Figure 2:** H>E. 10x. Hyperkeratosis, papillomatosis and mild epithelial hyperplasia, with dissociation of the cells of the spinous layer

for avoiding systemic treatment, although their use is not as effective, with high potential for local irritation. [3]

Many reports exist regarding the skeletal changes induced by retinoids. [6] In adults, abnormalities are identical to Diffuse Idiopathic Skeletal Hyperostosis (DISH), which consists of spinal and extra-spinal cord hyperostosis and calcification of tendons and ligaments. Other changes include the thinning of the long bones and osteoporosis. [6,7] In children, thickening of the periosteum, bone resorption, disc narrowing and premature closure of epiphyses may occur. [6,7] No consensus has been reached on the frequency and magnitude of these effects. [6,7] A recent study found no relationship between duration of treatment with oral retinoids or the cumulative dose and the prevalence and severity of DISH, degenerative changes and osteoporosis. [6] Annual routine spinal radiographs during the treatment with retinoids are therefore not recommended. [6,7] Patients should be asked to report skeletal pain and restriction of joint mobility. [6]

Other systemic effects of retinoids depend on

**Chart 1:** Patients treated with keratinization disorders with acitretin, and its side effects

| Patients with keratinization disorders treated with acitretin | Authors | Results | Side effects |
|---|---|---|---|
| Study involving 28 patients aged between 1 and 13 treated with acitretin at an average dose of 0.86mg/kg/day over 2-36 months. | Xi-Bao Zhang, Quan Luo, Chang-Xing Li, Yu-Qing He and Xiao Xu. (8) | 23 cases cured<br>5 showed improvement of clinical condition. | Cheilitis 46.3%<br>Skin Fragility 35.7%<br>Dry mouth 21.4%<br>Lipid Ch* 17.9%.<br>Ch-* AF** 25%<br>Ch *liver function 21%<br>No effect on growth or bone.. |
| Study involving 3 patients aged 5, 6 and 15 receiving 0.75-0.8 mg/kg/day of acitretin for between 9 to 28 months respectively | Xibao Zhang, Yuquing He, Hua Zhou, Quan Luo and Chang-Xing Li. (1) | Substantial improvement in the 3 cases | Mucocutaneous Ch.* in all 3 cases<br>Mild hepatic alterations<br>No effect on growth or bone |
| Study involving 3 patients, aged 45, 60 and 69, receiving 0.5-0.75mg/kg day of acetrin for 14, 22 and 28 years respectively | Mork,NJ, Austad,J, Kolbenstvedt, A. (9) | Clinical condition improved | Spinal hyperostosis (bamboo spine) in the 3 cases. |
| Study involving 2 patients:<br>Case 1- 75 year old treated with 25 mg/day of acetrin over 20 years<br>Case 2- 26 year old treated with acetrin doses of 25 mg/day over 5 months | Bondson,ML, Nystrom,AM, Gunnarson,U, VAhlquist,A (10) | Case 1: partial improvement of the ichthyosis and keratodermia<br>Case 2: improvement of hyperkeratosis | Case 1: hiperlipidemia controlled with Gemfibrozil and Ch.* in transient transaminase elevations<br>Case 2: cutaneous irritation |
| 3-year-old patient treated with 1 mg/kg/day dose of acetrin over 6 months. | S Khandpur, R Bhat, M Ramam.(11) | Improvement in the cutaneous Ch* and corneal erosions | No response in photophobia and alopecia |
| 10 day-old patient ('Baby Harlequin') treated with 1mg/kg/day dose of acetrin over 2 years | Singh S, Bhura M, Maheshwari A, Kumar A, Singh CP, Pandey SS (12). | Improvement in scaling, ectopy and contractions after one month of treatment | No change in laboratory and skeleton tests |

* Ch = changes
** AF = Alkaline Phosphatase

the dose and treatment duration, as seen in Table 1. *Zhang et al.,* in a study of 28 patients aged 1 - 13 years, patients were treated with acitretin (average dose of 0.86 mg/kg / day) for between 2 and 36 months. The most frequent changes observed were cheilitis, skin fragility, dry mouth, lipid abnormalities and liver function, but with no effect on growth or bone. [8] By contrast, a study by *Mork et al.* with three patients dosed with 0.5 to 0.75 mg/kg day for 22, 28 and 14 years, spinal hyperostosis was observed in all three 3 cases. [9] These findings are consistent with those of *Bondson et al.* who report that in a case where the retinoid dose was 25 mg/day for 20 years, changes in lipid levels and transaminases were observed. [10] Reports of use of the medication for shorter periods (6 months to 2 years), no significant systemic adverse events even at higher dosage (1mg/kg/day) were noted. [11-12]

Regardless of all the possible side effects of retinoids decribed in the literature, the patient reported in this case showed only slight changes in lipid and transaminase levels, in addition to hair loss. These were reversible with dose reduction and diet. This strengthens the proposition that, while treatment must be continuously monitored, the use of retinoids over the long term appears to be safe and significantly improves patients´ quality of life. ❑

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