Treatment Of Congenital Ichthyosis With Acitretin
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follcules forming keratotic follicular plugs. (Figure 2: 200X, HE)

The patient was clinically followed up regularly for six months. A post-treatment rebiopsy was performed and it revealed significant improvement of epidermal changes as continuous granular cell layer (Figure 3: 200 X, HE).

In accordance with histologic improvements, the patient's clinical appearance improved significantly as well (Figure 4).

**Figure 1**
Figure 1: Pretreatment appearance of the patient.

**Figure 2**
Figure 2: Pretreatment punch biopsy material showing moderate degree of hyperkeratosis with complete absence of granular cell layer. Hyperkeratosis extends into the hair follicle forming keratotic follicular plug. (200X, HE)

**Figure 3**
Figure 3: Posttreatment punch biopsy showing continuous granular cell layer. (200 X, HE)
DISCUSSION

Many surviving congenital ichthyosis patients have been treated with retinoids and survival is often attributed to early therapeutic intervention. However, the role of retinoids in improved survival still remains to be determined (11,12,13,14,15). Many perinatal congenital ichthyosis deaths are caused by interference of severe infections causing loss of vital functions and the late onset of retinoid action; therefore, other factors such as improved intensive care of severely compromised neonates, are likely to be important in survival of the patient (16).

The clinical features of infants with congenital ichthyosis are generally similar to our case, which is typical. No visceral malformation is reported, the disorder consisting exclusively of an error of epidermal keratinization. Respiratory movements are restricted; secondary infection and septicemia are frequent complications. Death usually occurs in the first few weeks of life.

Prenatal diagnosis is now possible, using sonography, which shows ectropion, ecbabium, nasal or aural abnormalities, and hypoplasia of the extremities. However, a precise diagnosis needs fetal skin biopsy made between 20 and 22 weeks of gestation (17). If the number and size of the biopsy specimens are small, it may be possible to misdiagnose an affected fetus as normal (17). Prenatal diagnosis is vital in genetically inherited lethal diseases. According to the prenatal diagnosis, the patients should thoroughly be evaluated and the families be informed about the disease (18).

At light microscopic examination, a thick compact stratum corneum with parakeratosis, hypogranulosis and hyperkeratosis of the hair canals is seen (19). On ultrastructural examination, the granular layer keratinocytes present abnormalities of lamellar granules. Between the cornified cell and the granular cell layers, extracellular lamellar structures are lacking (17). In our case histopathologic evaluation revealed moderate degree of hyperkeratosis and complete absence of granular cell layer in the epidermis with keratotic follicular plugs.

Control biopsy performed after a acitretin (1 mg/kg/day/ 6 month) therapy showed that the prior findings had completely ceased.

Some rare long-term survivals of congenital ichthyosis are reported. This survival is often attributed to early treatment with retinoids. The clinical presentation then evolves with age into a viable form of generalized ichthyosis (20). However, the persisting dermatosis remains severe and the quality of life of affected children is poor.

El-Ramly et al (21) presented eight cases of ichthyosis treated with retinoids. They reported that aromatic retinoid treatment resulted in a satisfactory improvement of skin condition. Tamayo et al (22), also recommended oral retinoid treatment after their experience in eight children with lamellar ichthyosis.

Gicquel et al (23) reported bilateral ectropion treatment in an infant with severe lamellar ichthyosis by N-acetylcysteine applied directly to the skin with association of oral acitretin. Topical N-acetylcysteine has been proved to have an antiproliferative effect on keratinocytes in vitro and in vivo. It may be useful in the treatment of major forms of ectropion in children with lamellar ichthyosis. Its association with conventional acitretin treatment may prevent unnecessary surgery. In accordance with the prior studies in literature, our patient showed dramatic improvement in skin lesions and ectropion with oral acitretin treatment.

Verfaille et al. (24) investigated the efficacy, tolerability and safety of oral liarozole, a retinoic acid metabolism blocking agent, with acitretin in patients with ichthyosis. Between-group comparisons for efficacy and tolerability revealed no statistically significant differences except for scaling on the trunk at baseline which was significantly worse in the liarozole group and showed a more pronounced
improvement in this group than in the acitretin-treated patients. The expected retinoic acid-related adverse events were mostly mild to moderate and tended to occur less frequently in the liarozole group. The results of this trial warrant further clinical trials to confirm efficacy and safety of liarozole as an orphan drug in ichthyosis. Saracoglu et al. treated two newborn infants with ichthyosis with acitretin (1 mg/kg/day). Clinical improvement was achieved shortly after treatment. They concluded that early management of severe ichthyosis cases could prevent life-threatening events.

Furthermore, long-term retinoid therapy is responsible for toxicity. Long-term therapy with oral retinoids provokes anxiety and shows adverse effects on bone mineralization. The most commonly reported effect is the production of osteophytes and calcification of ligaments. Paige et al. observed no evidence of skeletal toxicity in 42 children treated over an 11-year period. No complication due to oral acitretin treatment was observed in our patient.

In conclusion, early management of severe ichthyosis cases can prevent life-threatening events. In severe congenital ichthyosis cases, mortality due to the complications, is high in the neonatal period. Therefore, acitretin treatment seems to be the most efficient treatment in severe congenital ichthyosis with no major side effects and easy oral application.

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