

Keratosis Linearis with Ichthyosis Congenita and Sclerosing Keratoderma (CLICK-syndrome): A Rare, Autosomal Recessive Disorder of Keratohyaline Formation?

A. VAHLQUIST¹, F. PONTÉN² and A. PETTERSSON³

¹Department of Dermatology, Faculty of Health Sciences, Linköping University, ²Department of Pathology, Uppsala University, and ³County Hospital, Östersund, Sweden

We report a 32-year-old man with an unusual combination of congenital ichthyosis, sclerosing palmoplantar keratoderma with pseudoainhum, and bizarre striate hyperkeratosis in the flexures, but no systemic involvement. The condition, which improved on oral etretinate therapy, had not appeared previously in the family. On light microscopy the involved epidermis showed marked acanthosis with hypergranulosis and hyperkeratosis. Electron microscopy disclosed numerous large keratohyaline granules in superficial keratinocytes. The clinical picture and histology are virtually identical to those of a Spanish family suffering from an autosomally recessive skin disease of unknown etiology. We hypothesize that the condition is due to a genetic defect in the formation of keratohyaline granules. **Key words:** etretinate; inborn errors of keratinization; epidermal differentiation; genodermatosis.

(Accepted November 18, 1996.)

Acta Derm Venereol (Stockh) 1997; 77: 225–227.

Anders Vahlquist, MD, PhD, Department of Dermatology, University Hospital, S-581 85 Linköping, Sweden.

The variability in the symptoms associated with inherited disorders of keratinization is immense, reflecting the very complex regulation of epidermal differentiation. To elucidate the genetic basis of this complexity, it is important to delineate new forms of keratinizing disorders with pathognomonic symptoms implying monogenetic aetiology. We have recently identified a patient with an unusual combination of ichthyosis, palmoplantar keratoderma and striate hyperkeratosis, present since early childhood. A search in the literature revealed only one previous description of a similar triad of symptoms (1). We wish to report our case, adding electron microscopy to the list of investigations performed in this disease.

CASE REPORT

The patient, a 32-year-old unmarried man with healthy, non-consanguineous parents of Scandinavian extraction, was referred to us in May 1995 for investigation. He had a moderate, non-blistering ichthyosis since birth and long-standing palmoplantar keratoderma with pseudoainhum and a sclerosing flexion deformity of the fingers (Fig. 1a,b). Longitudinal, non-inflamed keratotic striae, which had appeared spontaneously, were seen around his wrists and in the armfolds and behind the knees (Fig. 1c,d). He also had several soft, slightly raised patches on the left side of the trunk, and a few hyperkeratotic, slightly inflamed (and sometimes haemorrhagic) verrucous lesions along the dorsal axillary folds (Fig. 1e,f). The patient was otherwise healthy, both physically and mentally, and had no history of either dental, nail, hair or mucous membrane problems. He had 5 half-siblings, all of whom were healthy and without skin symptoms, but no children of his own.

Laboratory tests, including haematologic, renal and hepatic parameters, were normal. A serum lipoprotein electrophoresis showed normal findings, thus excluding e.g. steroid sulfatase deficiency (2).

Histology

Several biopsy specimens taken from the keratotic lesions (including those on the trunk) revealed similar features of acanthosis, papillomatosis, hypergranulosis, hyperkeratosis with focal parakeratosis, some follicular plugging, and a mild, unspecific inflammatory infiltrate in the dermis (Fig. 2). Electron microscopy of upper epidermis disclosed numerous large keratohyaline granules with abnormally rounded configuration (Fig. 3).

Clinical course

According to the patient his symptoms had been fairly constant over time, although increased skin xerosis and finger stiffness were noted in the winter. His plantar keratoderma has twice been complicated by a dermatophytic infection. In 1983 he had been given etretinate 25 mg bid for 3 months. The therapy was well tolerated and resulted in a considerable improvement in the skin symptoms (thinner keratoderma and less scaly ichthyosis). However, a relapse was noted a few weeks after stopping therapy. Over the next years three repeated courses of etretinate (20–25 mg daily for 2–3 months) were given, with similarly successful results. However, in 1986 the patient developed slightly elevated liver transaminases whilst on etretinate and was advised to stop therapy for good. He has since been using emollients and occasional UVB therapy. He does not consider himself handicapped by the disease.

DISCUSSION

Our patient's skin symptoms are virtually identical to those of 4 Spanish siblings, previously reported to have an autosomal recessive keratinizing disorder probably representing a new entity that should be classified among congenital ichthyosiform syndromes (1). The most striking feature of the patient's skin was the early appearance of linear hyperkeratosis without evidence of Koebner's phenomenon. Although some of the symptoms – e.g. massive keratoderma, pseudoainhum and star fish-like keratotic extensions beyond the margins of the palms and soles – are similar to those in Vohwinkel's syndrome without sensory hearing loss (3, 4), the combination with generalized ichthyosis, striate lesions in many flexure sites, and a skin histology characterized by epidermal acanthosis and hyperkeratosis with abnormal keratohyaline granules is not seen in this or any other syndrome. For instance, *keratosis liquénoid striée* is usually characterized by more intensely inflamed, linearly arranged hyperkeratoses appearing in adulthood and without a previous family history (reviewed in ref. 5). However, a congenital variant of this condition has been described (6), which may in fact have represented a less



Fig. 1. Clinical pictures of the patient showing diffuse keratoderma with pseudoainhum on the 4th and 5th fingers (a) (arrow heads) and striate hyperkeratoses around the wrists (b), ichthyosis and striate hyperkeratosis in the arm (c) and kneefolds (d), and close-up views of the soft patches on the ichthyotic abdomen (e) and the plaque-like follicular plugging and erythematous scaling around the axillae (f).

severe case of the disease that we prefer to call **KLICK-syndrome**: keratosis linearis with ichthyosis congenita and keratoderma.

Ongoing studies will hopefully clarify if this disease is caused by a defect in the formation of keratohyaline granules, warranting a search for a candidate gene belonging to the cluster of differentiation-related genes on chromosome 1. In the mean-

time, it is reassuring to note that retinoids given as oral etretinate therapy may reduce the sclerosing keratoderma to about the same extent as it does in Vohwinkel's syndrome (7, 8).

ACKNOWLEDGEMENTS

We thank Drs. E Burstöm (Boden) and A Lundström (Umeå) for valuable discussion.

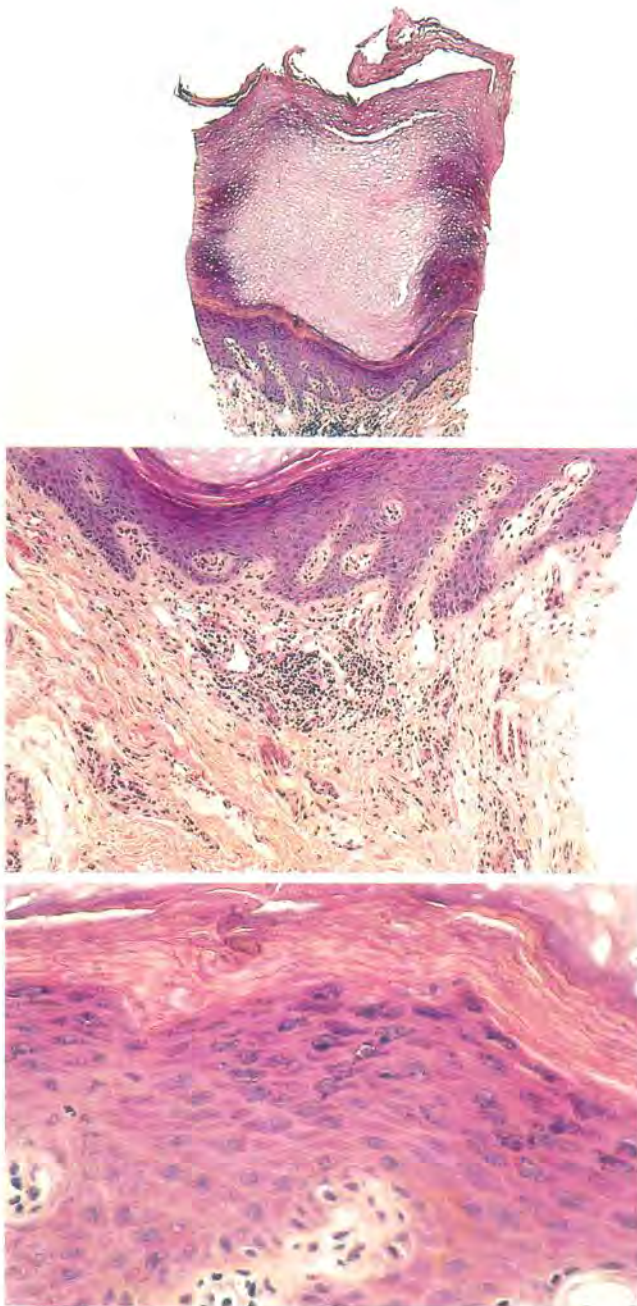


Fig. 2. Section of skin biopsy stained with hematoxylin-eosin. Low-power magnification (top) shows marked orthokeratotic hyperkeratosis with parakeratotic stratum corneum at both edges of the biopsy. Higher magnification (middle) displays slight acanthosis and inverted papillomatosis. Note the sparse infiltrate of mononuclear inflammatory cells in upper dermis. High-power (bottom) exposing hypergranulosis with irregular keratohyaline bodies. There are no signs of epidermolysis.

REFERENCES

1. Pujol R, Moreno A, Alomar A, de Moragas J. Congenital ichthyosiform dermatosis with linear keratotic flexural papules and sclerosing palmoplantar keratoderma. *Arch Dermatol* 1989; 125: 103-106.
2. Ibsen H, Brandrup F, Blaabjerg I, Lykkesfeldt G. Lipoprotein electrophoresis in recessive x-linked ichthyosis. *Acta Derm Venereol (Stockh)* 1986; 66: 59-62.

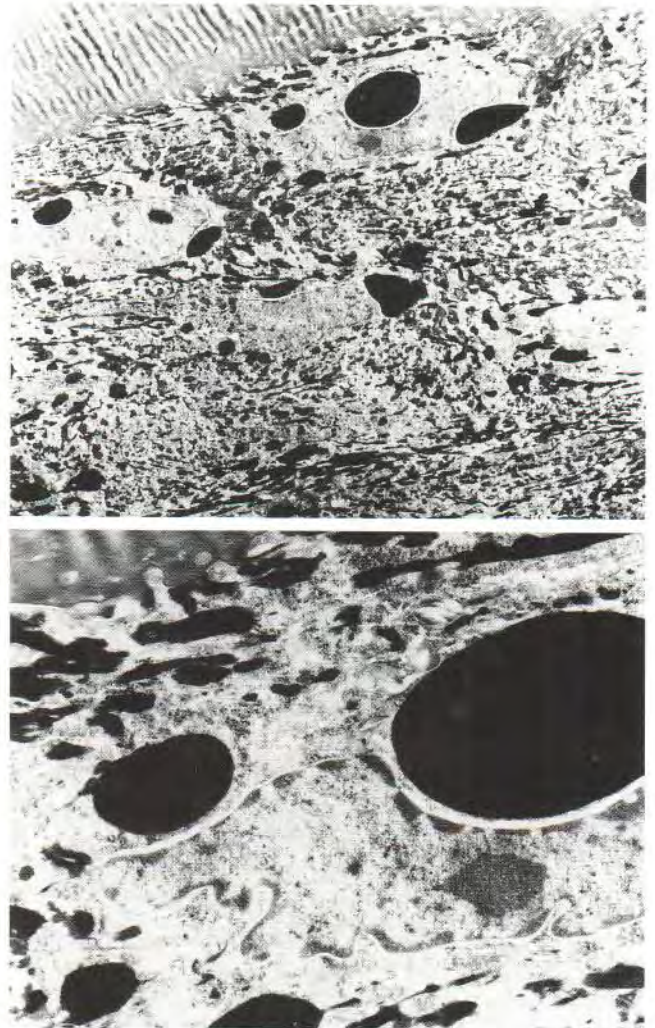


Fig. 3. Ultrastructural picture of upper epidermis. Top ($\times 4,000$) shows orthokeratotic stratum corneum with ample electron-dense intracytoplasmic bodies in superficial keratinocytes. Higher magnification ($\times 8,000$) of rounded globular structures, probably representing abnormal keratohyaline granules. Desmosomes appear normal.

3. Cole D, McCauley M, Way B. Vohwinkel's keratoma hereditarium mutilans. *Int J Dermatol* 1984; 23: 131-134.
4. Camisa C, Rossana C. Variant of keratoderma hereditaria (Vohwinkel's syndrome). *Arch Dermatol* 1984; 120: 1323-1328.
5. Masouyé I, Saurat J. Keratosis lichenoides chronica: the centenary of another Kaposi's disease. *Dermatology* 1995; 191: 188-192.
6. Barrière H, Litoux P, Bureau B, Welin J, Guyader C. Kératose lichénoïde striée. Forme congénitale. *Ann Derm Vénéréol (Paris)* 1977; 104: 767-769.
7. Chang Sing Pang A, Oranje A, Vuzevki V. Successful treatment of keratoderma hereditaria mutilans with an aromatic retinoids. *Arch Dermatol* 1981; 117: 225-228.
8. Vahlquist, A. Role of retinoids in normal and diseased skin. In: Blomhoff R, ed. *Vitamin A in health and disease*. New York: Marcel Dekker, Inc., 1994: 365-424.