COMEL-NETHERTON SYNDROME CASE PRESENTATION WITH REVIEW OF LITERATURE

Mohammed Mohy El-din Selim*
Hassan Ali Al-Abdulla*
Aida Al-Saleh*
Bahram Azadeh**

*From: Department of Dermatology & Venereology**
Department of Pathology, Hamad Medical Corporation
*Doha - Qatar***

Abstract:

We report a case of Comel-Netherton syndrome (NS) in a boy who was born full term with no family history of consanguinity. An initial neonatal diagnosis of infantile seborrhoeic dermatitis progressed through atopic dermatitis and juvenile psoriasis before icthyosis linearis circumflexa (ILC or N.S) was confirmed at the age of two and a half years on the basis of clinical and histopathological findings and characteristic hair changes. We discuss the reasons for Comel-Netherton syndrome being a challenge to the dermatologist [1], The diagnosis is usually delayed because ILC and hair shaft abnormalities do not become evident until after the first year of life [2] .NS is often misdiagnosed as immunodeficiency with seborrhoeic dermatitis (Leiner disease) or congenital erythrodermic psoriasis [3] and nonbullous icthyosiform erythroderma. [4]

Case report:

GF, a Palestinian boy, was born June 1997 after an uneventful pregnancy and normal vaginal delivery to a family with no history of consanguinity. From birth he had a generalized erythematous scaly rash, including the face and scalp but with the eyes and mucous membranes free, and at two days of age he was diagnosed as having infantile seborrhoeic dermatitis (Leiner) with the possibility of icthyosis. All the lesions cleared within three days on treatment with potassium permanganate lotion and 2%fucidic acid ointment (Fucidin ointment Leo Pharmaceuticals).

Fourteen weeks later he was seen again with scaly erythroderma, mainly on the trunk and with a cradle cap of scalp. He was treated for three weeks with Ketoconazol shampoo (Nizoral shampoo) and Flumetasone pivalate 0.02%, Clioquinol 3% cream (Locacortin vioform cream. Novartis Pharmaceuticals). Six weeks later he had dry skin with severe itching which was diagnosed as atopic dermatitis and treatment was started with aqueous cream, hydrocortisone cream and antihistamine. After two days he developed erythroderma and scales and was given decadron 0.5 mg/day for one week.

Four months later his condition deteriorated with an extensive itchy generalized excoriated erythematosquamous rash and failure to thrive. Juvenile psoriasis was diagnosed in addition to atopic dermatitis. A skin biopsy showed spongiotic dermatitis with psoriasiform epidermal hyperplasia. He was given a week of treatment with decadron 0.5 mg/day but his rash recurred frequently and his mother commented that the lesions cleared irrespective of treatment being given or withheld.

Three biopsies taken at different stages all showed psoriasiform and dermatitic tissue reactions.

Immunoglobulin assays repeatedly showed very high levels of IgE (2235 mg/dl) and normal levels of IgG, IgA and IgM. White cell counts showed a leukocytosis with neutropenia, relative lymphocytosis and a high eosinophilia (15.7%). Blood biochemistry, including serum electrolytes, was normal. The CD4-CD8 ratio was low (0.6; normal range 1.0-1.6). Complements C3 and C4 were normal. Urine was negative for aminoacids. Abdominal ultrasound, chest x-ray and skeletal survey all gave normal results.

A year later his condition, which had been assumed to be juvenile psoriasis, did not respond to treatment with cyclosporin A for one month. Another skin biopsy was taken and his

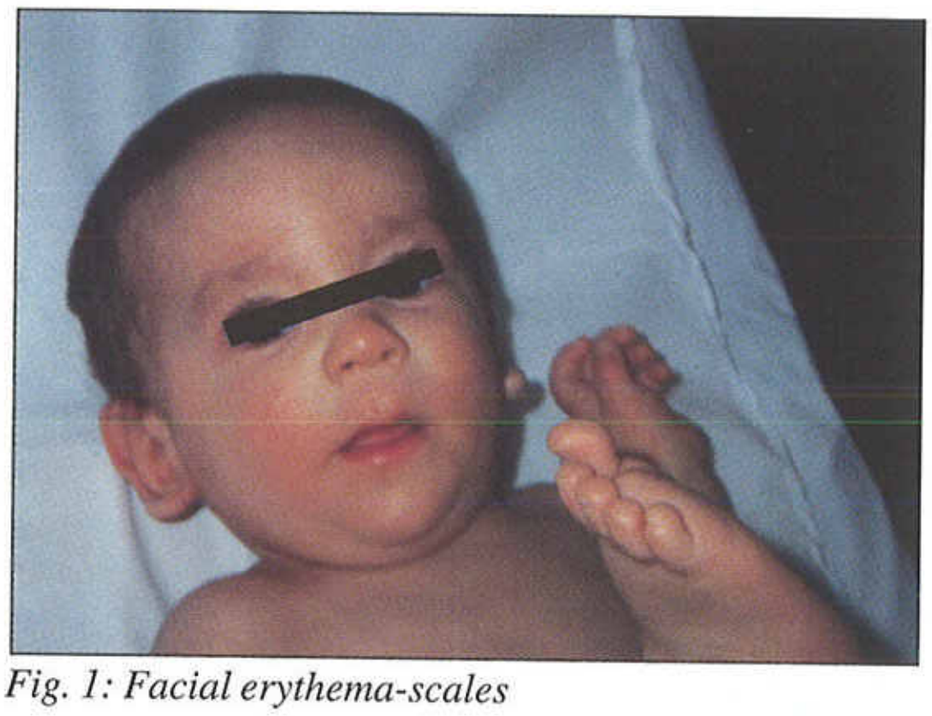

Fig. 1: Facial erythema-scales

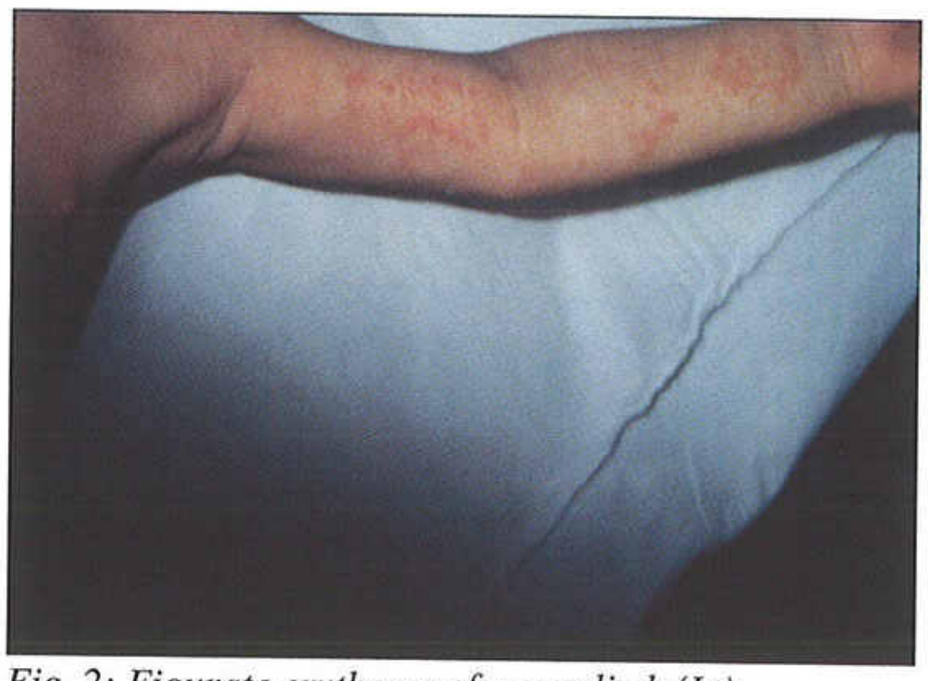

Fig. 2: Figurate erythema of upper limb (Lt)

Correspondence:
P.O. Box 3050, Doha - Qatar
M. M. Selim - Department of Dermatology

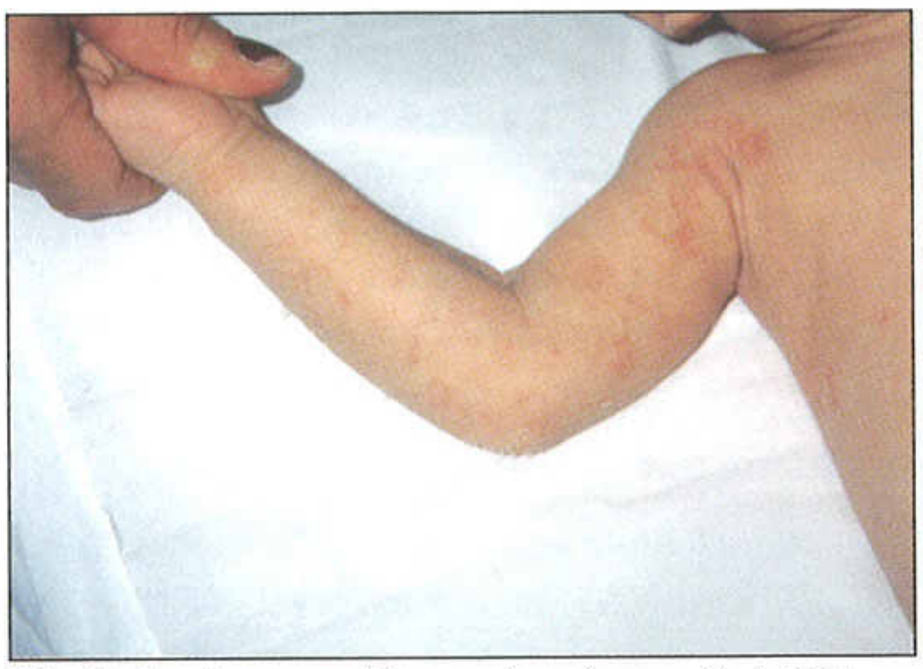

Fig. 3: Erythema and fine scales of upper limb (Rt)

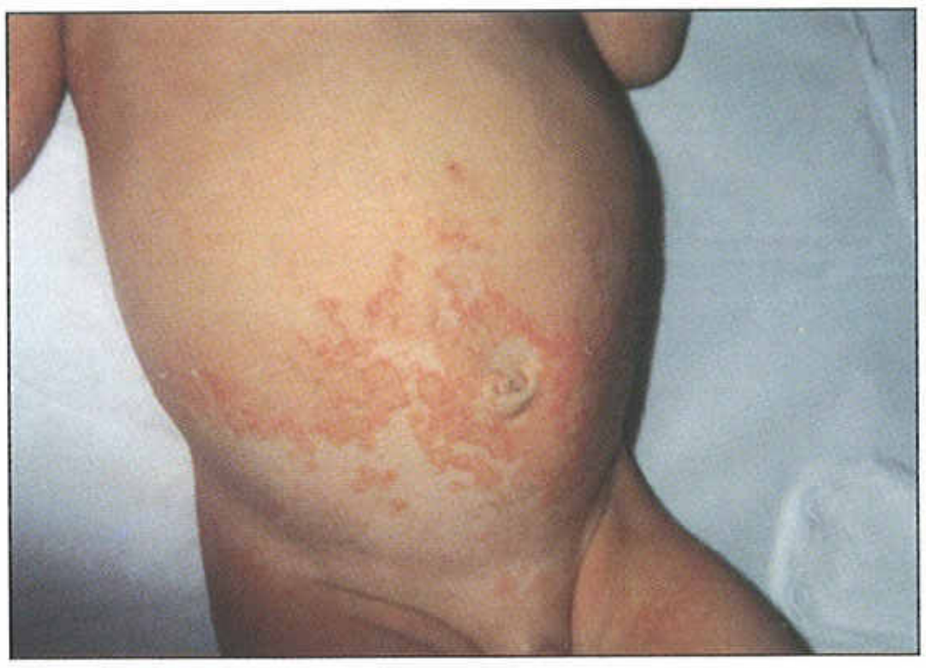

Fig. 4: Figurate erythema of abdomen

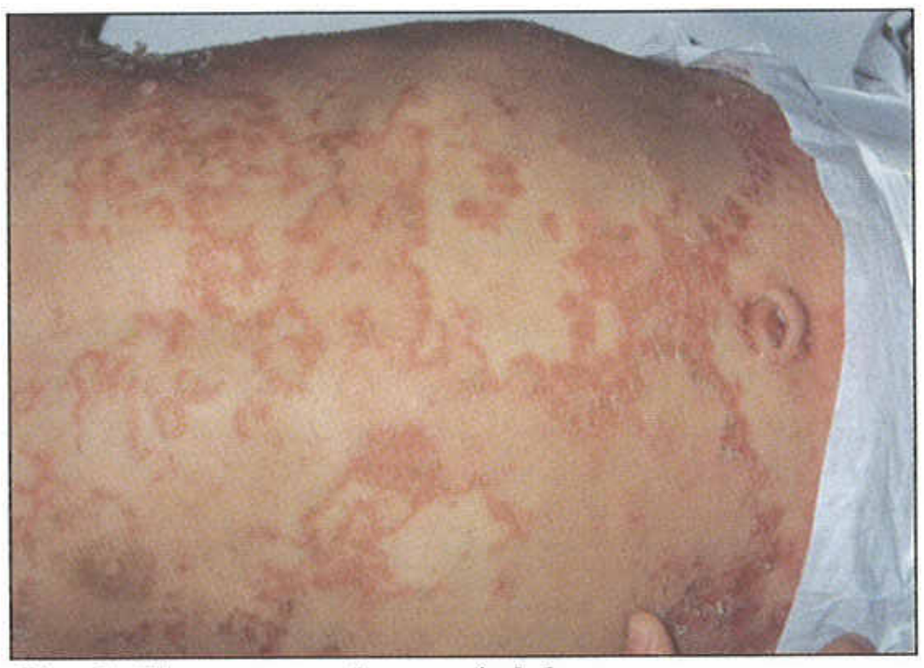

Fig. 5: Figurate erythema of abdomen

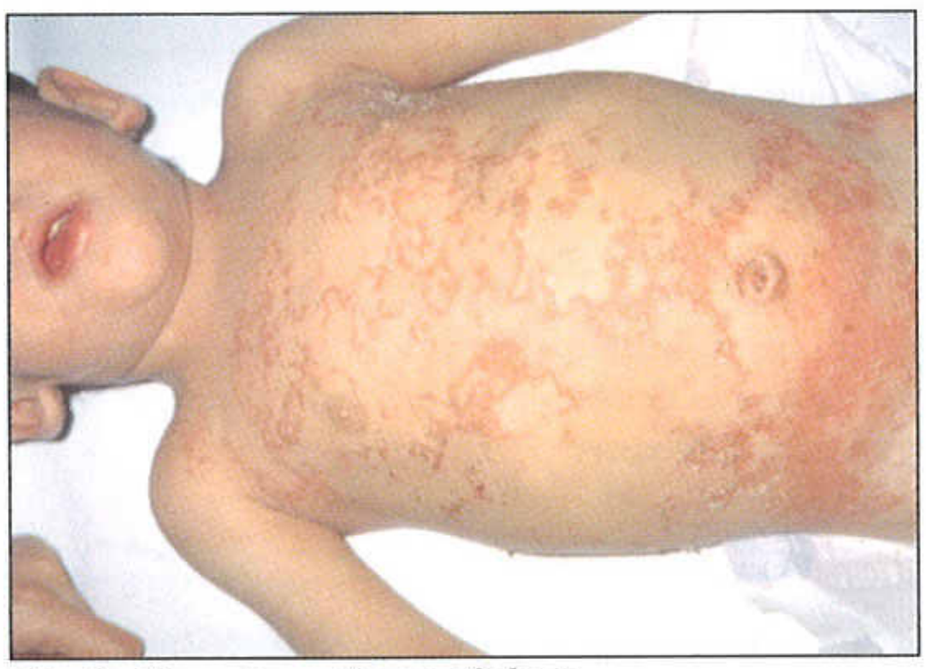

Fig. 6: Figurate erythema of chest

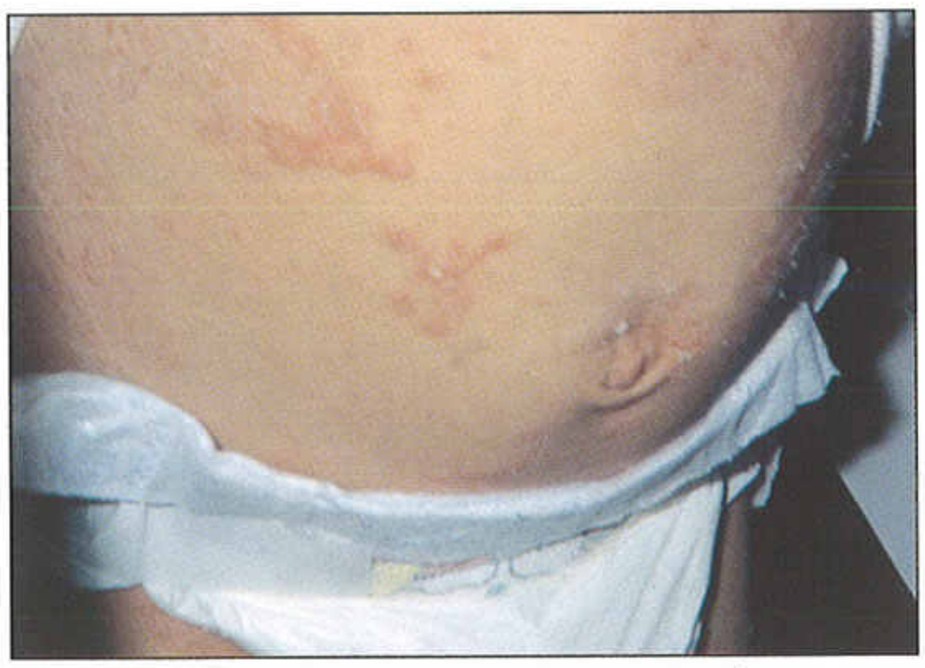

Fig. 7: Small erythematous patchs, psoriasiform

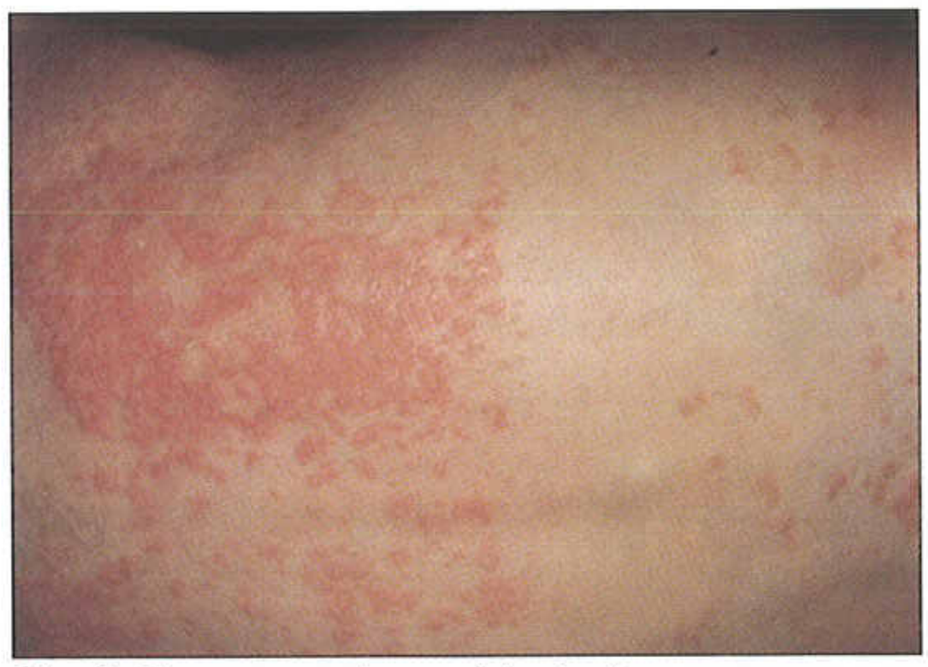

Fig. 8: Figurate erythema of the back

condition was reviewed. This time a diagnosis of Comel-Netherton was made based upon the neonatal onset of erythema, psoriasiform migratory polycyclic scaly erythema (Figs.1-9), an association with atopic manifestations (itching and raised IgE), hair shaft anomalies (Figs.10-19) and the histopathological findings of Biopsy No.1 (performed in 1997) showed a psoriasiform tissue reaction (Fig.20-21) which is considered to be consistent with juvenille psoriasis or seborrhoeic dermatitis. Biopsy No.2 (performed in early 1998) showed a sub-acute dermatitic reaction (Fig.22 & 23) consistent with seborrhoeic dermatitis. Biopsy No.3 (performed in late 1998) showed histological changes (Fig.24 & 25) of a chronic psoriasiform reaction probably chronic seborrhoeic dermatitis or chronic psoriasis.

Patient responded to Acetretin (Neotigason-La Roche) given by mouth in the low dose of 0.3 mg per kg per day together with topical emolients mainly aquous cream and vaseline gel (Fig-26, 27). After 3 months child was put on interrupted courses

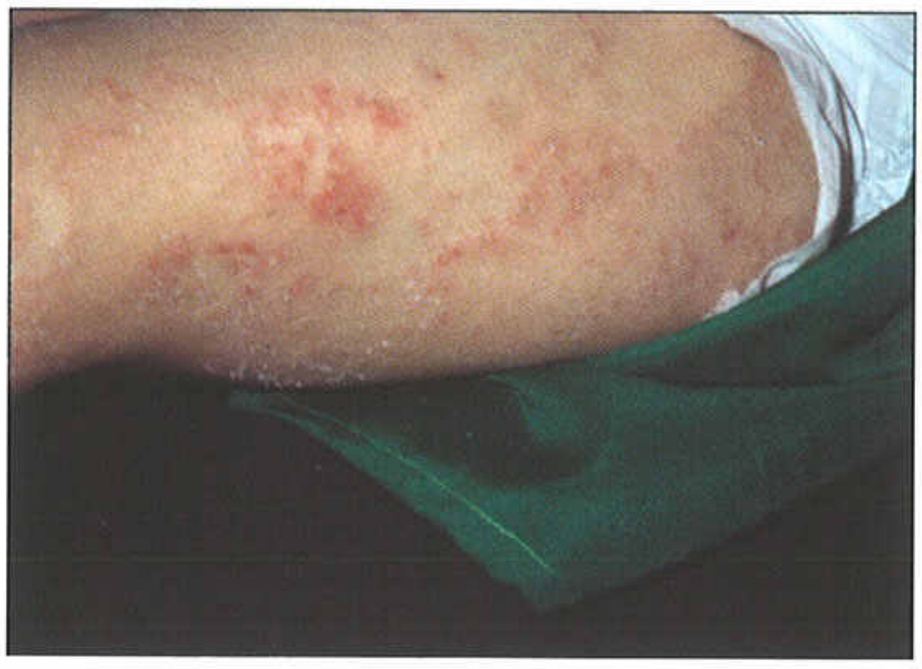

Fig. 9: Figurate erythema of the thighs

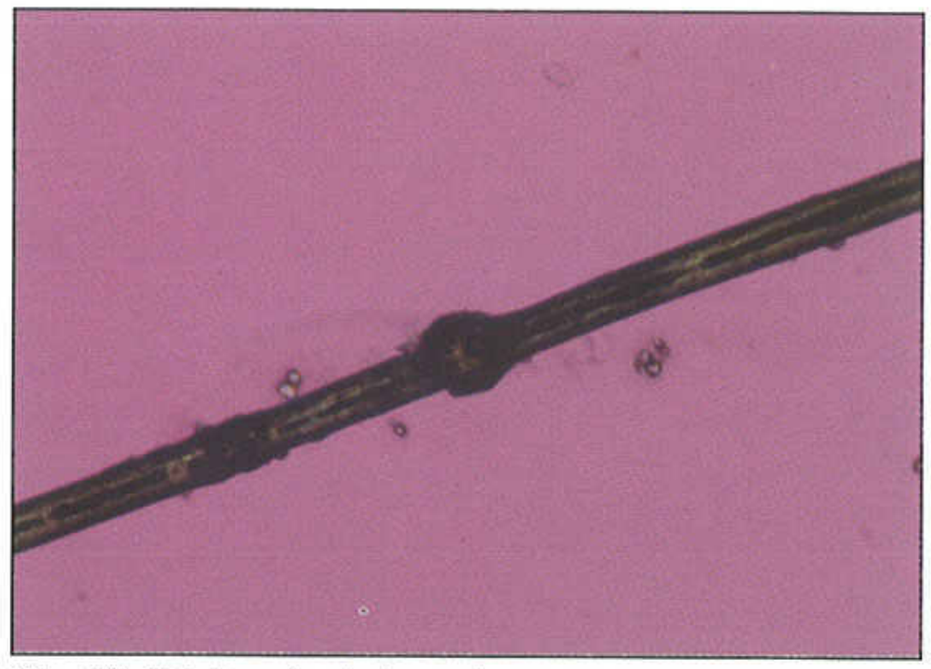

Fig. 10: Trichorrhexis invaginata

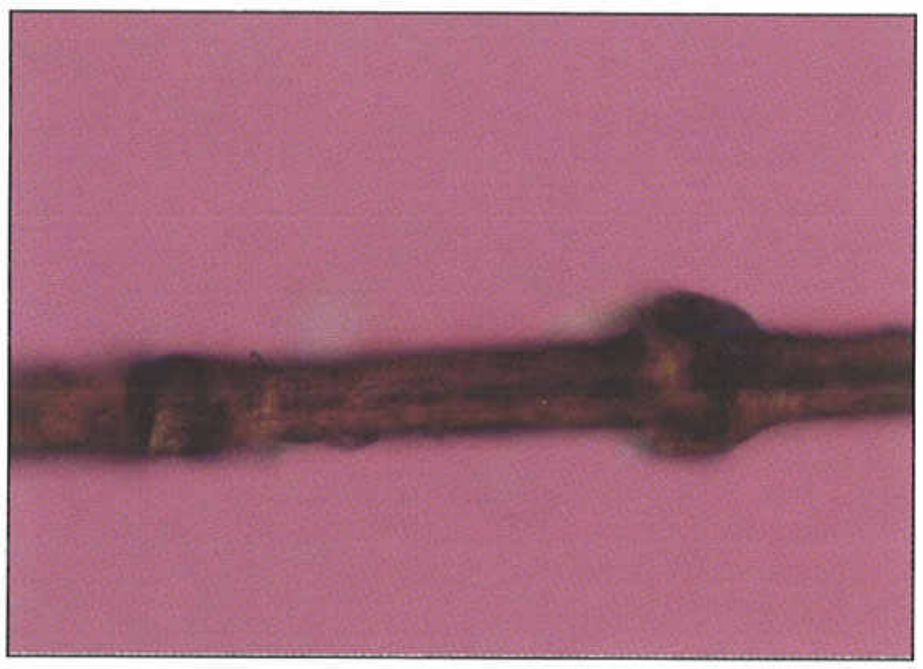

Fig. 11: Trichorrhexis invaginata

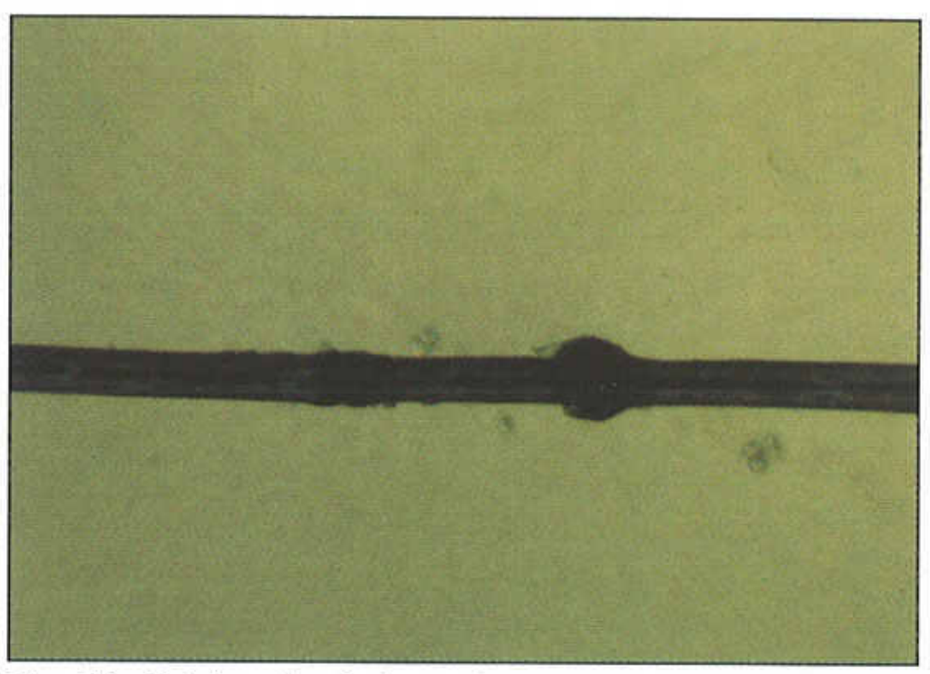

Fig. 12: Trichorrhexis invaginata

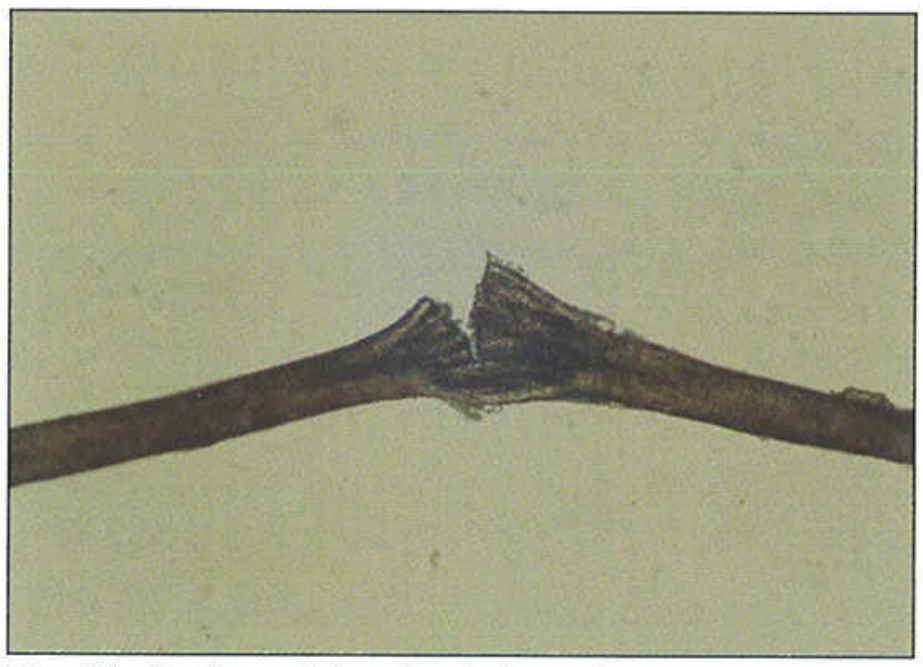

Fig. 13: Broken trichorrhexis invaginata

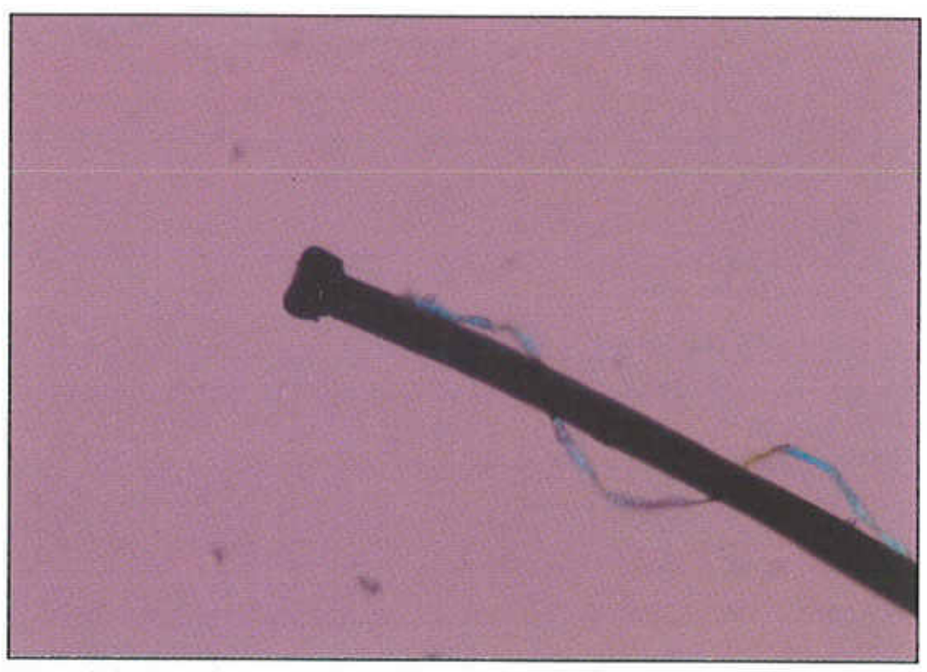

Fig. 14: Broken trichorrhexis invaginata

for over 1.5 year without any side effect. The mother was advised to use acetretin one week per month. Condition is well controlled without any recurrence and the child is regularly investigated for known side effects.

Discussion:

Icthyosis linearis circumflexa is a rare autosomal recessive genodermatoses [5] first described by Comel [6]. The disease is characterized by migrating polycyclic erythema with scales on both edges of the figurate erythema. The lesions occur on the trunk and proximal extremities, spread rapidly peripherally and vary in size, shape and location from day to day. The condition appears at or soon after birth, runs a chronic course and many patients show signs of atopy and bamboo hairs [7]. It can take a considerable time to establish a diagnosis [8].

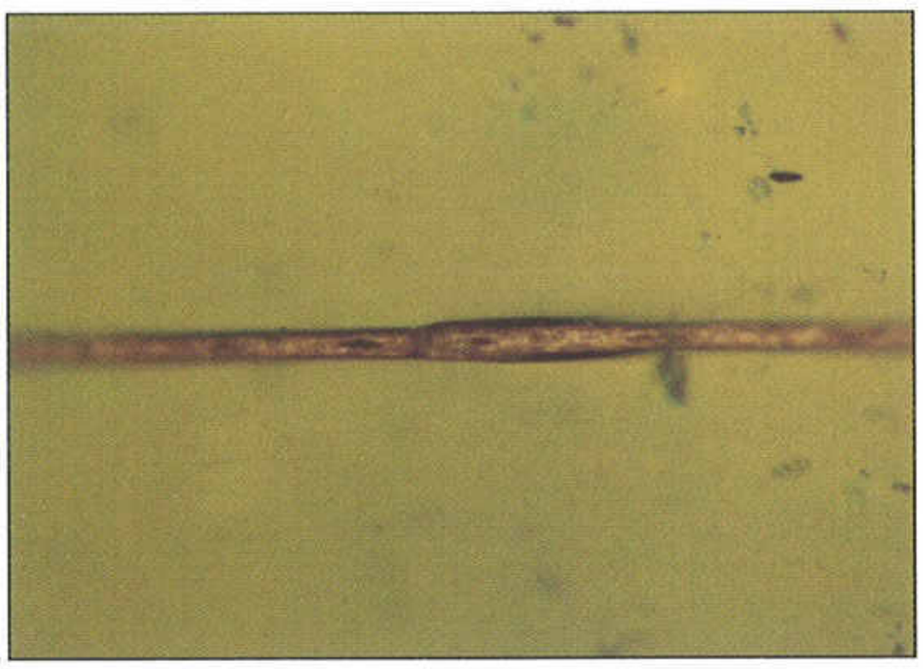

Fig. 15: Trichorrhexis nodosa

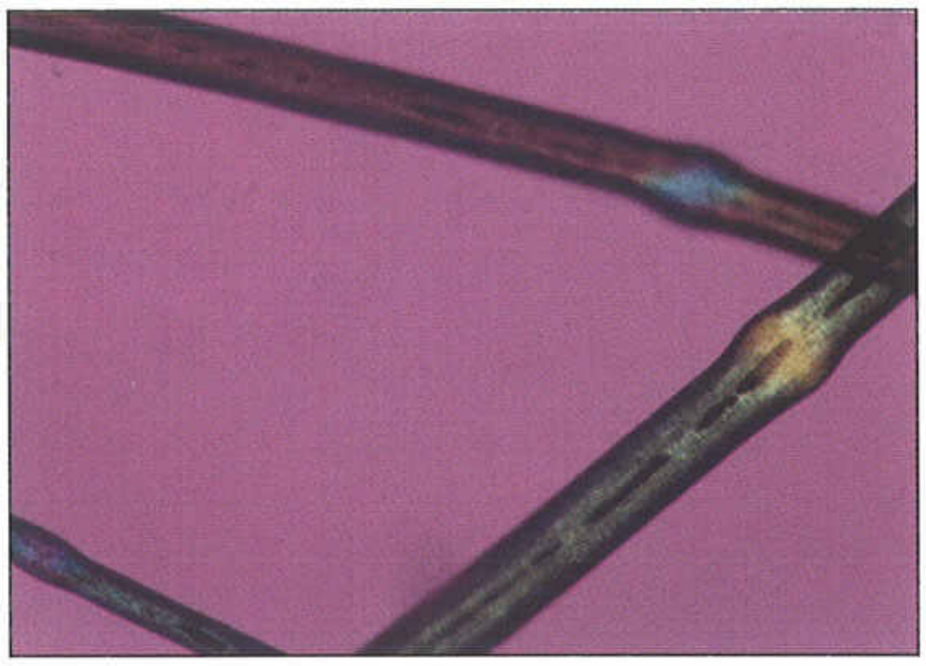

Fig. 16: Trichorrhexis nodosa

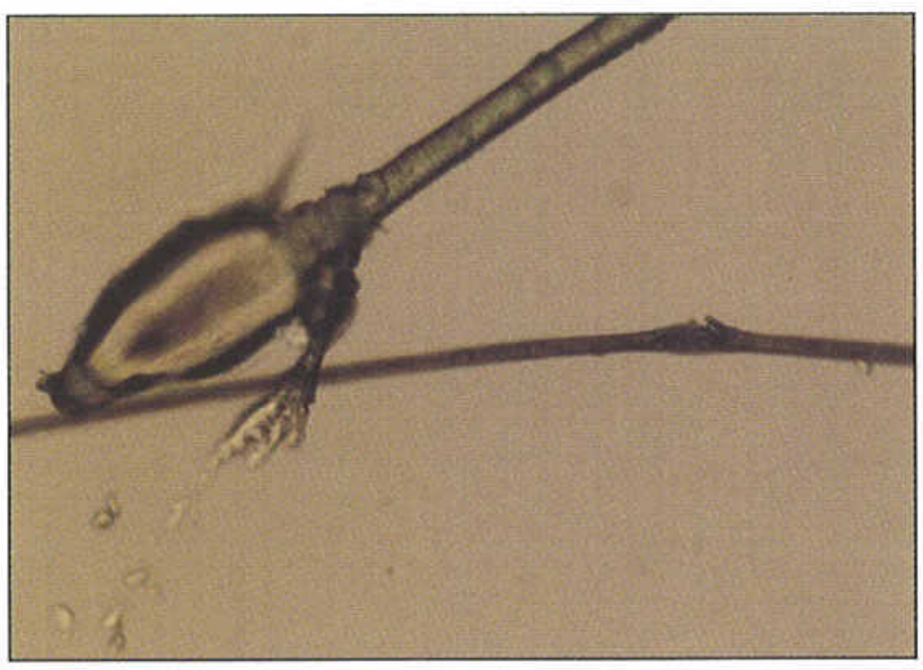

Fig. 17: Broken trichorrhexis nodosa

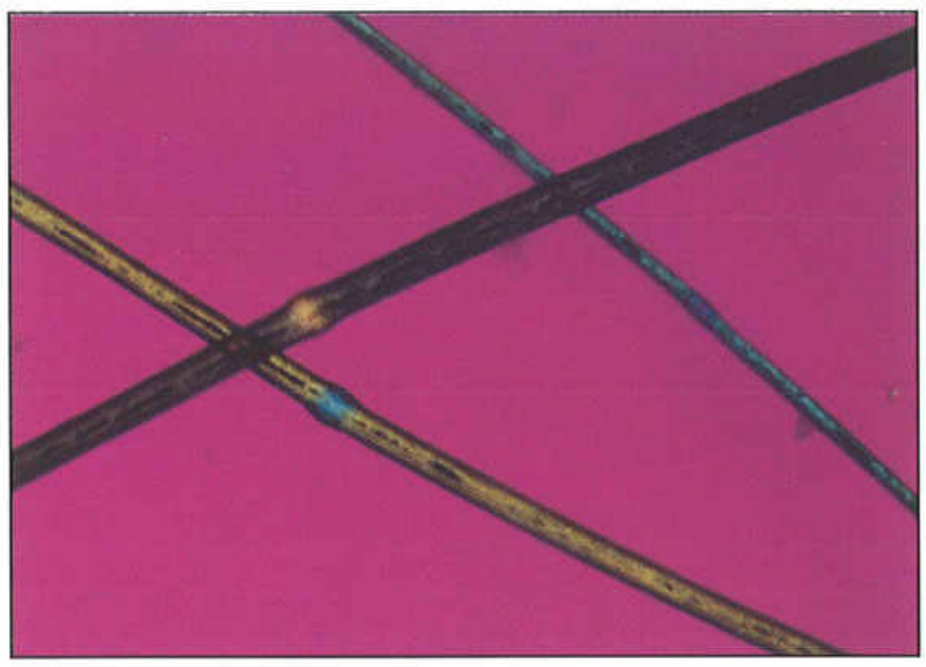

Fig. 18: Trichorrhexis invaginata and nodosa

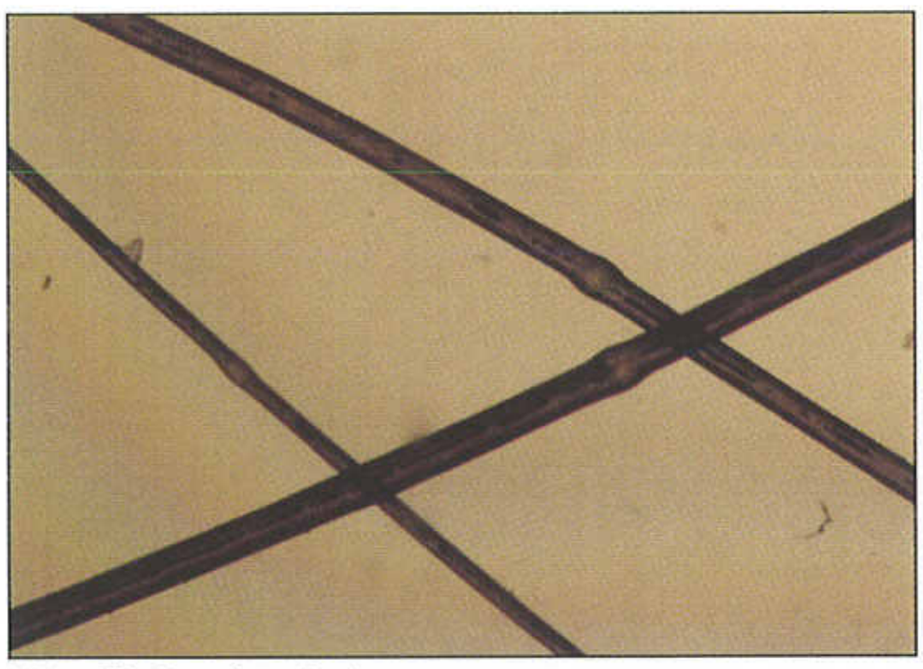

Fig. 19: Bamboo hairs

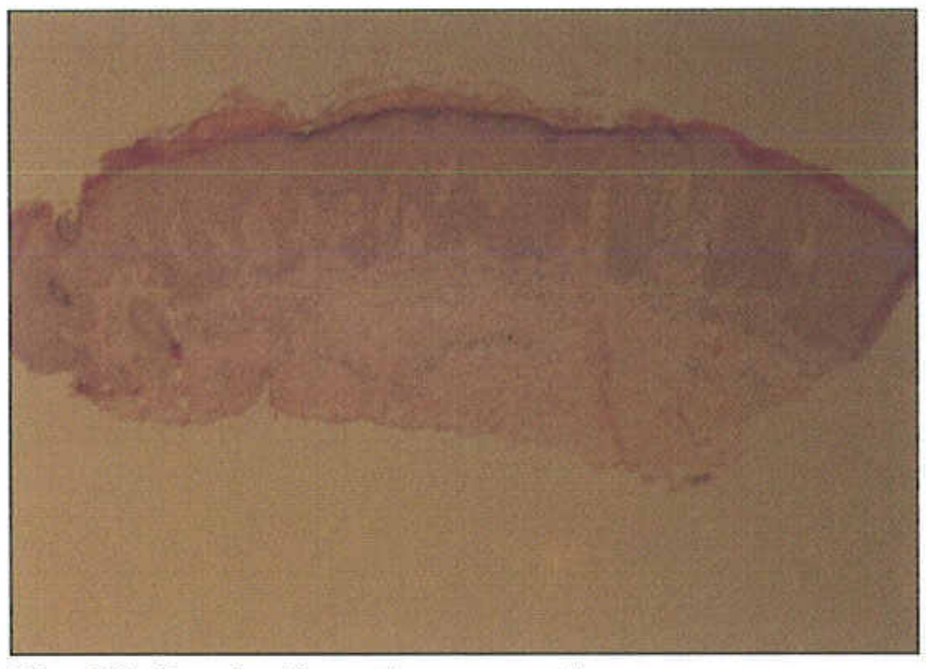

Fig. 20: Psoriasiform tissue reaction

Patients have high levels of IgE [9] and there may be hypernatremia, recurrent infection and failure to thrive [10]. Netherton syndrome should be suspected in infants showing generalized exfoliative, seborrhoeic or psoriasiform erythroderma [10].

Ultrastructurally the stratum corneum appears less cohesive and displays less desmosomes and individual corneocytes show numerous intracellular lipid droplets and nuclear remnants[11].

The disease is characterized by a specific keratinization disorder where synthesis of keratinization proteins is suppressed with disturbance of cutaneous permiability barrier.The normal skin barrier is provided by secretion of lamellar body contents which organize to form organized arays of hydrophobic membranes structures [11]. In NS there is marked abnormality

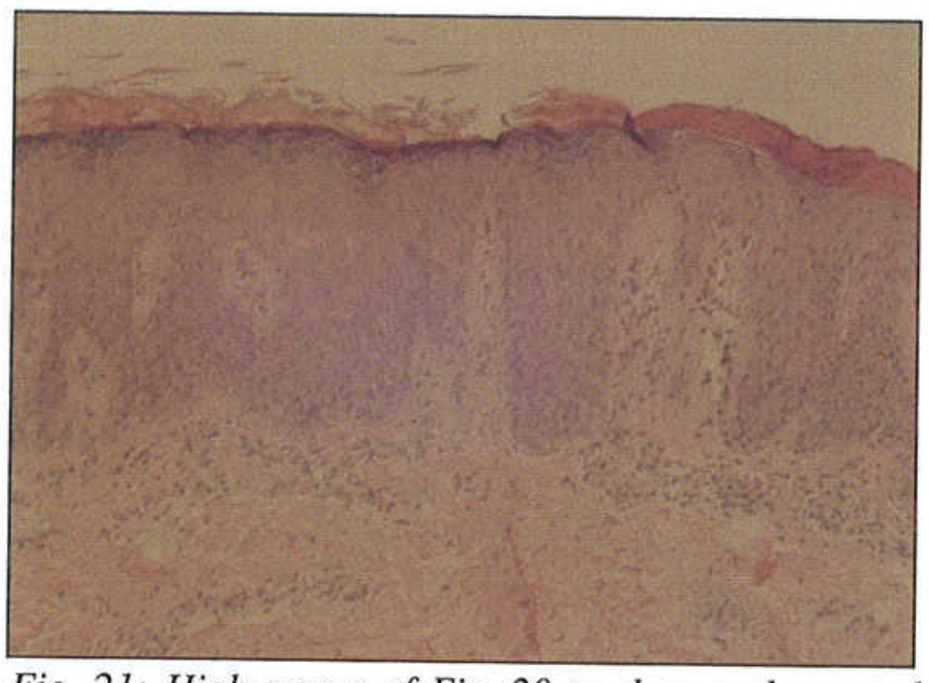

Fig. 21: High power of Fig. 20 to show oedema and inflammatory seen in upper dermis

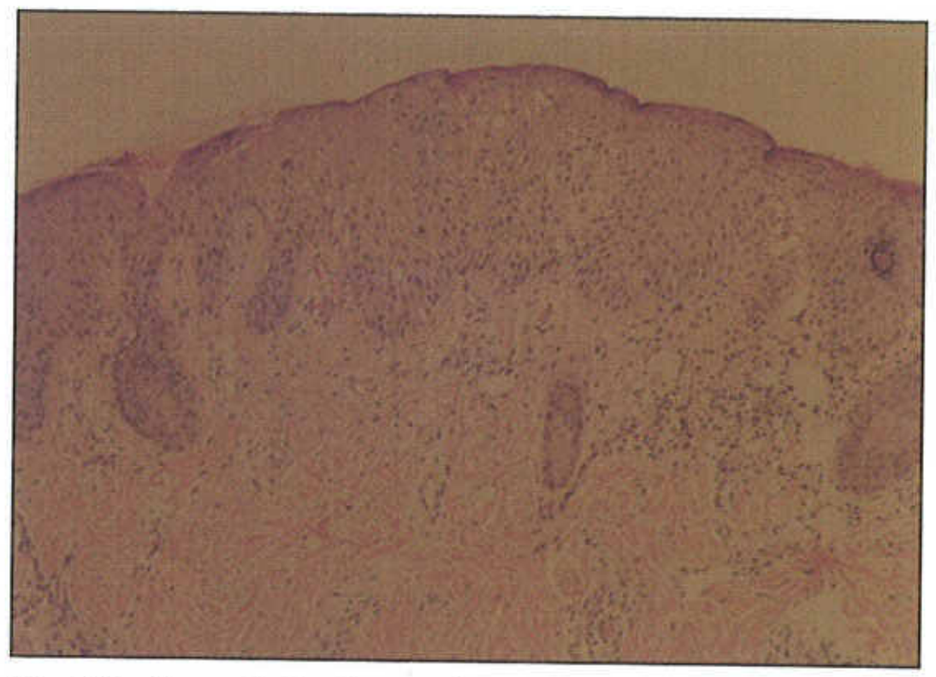

Fig. 22: Spongiotic dermatites

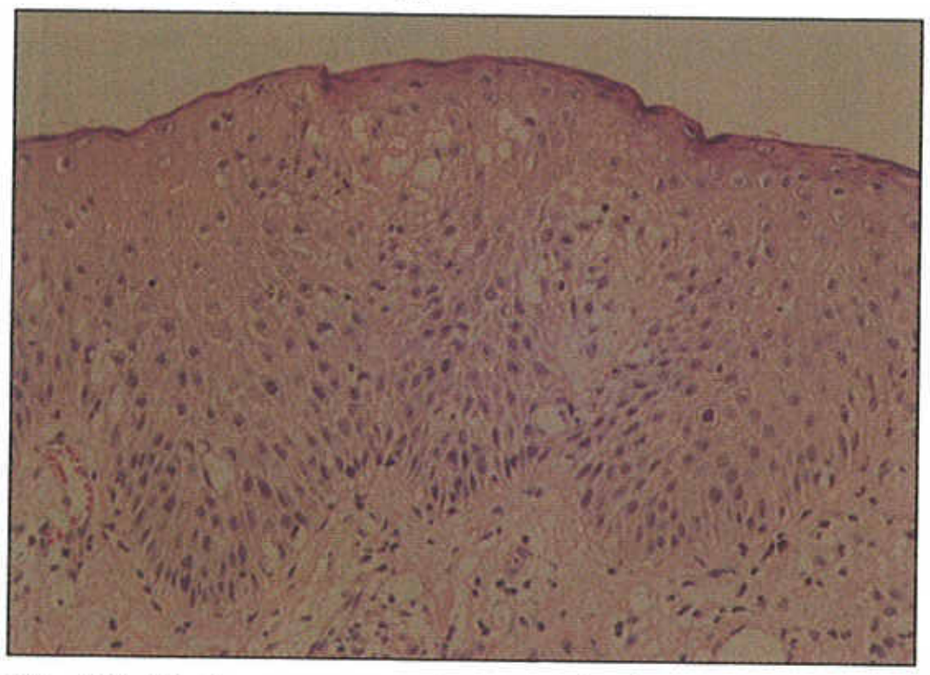

Fig. 23: Higher power to show psoriasis, exocipores and upper dermal inflammation

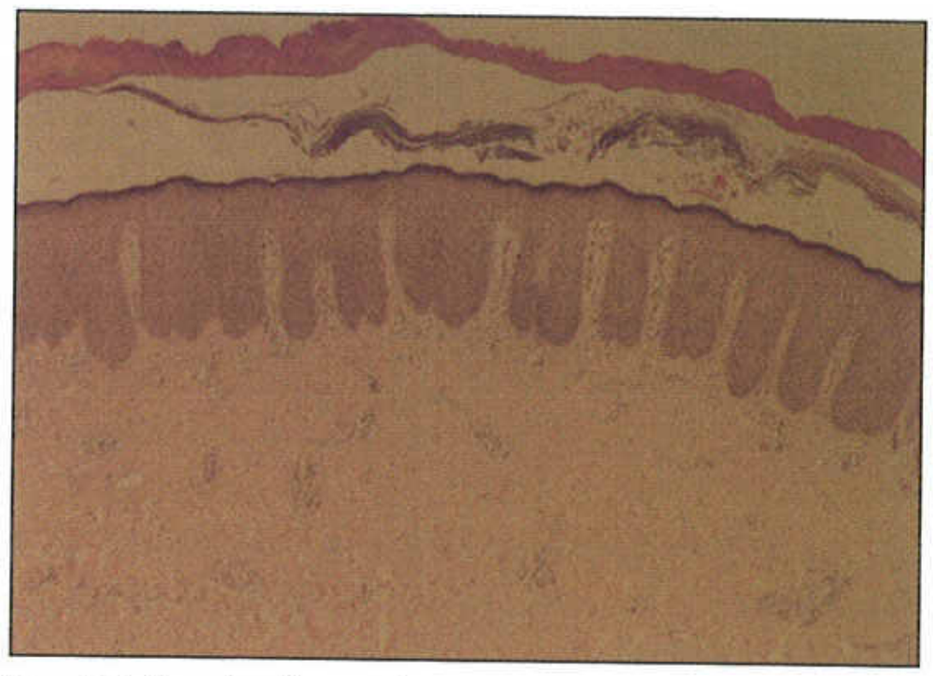

Fig. 24: Psoriasiform tissue reaction

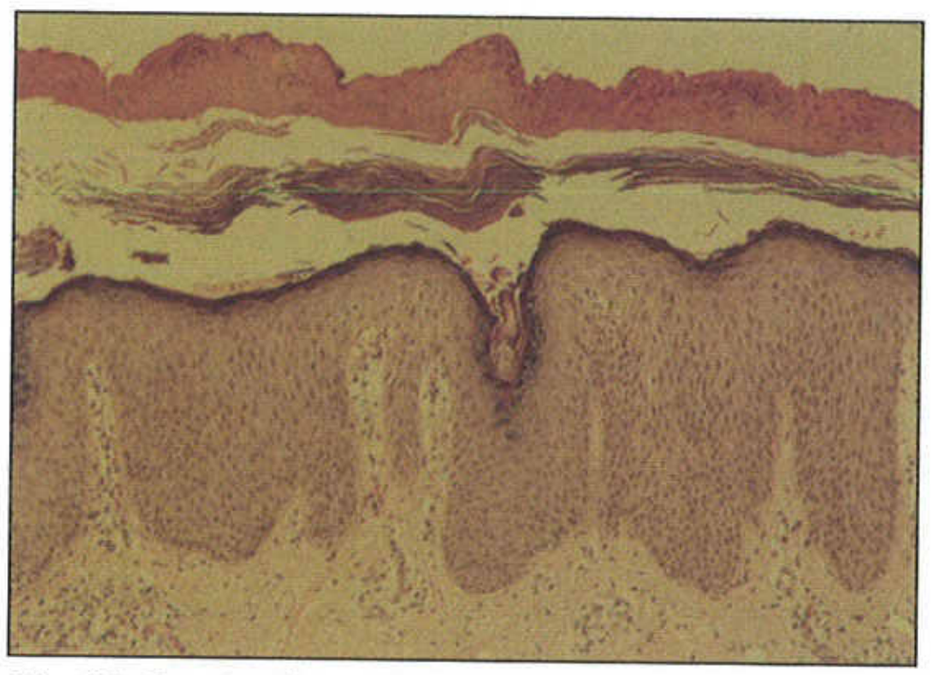

Fig. 25: Psoriasiform tissue reaction with parakeratosis

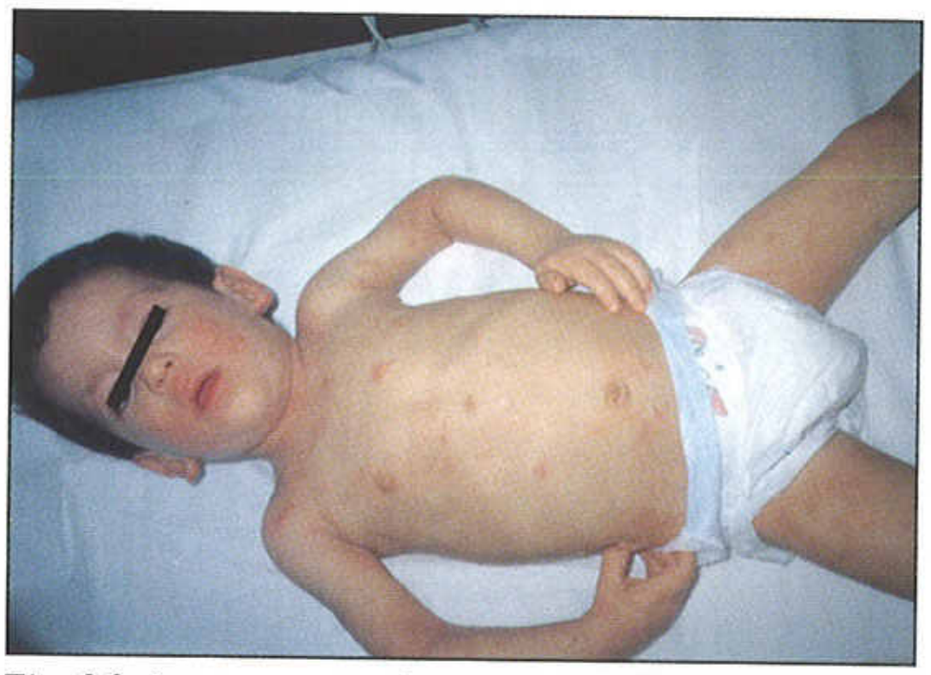

Fig. 26: Improvement after acitretin - face and front of trunk.

of lamellar body, secretion, architecture and reorganization that likely signify a severe disturbance in permeability function. The epidermis is invaded by exudating serum which fills the intercellular spaces of the upper spinous and granular layers or the exudate becomes partly included intracellularly [12].

Premature lamellar body secretion and foci of electron-dense material in the intercellular spaces of the stratum corneum appear frequently and this could explain the impaired permeability barrier in Netherton syndrome and account for the hypernatremia and dehydration in affected infants' [11].

The diagnosis of NS is made possible only by finding trichorrhexis invaginata (bamboo hair) [2, 13]. In the present case the hair of the eyebrows showed classical trichorrhexis invaginata and nodosa. Some patients show persistently

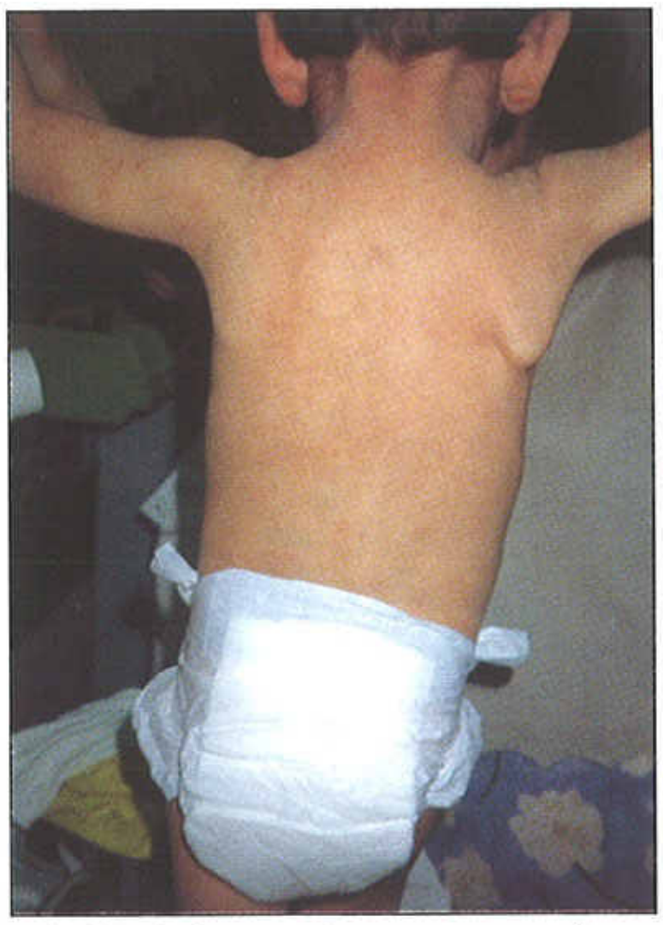

Fig. 26: The back showing improvement after acitretin.

recurrent icthyosiform erythroderma [2]. Our case showed icthyosiform erythroderma before developing the classical icthyosis linear circumflexa. NS should be considered amongst other disorders with elevated IgE [14] and since it shows greatly elevated IgE and atopic manifestation, as in the present case, it can be confused with atopic dermatitis although it does not respond to topical steroids.

It has been suggested also that NS is part of the group of immunodeficiency syndromes with atopic diatheses and may show reduced cellular immunity and develop widespread viral warts [15]. Our patient had a low T4-T8 ratio (0.6). Immunological studies of NS showed an absence of consistent immunological abnormalities [2]. Although quantitative serum immunoglobulin levels are generally normal it has been reported that some patients had selective antibody deficiency to bacterial polysaccharide antigen or to protein antigens. Consequently it is important to evaluate functional antibody response and not to rely upon immunoglobulin subclass determination [16].

In N.S. proliferation of epidermal cells increases, keratin 6 is enhanced and keratin 10 reduced [17]. The epidermal barrier function is impaired resulting in loss of water, electrolytes and protein by fluid exudation causing metabolic problems and recurrent infection [10] which may result in death of the patient from hypernatremia, infection and failure to thrive. In severe cases, where the fluid balance is further disturbed by additional fluid loss due to diarrhea, complications such as renal vein thrombosis and kidney failure may arise [18].

Some systemic conditions have been reported occurring sporadically in NS such as mental retardation [5], cystinurea [19], increased risk of secondary hyper-parathyroidism [20] and epileptogenous encephalopathy [21].

The histopathology of NS is described as psoriasiform [3]. There is pronounced dermal perivascular and interstitial infiltration and exocytosis of lymphocytes, macrophages and neutrophils [10]. The horny and the granular layers are replaced by parakeratotic cells [22]. There is suppression of synthesis of keratinization proteins [23]. Thus terminal differentiation is suppressed with a thin or, in part, completely absent stratum corneum, a decrease in keratin filaments and a decrease or lack of keratohyalin granules and of keratinosomes containing stacks of lipid membranes [10]. As a result the formation and discharge of epidermal barrier lipids from the keratinosomes that normally provide intercellular lamellar sheets at the granular-horny layer interface is highly disturbed leading to a loss of water, electrolytes and proteins by fluid exudation [10]. There is four fold increase in the rate of transepidermal water loss than nomal. This exudate invades the epidermis either filling the intercellular spaces of the upper spinous and the granular layer as finely granular amorphous material or is partly phagocytosed and lies within intracellular round-oval inclusions [23, 24].

Treatment of N.S.:

In meticulous surveillance of the fluid balance is important and aggressive treatment is indicated in cases of additional fluid loss [18].

Oral therapy with acitretin has been successful [8] with low doses of 0.5 mg/kg/day dramatically reducing the deposition of extra- and intra-cellular material and normalizing keratinization [24] but, as inherited keratinization disorders require long term treatment, the side effects of retinoids have to be carefully weighed against the benefits. Intermittent therapy should be used whenever possible [25]. The present case responded well to low daily dose of a acitretin (Neotigason Hoffman-La Roche) for three months and thereafter has been maintained on one week acitretin per month and was followed up for 15 months without recurrence or side effects and shifting to phototherapy is considered after discontinuing acitretin.

A low dose of systemic cyclophosphamide has been used effectively in the control of NS, reducing the affected skin from 80% or 90% to 15% of the body surface. The beneficial effect is possibly due to an effect on the lymphocyte sub-population in the dermis [26].

NS has been treated successfully also with PUVA [5]. The photo-chemotherapy is recommended to treat NS because it has been observed clinically that ILC lesions do not appear on sun exposed areas and the slight improvement of ILC in summer. The psoriasiform appearance of ILC is one of the basis on which PUVA is recommended to treat ILC because of the well known

beneficial effect in psoriasis. Although the mechanism by which PUVA improves ILC is not clear, it does reduce the erythemato-squamous lesions and the patients obtain long term remission.

N.S. is reported to respond also to local treatment with 12% ammonium lactate lotion [14]. Topical steroids and keratolytic agents are effective to a certain degree to improve lesions of ILC. Tacrolimus ointment 0.1% applied to the whole body was reported to induce significant improvement in ILC with no adverse effects [26].

Conclusion:

Comel-Netherton syndrome should be suspected in infants who show generalized exfoliative erythroderma, seborrhoeic or psoriasiform erythroderma. As concluded by Fartasch et al [12], the ultrastructural features of NS which show premature lamellar body secretion and foci of electron dense material in the intercellular spaces of the stratum corneum are specific markers of NS. These could permit early diagnosis of NS before the appearance of the hair shaft abnormalities, the trichorrhexis invaginata and trichorrhexis nodosa which are also diagnostic.

REFERENCES:

1- *De-Felipe I; Vazquez-Doval-FJ; Vincente-J: Comel Netherton Syndrome - A diagnostic challenge [letter]. Br.J. Dermatol 1997; 137(3): 468-9.*

2 - *Judge-MR, Morgan-G, Harper-JI: A clinical and immunological study of Netherton's Syndrome (see comments). Br.J. Dermatol 1994; 131: 615-21.*

3- *Shwayder-T, Banerjee-S: Netherton Syndrome presently as congenital psoriasis. Paediatr-Dermatol 1997; 14(6): 473-6.*

4- *Greene-SL; Muller-SA: Netherton's syndrome. J. Am Acad. Dermatol 1985; 13:329-37.*

5- *Manab M; Yoshiike - T; Negi M: Successful therapy of icthyosis linearis circumflexa with PUVA. Journal of American Acad. Dermatology 1983: 8(6): 905-6.*

6- *Comel-M: Icthyosis linearis circumflexa, Dermatologica 1949; 93: 133-36*

7- *Netherton EM: A unique case of trichorrhexis nodosa "bamboo hairs" Arch-Dermatol. 1958; 78: 483-87*

8- *Blaschke-S; Moller-R, Hausser-I et al Comel-Netherton syndrome Hautarzt 1998; 49 (6): 499-504.*

9- *Smith-DI; Smith-JG; Wong-SW et al: Netherton's syndrome : a syndrome of elevated IgE and characteristic skin and hair findings. Journal of Allergy-Clin. Immunol. 1995; 95 (1Pt 1): 116-23.*

10- *Hausser-I; Anton-Lamprescht-I; Severe congenital generalized exfoliative erythroderma in newborns and infants: a possible sign of Netherton syndrome. Pediatric Dermatol 1996; 13(3): 183-99.*

11- *Fartasch-M; Williams-ML and Elias-PM: altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome - Differentiation from other infantile erythrodermas and pathogenic implications. Arch. Dermatol. 1999; 135:823-832.*

12- *Hausser-I; Anton-Lamprecht-I; Harlscuch-W et al Nethertons syndrome: ultrastructure of the active lesions. Arch. Dermatol-Res. 1989; 281(3): 165-72.*

12- *Thorne-EG; Zelickson-AS; Mottaz-JH et al: Netherton's syndrome: an electron microscopic study. Arch-Dermatol-Res. 1975; Sept 12: 253(2): 177-83.*

13- *Smith-DL; Smith-JG; Wong-SW et al: Netherton's syndrome: a syndrome of elevated IgE and characteristic skin and hair findings. J-Allergy-Clin-Immunol.1995; 95(1pt1): 116-23.*

14- *Hintner-H; Jaschke-E; Fritsch-P: Netherton syndrome: weakened immunity, generalized verrucosis and carcinogenesis. Hautarzt. 1980; 31(8): 428:32.*

15- *Stryk-S; Siegfried-EC; Knulsen-AP: selective antibody deficiency to bacterial polysaccharide antigens in patients with Netherton syndrome. Pediatr. Dermatol. 1999; 16(1): 19-22.*

16- *Lucker-GP; Steijen-PM; Suykerbuyk-EJ; Knagballe-K et al Flow-Cytometric investigations of epidermal cell characteristics in monogenic disorders of keratinization and their modulation by topical calcipotriol treatment. Acta-Derm-Venereol. 1996; 76(2):97-101.*

17- *Pohl-M; Zimmerhackl-LB; Hausser-I et al: Acute bilateral renal vein thromboses complicating Netherton syndrome. Eur-J. Pediatr.1998; 157(2): 157-60.*

18- *Moragon-M; Botella-R; Jimenez-A et al: Netherton syndrome Med-cutan-Ibero-Lat-Am.1986; 14(6): 347-400.*

19- *Milstone-LM; Ellison-AF; Insogna-KL: serum parathyroid hormone level is elevated in some patients with disorders of keratinization [see comments]. Arch.Dermatol,1992; 128(7): 926-30.*

20- *Dupre-A; Bonafe-JL; Carrere-S: Comel's Linear circumflexa icthyosis and Netherton's syndrome. General conception based on study of 4 cases [author's transl.). Ann-Dermatol-Venereol. 1978; 105(1): 49-54.*

21- *Zina-AM; Bundino-S: Icthyosis linearis circumflexa comel and Netherton's syndrome; an ultra structural study. Dermatologica 1979; 158(6): 404-12.*

22- *Hausser-I; Anton-Lamprecht-I; Hartschuh-W et al Netherton's syndrome: ultra structure of the active lesion under retinoid therapy. Arch-Dermatol-Res. 1989; 281(3): 165-72.*

23- *Hartschuh-W; Hausser-I; Petzoldt-D: successful retinoid therapy of Netherton syndrome. Hautarzt 1989; 40(7): 430-3.*

24- *Happle-R; Van-de-Kerkhof-PC; Traupe-H: Retinoids in disorders of keratinization: Their use in adults Dermatologica 1997; 175 Suppl 1: 107-24.*

25- *Klein-E; Hahn-GM; Salmon-JA et al: Explorations of antimitotic agents in the treatment of a congenital disease, icthyosis linearis circumflexa. J. Surg. Oncol. 1979; 11(2): 85-8.*

26- *Suga Y; Tsubai R; Hashimoto Y; et al: A case of icthyosis linearis circomflexa successfully treated with topical tacrolimus. J. Am Acad Dermatol 2000; 42: 520-2.*