ILVEN: Is it Psoriasis? Debate Based on Successful Treatment with Etanercept

Regina Renner[1], Andreas Colsman[2] and Michael Sticherling[2]
[1]Department of Dermatology, Venerology and Allergology, University of Leipzig, Ph.-Rosenthalstraße 23–25, DE-04103 Leipzig, and [2]Clinic of Dermatology, University of Erlangen, Germany. E-mail: Regina.renner@medizin.uni-leipzig.de
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Sir,

Inflammatory linear verrucous epidermal naevus (ILVEN) is an epidermal naevus that resembles linear psoriasis clinically and histologically, and which may respond to classical topical anti-psoriatic treatment (1, 2). Sometimes only the clinical course of the disease, its therapeutic resistance, and strong itching suggests the diagnosis of ILVEN. Therefore, there is controversy as to whether ILVEN is a disease entity distinct from linear psoriasis (3). The treatment options for ILVEN have not been defined. Oral retinoids and new biologicals, such as etanercept, represent promising drugs.

CASE REPORT

In 2005, we first reported a 36-year-old woman (4) who presented with widespread skin lesions that had been present from birth and which had been diagnosed and treated as psoriasis vulgaris. The patient was re-evaluated in our clinic and diagnosed as having systematized ILVEN that covered more than 50% of her skin surface. Oral acitretin was given up to 1 mg/kg bodyweight, which improved the patient's symptoms apart from slight itching and varyiable erythema.

Due to the high dosage of acitretin, slightly elevated liver enzymes and only partial clinical improvement, alternative therapeutic options were discussed. Because of the possible shared aetiopathogenic pathways between ILVEN und psoriasis, infliximab infusions were initiated at a dose of 5 mg/kg bodyweight on weeks 0, 2 and 6, and then every 8 weeks for 6 cycles. The treatment was well tolerated, but no significant clinical effects were seen.

After 7 months, therapy was switched to etanercept, commencing at 25 mg twice a week for 4 weeks, and subsequently 2×50 mg/week for 3 months, which resulted in a significant reduction in skin lesions, and finally 2×25 mg/week until the present time to stabilize the effect. After only 6 injections (2×25 mg/week for 3 weeks), the patient described a significant reduction in her itch, but unsatisfactory improvement of skin lesions. We therefore increased the dosage to 2×50 mg/week. After another 4 weeks, erythema and scaling were significantly reduced. The acitretin dosage could be reduced gradually to the current 40 mg/day without exacerbation of the skin lesions. The treatment remains well tolerated. The patient's skin lesions improved significantly compared with the at the beginning initiated monotherapy with retinoid, particularly the very distracting symptoms for the patient of itching and erythema.

DISCUSSION

The pathogenesis of ILVEN is unknown. It is regarded as a genetic dyskeratotic disease reflecting genetic mosaicism (5). Because of its clinical and histological similarity to linear psoriasis, shared pathogenic traits such as the central involvement of T cells (6) may be hypothesized. Some authors have suggested that these similar pathways are probably mediated by interleukins 1 and 6 or tumour necrosis factor α (TNF-α) (7, 8).

Recent data and discussion focus on the correlation of ILVEN with epidermal naevus and/or psoriasis. The latter aspect was addressed by Vissers et al. (9), who were able to differentiate ILVEN from psoriasis by quantitative immunohistochemical examination. Various markers were investigated in skin biopsies taken from patients with psoriasis and with ILVEN. In patients with ILVEN the number of Ki-67-positive nuclei tended to be reduced, whereas the number of keratin-10 positive cells and HLA-DR expression was increased compared with psoriasis. In addition, T-cell subsets expressing CD8+, CD45RO+ and CD2+, CD94 and CD161 showed a marked difference between ILVEN and psoriasis.

Regarding the relations of ILVEN to epidermal naevi, Welch et al. (10) concluded from immunohistochemical features that different mechanisms govern the growth dysregulation observed in both entities. Elevated ICAM-1, ELAM-1 and HLA-DR expression in ILVEN suggested an inability to down-regulate the inflammatory infiltrate.

Hofer (5) attempted to integrate these different aspects by defining four different groups of diseases that stress the intimate correlation of ILVEN, linear psoriasis and epidermal naevus:

- ILVEN with or without concomitant psoriasis, which responds only in part to anti-inflammatory/anti-psoriatic treatment;
- ILVEN without concomitant psoriasis;
- linear psoriasis with concomitant psoriasis vulgaris; and
- linear psoriasis without concomitant psoriasis vulgaris.

The last three subtypes respond well to anti-psoriatic treatment. This hypothesis is based on the clinical observation that some ILVEN cases respond to anti-

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psoriatic and anti-inflammatory treatment with only a slight reduction in itching and the inflammation (11). These cases are due to an underlying (verrucous) epidermal naevus. In contrast, cases treated successfully with anti-inflammatory and anti-psoriatic therapy implicate that they have no underlying naevus. According to Hofer (5), these should rather be called inflammatory linear verrucous eruption (ILVE(N)). According to the dichotomy model, ILVE(N) could thus represent a psoriatic manifestation with segmental type 1 mutation, which arises as an early post-zygotic mutation in a healthy embryo or as an epigenic event. ILVE(N) with co-occurrence of psoriasis vulgaris may be interpreted as a type 2 segmental manifestation (5). These are characterized by an additional segmental loss of post-zygotic heterozygosity. Most of these patients present a distinct involvement of the affected dermatomes in addition to diffuse and widespread lesions on the integument. However, it is necessary to bear in mind that these terms are restricted to monogenetic skin disorders with an autosomal dominant inheritance. As psoriasis is a polygenetic disorder, these ideas should only cautiously be transferred. In addition, our case represents a systematized ILVEN, which might partially be sorted to that first ILVEN entity defined by Hofer (5), which has no psoriasis, but partial response to anti-psoriatic treatment (Fig. 1). Thus, our case pinpoints both the similarities and differences of ILVEN and psoriasis.

Whereas in localized ILVEN, topical anti-psoriatic treatment may suffice and surgical excision, CO_2 laser or dermabrasion (12) may represent alternative therapeutic options, none of these are satisfactorily applicable for systematized ILVEN, but systemic therapy seems to be the only debatable option. Among these, oral retinoid therapy is very effective, but side-effects and contraindications limit its clinical use.

	ILVEN +/- pso	ILVEN no pso	Linear pso no pso	Linear pso + pso
Therapeutic response	-	+	+	+
Nevus	+	-	-	-
		ILVE(N)		
Segmental Mutation		type I	type I	type II

Fig. 1. Similarities and differences between ILVEN and psoriasis (pso). ILVEN: Inflammatory linear verrucous epidermal naevus.

Regarding the similarities of ILVEN and psoriasis discussed above, TNF-α-blockers might be a therapeutic alternative (13). TNF-α-blockers are not equally effective in clinical use. Infliximab is a chimeric monoclonal antibody that binds both soluble and receptor-bound TNF-α and is most effective in psoriasis. In contrast, etanercept only binds soluble TNF-α and thus inhibits its interaction with specific receptors. In our case, the chimeric antibody infliximab and the soluble fusion protein etanercept seemed to induce differential clinical responses, which supports the clinical experience seen in psoriasis. In contrast to the oral retinoids, etanercept appeared to be very effective in the treatment of the inflammatory processes, reducing both the erythema and the underlying pruritus of the skin lesions.

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