

Successful Treatment of Therapy-resistant Pruritus in Lichen Amyloidosis with Menthol

Martha Fröhlich¹, Alexander Enk², Thomas L Diepgen¹ and Elke Weisshaar^{1*}

¹Clinical Social Medicine, Occupational and Environmental Dermatology, and ²Department of Dermatology, University Hospital Heidelberg, University Hospital Heidelberg, Thibautstrasse 3, DE-69115 Heidelberg, Germany. *E-mail: elke.Weisshaar@med.uni-heidelberg.de
Accepted June 4, 2009.

Sir,

Lichen amyloidosis, a variant of localized cutaneous amyloidosis, is characterized by discrete, intensely pruritic, hyperkeratotic brown-coloured papules and plaques (1). Genetic and viral factors, as well as chronic friction due to scratching, are possible causes (2–4). Therapeutic management of lichen amyloidosis comprises the use of topical treatments, such as glucocorticosteroids, calcipotriene, hydrocolloid dressings, psoralen plus ultraviolet A (PUVA) photochemotherapy, intralesional glucocorticosteroids, systemic treatments, such as acitretin, cyclophosphamide, and cyclosporine, as well as curettage, cryotherapy, surgical excision, electrodesiccation, dermabrasion and laser therapy. All are characterized by variable and limited response frequently followed by reoccurrence of lichen amyloidosis.

CASE REPORT

A 67-year-old Caucasian woman with a history of lichen amyloidosis on the upper back for more than 26 years presented to the itch clinic of the Department of Dermatology in 2007 because of severe therapy-resistant pruritus within the affected skin area. The lichen amyloidosis had begun in 1982, the size of a hens egg, constantly extending in a triangular area of the upper and lower back up to a size of 30 × 25 cm in 2007.

The patient's history, including that of her family, was free of any dermatological diseases, atopy or allergies. She denied any sun or ultraviolet (UV) exposure before lichen amyloidosis had begun. Her past medical history comprised arterial hypertension, which had started 20 years after onset of lichen amyloidosis. She had been treated with losartan, hydrochlorothiazide and oestradiol/norethisterone acetate since menopause. Systemic amyloidosis, including any systemic disease, had been excluded. In 1993 and 2006, a skin biopsy was taken of the affected skin. Light microscopy revealed orthokeratotic hyperkeratosis with prominent stratum granulosum and elongation of the rete ridges, as well as slight lymphocytic inflammatory infiltrate. Congo red staining could not be seen under polarized light. Staining with methylene blue revealed light blue hyaline-like bodies. In electron microscopy, no changes were observed in the keratinocytes. Globular deposits of fibrillary material were seen at the papillary dermis (amyloid deposits).

Over the past 25 years, the patient had tried various therapies, but none were effective long-term: local PUVA bath therapy, topical glucocorticosteroids, oral antihistamines, dermabrasion (performed in 1995 leading to a temporary reduction in pruritus with reoccurrence 12 months later), various laser therapies in 2003, oral pregabalin and gabapentin in 2004, topical

immunomodulators in 2004 and 2007, various over-the-counter products (moisturizers, urea and herbal-containing topicals). Topical capsaicin cream had not been tolerated due to severe burning sensations. In 2007, she was treated with paroxetine, 10 mg daily for 2 weeks, increasing to 20 mg daily after 2 weeks, but discontinued after a total of 2 months because of ineffectiveness.

In February 2007, dermatological examination revealed a rippled hyperpigmented rectangular plaque including erythematous to brownish lichenified plaques and papules, as well as 2–3 monomorphous shiny light-brown papules alongside with hyper- and hypo-pigmented skin on the upper back sized 30 × 25 cm (Fig. 1). She complained of severe itching (visual analogue score (VAS) 8–9; VAS = 0 (no itch) – 10 (maximum imaginable itch)). Pruritus was reported to be less in summertime and particularly strong at night, which regularly kept her awake. Topical treatment with menthol 2% cream (oil-in-water emulsion) twice daily was started in February 2008. After 3 weeks the pruritus disappeared almost completely (VAS 2) with no sleep disturbance. The appearance of the lichen amyloidosis improved continuously with a decrease in papules, infiltration and pigmentation. The patient has been continuing topical menthol treatment twice daily for one year, in a combination preparation with 10% urea. She still uses antihistamines, such as cetirizine, loratadine and hydroxyzine, intermittently approximately once a week. The patient's lichen amyloidosis has improved significantly (Fig. 2) and she remains almost free of pruritus (VAS 1–3).

DISCUSSION

The origin of lichen amyloidosis is unclear. It is debated whether pruritus and scratching are symptoms or requisite causal factors (2–4). It is evident that lichen amyloidosis corresponds to areas of the body that are prone to rub-



Fig. 1. Clinical photo in February 2007 before start of treatment with topical menthol. The skin shows light-brown scaly 2–3 mm monomorphous papules on hyper- and hypo-pigmented skin on the upper back.



Fig. 2. Upper back of the patient after 9 months of topical treatment with menthol 2%.

bing. This habit was also confirmed in our patient using towels and/or scrubbing brushes. Some consider lichen amyloidosis to be a variant of lichen simplex chronicus, with chronic scratching as the cause, and not the result, of amyloid deposition (2, 4). Lichen amyloidosis has been reported in association with several skin and internal diseases that were all excluded in our patient.

A relationship between macular amyloidosis and notalgia paresthetica has been proposed (3, 4). This is a sensory nerve entrapment syndrome involving the posterior rami of T2–T6 nerve root associated mainly with degenerative changes in the vertebra. Patients typically present with unilateral pruritus of the mid-upper back in the distribution of T2–T6 dermatomes, occasionally accompanied by burning pain, paraesthesia and/or hyperesthesia, which results in a well-circumscribed hyperpigmented patch in the symptomatic area. It has been discussed whether macular amyloidosis and notalgia paresthetica represent three stages of one disease, are overlapping conditions, or are rarely associated (2–4). As notalgia paresthetica leads to itching, rubbing and scratching may secondarily lead to macular amyloidosis. A number of patients with clinical, but without histological, features of macular amyloidosis have been classified with “macular posterior pigmentary incontinence” (4). Our patient had no history of any spine or back disease and refused any radiological examinations. In addition, the clinical picture in this case differed greatly; the skin was affected on both sides of the vertebrae and the typical distribution around the scapula was missing.

Menthol is an old remedy containing major monoterpene in the essential oils of some menthe species (Lamiaceae) e.g. *Mentha piperita*, *Mentha arvensis*. It is a widely used over-the-counter topical for the treatment of, for example, pain. The antipruritic effect of menthol has been described for hydroxyethyl starch-induced (5), histamine-induced (6) and mustard gas-induced

pruritus (7). A 1% menthol preparation had a significant antipruritic effect (6), whereas a 10% solution did not (8). Our patient describes topical menthol therapy as the best therapy she has ever received. The mechanism of antipruritic action in our patient is not clear, but the following aspects may be considered relevant: patients with chronic pruritus sometimes report relief of pruritus by applying cool showers or cool packs. The ability of menthol to chemically trigger the cold-sensitive TRPM8 receptors in the skin is responsible for the well-known cooling sensation that it provokes when inhaled, is eaten or applied to the skin (9). In this sense it is similar to capsaicin (10). Menthol has been shown to disperse through the stratum corneum, disrupt the regular organization of these structures, and increase drug partition and diffusion

parameters (9, 11). The transient increase in transepidermal water loss (TEWL) suggests a possible role as a percutaneous penetration enhancer (8), e.g. for urea used in topical preparations. One study proposed that menthol fulfils the definition of a counter-irritant, but did not show any effects on histamine-induced itch, cold detection or cold pain sensations (8). Menthol has been shown to selectively activate κ -opioid receptors possibly explaining its antipruritic properties (12). A missense mutation in the OSMRE gene, encoding oncostatin M-specific receptor β (OSMR β), a component of the oncostatin M (OSM) type II receptor and the interleukin (IL)-31 receptor was found in three families with familial primary localized cutaneous amyloidosis (13). The expression of IL-31 receptor and OSMR β was detected in afferent fibres in the spinal cord and the dermis of the skin (14). It was speculated that the diminished innervation of epidermis and dermoepidermal junction in lichen amyloidosis with hypersensitivity of the remaining nerve fibres may explain chronic and severe pruritus in lichen amyloidosis (15). A cross-talk between nerve fibres and cytokines might induce pruritus in lichen amyloidosis (13–15).

The authors declare no conflict of interest.

REFERENCES

1. Kibbi AG, Rubeiz NG, Zaynoun ST, Kurban AK. Primary localized cutaneous amyloidosis. *Int J Dermatol* 1992; 31: 95–98.
2. Cerroni L, Kopera D, Soyer HP, Kerl H. Notalgia paresthetica, posterior pigmented pruritic patch and macular amyloidosis. Three stages of the same disease. *Hautarzt* 1993; 44: 777–780.
3. Westermark P, Ridderström E, Vahlquist A. Macular posterior pigmentary incontinence: its relation to macular amy-

- loidosis and nostalgia paresthetica. *Acta Derm Venereol* 1996; 76: 302–304.
4. Bernhard JD. Notalgia paresthetica, macular posterior pigmentary incontinence, macular amyloidosis and pruritus. *Acta Derm Venereol* 1997; 77: 164.
 5. Haught JM, Jukic DM, English JC. Hydroxyethyl starch-induced pruritus relieved by a combination of menthol and camphor. *J Am Acad Dermatol* 2008; 59: 151–153.
 6. Bromm B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neurosci Lett* 1995; 187: 157–160.
 7. Panahi Y, Davoodi SM, Khalili H, Dashti-Khavidaki S, Bigdelli M. Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. *Singapore Med J* 2007; 48: 392–395.
 8. Yosipovitch G, Szolar C, Hui XH, Maibach H. Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. *Arch Dermatol Res* 1996; 288: 245–248.
 9. Patel T, Ishiiji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol* 2007; 57: 873–878.
 10. Anand P. Capsaicin and menthol in the treatment of itch and pain: recently cloned receptors provide the key. *Gut* 2003; 52: 1233–1235.
 11. Obata Y, Hatta I, Ohta N, Kunizawa N, Yagi N, Takayama K. Combined effects of ethanol and L-menthol on hairless rat stratum corneum investigated by synchrotron X-ray diffraction. *J Control Release* 2006; 115: 275–279.
 12. Galeotti N, DiCesare ML, Mazzanti G, Bartolini A, Ghelardini C. Menthol: a natural analgesic compound. *Neurosci Lett* 2002; 322: 145–148.
 13. Arita K, South AP, Hans-Filho G, Sakuma TH, Lai-Cheong J, Clemets S, et al. Oncostatin M receptor-beta mutations underlie familial primary localized cutaneous amyloidosis. *Am J Hum Genet* 2008; 82: 73–80.
 14. Bando T, Morikawa Y, Komori T, Senba E. Complete overlap of interleukin 31 A and oncostatin M receptor beta in the adult dorsal root ganglia with distinct development expression pattern. *Neuroscience* 2006; 141: 1263–1271.
 15. Maddison B, Namazi MR, Samuel LS, Sanchez J, Pichardo R, Stocks J, et al. Unexpected diminished innervation of epidermis and dermoepidermal junction in lichen amyloidosis. *Br J Dermatol* 2008; 159: 403–406.