

Case Report

Taming elephantiasis with acitretin

阿曲汀對象皮病的療效

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We present two patients with elephantiasis nostras verrucosa of the lower limbs which improved with oral acitretin. One patient was young and otherwise well while the other was a diabetic with multiple co-morbidities. The treatment was well tolerated and resulted in flattening of verrucous and hyperkeratotic skin lesions and a reduction in frequency and severity of cellulitic events. There was also an improvement in cosmetic appearance and mobility. Treatment with oral acitretin may improve the quality of life of patients with this chronic dermatosis and should be considered in carefully selected patients.

我們報告兩名疣狀非血絲蟲性象皮病患者的下肢患處，在服用阿曲汀後情況得以改善。他們分別為一名健康良好的年輕人，及一名患有多種疾病的糖尿病患者。病人對此藥物治療耐受性良好，治療不但使其疣狀及角化皮損得以變平，亦令蜂窩性組織炎發生的次數及嚴重性減少。同時間，病人的外觀及活動能力亦得以改善。阿曲汀可改善此等慢性皮膚病患者的生活質素，如有合適的患者，應考慮給予此藥物作為治療。

Keywords: Acitretin, elephantiasis nostras verrucosa, lymphoedema, retinoid

關鍵詞： 阿曲汀，疣狀非血絲蟲性象皮病，淋巴水腫，類維生素 A

Introduction

Elephantiasis nostras verrucosa (ENV) is an uncommon dermatosis characterised by hyperkeratotic and verrucous lesions with

dermal fibrosis. ENV develops after chronic, non-filarial lymphoedema.¹ Currently the clinical management of chronic lymphoedema consists of a multimodality approach including elevation, exercise, compression garments, manual lymphatic drainage, intermittent compression pumps and prevention of infection.²⁻⁴ Unfortunately, such therapy is labour-intensive and time-consuming. Consequently it is often difficult to maintain good compliance and achieve positive outcomes.

In recent years, there have been reports regarding the use of oral retinoids in the treatment of ENV.^{5,6} We present two cases of ENV which responded well to oral acitretin. One case involves an

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otherwise well young man while the other had multiple co-morbidities including diabetes mellitus and peripheral vascular disease. The treatment was well tolerated in both cases without significant side effects.

Case report 1

A 31-year-old, otherwise well man presented with primary lymphoedema tarda of the lower limbs which commenced ten years previously. The protracted lymphoedema resulted in gross ENV, particularly of his left foot. All investigations, including X-ray, computed tomography, venogram and Doppler ultrasound, were normal except for lymphoscintigraphy which revealed significant hyperplasia of lymphatic channels in keeping with primary lymphoedema tarda. Clinically, the most dramatic cutaneous changes were malodorous, verrucous and papillomatous lesions over his feet and toes, with significant plantar hyperkeratosis (Figure 1a).

Despite usual conservative management, such as compression bandages, elevation and lymphatic massage, the patient developed multiple episodes of cellulitis with 15 episodes over the preceding three and a half years. This impacted significantly on his employment and quality of life in general. His toes, particularly on the left foot, were so badly affected and disfigured that they caused constant discomfort and embarrassment. Moreover, because of the bulkiness of the left foot he had to wear shoes of different sizes on each foot. Not so long after, he was unable to find shoes to fit his left foot at all.

After detailed discussions regarding management options and potential side effects, he was commenced on oral acitretin at a dose of 0.3 mg/kg/day. This was well tolerated and the dosage was increased to 0.6 mg/kg/day after 1 month. During his oral retinoid therapy, the patient did not develop cellulitis, nor did he experience any notable side effects. After 12 weeks there was an appreciable cosmetic improvement, with a

reduction in hyperkeratosis, papillomatosis and fissuring (Figure 1b). The bulk of the affected toes was also appreciably reduced. Indeed, the patient was once again able to wear shoes of the same size on both feet! Soon after, a decision was made mutually to cease acitretin therapy partly because he was satisfied with the treatment outcome thus far. Two years later his problem flared with recurrent cellulitis once again. Recommencement of retinoid therapy was considered, but the patient declined and was subsequently lost to follow-up.

Case report 2

A 71-year-old man with primary lymphoedema tarda of the lower limbs for many years presented for review. His medical background included type II diabetes mellitus, ischaemic heart disease, peripheral vascular disease, hypertension and alcoholic liver disease. He had suffered recurrent cellulitis of both legs over many years.

A recalcitrant ulcer on the dorsal aspect of his left foot developed and it was treated with a full-thickness skin graft. Within three years, he developed ENV which was confined to the grafted area only, with sparing of the rest of his left leg. These changes consisted of hyperkeratotic, verrucous and papillomatous lesions which were malodorous and chronically weeping (Figure 2a). He developed several episodes of cellulitis in this leg every year which resulted in hospitalisation and treatment with intravenous antibiotics.

He was commenced on oral acitretin at a relatively low dose of 0.15 mg/kg/day. The dose was increased to 0.3 mg/kg/day after two months. Within three months of therapy, the lesions had markedly flattened. There was an appreciable reduction in the bulk of the affected toes and the foot was no longer weeping and malodorous (Figure 2b). He was treated for eight months in total and during this period, he did not experience any cellulitic episodes or significant side effects. Moreover, his diabetic control was not compromised and his liver function and serum

lipids were unchanged. Acitretin was ceased because of medical problems unrelated to his oral retinoid therapy. He subsequently died of an internal medical crisis.

Discussion

Acitretin has a well-established use in the treatment of various hyperkeratinisation disorders and

epidermal proliferative problems.⁷ Its clinical efficacy in psoriasis and disorders of keratinisation suggests that it leads to a normalisation of differentiation and proliferation of keratinocytes, while its usefulness in the treatment of pustular psoriasis implies a modification of inflammation.⁸

The pathophysiology of ENV involves a vicious cycle of infection and lymphatic damage. Damaged lymphatic vessels lead to impaired

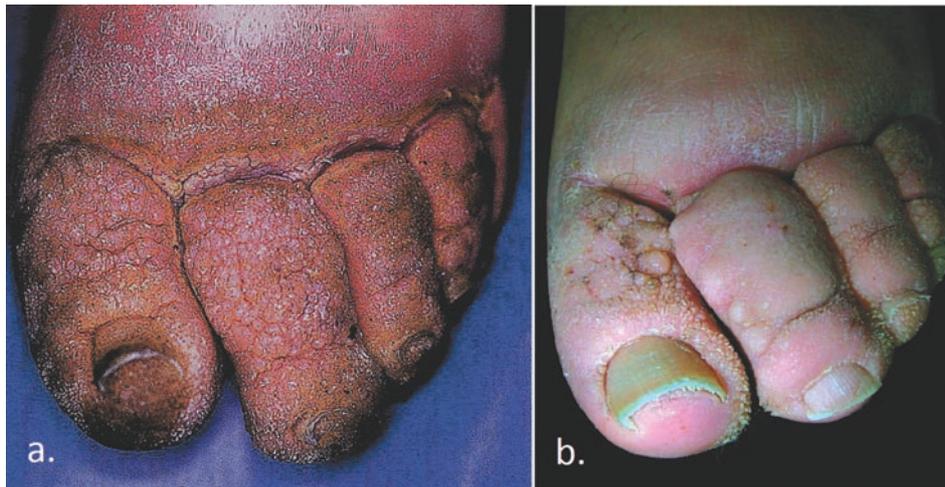


Figure 1. Case 1 (a) ENV of the left foot at baseline with hyperkeratotic and verrucous lesions contributing to increased bulk; (b) after 12 weeks of oral acitretin, skin lesions have flattened significantly and the bulk of the foot has been reduced.



Figure 2. Case 2 (a) ENV of the left foot confined to a previously skin grafted area; (b) after 12 weeks of oral acitretin, there is significant flattening of verrucous and hyperkeratotic skin lesions.

lymphatic drainage and subsequent lymphoedema.⁹ The inability to remove excess plasma proteins causes chronic inflammation which results in epidermal hyperplasia and dermal fibrosis.¹⁰ Subsequently, fissures and verrucous lesions that provide a portal of entry for pathogens develop. Each episode of cellulitis then causes further lymphatic damage in the affected limb.

The histopathology of ENV typically reveals a hyperplastic pseudoepitheliomatous epidermis with significant acanthosis. Often there is overlying hyperkeratosis and/or parakeratosis. The dermis is fibrotic with irregular whorls of collagen and a variable number of fibroblasts. Dilated lymphatic spaces, vascular proliferation and a perivascular lymphocytic inflammatory infiltrate may be present in the dermis.¹¹ An example of the typical histopathology of ENV can be seen in Figure 3.

We presented two very different cases of ENV that responded well to oral acitretin. Their problems were not cured but were well-tamed nevertheless. The first patient was an otherwise well man with extensive disease, while the second patient was an older patient with significant co-morbidities whose ENV was confined to an area of skin grafting only. In both cases, a significant

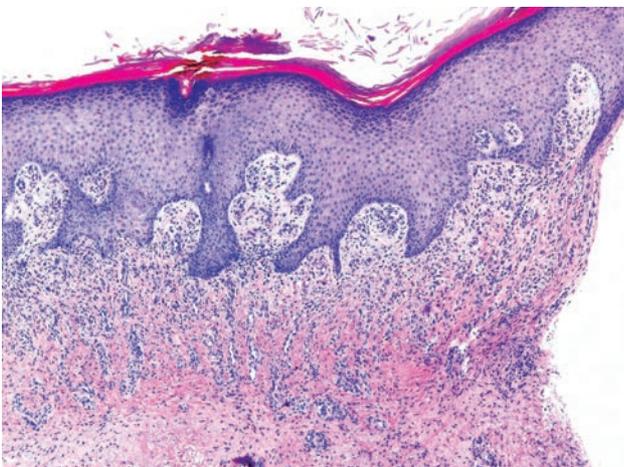


Figure 3. Typical histopathology of ENV with pseudoepitheliomatous hyperplasia and dermal fibrosis. Photomicrograph courtesy of Dr. Stephen Mann, Histopathologist, Sydney, Australia.

improvement of ENV was achieved within a relatively short treatment period. Importantly, oral acitretin led to a reduction in the number of cellulitic episodes in both cases.

Table 1 summarises the published reports of oral retinoid treatment of ENV. In all cases, a significant improvement was seen after a relatively short treatment period. One patient experienced a relapse of skin changes after stopping oral retinoid treatment, although restarting treatment improved the skin once again. Only one patient discontinued treatment and this was due to raised serum triglycerides. Although side effects of oral acitretin such as hyperlipidaemia may be encountered, with adequate monitoring and appropriate treatment this is not an absolute contraindication.¹²

Chronic lower limb lymphoedema occurring in the diabetic patient is a potentially serious problem. Such patients often have multiple factors that place their lower limbs at increased risk for the development of lymphoedema. Peripheral neuropathy, vascular disease, chronic ulcers, impaired immunity and poor healing all predispose the limb to recurrent infection and damaged lymphatics. Early treatment of diabetic patients with ENV could potentially save a limb.

Treatment of ENV with an oral retinoid reduces epidermal hyperplasia, with flattening of the papillomatous and verrucous lesions and reduced fissuring. The consequent reduction in the number of associated soft tissue infections may slow the progression of the disease. Ideally, oral acitretin should be initiated at an early stage of the disease, both to maximise the beneficial effect of retinoid treatment and possibly slow the progression of disease.

Although not a cure and there are side-effects to consider, oral retinoids may nonetheless offer significant improvement in terms of function and quality of life, with the possibility of some enduring benefit beyond the treatment period. Furthermore, even in later stages of the disease, it would appear that improvement may still be achievable with oral

Table 1. Published reports of ENV treated with oral retinoids

Reference	Patient details	ENV site	Co-morbidities	Treatment	Complications	Outcome of ENV
Zouboulis et al. ⁶	98-year-old female	Lower legs	Obesity CRF CCF	Oral etretinate 0.6-0.75 mg/kg/day for 4-6 wks	Raised serum triglycerides	Marked improvement
	82-year-old female	Lower legs	Obesity		Nil	Marked improvement
	67-year-old female	Lower legs	Obesity CCF		Nil	Marked improvement Relapsed after ceasing therapy but improved with re-introduction
Feind-Koopmans et al. ⁵	53-year-old male	Lower legs	Obesity CCF	Oral acitretin 0.3 mg/kg/day for 7 weeks	Nil	Marked improvement Remained in remission for 7 months follow-up
Current paper	31-year-old male	Lower legs	Nil	Oral acitretin 0.6 mg/kg/day for 8 weeks	Nil	Marked improvement
	71-year-old male	Left foot skin graft	T2DM Alcoholic liver disease IHD PVD	Oral acitretin 0.3 mg/kg/day for 6 months	Nil	Marked improvement

CCF, congestive cardiac failure; CRF, chronic renal failure; ENV, elephantiasis nostras verrucosa; IHD, ischaemic heart disease; PVD, peripheral vascular disease; T2DM, type II diabetes mellitus.

acitretin. However, it is unclear at present whether intermittent courses of therapy would provide similar benefits compared to continuous therapy. Further studies are needed to adequately address these questions. For now, with judicious care, for patients with elephantiasis acitretin could successfully produce an ameliorating and taming effect.

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