

CLINICAL REPORT

Terbinafine-induced Subacute Cutaneous Lupus Erythematosus

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Oral terbinafine is licensed for use in onychomycosis after positive confirmation of infection. We describe five cases of subacute cutaneous lupus erythematosus associated with terbinafine therapy. All cases had positive antibodies to extractable nuclear antigens, predominantly anti-Ro, and several had a history of pre-existing autoimmune disease. Terbinafine should only be prescribed after confirmation of infection by microscopy or culture.
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Terbinafine is a synthetic allylamine that has been licensed in the UK since 1991 as a systemic treatment for dermatophyte infections of the nails and skin. Patients with these infections commonly present to general practitioners who should only initiate therapy after confirmation of infection by microscopy and culture of skin or nail specimens. Side effects associated with terbinafine are uncommon, but can include cutaneous reactions. We describe a series of five patients from South East Scotland who presented to our department over a 12-month period with terbinafine-induced subacute cutaneous lupus erythematosus.

CASE REPORTS

Five women (median age 46 years, range 39–64 years) had received oral terbinafine for presumed fungal nail infection. Infection had been confirmed in only one of the five patients by mycological assessment of appropriate skin and nail specimens prior to commencement of therapy by their general practitioners. All five patients had previously documented medical problems which included autoimmune thrombocytopenic purpura, essential thrombocythaemia, vitiligo, psoriasis, diabetes and seronegative arthritis (Table I).

Our patients presented as emergencies to the dermatology department with annular, erythematous, almost bullous eruptions on light-exposed sites, particularly the upper trunk (Fig. 1). All had been on oral terbinafine therapy for at least 4 weeks (range 4–12 weeks) before the development of cutaneous side

effects. Examination of skin biopsies showed an inflammatory cell infiltrate and immunofluorescence consistent with lupus erythematosus. At presentation the majority had a lymphopenia (median $0.76 \times 10^9/l$). Erythrocyte sedimentation rate was not significantly elevated, and biochemical markers of hepatic and renal function were normal in all patients except one who had a transient derangement of liver function tests. Immunological studies showed a positive anti-nuclear factor in only two patients, at a titre of $\geq 1/640$. However, all patients had positive antibodies to extractable nuclear antigens: all five had anti-Ro titres $>100 \mu/ml$, one of five had positive anti-La antibodies. Anti-histone antibodies were present in only one patient of three tested.

Following discontinuation of terbinafine therapy, four patients experienced slow resolution of their cutaneous eruption over several weeks; one required a protracted course of systemic steroids over 5 months for disease progression associated with haemolytic anaemia, but made a full recovery. No patients have experienced any relapse in their symptoms to date (all at least 12 months following their original presentation) despite persistence of anti-Ro positivity in clinical remission in all cases.



Fig. 1. Photo-aggravated distribution of terbinafine-induced subacute cutaneous lupus erythematosus.

Table I. Clinical, serological and histological characteristics of patients and the outcome after discontinuation of terbinafine

	Patients									
	1	2		3		4		5		
Age (years)	58	39		43		64		46		
Time of year at presentation	July	January		April		July		February		
Time on terbinafine (weeks)	8	5		5		12		4		
Past medical history	Sero-negative arthritis	Type I diabetes Vitiligo Psoriasis		Drug-induced urticaria		Essential thrombocythaemia		Autoimmune thrombocytopenic purpura		
ESR (mm/h)	15	17		12		12		13		
Lymphocytes ($\times 10^9/l$) (normal: $1.5-4.0 \times 10^9/l$)	0.73	1.50		0.53		0.76		2.00		
	Acute	Remission	Acute	Remission	Acute	Remission	Acute	Remission	Acute	Remission
Anti-nuclear factor	Negative	1:160	Negative	Negative	>1:640	Negative	>1:640	1:640	Negative	Negative
Anti-dsDNA (IU/ml)	NT	<15	NT	NT	66.1	NT	<15	<15	NT	NT
Anti-Ro (U/ml)	>100	>100	>100	>100	>100	>100	>100	>100	>100	99.0
Anti-La (U/ml)	<25	<25	<25	<25	<25	<25	>100	>100	<25	<25
Anti-Jo-1 (U/ml)	<25	<25	<25	<25	<25	<25	<25	<25	<25	<25
Anti-Sm/Sm-RNP (U/ml)	<25	<25	<25	<25	<25	<25	<25	<25	<25	<25
Anti-Scl70	30	26	<25	<25	<25	<25	<25	<25	<25	<25
Anti-histone	Positive	Weak positive	Negative	NT	Negative	NT	NT	NT	NT	NT
Direct immunofluorescence	Positive (IgA, C3)		Positive (IgG)		Negative		Negative		Positive (IgM)	
Outcome after discontinuation of terbinafine	Resolved, short course of oral steroids		Resolved		Resolved		Resolved		Progressed, haemolytic anaemia, long course of oral steroids	

NT: Not tested.

DISCUSSION

Terbinafine has significant fungicidal activity (1) and is the drug of choice for onychomycosis. It has increased efficacy and more prolonged remission than other anti-fungal agents such as griseofulvin and itraconazole (2). Culture of nail specimens takes time and has a high false-negative rate when compared with identification of fungal hyphae by microscopy (3). This may influence the clinician's decision to treat on clinical signs alone. However, although direct microscopy may not yield information on organism type and sensitivity to therapy, it does provide objective evidence of onychomycosis.

In the last 10 years prescriptions for oral terbinafine in Scotland (with a population size of just over 5 million) have more than doubled to 50,000 per year (4). Prescribing of griseofulvin has fallen over the same time period. Cutaneous adverse reactions associated with terbinafine are rare, but include photosensitivity, erythema multiforme/Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, generalized pustulosis and worsening of psoriasis (5–8). Up until recently, in the UK there has been only one isolated report of terbinafine-associated subacute cutaneous lupus erythematosus (SCLE) (9), suggesting a chance association only. However, an SCLE-like eruption was described in a further three patients treated with the drug (10) as

well as two reports of systemic lupus erythematosus (SLE) in association with terbinafine (11, 12).

Classic SCLE affects predominantly females and comprises a small subset of the LE population. The condition presents with sudden onset of annular or psoriasiform patches and plaques affecting particularly the sunlight-exposed areas typically involving the outer upper arms, shoulders, neck and face. Histological changes include a lymphocytic infiltrate at the dermo-epidermal junction with basal cell liquefaction and colloid bodies. Immunofluorescence is frequently, but not always, positive for immunoglobulin and C3. Overall the condition carries a more favourable prognosis than SLE, with which it may share some common features such as photosensitivity, lymphopenia and positive anti-nuclear factor. Almost all patients have positive antibodies to Ro, some to La.

Drug-induced SCLE has been described particularly with thiazide diuretics (13), but other implicated agents include angiotensin converting enzyme inhibitors (14), calcium channel blockers (15), interferon- β (16) and griseofulvin (17). Our data, together with recently published series in the American literature (18, 19), support an association with terbinafine therapy. Virtually all reported cases have had positive anti-Ro antibodies; some but not all had positive anti-histone

antibodies that may disappear with resolution of the condition, after cessation of therapy. In some reports terbinafine appears to have exacerbated a pre-existing connective tissue disease, and although this was not apparent with our patients, three had a history of other autoimmune diseases.

Given the relatively high prescribing levels in the UK, terbinafine-associated SCLE appears to be an uncommon phenomenon. Despite this it would seem prudent to enquire about symptoms suggestive of possible connective tissue disease, photosensitivity or other autoimmune disorders when considering terbinafine treatment. More important, however, is the need to follow prescribing guidelines by demonstration of the presence of fungal hyphae and preferably positive fungal culture before commencement of therapy.

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