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Case Report

Erythema Nodosum Associated with Terbinafine Therapy- A Case Report

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Abstract

Terbinafine is a commonly used anti-fungal agent in dermatological practice but not one clearly associated with erythema nodosum. There is only one published report in 2014 that described a delayed onset of erythema nodosum after cholestasis complicated terbinafine therapy. We report the case of a woman who developed erythema nodosum whilst on terbinafine therapy for onychomycosis to further consider this link and its potential implications.

Keywords: Erythema Nodosum; Terbinafine, Lamisil; Forearm; Onychomycosis

Introduction

Erythema nodosum is a painful and uncommon panniculitis which should be avoided if and where possible [1,2]. Terbinafine is a commonly prescribed drug in dermatology, particularly for onychomycosis and tinea [3,4]. Although it is considered a relatively safe anti-fungal agent, several rare but important cutaneous adverse effects can occur [4,8]. Studied reactions include but are not limited to lupus erythematosus, acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis [5]. With only a single prior case report associating erythema nodosum to terbinafine we present our case to further strengthen this rare association [6].

Case Report

A 69-year-old Australian woman with a history of hypertension, hypercholesterolemia, osteoporosis and sub-clinical hypothyroidism presented to her primary care practitioner worried about a reaction to terbinafine.

She was being treated for mild onychomycosis of both her great toenails with terbinafine at a dose of 250 mg orally once a day. She noted that by the second day of therapy she started developing ankle swelling and pain followed by worsening erythematous and tender nodules in subsequent days on both her anterior legs and left forearm. She continued to take terbinafine for another six days prior to presentation by which time she had ceased the medication for eight days.

Additional history was sought based on this presentation. She denied any sore throat, cough, or nasal congestion. There was no history of previous COVID-19 infection. There were also no risk factors for tuberculosis, and she reported no constitutional, bowel or bladder symptoms. Furthermore, there was no recurrent oral or genital ulcerations or eye inflammation on history. Her most recent vaccination was her Cominarty COVID-19 booster which had been given six months prior.

Past adverse drug reactions included aspirin, cephalexin, penicillin and iodidies but not terbinafine. She also gave no history of previous erythema nodosum episodes. Terbinafine had been previously used with no issues four years prior for onychomycosis.

She had undergone a colonoscopy a day prior to the start of her terbinafine therapy for follow up of previous colonic polyps. The colonoscopy had found a single non- malignant polyp in her sigmoid colon and pre-existing diverticular disease. This was her third colonoscopy in a decade and no evidence of inflammatory bowel disease was found in all endoscopies. The medications administered during her colonoscopy were midazolam, fentanyl and propofol intravenously. She reported feeling well post procedure.

Her long-term medications included rosuvastatin 5 mg daily, cholecalciferol 1000 IU daily, telmisartan 80 mg/amlodipine 5 mg daily and denusomab subcutaneous injections six monthly the last of which had been administered two months prior.
She reported no other supplement or over the counter medication use.

On physical examination she was afebrile with normal vitals. Her chest and abdomen examined normally. There was no clinically palpable lymphadenopathy and her oropharynx was normal on examination. Skin examination as photographed in Fig. 1 revealed erythematous and tender nodules over the extensor surfaces of both legs and her left forearm.

A deep incisional skin biopsy was subsequently performed which supported the diagnosis of erythema nodosum as shown in Fig. 2.

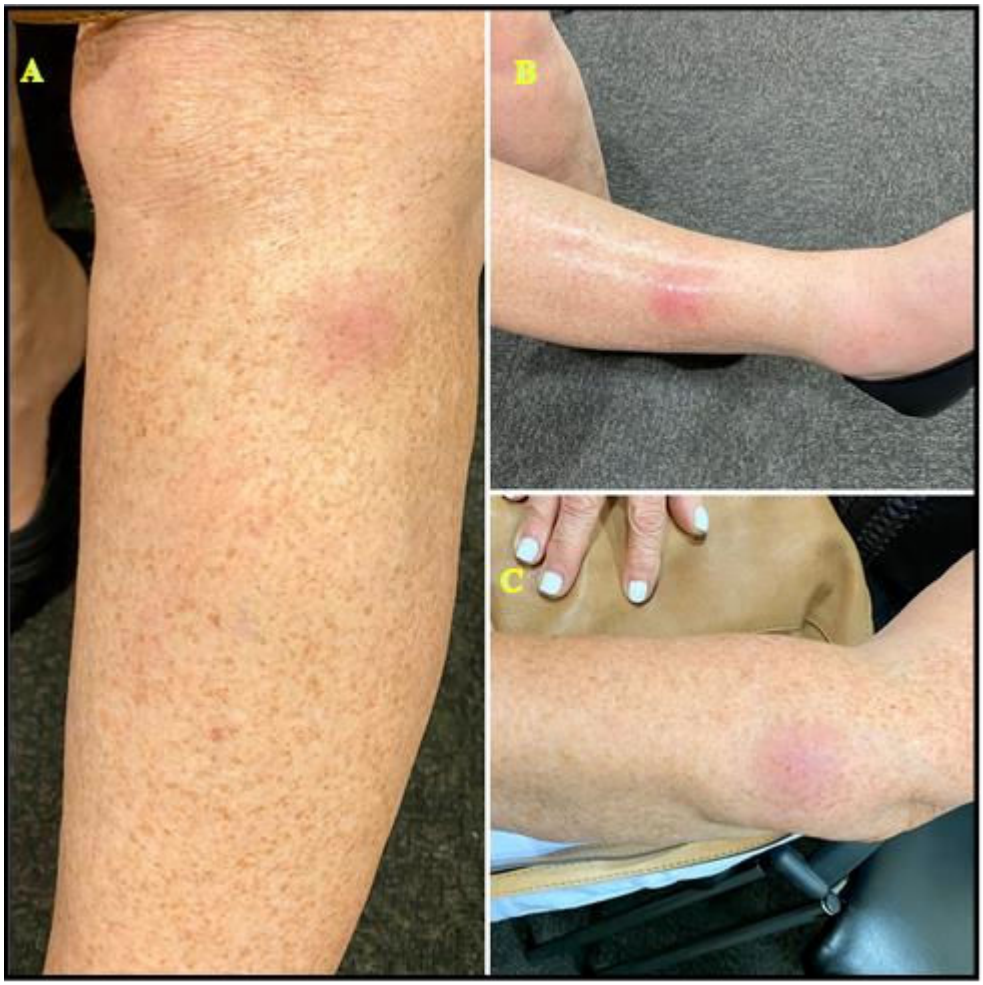

Figure 1: Clinical photos. A: Left Leg; B: Right Leg; C: Left forearm

Her blood work as shown in Table 1 did not point to an alternate diagnosis that could be attributed to her erythema nodosum. There was a mild neutrophilia and monocytosis without any blood film evidence of malignancy and a mild elevation of her inflammatory markers. Her autoimmune screen, liver panel, thyroid and tuberculosis testing amongst others was normal.

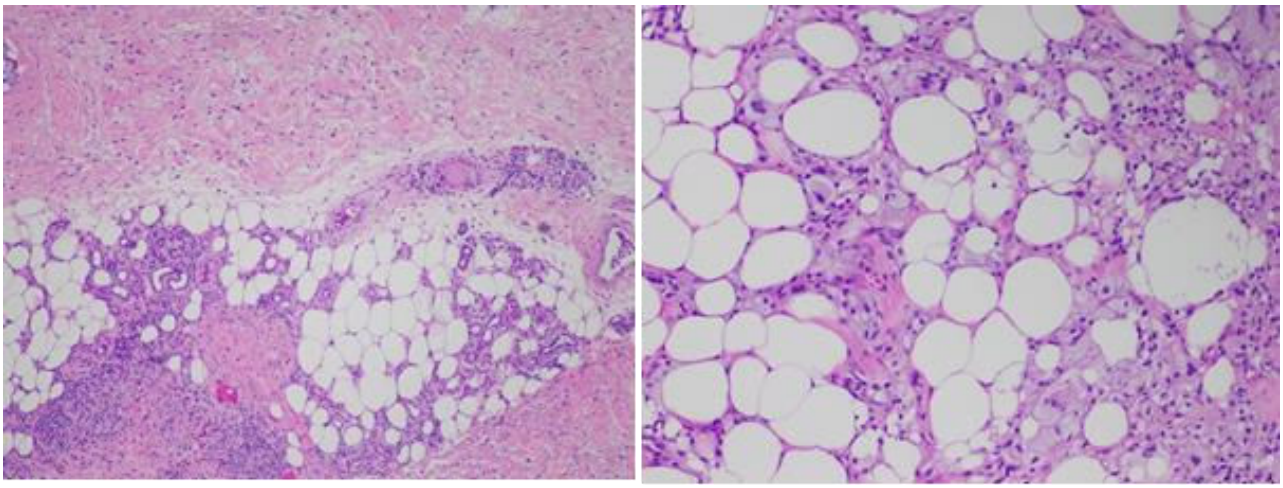

Figure 2: Histology displayed both septal and lobular panniculitis with marked subdermal fibrosis infiltrated by lymphocytes, histiocytes and granulomas with multinucleated giant cells. Although there was a perivascular lymphocytic infiltrate, no definite vasculitis was seen.

Investigation	**Results**						
Full Blood Count	Hb 139	*White Cell Count 14.7**	*Neutrophils 11.0 **	Lymphocytes 2.1	*Monocyte s 1.3 **	Eosinophils 0.1	Basophils 0.1
Blood film	Other than mild neutrophilia and monocytosis this was reported normal and so were subsequent films.						
CRP	*33 mg/L**						
ESR	*60 mm/hr**		*29 mm/hr* (12 days later)*				
Electrolytes (mmol/L)	Sodium 137	Potassium 4.5	Chloride 102	Urea 4.7	eGFR 74 ml/min	Calcium 2.54	
Liver Enzymes (U/L)	ALT 18	AST 17	ALP 75	GGT 20	Bilirubin 12 umol/L	Albumin 37 g/L	Globulin 37 g/L
Serum LDH	218 U/L						
Serum ACE	37.8 U/L						
ANA	Negative						
ENA	Negative						
Quantiferon TB Gold	Negative						
ASOT	< 20 IU/ml						
Anti-DNAse B	< 100 U/ml						
Serum Electrophoresis (g/L)	*Alpha 1 Globulin 4.9 **	*Alpha 2 globulin 10.4 **	*Beta 1 Globulin 5.8 **	Beta 2 Globulin 3.4	IgG 10.1	IgA 2.78	IgM 2.31
	Polyclonal increase in gamma globulins suggestive of a reactive process. No banding of significance.						
Anti CCP	1.0 U/ml						
Rheumatoid Factor	< 10 IU/ml						
Anti -dsDNA	1 IU/ml						
Thyroid Testing	TSH 2.91 mIU/L		Anti-Thyroid Peroxidase 34 IU/ml		Anti-Thyroglobulin < 1.3 IU/ml		

Table 1: Blood results - abnormal elevated results marked with * otherwise all normal results.

Her chest plain film which was compared to a decade prior showed no evidence of mediastinal widening, adenopathy or lung changes and was reported normal. A reaction to terbinafine could not be confidently excluded given the temporal relationship of the drug to her rash. As a result of her previous reaction to aspirin she was prescribed a weaning dose of prednisolone rather than a non-steroidal anti-inflammatory which subsequently helped with symptomatic management.

Discussion

Erythema nodosum is postulated to be a delayed-type hypersensitivity reaction. It is interesting that our case had tolerated terbinafine in the past but it is not uncommon for drug reactions to occur with subsequent exposures despite initial tolerability. The possibility of her Cominarty vaccine booster causing her erythema nodosum at six months is unlikely.

The current literature suggests that the median time to an erythema nodosum reaction post vaccination either with ChAdOx1 (Astra Zeneca) or Cominarty (Pfizer-BioNTech) was 2.5 days with a range of 1 to 28 days [9]. Comparing our case to the prior 2014 report on terbinafine and erythema nodosum it is notable our patient showed no signs of liver injury and we suspect this is likely due to her ceasing the medication by six days. The typical period for terbinafine induced hepatotoxicity is from the third to sixth week of therapy [6]. The temporal onset of her symptoms with her terbinafine use makes a compelling case for it being a causal factor perhaps with a superimposed genetic predisposition to erythema nodosum.

Conclusion

Given the rarity of erythema nodosum secondary to terbinafine it is unknown if patients with a prior history of erythema nodosum are at greater risk of recurrence when exposed to terbinafine. The case however provides a worthwhile exercise for clinicians to determine whether an alternative anti-fungal might be more prudent in patients with risk factors for erythema nodosum. Just as importantly should signs of panniculitis develop in a patient recently treated with terbinafine it is worth contemplating erythema nodosum as the potential pathology and consider cessation and an alternative method of treatment where possible.

Conflict of Interest

The authors have no conflict of interest to declare.

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