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Research Article

Clinical Manifestations and Management of Terbinafine-Induced Acute Generalized Exanthematous Pustulosis

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Background. Acute generalized exanthematous pustulosis (AGEP) is a rare and serious adverse reaction of terbinafine. Understanding AGEP and terbinafine is primarily based on case reports. The purpose is to explore the clinical characteristics of terbinafine-induced AGEP, and to provide reference for clinical diagnosis and treatment. *Methods*. Case reports and original studies of terbinafine-induced AGEP were retrieved by searching Chinese and English databases from January, 1991, to May 31, 2022. *Results*. The median age of the 32 patients (17 males and 15 females) was 55 years (range: 6–84). The median time to onset of AGEP is 8 days (range: 1–77) and is usually accompanied by fever (>38°C) and elevated neutrophil levels (>8000/mm^3). Four patients (12.5%) had oral mucosal involvement, and 10 patients (31.3%) developed postpustular desquamation. The lesions were mainly distributed in the trunk (43.8%), the whole body (34.4%), and the extremities (53.1%). Skin biopsy revealed subcorneal pustules (65.6%), intraepidermal cavernous pustules (43.8%), necrotic keratinocytes (15.6%), spongy hyperplasia (25.0%), neutrophil exocytosis (34.4%), and papillary dermal edema (40.6%). AGEP resolved completely in all patients at a median time of 12 days (range: 2–90) after discontinuation of terbinafine and symptomatic therapy. *Conclusion*. Clinicians should be aware that terbinafine-induced AGEP is a rare cutaneous adverse reaction. AGEP usually occurs within 2 weeks after administration and has a good prognosis after discontinuation.

1. Introduction

Terbinafine is a commonly used antifungal drug whose mechanism of action includes inhibition of squalene epoxidase, preventing sterol biosynthesis in fungi, ultimately leading to cell death, and has been shown to be effective in the treatment of dermatophytes, including onychomycosis [1]. Terbinafine, administered once daily, remains the best treatment option for patients with multiple comorbidities taking other prescription medications due to its minimal drug-drug interactions [2].

In a postmarketing surveillance study, the most common side effects of terbinafine were gastrointestinal (4.9%), such as nausea or diarrhea, and dermatological events (2.3%) [3]. The incidence of severe side effects was only 0.04%, including Stevens-Johnson syndrome, toxic epidermal necrolysis, subacute cutaneous lupus, and erythema multiforme [4]. Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction characterized by the rapid formation of nonfollicular, sterile pustules on an erythematous base [5]. Whereas knowledge of terbinafine and AEGP is largely based on case reports. AGEP can be a critical clinical condition and is rarely described, requires prompt diagnosis and treatment, and may be missed by the clinic. The clinical characteristics of terbinafine-induced AGEP are unclear. Given that terbinafine is an important choice for dermatophyte infections, here we discussed the clinical features of terbinafine-induced AGEP, to provide a reference for clinical diagnosis and treatment.

2. Methods

2.1. Retrieval Strategy. We searched all original research reports and clinical reports of terbinafine-induced AGEP

through Chinese and English data (PubMed, Embase, Cochrane Library, ScienceDirect, Web of Science, Wanfang, VIP, CNKI) from January, 1991, to May 31, 2022. No language restrictions will be applied to the search. MeSH terms and keywords include terbinafine, antifungal, AEGP, Acute generalized exanthematous pustulosis, pustules, adverse reactions, anaphylaxis, and cutaneous adverse reactions. Terbinafine-inducedAGEP-related case reports and case series were included. Reviews, mechanistic studies, animal studies, and duplicate cases were excluded.

2.2. Data Extraction. The following information was extracted from each patient: gender, age, country, past medical history, concomitant medications, drug dose, time of onset, clinical features of AGEP eruptions, laboratory tests, skin biopsy, treatment, and prognosis.

2.3. AGEP Diagnosis. AGEP diagnosis is made by the modified EuroSCAR scoring system [6]. Scores interpreted as no (0), possible (1–4 points), probable (5–7 points), and definite (8–12 points).

2.4. Correlation Evaluation. The association of terbinafine with AGEP was assessed using the Naranjo scale [7]. The final score interpretations are stratified into four categories, with a score of ≥9 considered "definite," 5 to 8 "probable," 1 to 4 "possible," and ≤0 "doubtful."

2.5. Statistical Analysis. Statistical analysis was performed using SPSS Statistics 22.0 (IBM, Armonk, NY, USA). The count data are represented by *n* (%), and the continuous data are represented by the median value (minimum and maximum).

3. Results

3.1. Basic Information. After inclusion and screening, a total of 32 patients from 29 literature studies were included (Figure 1). The patient's basic information is summarized in Table 1. Of these patients (17 males and 15 females), 18 (56.3%) were mainly from Europe and 7 (21.9%) from North America, with a median age of 55 years (range: 6–84). Terbinafine is mainly used for the treatment of onychomycosis and skin fungal infections with 250 mg daily. The median time to onset of AGEP was 8 days (range: 1–77). Previous skin history was present in 4 patients (12.5%), including 3 patients (9.4%) with psoriasis and 1 patient (3.1%) with bullous pemphigoid. Five patients (15.6%) had underlying diseases and 6 patients (18.8%) were taking other drugs concurrently.

3.2. Clinical Manifestations. Table 2 summarizes the clinical manifestations of terbinafine-induced AGEP. Thirty-one patients had nonfollicular pustules, 27 had erythema, 16 had rash, and 8 had pruritus. The remaining symptoms included pain (9.4%) in the affected area, edema (9.4%), target lesions (6.3%), burning sensation (6.3%), and chills (6.3%). Four patients (12.5%) had oral mucosal involvement and ten patients (31.3%) developed postpustular desquamation. Twenty patients (62.5%) had fever, 19 of (59.4%) whom had a temperature over 38°C. The lesions were mainly distributed in the trunk (43.8%), the whole body (34.4%), and the limbs (53.1%). Palms and soles were involved in 1 patient (3.1%).

3.3. Laboratory Test. Laboratory results of terbinafine-induced AGEP are summarized in Table 2. Twenty-seven patients (84.4%) reported white blood cell counts, of which 24 patients (75.0%) had elevated white blood cell levels, with a median of 18100 cells/mm^3 (range: 1000–38100). Neutrophil counts were reported in 19 patients (59.4%), 18 (56.3%) of whom had elevated neutrophil levels, with a median of 14999 cells/mm^3 (range: 8154.5830330). Normal eosinophil levels were reported in 6 patients (18.8%). Erythrocyte sedimentation rate was elevated in 3 of 6 patients (9.4%). The erythrocyte sedimentation rate was elevated in 3 of 6 patients (9.4%) and *C*-reactive protein was elevated in 7 of 8 patients (21.9%). Two patients (6.3%) developed acute kidney injury and one patient (3.1%) developed liver injury. Two of the five patients (6.3%) showed positive through Patch tests. Two patients (6.3%) showed positive after lymphocyte transformation test in 3 patients.

3.4. Skin Biopsy. Skin biopsies for terbinafine-induced AGEP are summarized in Table 2. The most common findings of the histopathological examination were subcorneal pustule (65.6%), intraepidermal spongiform pustules (43.8%), necrotic keratinocytes (15.6%), spongy tissue hyperplasia (25.0%), exocytosis of neutrophils (34.4%), and papillary dermal edema (40.6%). Fourteen patients (43.8%) had mixed inflammatory infiltrates in 21 patients with perivascular inflammatory infiltrates.

3.5. Treatment. The treatment and prognosis of terbinafine-induced AGEP are summarized in Table 3.

Terbinafine was discontinued immediately in all patients; 15 patients (46.9%) received systemic corticosteroids; 11 patients (34.4%) received topical steroids; 5 patients (15.6%) received antihistamines; and 10 patients (31.3%) received systemic supportive care, including wet dressings, preservatives, and so on. All patients achieved full resolution of their AGEP eruption post-treatment. The median time to AGEP recovery was 12 days (range: 2–90) in 26 patients. AGEP relapsed within 2 days in 1 patient who received terbinafine again.

3.6. Correlation Evaluation. All patients scored 5–8 on the Naranjo probability scale, indicating a probable relationship between terbinafine and AGEP (Table 3). Six patients (18.8%) scored between 5 and 8 by the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR), indicating a probable AGEP diagnosis and 26 patients had a score ≥9, indicating a definite AGEP diagnosis.

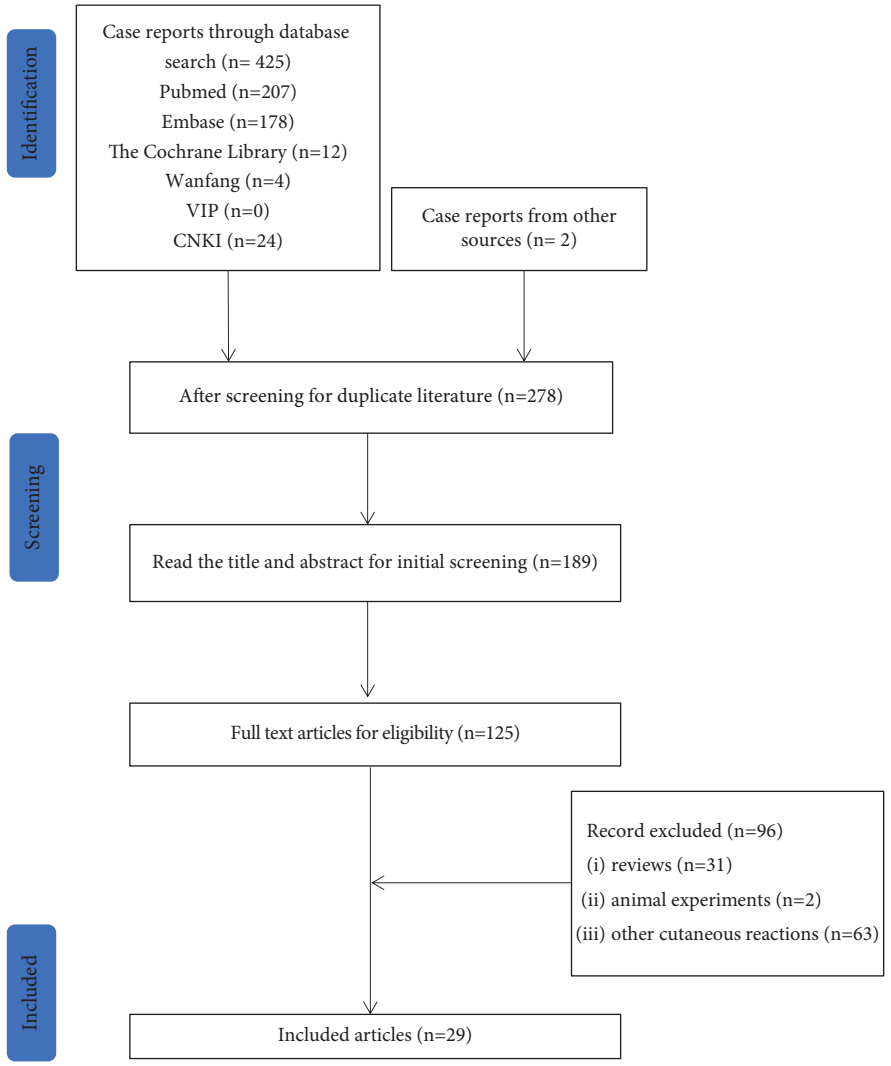

Figure 1: Flow chart of study selection process for reported cases of terbinafine-induced acute generalized exanthematous pustulosis.

4. Discussion

AGEP has been attributed to a variety of causes, such as viral infections or allergy to mercury, while more than 90% of AGEP cases are caused by systemic drugs [8]. The most common drug classes that induced AGEP were beta-lactam antibiotics (25.9%), other antibiotics (20.8%), iodine contrast agents (7.3%), and corticosteroids (5.4%). The most commonly involved drugs are amoxicillin, pristinamycin, and diltiazem [9]. A multinational case-control study of AGEP showed that terbinafine was the most common drug after pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxy) chloroquine, and sulphonamides [8]. The appearance time of AGEP varies with different drugs. AGEP was triggered after 1 day of antibiotic exposure [8]. The onset time of AGEP induced by diltiazem varied from 1 day to 3 weeks, while the average time of AGEP induced by hydroxychloroquine was 40 days [10, 11]. In contrast, terbinafine-induced AGEP had a longer incubation period, ranging from 1 to 77 days. Drug-induced AGEP resolved spontaneously within 15 days after discontinuation. The resolution time of terbinafine-induced AGEP was longer, ranging from 2 days to 90. This long duration can be explained by the pharmacodynamic and pharmacokinetic properties of terbinafine. Terbinafine remains in sebaceous-rich areas of the body for up to 15–20 days after stopping treatment [12].

The risks of severe acute adverse reactions (SCAAR) include genetic and nongenetic risk factors. Host factors include potential malignancies or systemic lupus erythematosus, as well as potential infections, such as tuberculosis and HIV. However, none of the above risk factors were found in terbinafine-induced AGEP. Although several patients had a positive history of psoriasis, EuroSCAR strongly recommended that AGEP be unrelated to the individual or family history of psoriasis [8].

The mucocutaneous features of terbinafine-induced AGEP are characterized by sterile, nonfollicular pustules on an erythematous base with minimal mucosal involvement and are usually pruritic. Leukocytosis with an elevated neutrophil count

Table 1: Basic information on 32 patients with terbinafine-induced acute generalized exanthematous pustulosis.

Parameters		Values
Sex	Male	17 (53.1%)
	Female	15 (46.9%)
Age	Years	55 (6,84)
Country	USA	7 (21.9%)
	UK	5 (15.6%)
	Belgium	3 (9.4%)
	France	3 (9.4%)
	Tunisia	3 (9.4%)
	Turkey	4 (12.5%)
	Switzerland	2 (6.25%)
	Japan, India, Italy, Australia, and Portugal	1 (3.1%)
Dosage	250 mg daily	16 (50.0%)
Onset time	Days	8 (1, 77)[b]
	≤7	14 (43.8%)
	7–14	11 (34.4%)
	21–77	7 (21.9%)
Indication (31)[a]	Onychomycosis	17 (53.1%)
	Tinea cruris	5 (15.6%)
	Tinea corporis	3 (9.4%)
	Tinea pedis	3 (9.4%)
	Tinea capitis	1 (3.1%)
	Tinea manum	1 (3.1%)
	Cutaneous candidiasis	1 (3.1%)
Past skin diseases (4)[a]	Psoriasis	3 (9.4%)
	Bullous pemphigoid	1 (3.1%)
History of disease (5)[a]	Diabetes	3 (9.4%)
	Hypertension	2 (6.3%)
	Ischaemic heart disease	1 (3.1%)
	Chronic heart failure	1 (3.1%)
	Hypercholesterolemia	1 (3.1%)
	Chronic obstructive pulmonary disease	1 (3.1%)
Concomitant drugs	Ciclopirox, enalapril, simvastatin, warfarin, isosorbide, diltiazem, metoprolol, glyburide, glucophage, prednisolone, hydrochlorothiazide, gemfibrozil, and aspirin	6 (18.8%)

[a]represents the number of patients out of 32 on which information regarding this particular parameter was provided. [b]Median (minimum-maximum).

Table 2: Clinical features, laboratory tests, and skin biopsies of 32 patients with terbinafine-induced acute generalized exanthematous pustulosis.

Parameters		Values
Clinical features	Nonfollicular pustules	31(96.9%)
	Erythematous plaques	27 (84.4%)
	Rash1	16 (50.0%)
	Pruritic	8 (25.0%)
	Pain	3 (9.4%)
	Edema	3 (9.4%)
	Targetoid lesion	2 (6.3%)
	Burning sensation	2 (6.3%)
	Chills	2 (6.3%)
	Mucosal involvement	4 (12.5%)
	Desquamation	10 (31.3%)
Fever (20)[a]	>38°C	19 (59.4%)
	37.6°C	1 (3.1%)
Location	Trunk	14 (43.8%)
	Entire body	11 (34.4%)
	Extremities	17 (53.1%)
	Abdomen	4 (12.5%)
	Inguinal areas	8 (25.0%)
	Back	5 (15.6%)
	Thighs	4 (12.5%)
	Chest	3 (9.4%)
	Axilla	3 (9.4%)
	Buttocks	3 (9.4%)
	Neck	2 (6.3%)
	Facial involvement	2 (6.3%)
	Palms and soles	1 (3.1%)
	Genitals	1 (3.1%)
Laboratory test		
White blood cell count (27)[a]	Elevated	24 (75.0%)
	Cells/mm^3	18100 (1000, 38100)[b]
Neutrophil count (19)[a]	Elevated	18 (56.3%)
	Cells/mm^3	14999 (8154.58, 30330)[b]
Eosinophils (6)[a]	Normal	6 (18.8%)
Erythrocyte sedimentation rate (6)[a]	Elevated	3 (9.4%)
	Normal	3 (9.4%)
C-reactive protein (8)[a]	Elevated	7 (21.9%)
	Normal	1 (3.1%)
Kidney function (12)[a]	Acute kidney injury	2 (6.3%)
Liver function (11)[a]	Acute liver injury	1 (3.1%)
Patch tests (5)[a]	Negative	3 (9.4%)
	Positive	2 (6.3%)
Lymphocyte transformation test (3)[a]	Negative	1 (3.1%)
	Positive	2 (6.3%)
Skin biopsy	Subcorneal pustule	21 (65.6%)
	Intraepidermal spongiform pustules	14 (43.8%)
	Necrotic keratinocytes	5 (15.6%)
	Spongy tissue hyperplasia	8 (25.0%)
	Exocytosis of neutrophils	11 (34.4%)
	Papillary dermal edema	13 (40.6%)
	Perivascular inflammatory infiltrates with neutrophils	1 (3.1%)
	Eosinophils	3 (9.4%)
	Lymphocytic	2 (6.3%)
	Mixed inflammatory infiltrate	14 (43.8%)

[a]represents the number of patients out of 32 on which information regarding this particular parameter was provided. [b]Median (minimum-maximum).

Table 3: Treatment and prognosis of 32 patients with terbinafine-induced acute generalized exanthematous pustulosis.

Parameters		Values
Treatment	Discontinued	32 (100%)
	Topical steroids	11 (34.4%)
	Systemic steroids	15 (46.9%)
	Antihistamines	5 (15.6%)
	Systemic supportive care	10 (31.3%)
Outcome	Recovery	32 (100%)
Recovery time (26)[a]	Days	12 (2, 90)[b]
Naranjo probability scale*	Probable	32 (100%)
EuroSCAR#	Probable	6 (18.8%)
	Definite	26 (81.3%)

NA, not available and EuroSCAR, European Study of Severe Cutaneous Adverse Reactions. [a]represents the number of patients out of 32 on which information regarding this particular parameter was provided. [b]Median (minimum-maximum). *Score interpretation: doubtful (0), possible (1–4), probable (5–8), and definite (≥9). #Score interpretation: no (≤0), possible (1–4), probable (5–7), and definite (8–12).

($>8.0\times10^9$/L) and fever (≥38°C) were another feature of terbinafine-induced AGEP. During AGEP resolution, some patients have desquamation of the affected area. It is reported that up to 20% of AGEP elderly patients have visceral organ involvement, the most common of which are the liver, kidney, and lung [13]. In patients with terbinafine-induced AGEP, liver involvement manifested only as elevated aspartate aminotransferase and alanine aminotransferase [14]. Renal involvement manifests as elevated creatinine and acute prerenal failure [15, 16]. After discontinuation of terbinafine and supportive care, liver enzymes and renal function returned to normal levels.

The diagnosis of AGEP relies on clinical and histology. The differential diagnosis of generalized pustular eruptions can be difficult due to the similar clinical and histopathologic features of AGEP and generalized pustular psoriasis (GPP). AGEP differs from GPP mainly in drug exposure, no relapse, faster recovery time after discontinuation, and no personal and family history of psoriasis. One patient started terbinafine and initially showed a generalized outbreak of AGEP, but later seemed closer to the pustular psoriasis (PP) [17]. The typical pathological manifestations of AGEP are the formation of subcorneal and/or intraepidermal cavernous pustules, marked edema of the papillary dermis, perivascular infiltration of neutrophils, and eosinophil exocytosis in some patients. Terbinafine-induced AGEP conforms to the above characteristics.

Patch and in vitro tests have confirmed that AGEP is a delayed-type hypersensitivity reaction mediated by T lymphocytes [18, 19]. The possible mechanism of AEGP is the activation of specific CD4+ and CD8 + T lymphocytes through antigen-presenting cells after pathogenic factors (mainly drugs) come into contact with the body. Activated lymphocytes rapidly proliferate and migrate into the dermis and epidermis. Activated CD8 T cells release perforin and granzyme B, which, through interaction with Fas ligands, induce apoptosis of intraepidermal keratinocytes, resulting in tissue destruction and intraepidermal blistering form [20].

Specific CD4 + T lymphocytes release a large amount of neutrophil chemokine CXCL8, which chemotactic neutrophils into blisters and eventually form sterile pustules. [21] In addition, Th17 cells may also play a role in the pathogenesis of AGEP. IL-17, a potent pro-inflammatory cytokine capable of recruiting neutrophils, can also synergize with CXCL8, released by keratinocytes to promote pustule formation. [22] Individuals with IL-36RN mutations may be at increased risk of developing AGEP. Mutations in the IL36RN gene lead to an uncontrolled IL-36 pathway, which further leads to increased production of IL-6, IL-8, IL-1α, and IL-1β, and may predispose to pustules [23]. Navarini et al. studied the IL36RN gene mutation in AGEP and found that the IL36RN gene mutation in AGEP patients was significantly higher than that in the control group (1.6% vs. 0.4%) [24]. These results suggest that patients with mutations in the IL36RN gene are susceptible to AGEP.

fAGEP and GPP are difficult to distinguish, which is particularly important when choosing a therapy. Identification and immediate withdrawal of suspected medications remain the most important measures in the management of AGEP patients [5]. However, there is still no consensus on the optimal treatment regimen for AGEP. Antibiotics should be avoided unless there are clear and significant signs of infection [25]. Antiseptic solutions prevent infection, moisturizers and emollients can help restore the skin barrier, and topical corticosteroids can relieve itching and inflammation [5, 26]. Most AGEP cases clear rapidly with systemic corticosteroids, but severe or refractory cases may require other systemic treatments such as cyclosporine, infliximab, and intravenous immune globulin [26]. To date, the therapeutic value of glucocorticoids in AGEP remains questionable. In one patient, pustules worsened with oral steroids but improved with intravenous steroids [27]. Further research is needed on which treatment regimen is more effective for AGEP. Interleukin 17 may be a therapeutic target for AGEP [28]. Although AGEP is usually self-limiting and has a good prognosis, re-exposure of terbinafine may lead to re-occurrence of AGEP, so patients must be advised to avoid re-exposure [29].

5. Conclusion

Terbinafine-induced AGEP is a rare cutaneous adverse reaction. The development of impetigo during the administration of terbinafine should consider the possibility of AGEP. Terbinafine discontinuation is the mainstay of treatment for AGEP. The prognosis is good after discontinuation.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Chunjiang Wang, Tian Wu, and Yang He conceptualized and designed the study, performed analysis and interpretation, and revised the manuscript. Tian Wu, Yang He, Zhiqiang Fan, Wei Sun, Zuojun Li, and Chunjiang Wang wrote, reviewed, and retrieved the data. All authors have read and approved the final manuscript.

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