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Low-dose venlafaxine-induced erythema multiforme: a case report

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Abstract

Background Venlafaxine, a serotonin–norepinephrine reuptake inhibitor, is commonly prescribed for depressive and anxiety disorders, with a safety profile comparable to selective serotonin reuptake inhibitors. Although venlafaxine's adverse effects are generally mild, serious cutaneous reactions such as erythema multiforme are exceedingly rare.

Case presentation To the best of our knowledge, we report the first known case of venlafaxine-induced erythema multiforme in a 74-year-old Iranian male with generalized anxiety disorder, who developed an erythematous, papular rash after initiating low-dose venlafaxine. The patient's comorbidities and polypharmacy increased his risk for hypersensitivity, and the development of delayed skin lesions aligned with drug-induced erythema multiforme. Differential diagnoses, including drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, and viral exanthems, were ruled out on the basis of lesion morphology, distribution, and absence of systemic symptoms. Although histopathologic confirmation was not obtained, the rapid resolution of symptoms following venlafaxine discontinuation supports the diagnosis of drug-induced erythema multiforme.

Conclusion This case highlights the complexities of managing cutaneous drug reactions in elderly patients with multiple medications and emphasizes the importance of vigilance for rare adverse reactions with psychiatric medications, particularly in high-risk populations. Prompt recognition and withdrawal of the offending agent are crucial to prevent progression to severe drug reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis. Prompt drug discontinuation can prevent progression to severe reactions. This case also underscores the need for further research into the mechanisms and management of rare drug-induced reactions, particularly in elderly patients with complex medical histories.

Keywords Antidepressant, Drug hypersensitivity, Drug reaction, Dermatologic reaction, Case report

Introduction

Venlafaxine, a serotonin–norepinephrine reuptake inhibitor (SNRI), is a versatile antidepressant widely used to treat major depressive disorder (MDD), generalized anxiety disorder (GAD), panic disorder, and neuropathic pain [1]. Its primary mechanism of action involves the inhibition of serotonin and norepinephrine reuptake, with additional effects on dopamine at higher doses. Although not as extensively studied as selective serotonin reuptake inhibitors (SSRIs), venlafaxine exhibits dose-dependent activity, with serotonin reuptake inhibition at lower doses and norepinephrine reuptake inhibition at higher doses [1–3]. Optimal doses for achieving a balance between efficacy and tolerability range from 75 to 150 mg daily, with higher doses increasing adverse effects without a corresponding increase in efficacy [4]. Common side effects include nausea, dizziness, and increased blood

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pressure at higher doses, and abrupt discontinuation may cause withdrawal symptoms [2, 5].

Erythema multiforme is a condition caused by a cell-mediated immune response, with infections accounting for 90% of cases. Herpes simplex virus (HSV) type 1 is the most common etiology of erythema multiforme, followed by HSV type 2 and *Mycoplasma pneumoniae*, particularly in children. While medications are responsible for fewer than 10% of cases, drugs such as nonsteroidal antiinflammatory drugs, antiepileptics, and antibiotics (e.g., sulfonamides, penicillins, and tetracyclines) have been implicated. Rare causes of erythema multiforme include vaccines and autoimmune diseases (e.g., inflammatory bowel disease) and malignancies (e.g., leukemia, lymphoma, and solid organ cancers). Persistent or refractory cases are more often associated with malignancies [6]. While rare, antidepressants have occasionally been implicated in drug-induced erythema multiforme (EM). To the best of our knowledge, venlafaxine-induced EM has not been reported before, making this case unique. This report underscores the importance of recognizing such rare reactions and provides a foundation for further exploration into their mechanisms and management.

Case presentation

A 74-year-old Iranian male with generalized anxiety disorder (GAD) was initially treated with escitalopram (10 mg), but the medication was discontinued after 4 weeks owing to exacerbated anxiety, irritability, and persistent sleep disturbances. Sertraline (50 mg) was then initiated, resulting in improved sleep, but significant side effects, including increased myoclonus and cranial tremors. Brain magnetic resonance imaging (MRI) yielded normal results, and sertraline was discontinued in favor of venlafaxine, starting with a 9.375 mg dose (one quarter of a 37.5 mg tablet). Subsequently, 2 weeks after initiating venlafaxine, the patient showed significant improvement in anxiety and a reduction in myoclonic symptoms, with only minor complaints of dry mouth. Encouraged by these improvements, the treatment plan was continued with venlafaxine.

However, approximately 1 month after starting venlafaxine, the patient developed a nonpruritic, erythematous, papular rash involving the skin and oral mucosa, raising concerns about a possible adverse reaction to the medication. Cutaneous lesions were primarily located on the distal lower extremities, bilateral buttocks, and one elbow. The patient's vital signs were normal, and he reported no systemic symptoms, such as fever or arthralgia.

The patient's medical history included ischemic heart disease, hypertension, and benign prostatic hyperplasia. His medication regimen consisted of aspirin 80 mg, clopidogrel 75 mg, metoprolol tartrate 50 mg, rosuvastatin 20 mg, losartan 25 mg twice daily, tamsulosin 0.4 mg, and pantoprazole 40 mg, all administered orally.

A dermatologist was consulted for evaluation of the suspected drug reaction. The dermatologist diagnosed erythema multiforme minor and advised the patient about its potential to progress to more severe conditions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Appropriate pharmacotherapy included an oral antihistamine (cetirizine) and a topical corticosteroid (betamethasone) combined with a gentle emollient (Eucerin). Neither laboratory tests nor a biopsy were performed. His lesions showed improvement within about 7 days of discontinuing the drug.

Patient's timeline

Day	Event	Actions taken	Outcome
0	Patient begins treatment with low-dose venlafaxine for generalized anxiety disorder (GAD)	–	–
~30	Patient develops erythematous, papular rash involving skin and oral mucosa	Venlafaxine discontinued owing to suspicion of drug-induced erythema multiforme (EM); Appropriate pharmacotherapy initiated	Rapid improvement of rash noted, with significant resolution of skin lesions
~37	Complete resolution of cutaneous lesions observed, confirming diagnosis of venlafaxine-induced EM	–	–

Discussion

Diagnosing drug-induced cutaneous reactions presents challenges owing to their unpredictable nature, polymorphic manifestations, and frequently multifactorial causes. Such reactions may be classified as immediate, appearing within 1 hour following drug administration and manifesting as urticaria, angioedema, or anaphylaxis. Conversely, delayed reactions can emerge after 6 hours and may even take weeks to months to develop post administration [7].

This case underscores the complexities in diagnosing drug-induced cutaneous reactions in elderly patients with multiple comorbidities and polypharmacy. The patient's presentation of erythematous, papular rash following the initiation of venlafaxine aligns with a delayed cutaneous drug reaction. Venlafaxine, while effective in treating generalized anxiety disorder, has been documented in

rare cases to induce skin reactions, further complicating diagnosis, especially in the context of concurrent use of multiple medications with potential for adverse cutaneous effects.

Risk factors contributing to cutaneous drug reactions include advanced age, concurrent systemic diseases, and coexisting viral infections [8]. Age-related physiological factors likely compounded the patient's risk of a cutaneous reaction. Reduced hepatic and renal function in the elderly can alter the pharmacokinetics of drugs such as venlafaxine, potentially increasing serum concentrations and enhancing drug bioavailability beyond the therapeutic range [8].

In addition, the patient's polypharmacy regimen, including cardiovascular agents such as aspirin, clopidogrel, and metoprolol, further underscores the challenge, as polypharmacy increases the risk of drug–drug interactions and hypersensitivity responses, particularly in a setting of chronic systemic illness [8]. In cases of concurrent viral infection, immune tolerance to medications may be compromised, resulting in heightened immune-mediated skin reactions [8].

Erythema multiforme-like eruptions, although uncommon in association with antidepressants and antipsychotics, have been documented with agents such as fluoxetine, paroxetine, bupropion, clozapine, and risperidone [7, 8]. Similar cutaneous reactions have also been observed in patients receiving treatment with anticonvulsant medications, including carbamazepine, valproic acid, lamotrigine, gabapentin, and oxcarbazepine [8].

Erythema multiforme (EM) is an immune-mediated condition characterized by distinctive targetoid skin lesions, often involving the mucosal membranes in severe cases. Historically confused with Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), EM is now recognized as a distinct clinical entity. The condition is most frequently triggered by infections, particularly herpes simplex virus (HSV), and less commonly by medications or other factors [9, 10].

EM is a rare condition with an annual incidence estimated at less than 1%. It predominantly affects individuals under 40 years of age, with a slight male predominance. Although it occurs across all ethnicities and regions, EM is more prevalent in young adults and occasionally in children [6, 10].

The pathogenesis of EM is primarily driven by a cell-mediated immune response, often triggered by infections such as herpes simplex virus (HSV) or by drug hypersensitivity [6, 9]. In HSV-associated EM, viral antigens deposited in the skin initiate an immune response involving $CD4^+$ and $CD8^+$ T cells, with the latter releasing interferon-gamma (IFN-γ), leading to keratinocyte apoptosis and characteristic target lesions [9].

Drug-induced EM, however, is associated with tumor necrosis factor-alpha (TNF-α), which contributes to epithelial damage [11]. Genetic predisposition, such as associations with specific human leukocyte antigen (HLA) types, also plays a role, particularly in recurrent cases [10]. Histologically, EM lesions exhibit keratinocyte necrosis, lymphocytic infiltrates, and basal cell vacuolization [11]. These processes highlight the interplay between immune dysregulation and triggering antigens, distinguishing infectious from drug-induced EM and emphasizing the need for targeted interventions [9]. With venlafaxine, the mechanism behind EM remains speculative but may be linked to its metabolism. In some patients, venlafaxine or its metabolites may inadvertently bind to skin proteins or modify immune processing pathways, thus sensitizing the immune system. Variability in drug metabolism, especially in older adults with reduced hepatic and renal function, may increase drug bioavailability and lead to higher systemic levels, potentially enhancing this hypersensitivity response.

EM presents with polymorphous lesions, including the hallmark target lesions comprising concentric rings of erythema. These lesions predominantly appear on the extremities and spread centripetally. The condition is classified into EM minor, involving skin lesions without mucosal involvement, and EM major, which includes mucocutaneous manifestations such as oral, ocular, or genital involvement. Prodromal symptoms such as fever and malaise may precede mucosal lesions [10, 12].

Target lesions are a hallmark of EM, although they may not be universally present. Initial lesions commonly appear as round, erythematous papules that progress into the classic target-shaped morphology. Cutaneous manifestations generally exhibit a symmetrical distribution, predominantly involving the extensor surfaces of the distal extremities [13]. The absence of pruritus in this patient's lesions is consistent with drug-induced EM, which generally presents as asymptomatic, nonpruritic lesions [10].

Mucosal involvement frequently manifests as diffuse erythematous areas, painful erosions, or bullae. Oral mucosal involvement is especially prevalent, observed in up to 70% of erythema multiforme cases, and typically affects the vermilion border, buccal and labial mucosa, non-attached gingiva, and tongue [11].

The development of erythema multiforme lesions typically spans 3–5 days, with resolution usually occurring within approximately 2 weeks [6]. In cases associated with HSV, eruptions typically arise within 2–17 days following an HSV episode [11].

Diagnosis of EM is primarily clinical, relying on the history of preceding infections or medications and the presence of characteristic skin lesions. Histopathological

examination can confirm the diagnosis in atypical cases, revealing necrotic keratinocytes and a lymphocytic infiltrate. Differentiation from SJS and TEN is critical, as these conditions present with more extensive epidermal detachment and higher mortality [6, 11].

The differential diagnoses for this patient included urticaria, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), viral exanthems, acute generalized exanthematous pustulosis (AGEP), fixed drug eruption (FDE), autoimmune bullous diseases, and leukocytoclastic vasculitis (LCV). However, these were systematically ruled out for various reasons [6]. Histological examination and clinical correlation remain essential for accurate differentiation. The patient's characteristic targetoid lesions, limited mucosal involvement, and absence of systemic symptoms strongly support a diagnosis of EM.

DRESS, which is characterized by systemic symptoms such as fever, lymphadenopathy, and eosinophilia, could not be fully excluded since a complete blood count (CBC) was not provided; however, the absence of systemic symptoms makes it less likely [6]. SJS involves extensive mucosal involvement and epidermal detachment, features not observed in this case [11]. Viral exanthems typically present with systemic symptoms such as fever or malaise, which were absent here [6]. AGEP is marked by pustules and fever, neither of which were noted in this presentation [13]. FDE is localized and recurs at the same site upon re-exposure, differing from the widespread targetoid lesions seen here [12]. Autoimmune bullous diseases, such as bullous pemphigoid, typically manifest with tense bullae and chronic recurrence, which did not align with the patient's findings [6]. Leukocytoclastic vasculitis (LCV), characterized by palpable purpura and histopathological findings of neutrophilic infiltration and fibrinoid necrosis, was also considered. However, LCV is typically associated with palpable purpura rather than targetoid lesions, and the absence of purpura in this case makes this diagnosis less likely [14].

The chronicity and fixed duration of erythema multiforme (EM) lesions, lasting 7–14 days, further distinguish it from transient conditions such as urticaria [11].

Differential diagnosis	Key features	Reason ruled out
Urticaria	Transient, pruritic wheals that typically resolve within 24 hours	Lesions in this case were fixed and lasted 7–14 days, inconsistent with urticaria
DRESS	Systemic symptoms such as fever, lymphadenopathy, eosinophilia; delayed onset	Systemic symptoms absent; CBC not performed but no clinical signs of systemic involvement
Stevens–Johnson syndrome (SJS)	Extensive mucosal involvement, epidermal detachment, systemic symptoms (e.g., fever)	No epidermal detachment or extensive mucosal involvement observed
Viral exanthems	Diffuse rash often accompanied by fever, malaise, and other systemic symptoms	Lack of systemic symptoms such as fever or malaise in this patient
Acute generalized exanthematous pustulosis (AGEP)	Widespread pustules with fever; rapid onset	No pustules or fever noted
Fixed drug eruption (FDE)	Localized, recurring lesions at the same site upon re-exposure to the offending drug	Lesions were widespread and not localized or recurring at the same site
Autoimmune bullous diseases	Tense bullae, chronic recurrence, systemic associations (e.g., bullous pemphigoid)	No bullae or chronic recurrence noted; presentation inconsistent with autoimmune bullous diseases
Leukocytoclastic vasculitis (LCV)	Palpable purpura, histological findings of neutrophilic infiltration, and fibrinoid necrosis	No palpable purpura; biopsy not performed but no clinical features of vasculitis
Erythema multiforme (EM)	Targetoid lesions, limited mucosal involvement, absence of systemic symptoms, fixed duration	Patient's presentation matches this diagnosis, supported by clinical features and response to treatment

Management of EM focuses on addressing the underlying cause and alleviating symptoms. For HSV-associated EM, antiviral prophylaxis with acyclovir is effective in preventing recurrences. Acute episodes may require topical corticosteroids and antihistamines to manage symptoms. Severe cases with mucosal involvement may necessitate hospitalization for supportive care, including intravenous fluids and electrolyte repletion. For refractory or recurrent EM, systemic immunosuppressants such as corticosteroids, thalidomide, or dapsone may be considered [9, 12, 13].

Accurate identification of drug-induced erythema multiforme can be challenging owing to its variable presentation and the absence of specific laboratory marker. Histopathologic examination, while helpful in ambiguous cases, was deemed unnecessary in this patient given the clear clinical picture and rapid response to drug cessation. A high index of clinical suspicion should be maintained when there is an acute onset of multiple target or atypical lesions. The presence of multiple, distinct target lesions, particularly on the extremities, and measuring less than 3 cm in diameter, is strongly suggestive of EM. However, when diagnosis is uncertain, skin biopsy can help distinguish EM from other drug reactions and dermatologic conditions [6].

The lack of biopsy confirmation in this case weakens diagnostic certainty, as a biopsy could provide histopathologic evidence to confirm erythema multiforme minor (EMM) and help rule out other cutaneous drug reactions. Histopathological findings typical of EM, such as epidermal necrosis, subepidermal bullae, and lymphocytic infiltration, are valuable in distinguishing EM from conditions such as DRESS or SJS/TEN, which display distinct histopathologic patterns [11].

However, it is important to acknowledge the potential limitations of biopsy. In some cases, biopsy results may be nonspecific, failing to provide a definitive diagnosis. In addition, sample variability can affect accuracy, especially if the biopsy is taken from a less active lesion, potentially missing key diagnostic features [6, 11].

The rapid improvement of this patient's lesions after venlafaxine discontinuation highlights the importance of prompt drug withdrawal when a cutaneous drug reaction is suspected, as continued exposure may increase the risk of progression to more severe conditions, such as Stevens–Johnson syndrome or toxic epidermal necrolysis. This risk is particularly relevant in elderly patients with comorbidities and concurrent use of other medications that may exacerbate hypersensitivity reactions.

Conclusion

This case highlights the critical importance of careful assessment of cutaneous symptoms in patients with complex medical backgrounds, particularly among the elderly, who are at an elevated risk for drug-related adverse effects owing to polypharmacy and age-related physiological changes. It contributes to the expanding body of literature on rare cutaneous reactions associated with antidepressant therapy and underscores the need for heightened vigilance when new-onset cutaneous eruptions arise following the initiation of psychiatric medications.

Clinicians should maintain a high index of suspicion for drug-induced erythema multiforme (EM), especially in cases presenting with target lesions or atypical papular eruptions in the absence of systemic symptoms. Prompt recognition and discontinuation of the offending agent are crucial to prevent the progression to severe drug reactions and to mitigate risks in managing patients with complex psychiatric and medical comorbidities.

Moreover, this case underscores the importance of ongoing research into the mechanisms underlying rare drug-induced reactions, particularly those associated with psychiatric medications. As the use of such medications continues to grow in diverse populations, future studies should focus on identifying specific risk factors and molecular pathways that predispose individuals to these adverse events. Establishing robust pharmacovigilance systems and developing tailored guidelines for monitoring high-risk patients will be critical in enhancing patient safety and therapeutic outcomes. These efforts have the potential to bridge current gaps in knowledge and pave the way for more precise and personalized approaches to managing and preventing rare adverse drug reactions.

Abbreviations

EM	Erythema multiforme
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
GAD	Generalized anxiety disorder
DRESS	Drug reaction with eosinophilia and systemic symptoms
SJS	Stevens–Johnson syndrome
TEN	Toxic epidermal necrolysis
MRI	Magnetic resonance imaging
FDA	Food and Drug Administration
AGEP	Acute generalized exanthematous pustulosis
FDE	Fixed drug eruption
HSV	Herpes simplex virus
IFN-γ	Interferon-gamma
TNF-alpha	Tumor necrosis factor-alpha
EMM	Erythema multiforme minor

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Author contributions

AM was responsible for conceptualizing the study, curating the data, and drafting the initial manuscript. MR provided critical review and editing of the manuscript. She also supervised the study, providing guidance throughout the writing process and ensuring the manuscript's final form. Both authors read and approved the final manuscript.

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Availability of data and materials

All data are included within the article.

Declarations

Ethics approval and consent to participate

Owing to the observational nature of this case report, which does not involve any interventions or experimental procedures, formal ethical approval was not required.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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