Published by
Saidu Medical College

OPEN ACCESS

ISSN (P): 1819-4583
ISSN (E): 3007-9470

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Citation:
Khan A, Ahmad K, Khalil A, Shah A, Muhammad A, Khan I. Clozapine-induced acute generalized exanthematous pustulosis: a case report. J Saidu Med Coll. 2025;15(4):714–717.

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Funding:
The authors received no external funding for this study.

Conflicts of Interests:
The authors have declared that no competing interests exist.

Data Sharing Statement:
The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

Received: October 07, 2024
1st Revision: September 21, 2025
Accepted: October 05, 2025

Case Report

Clozapine-Induced Acute Generalized Exanthematous Pustulosis: A Case Report

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https://doi.org/10.52206/jsmc.2025.15.4.1095

Abstract

Background: Background: Clozapine is one of the most effective treatments for resistant schizophrenia; however, it can cause severe hematological and, rarely, dermatological reactions.

Case Presentation: We describe a 25-year-old woman with treatment-resistant schizophrenia who developed acute generalized exanthematous pustulosis (AGEP) four days after clozapine initiation. The rash appeared as widespread erythematous pustules over the face, trunk, and limbs, confirmed clinically as AGEP. Clozapine was discontinued, and she was treated with oral antihistamines and topical calamine, leading to full recovery within two weeks.

Discussion: Clozapine-induced AGEP is exceedingly rare, with few cases reported in the literature. The reaction is thought to result from a type IV hypersensitivity mechanism. Prompt recognition, drug withdrawal, and multidisciplinary care are crucial for favorable outcomes.

Conclusion: This case underscores the importance of dermatological monitoring in patients receiving clozapine. Early identification and intervention can prevent complications and optimize treatment continuity.

Keywords: Acute Generalized Exanthematous Pustulosis, Adverse drug reaction, Clozapine, Schizophrenia, Skin eruption.

Introduction

Clozapine is considered the gold standard for treatment-resistant schizophrenia because of its superior efficacy and impact on symptom control. However, its clinical use is restricted due to several potentially life-threatening adverse effects such as agranulocytosis, myocarditis, seizures, and less commonly, dermatological reactions [1,2]. Cutaneous manifestations associated with clozapine are rare but may range from benign urticaria to severe life-threatening reactions such as Stevens-Johnson syndrome and Acute Generalized Exanthematous Pustulosis (AGEP) [3].

While drug-induced AGEP is most often triggered by antibiotics and antifungal agents, antipsychotics including risperidone, olanzapine, and aripiprazole have occasionally been implicated [4–7]. Reports of clozapine-induced AGEP remain scarce in the literature. Here, we describe a rare case of clozapine-induced AGEP in a young woman with chronic schizophrenia, highlighting diagnostic challenges, interdisciplinary management, and the clinical need for vigilance among mental health professionals.

Patient Information

A 25-year-old unmarried female with a 14-year history of schizophrenia presented with persistent auditory hallucinations, delusions, disorganized thinking, and impaired daily functioning. Multiple prior pharmacological treatments, including risperidone, olanzapine, and haloperidol, had resulted in only partial symptomatic improvement. She also exhibited obsessive-compulsive behaviors and long-standing somatic delusions, notably the fixed belief of having a lizard stuck in her throat for 11 years.

Her medical history included a previous tonsillectomy and episodes of gastroenteritis. There was no known history of drug allergies or family history of dermatologic or autoimmune conditions.

Diagnostic Assessment

The diagnosis of AGEP was based on rapid onset of sterile pustules, absence of mucosal involvement, and resolution within days after drug withdrawal. Laboratory investigations did not show any evidence of infection or leukocytosis. Histopathological confirmation through skin biopsy was not performed, representing a limitation. However, the close temporal relationship between clozapine exposure and rash onset, coupled with rapid improvement after discontinuation, supported a diagnosis of clozapine-induced AGEP [2,4].

Clinical Findings

Due to limited response to previous medications, clozapine therapy was initiated. On day four of treatment, at a dose of 100 mg daily, she developed erythematous pustular eruptions on her neck, face, and forearms. With further titration to 150 mg, the rash worsened, spreading to the trunk and limbs, accompanied by mild facial swelling. Initial dermatologic evaluation suggested urticaria, but follow-up assessment favored AGEP based on the morphology and distribution of the lesions.

The Naranjo Adverse Drug Reaction Probability Scale yielded a score consistent with a "probable" adverse drug reaction, linking the eruption to clozapine. Differential diagnoses included viral exanthem, autoimmune blistering disorders, and drug-induced urticaria, all of which were ruled out clinically [1,8].

Timeline

- Day 0–3: Clozapine initiated, titrated to 100 mg daily.
- Day 4: Onset of erythematous pustular rash over neck and face
- Day 5–6: Lesions spread to trunk and limbs; facial swelling observed.
- Day 7: Clozapine discontinued; dermatology confirmed AGEP.
- Days 8–14: Managed with oral loratadine and topical calamine; marked improvement noted.
- Week 2: Complete resolution of rash; psychiatric stabilization achieved with risperidone (8 mg/day) and ECT.
- Week 4: Sustained remission of both dermatologic and psychiatric symptoms during follow-up.

Therapeutic Intervention

Clozapine was discontinued immediately after dermatologic confirmation of AGEP. Symptomatic treatment included oral loratadine (10 mg daily) and topical calamine lotion to relieve itching and erythema. Under dermatology supervision, the lesions improved without systemic corticosteroids. Given her psychiatric relapse risk, risperidone was initiated and gradually increased to 8 mg/day, along with a structured course of electroconvulsive therapy (ECT).

Follow-Up and Outcomes

Within one week of stopping clozapine, the pustular rash began to resolve, and by the second week, complete recovery was observed with no residual scarring. The patient remained stable on risperidone and continued outpatient psychiatric follow-up. No recurrence of dermatological symptoms was noted over a one-month period, indicating a favorable outcome following prompt discontinuation and appropriate symptomatic care [3,9].

Discussion

Clozapine-induced AGEP is an exceptionally rare adverse event, with very few reported cases in the literature [1,3,5]. AGEP is a severe cutaneous drug reaction characterized by the sudden appearance of sterile pustules on erythematous skin, often accompanied by fever and leukocytosis. It typically resolves within two weeks after the offending drug is withdrawn. The reaction is thought to result from a type IV hypersensitivity mechanism mediated by activated T cells releasing cytokines that attract neutrophils to the epidermis [6,9].

Most commonly, AGEP is associated with antibiotics such as aminopenicillins and macrolides; however, psychotropic drugs like risperidone, aripiprazole, and clozapine have also been implicated [4–7]. Previous reports have described clozapine-related dermatologic effects including phototoxicity [1], pityriasis rosea-like eruptions [5], and urticaria [3,8].

Our case shares similarities with earlier observations but also presented with facial swelling suggestive of mild angioedema, a feature that can complicate differentiation from other hypersensitivity reactions. Nevertheless, the temporal pattern of onset and complete resolution following cessation of clozapine strongly supported AGEP as the most likely diagnosis.

This case emphasizes the need for dermatologic awareness in psychiatric practice. Although hematologic monitoring is mandatory for clozapine, clinicians should also be alert to dermatologic symptoms that may indicate serious cutaneous adverse reactions. Early collaboration between psychiatrists and dermatologists is crucial for effective management and prevention of morbidity [2,9].

Conclusion

Clozapine, while highly effective for treatment-resistant schizophrenia, can cause rare but clinically significant dermatologic reactions such as AGEP. Early detection, immediate drug discontinuation, and appropriate dermatologic management are vital for recovery. Multidisciplinary coordination between psychiatry and dermatology ensures accurate diagnosis and safe therapeutic transition. Clinicians must remain vigilant to safeguard patient well-being when prescribing clozapine.

Learning Points

- AGEP should be considered in the differential diagnosis of acute pustular eruptions in patients receiving clozapine.
- Prompt recognition and withdrawal of the offending drug are essential for favorable outcomes.
- Dermatologic surveillance should accompany hematologic monitoring in clozapine therapy.
- Collaboration between dermatologists and psychiatrists enhances diagnostic accuracy and patient safety.
- Atypical features such as facial edema may indicate overlapping hypersensitivity reactions and warrant careful evaluation.

Authors' Contributions

All authors meet the ICMJE criteria for authorship. They have reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 6: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

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