

## Clozapine-induced angioneurotic edema

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### Abstract

Many prescribed drugs can cause cutaneous rashes and eruptions, which may present in various forms and severity. Most of these reactions are mild; however, the severe cases can lead to life-threatening complications. The most severe of these reactions may include angioedema, acute generalized exanthematous reactions, Stevens–Johnson syndrome and toxic epidermal necrolysis. We report two cases wherein the patients developed classical angioneurotic edema on clozapine therapy and improved rapidly when clozapine was stopped.

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### 1. Introduction

There are many prescribed drugs that can cause cutaneous rashes and eruptions, which may present in various forms and severity. Most of these reactions are mild; however, the severe cases can lead to life-threatening complications. Adverse reactions to drugs manifesting as cutaneous rashes occur in up to 8% of the general population and in 2% to 3% of hospitalized patients [1]. The most common of these include generalized rashes (50% to 95%) and urticaria (5% to 22%) [1–3]. Severe skin reactions may include angioedema, acute generalized exanthematous reactions, Stevens–Johnson syndrome and toxic epidermal necrolysis [4]. Some of the drugs associated with angioedema include angiotensin-converting enzyme inhibitors, insulin, aspirin, nonsteroidal anti-inflammatory drugs, beta-lactam antibiotics, sulfonamides and antipsychotics like risperidone [5,6], olanzapine [7], droperidol [8,9] and chlorpromazine [10], although these are extremely rare. Variants of allergic reactions to clozapine have also been reported [11–14]. We report two cases wherein the patients developed classical angioneurotic edema on clozapine therapy and improved rapidly when clozapine was stopped.

### 2. Case report 1

A 45-year-old married man with no significant past medical or psychiatric history and family history of bipolar illness on his father's side who was diagnosed as having undifferentiated schizophrenia was started on olanzapine 20 mg/day. He had shown poor response to adequate trials of both haloperidol and risperidone in the past. Admission laboratory tests, including serum chemistry, liver function and total and differential white blood cell count, were within

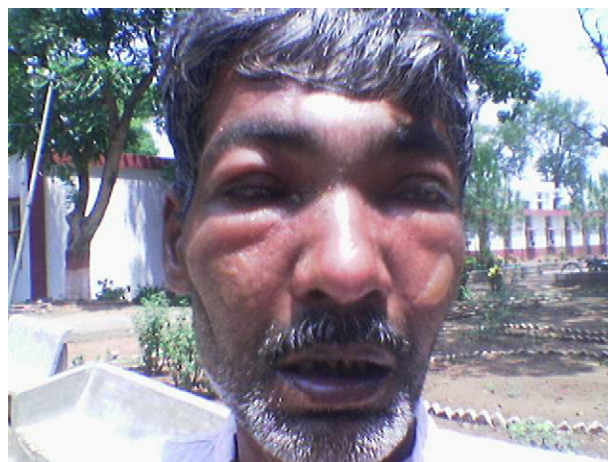


Fig. 1. Periorbital swelling, exfoliation and blisters on the cheek due to clozapine.

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normal limits. As the patient showed only partial improvement on olanzapine even after 6 weeks, it was discontinued, and he was started on clozapine, which was slowly increased to 150 mg/day after 15 days. On the second day after the clozapine dosage reached 150 mg/day, he developed vomiting followed by fever. This was associated with swelling over the periorbital region, exfoliation and blisters on the cheek. A dermatological consultation done at this time indicated that the patient had maculopapular rash and angioedema (Fig. 1). The total white blood count at this time was 17,900 (normal range, 4000–11,000), and the differential count showed a neutrophil count of 96%. Clozapine was stopped, and he was treated via injection of dexamethasone, 2 mg bid, and pheneramine, bid. The patient's angioedema improved dramatically, and he totally recovered in 3 days. He was restarted on olanzapine 15 mg/day upon discharge.

### 3. Case report 2

A 46-year-old married man with a past history of diabetes mellitus and hyperthyroidism, which were under treatment, was admitted with a diagnosis of bipolar affective disorder, mania with psychotic symptoms. On admission, he was elated and exhibited aggressive behavior. He could not be treated with lithium due to hyperthyroidism and could not afford sodium valproate due to his financial condition. He had shown poor response to carbamazepine in the past. Other antipsychotics could not manage his disruptive behavior, and hence, he was started on ECTs but did not show a significant improvement even after receiving eight ECTs. Baseline blood investigations, including total and differential counts, were within normal limits. He was then started on clozapine, which was slowly increased to 50 mg/day over 4 days, during which he developed fever with periorbital edema, exfoliating blisters on the cheek and flushing of the face. Through an in-house dermatological consultation done at the time, he was diagnosed as having angioedema. The total white blood count at that time was 11,900 (normal range, 4000–11,000), and the differential count showed a neutrophil count of 75%. Clozapine was stopped, and he was treated via injection of hydrocortisone, 2 mg bid, and pheneramine, bid. His symptoms subsided within 2–3 days. He was then started on sodium valproate, 1 g/day, which was made available through certain charitable organizations, and he was asymptomatic at discharge.

### 4. Discussion

Angioedema is characterized by painless, nonpruritic, nonpitting and well-circumscribed areas of edema due to increased vascular permeability mediated by histamine, serotonin and kinins (bradykinins), causing the arterioles to dilate while inducing a brief episode of vascular leakage in the venules. It can cause complications that range from

dysphagia to respiratory distress, to complete airway obstruction, to death due to laryngeal edema.

It is classified as hereditary, acquired, allergic, secondary (to medications) or idiopathic. It tends to occur more in women than in men, and the frequency increases after adolescence, with the peak in the third decade of life. The allergic form of angioedema may be mediated by immunoglobulin E, resulting from ingestion of drugs like clozapine, or it could be complement mediated [15]. An inherited deficiency of C1-esterase inhibitor may also have led to a genetic susceptibility to developing angioneurotic edema with clozapine [16]. Considering the past and family history and response to antihistaminics and steroids, it is most probable that our patient developed an allergic angioedema to clozapine.

Our patients developed maculopapular rash and angioedema upon the administration of a stable dose of clozapine, and symptoms resolved fairly rapidly with the discontinuation of the medication and administration of resuscitative measures. The above clinical picture occurring in both males, coupled with the absence of other associated clinical signs of hepatitis, lymphadenopathy, liver function test changes, leukopenia, eosinophilia or neutrophilia, supports a diagnosis of angioedema and maculopapular eruptions secondary to clozapine administration. However, skin testing was not performed due to the risk of developing erythroderma, and rechallenge was not possible due to ethical reasons. Complement assays also could not be performed due to the lack of testing facilities at our institute.

### 5. Conclusion

Drug-induced adverse reactions may vary in severity and have to be monitored closely to prevent life-threatening complications. The drug should be identified and withdrawn immediately, and appropriate supportive treatment measures should be undertaken. With the increasing use of clozapine, especially for treatment-resistant schizophrenia, psychiatrists should be fully aware of the potential complications of these medications.

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