SHORT COMMUNICATION

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Olanzapine-induced Drug Reaction with Eosinophilia and Systemic Symptoms: Case Report and Review of the Literature

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Hypersensitivity syndrome, also known as DRESS (drug reaction with eosinophilia and systemic symptoms), is a rare drug-induced systemic allergic reaction characterized by exanthema and extracutaneous symptoms (e.g., hepatitis, nephritis, lymphadenopathy, fever, eosinophilia). It frequently takes a severe, protracted course, with a mortality rate of up to 5–10% (1). The accompanying skin reaction ranges from mild maculopapular exanthema to erythroderma with pustules and/or tension blisters. Mucosal involvement is uncommon. A relatively long latency period of several weeks between the initiation of the drug and the onset of clinical symptoms is typical (1). Potential triggers include anticonvulsants, allopurinol, sulphonamides, and antiretroviral medication (2). Case reports described olanzapine, a second-generation neuroleptic used to treat schizophrenia and bipolar disorder, as an occasional trigger of DRESS, but did not include allergological skin testing to confirm the diagnosis (3–7). In this report, we present a case of olanzapine-induced DRESS, with diagnostic evidence of drug-specific sensitization by both patch and prick testing.

CASE REPORT

A 49-year-old female patient was started on olanzapine and lithium to treat bipolar affective disorder. In addition, metamizole was administered as an analgesic (the exact duration and frequency of metamizole intake could not be determined retrospectively). Three weeks after starting olanzapine and lithium, she developed a fever of up to 40°C, accompanied by a macular rash that started on her legs and rapidly spread to over 50% of her body surface area. Her condition deteriorated rapidly; she developed vigilance disturbances and anuria for 24 h, and was transferred to an internal medicine intensive care unit. Laboratory tests on admission confirmed acute renal failure and revealed moderately elevated liver enzymes (aspartate aminotransferase 53 [10–35] U/L, alanine aminotransferase 120 [10–35] U/L, gamma-glutamyl transferase 167 [<40] U/L), an elevated international normalized ratio (INR, 1.48 [0.85–1.18]), and marked blood eosinophilia (6,300 [30–270] /μL). Over the next few days, the exanthema worsened, with pronounced acral edema and tension blisters. There was no evidence of mucosal involvement. Computed tomography revealed generalized lymphadenopathy; bone marrow and lymph node biopsies showed no evidence of underlying hematological disease. The histological examination of a skin biopsy (obtained 8 days after the onset of symptoms) from the right forearm revealed subepidermal cleft formation and an increased lymphocytic inflammatory infiltrate in the upper dermis, consistent with a drug hypersensitivity reaction (**Fig. 1**A). A definite diagnosis of DRESS was made as the patient scored 8 out of a maximum of 9 points on the clinically validated Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) classification for DRESS (8). Prednisolone was started on admission at an initial dose of 250 mg per day and tapered over 2 months. Clinical symptoms gradually improved under steroid therapy. As the exanthema resolved, numerous milia formed on the dorsum of the hands, in the area of the former tension blisters.

Four months later, the patient was referred for allergy testing. The allergological history revealed no evidence of pre-existing drug allergy. The patient's history of atopy was positive for al-

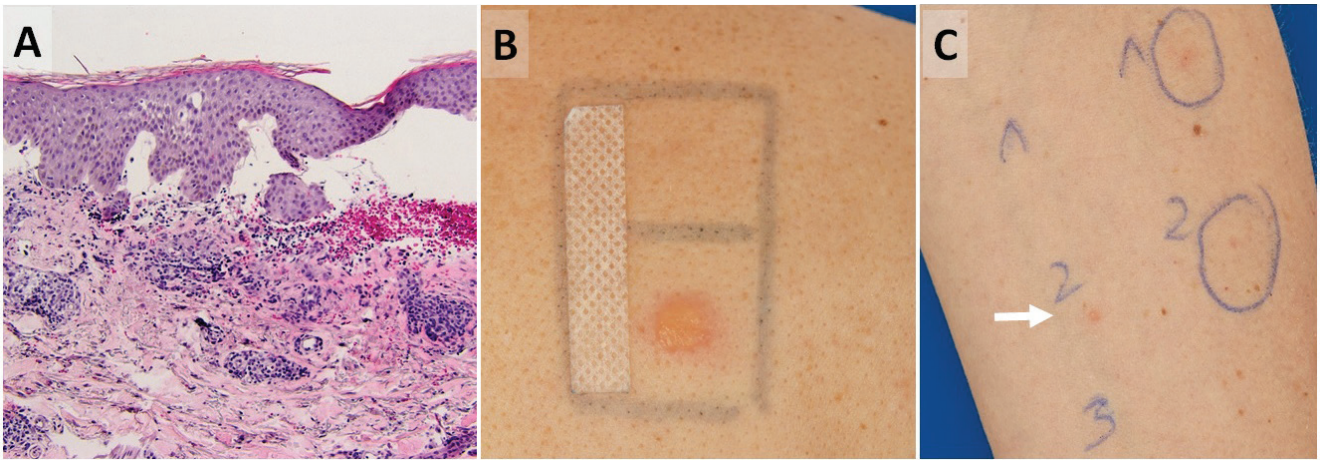

Fig. 1. Histology and skin test results in olanzapine-induced DRESS. (A) Histology from the right forearm (day 8 after the onset of symptoms) showing subepidermal edema/cleft formation, and lymphocyte-predominant inflammatory infiltrate in the upper dermis, consistent with drug hypersensitivity reaction (haematoxylin-eosin stain, 10x). (B) Patch testing with lithium (upper test site) and olanzapine (lower test site) showing sensitization to olanzapine, reading after 48 h. (C) Prick testing (1: lithium, 2: olanzapine, 3: metamizole) and intradermal testing (circled; 1: metamizole 1:100, 2: metamizole 1:1,000) showing sensitization to olanzapine (arrow), reading after 48 h.

lergic rhinoconjunctivitis and mild bronchial asthma, which did not require pharmacological treatment. Olanzapine, lithium, and metamizole had been discontinued at the onset of the hypersensitivity reaction. Skin prick and patch tests with readings after 24, 48, and 72 h were performed with olanzapine and lithium; prick and intradermal tests at concentrations of 1:1,000, and 1:100 were carried out with metamizole. From the 24-h reading onwards, patch test results showed sensitization to olanzapine with a bullous test reaction at 48 h (Fig. 1B). A positive prick test was observed at the 48 and 72-h reading (Fig. 1C). Skin tests with metamizole and lithium were negative. Skin testing was well tolerated, and there was no evidence of a systemic cutaneous or extracutaneous flare-up. The patient was provided with an allergy passport for olanzapine with a note regarding possible immunological cross-reactivity with tricyclic neuroleptics (e.g., clozapine, quetiapine), and tricyclic antidepressants (e.g., amitriptyline, nortriptyline, opipramol). The future use of lithium and metamizole according to medical indication was endorsed.

DISCUSSION

Since the first approval of olanzapine-containing products for the treatment of mental disorders in 1996 (9), sporadic cases of treatment-associated hypersensitivity including DRESS have been published in the medical literature (3–7) (**Table I**). A summary of 23 further cases was documented in a drug safety alert issued by the U.S. Food and Drug Administration (FDA) in 2016 (9). The latency period between treatment initiation and onset of symptoms has been reported to range from 4 to 60 days, with a median of 19 days in the FDA series. Reported symptoms include eosinophilia, fever, hepatitis, lymphadenopathy, diarrhea, respiratory symptoms, and exanthema. A severe course requiring hospitalization and prolonged steroid therapy was documented in the majority of cases. One fatal outcome is included in the FDA series; however, the authors state that the patient was on multiple medications and the cause of death was unclear (9). An important shortcoming is that published reports do not document allergy testing to confirm olanzapine-specific sensitization (3–7). Only the FDA series includes 6 patients reporting positive confirmatory test results, with sensitization detected by lymphocyte stimulation test, lymphocyte transformation test, patch test, and/or "other allergy workups" (details not given). One patient experienced a recurrence of symptoms upon resumption of olanzapine treatment (9). The majority of cases (all published case reports and 16/23 of the patients reported to the FDA) of olanzapine-associated DRESS must therefore be considered "unconfirmed". The lack of diagnostic results to confirm olanzapine as the culprit drug is an important issue when more than 1 medication has been discontinued and treatment of the psychiatric condition needs to be reinitiated.

The observed reluctance to perform skin testing after an episode of suspected olanzapine-induced DRESS may be due to (*i*) a lack of experience and/or validated diagnostic tests, or (*ii*) safety concerns. (*i*) A low quality of evidence for the role of skin testing in DRESS due to heterogeneity in methodology, result analysis, and reporting of cohorts was confirmed in a recent systematic review including 17 articles and overall 290 DRESS patients who underwent skin testing (10). Nevertheless, the authors emphasize the crucial role of cutaneous testing in determining the culprit drug in DRESS patients. They document a moderate sensitivity, which depends on the test method used. The highest proportion of positive results is obtained with the intradermal test using intravenous drug formulations (66.5%). Positive results are reported in 25.0% of prick tests and 58.4% of patch tests. (*ii*) Recurrence of exanthema and/or mild systemic symptoms has been sporadically reported to be induced by patch testing with the culprit drug in

Table I. Published reports of olanzapine-associated hypersensitivity (up to March 2025)

Author (year)	Sex (age)	Time to onset of skin reaction (days)	Comedication	Symptoms	Treatment	Outcome	Histology	Allergy testing
Raz A et al. (2001) (3)	M (34)	60	None	Eosinophilia, fever, hepatitis, axillary lymph node enlargement, exanthema	Prednisone	Restitutio ad integrum	Consistent with drug hypersensitivity	No
Penchilaiya V et al. (2017) (4)	M (17)	4	Chlorpromazine, promethazine, haloperidol, lorazepam, valproate	Eosinophilia, fever, diarrhea, bronchitis, exanthema	Supportive management and hydration	Restitutio ad integrum	No	No
Bixby AL et al. (2019) (5)	M (18)	17	Lithium, lorazepam, valproate	Thrombocytopenia, creatine phosphokinase elevation, fever, hypotension, diarrhea, exanthema	Prednisone	Restitutio ad integrum	Consistent with drug hypersensitivity	No
Sogo A et al. (2022) (6)	M (49)	10	Meropenem, vancomycin, levofloxacin, lansoprazole	Eosinophilia, fever, liver dysfunction, exanthema	Prednisolone	Restitutio ad integrum	Consistent with drug hypersensitivity	Lymphocyte stimulation test (negative)
Sohi MK et al. (2023) (7)	F (47)	17	None	Lymphadenopathy, exanthema	Prednisone, diphenhydramine	Restitutio ad integrum	No	No
Ickrath K et al. (present report)	F (49)	21	Lithium, metamizole	Eosinophilia, elevated liver enzymes, renal failure, fever, reduced vigilance, lymphadenopathy, exanthema	Prednisolone	Restitutio ad integrum (except milia)	Consistent with drug hypersensitivity	Patch and prick testing (sensitization to olanzapine)
FDA Drug Safety Communication (2016) (9)	Report of 23 cases of olanzapine-associated DRESS as identified by the FDA Adverse Event Reporting System database, 1996–2016. Median time to onset 19 days; hospitalization required in 18 cases; 1 fatality. Confirmatory test results specific for olanzapine in 6 cases (lymphocyte stimulation test, lymphocyte transformation test, patch test and/or "other allergy workups")							

F: female; M: male; FDA: U.S. Food and Drug Administration.

DRESS patients (11, 12). However, serious adverse events are very uncommon and the overall safety of skin tests to determine the culprit drug in DRESS is considered acceptable (10).

The case presented is an example of successful patch and prick testing in a case of definite DRESS that (*i*) was well tolerated, (*ii*) identified olanzapine as the culprit drug, and (*iii*) excluded alternative triggers, allowing resumption of lithium therapy to prevent further manic episodes in bipolar disorder. International collaboration including studies in larger cohorts is essential to standardize the methodology and reporting measures of hypersensitivity testing in patients with DRESS.

The authors have no conflicts of interest to declare.

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