Letter to Editor

Chlorpromazine-induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare condition affecting between 1 in 1,000 to 1 in 10,000 patients after exposure to associated drugs.[1] It is a life-threatening condition with a mortality rate of about 10%, which necessitates early identification and treatment.[2] We describe a case of DRESS syndrome secondary to the use of chlorpromazine in a female with paranoid schizophrenia, the diagnostic challenge encountered, and the successful treatment of the condition with corticosteroids.

CASE REPORT

Ms. Y, a 30-year-old female, was a known case of schizophrenia for 3 years. In view of significant aggression, the patient was admitted for inpatient care. Baseline physical examination and biochemical investigations were normal except for features suggestive of iron deficiency anemia, for which she was started on oral iron supplements. The patient had no history of any medical illness, and she was not on any medication apart from olanzapine (she was on olanzapine 20 mg for more than three months) at the time of presentation. She had not responded to a trial with olanzapine and had amenorrhea with the same. She was initiated on T. chlorpromazine at the dose of 50 mg/d. T. olanzapine was tapered and stopped over the period of 1 week, and the dose of chlorpromazine was gradually increased up to 600 mg/d over a period of 2 weeks. On the 21st day after initiating chlorpromazine, she developed itching all over the body along with easy fatigability, which progressed within the next 2–3 days to erythematous maculopapular rashes all over the body, tiny pustules over the face, xerosis over the legs, along with puffiness of face, periorbital swelling [Figures 1 and 2], and dizziness. T. cetirizine 10 mg three times daily and calamine lotion were started, and the dose of chlorpromazine was decreased to 100 mg/d. On the fourth day after the onset, the above symptoms exacerbated within 30 min of receiving T. chlorpromazine 100 mg. On systemic examination, she had persistent tachycardia of 150 beats per minute (bpm), blood pressure (BP) of 90/60 mmHg, and body temperature as measured in the axilla of 101°F. Chlorpromazine was immediately stopped. The vitals were monitored once every 4 h and hydration was adequately maintained.

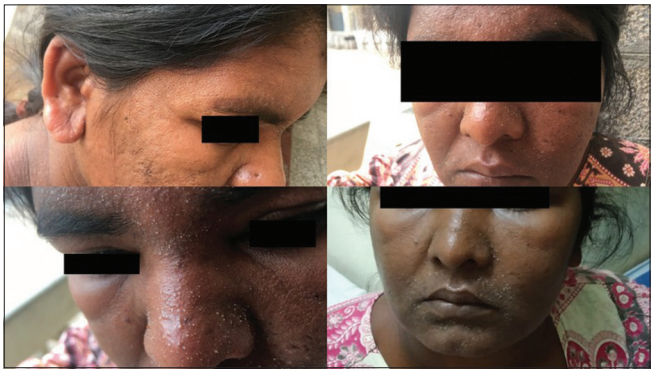

Figure 1: Facial puffiness, periorbital swelling, and a pustular rash over the face

Antipyretics were administered for fever. Hematological investigations revealed erythrocyte sedimentation rate (ESR) 30 mm/h (normal range 0–12 mm/h), eosinophilia (16.3%, normal range 0-6%), increased absolute eosinophilic count (1173.6 cells/μL, normal range 450–550 cells/μL), lymphocytopenia (15.4%, normal range 20–40%), and mildly raised alkaline phosphatase (152 U/L, normal range 30-120 U/L).

Initially, the possibility of chlorpromazine-induced photosensitive rash only was considered. Later, the patient was suspected of having DRESS syndrome, given the systemic involvement and rashes involving the nonsun-exposed areas of the body. Dermatologist consultation was sought, and a clinical diagnosis of DRESS syndrome was made. We liaised with a cardiologist to rule out myocarditis, in view of persistent tachycardia. On evaluation, there were no features suggestive of myocarditis—2D echocardiography, electrocardiogram, and cardiac enzyme profile (creatine kinase = 67 U/L, creatine kinase MB = 13 U/, troponin T = 0.004 ng/ml) were within normal limits. The patient scored nine on the Naranjo adverse drug reaction probability scale, which suggested the definitive role of chlorpromazine in the occurrence of DRESS.

For the treatment of DRESS syndrome, the patient was started on T. prednisolone 40 mg/day (tapered off over 10 days), T. cetirizine 10 mg twice daily, and calamine lotion local application over the skin lesions, with adequate hydration. Exogenous corticosteroid administration is known to induce or exacerbate

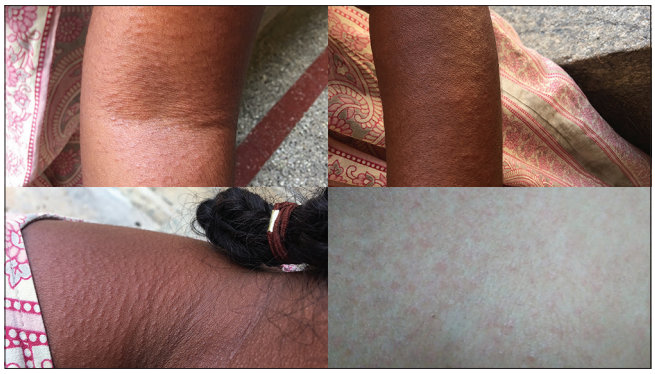

Figure 2: Maculopapular rashes over the upper limb, abdomen, neck, and shoulder region

psychosis.[3] Hence, close monitoring was done for psychotic symptoms as the patient was temporarily off antipsychotic medications while on oral prednisolone. However, we did not notice any new or worsening of pre-existing psychotic symptoms. Over a period of seven days, the patient's dermatological lesions and systemic manifestations gradually disappeared. The management of DRESS syndrome, in this case, was in line with the recommendation.[4]

After the resolution of DRESS syndrome, the patient was started on T. risperidone 2 mg/d for her psychotic symptoms. There was no cross-reaction or reappearance of dermatological symptoms after starting risperidone. The dose of risperidone was gradually increased up to 6 mg/d. The patient maintained improvement in her psychotic symptoms and was subsequently discharged from the hospital. The patient has been in follow-up for four months, and she is doing well with respect to her psychotic symptoms and there has not been any reappearance of DRESS symptoms.

DISCUSSION

DRESS syndrome usually manifests after a prodromal latency period of about 2-8 weeks.[5] The clinical feature consists of fever, rash, lymphadenopathy, hematological findings (eosinophilia, leukocytosis, thrombocytopenia, and anemia), and multisystem involvement (hepatic and renal systems are commonly involved).[6] The cutaneous manifestations typically consist of an urticarial maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma. Due to the wide variety of clinical manifestations mimicking various medical conditions, it poses a challenge for an appropriate, timely diagnosis. Currently, the DRESS syndrome is diagnosed primarily based on the clinical and laboratory abnormalities, and many diagnostic criteria are available. Our patient met the RegiSCAR criteria[2] (scored 4 out of 7) suggestive of a diagnosis of DRESS syndrome. However, compared to other commonly used diagnostic criteria for the diagnosis of DRESS, such as Bocquet's criteria,[7] in this case, only cutaneous manifestation and blood counts abnormality were predominantly present, but the systemic involvement was not prominent.

Among the psychotropic medications, the antiepileptic-mood stabilizers—carbamazepine, oxcarbazepine, valproate, and lamotrigine—have been reported to induce DRESS syndrome.[4] There is a case report of DRESS syndrome with a combination of olanzapine and sodium valproate,[8] and the same patient had earlier received chlorpromazine. However, it is unclear whether chlorpromazine had led to the sensitization for the development of DRESS syndrome. To our knowledge, this is the first report of chlorpromazine-induced DRESS syndrome. Cutaneous adverse effects of chlorpromazine are widely reported and include photo-sensitive reactions such as maculopapular rash, urticaria, pigmentation, subacute lupus erythematosus, lichenoid eruptions, severe exfoliative reactions, and toxic epidermal necrolysis.[9] Life-threatening side effects of chlorpromazine are reported in about 0.6% of the subjects who receive the drug.[10] Chronic administration of chlorpromazine is associated with the development of a lupus-like circulating anticoagulant and a variety of immunological abnormalities.[11] One of the well-studied mechanisms for the photosensitive reactions to chlorpromazine is a delayed hypersensitivity immune reaction.[9] Although the precise pathogenesis of DRESS remains elusive, hypothesized mechanisms include deficient drug metabolism and reactive metabolites, delayed cell-mediated immune response, genetic predisposition with specific human leukocyte antigen (HLA) haplotypes, and viral reactivation.[6,12] Hence, the appearance of DRESS syndrome in our patient might be due to a delayed hypersensitivity immune reaction. Although steroid administration is very well known to induce new or worsen pre-existing psychotic symptoms, psychiatrists should be aware that not all patients on steroids may experience psychosis, and life-threatening conditions such as DRESS syndrome take the precedence in management as demonstrated in this case. However, one should be cautious about the worsening of psychotic symptoms in already diagnosed patients with psychosis. In such instances, it might be beneficial to switch over to antipsychotic medications that are least likely to cause DRESS syndrome or to use alternative psychotropic medications, which include benzodiazepines for the temporary management of aggressive behavior.

An important limitation of our report is that we did not get the skin biopsy of the lesions, due to pragmatic constraints. Still, this report suggests that

DRESS syndrome can be one of the serious adverse effects of chlorpromazine. Patients on chlorpromazine developing serious dermatological adverse effects should be assessed to rule out DRESS syndrome, in view of the high mortality rate in patients with DRESS syndrome.[2,13] Further systematic clinical and genetic studies are needed to evaluate the association of DRESS syndrome and chlorpromazine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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