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Lithium dress: a pediatric case report

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Abstract: The reaction to drugs with eosinophilia and systemic symptoms called DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) is part of a broad spectrum called toxicodermas. The exact incidence is not known in children; However, a mortality rate that can be as high as 10% has been estimated in the literature. We present the case of a teenage patient with a personal history of bipolar affective disorder (BD), who received sertraline, quetiapine and trazodone on an outpatient basis. Due to the presence of hallucinations, lithium was added to the management. Ten days later she went to the emergency department due to the appearance of a skin rash and systemic symptoms, for which a clinical condition secondary to hypersensitivity to medications was suspected.

Key words: DRESS syndrome; lithium; eosinophilia

1 Introduction

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) is a drug-induced hypersensitivity reaction. It can be fatal and is common, involving skin rash, hematologic abnormalities, lymphadenopathy, and organ involvement [1]. It is found worldwide, and incidence rates of 0.9 per 100,000 patients per year have been reported in African populations, although this figure may be underestimated given the heterogeneity of its clinical presentation. Its frequency varies depending on the type of medication; a higher prevalence has been reported in women (male-to-female ratio of 0.8), but this finding is not consistent across different studies [2]. In our setting, records of DRESS cases are scarce, and even more so in the pediatric population. Diagnosis is primarily clinical and poses a challenge due to the variety of presentations; however, it should be considered in any child exposed to a new medication.

The following is a review of the clinical case of an adolescent female patient with a personal history of bipolar affective disorder (BD), who was receiving sertraline and quetiapine on an outpatient basis. Due to the presence of hallucinations, lithium was added to her treatment regimen. Ten days later, she presented to the emergency department with a skin rash and systemic symptoms, leading to suspicion of a clinical picture secondary to drug hypersensitivity.

2 Clinical case

A 13-year-old female patient presented to a high-complexity hospital in Medellín with a seven-day history of rounded, pruriginous macular lesions that initially appeared on her lower extremities and later spread throughout her body, without mucosal involvement. These were associated with cervical and retroauricular lymphadenopathy, headache, and subjective fever. She also reported odynophagia. Her significant medical history included bipolar affective disorder (BD) for which

she was being treated with sertraline, trazodone, and lithium; lithium therapy had been initiated 10 days prior.

She was initially evaluated by pediatrics; the patient was hemodynamically stable, with a blood pressure of 100/60 mmHg, heart rate of 87, respiratory rate of 18, temperature of 36.6 ° C, and oxygen saturation of 99%. On physical examination: left cervical lymphadenopathy measuring 1.5 × 1.5 cm; two right cervical lymph nodes measuring 1 × 1 cm; bilateral retroauricular lymph nodes smaller than 1 cm; bilateral axillary lymph nodes measuring 2 × 2 cm; smooth oropharynx with mild erythema; tenderness on abdominal palpation in the right hypochondrium, and erythematous maculopapular skin lesions that blanched on pressure and were located on the abdomen, the medial aspect of the lower extremities, and the lateral aspect of the right upper extremity, associated with edema.

On neurological examination, the patient presented with hyperreflexia, with no other additional findings. Infectious causes were ruled out. Subsequently, given the history of recent initiation of a new psychotropic medication, intoxication or an adverse drug reaction was suspected. Laboratory tests revealed a complete blood count with eosinophilia but no lymphocytosis; platelet counts were within normal limits; renal and hepatic function and electrolyte levels were normal; and serum lithium level was within normal ranges (Table 1).

Table 1. Results of laboratory tests performed upon admission

Test	Result
Complete blood count	Eosinophils 553 (7%), lymphocytes 3160 (40%)
Serum electrolytes	K 4.1 mmol/L, Na 140 mmol/L
Liver function	AST 21, ALT 22; AST 18, ALT 19; total bilirubin 0.4 mg/dL, direct bilirubin 0.4 mg/dL
Renal function	Creatinine 0.61 mg/dL, BUN 11 mg/dL
Serum lithium level	0.9 (Reference range: 0.6-1.2 mEq/L)

Although laboratory tests revealed no evidence of liver involvement, the elevated eosinophil count was notable, as the normal range for this age group (13 to 18 years) is 0 to 500 (0 to 3%) [3], which, in conjunction with the clinical presentation, raised suspicion of a DRESS diagnosis. The RegiSCAR score was calculated at a total of five points, classifying the case as probable. It was decided to hospitalize the patient for monitoring of symptoms, dermatological changes, and laboratory follow-up. She was evaluated by the toxicology department; during a follow-up interview, symptoms associated with the initiation of lithium were identified, and these symptoms improved following its discontinuation. Over the next three days, the patient's skin rash began to improve, resolving completely by the fourth day. By day six, a significant decrease in eosinophils, along with resolution of lymphadenopathy, fever, and rash, was observed. Consequently, she was discharged and placed on outpatient management with sertraline and valproic acid, which she tolerated well.

3 Discussion

DRESS syndrome is a severe hypersensitivity reaction to drugs or their active metabolites. Its latency period has not been clearly established in the literature; however, it has been suggested that it can range from two weeks to three months between drug exposure and the onset of symptoms [4]. It was classically described in association with anticonvulsants such as phenytoin; later, other anticonvulsants such as phenobarbital and carbamazepine were also reported, all of which shared the presence of arene oxide groups. Over time, the list expanded to include not only anticonvulsants (valproic acid, lamotrigine) but also antibiotics (sulfonamides, dapsone) and other medications (allopurinol) [5-7].

It is estimated that the incidence in adults can range from 1 in 1,000 to 1 in 10,000. Although there are no very clear data on the actual incidence in children, it is known to be lower than in adults. However, it should be noted that mortality

in children can reach 10%; therefore, it is important to consider it as a differential diagnosis in the pediatric population [8,9].

The pathophysiology of DRESS syndrome has not been fully elucidated. It is described as a Type IV hypersensitivity reaction resulting from a complex interaction between genetic factors, an altered immune response, and abnormalities in metabolism and detoxification mechanisms, which together lead to the formation of neoantigens. This leads to T-cell stimulation and, consequently, cytokine production and an increase in eosinophils in both the blood and peripheral tissues. Furthermore, the role of viral infections—particularly herpesvirus 6 and others (HHV-8, EBV, and CMV)—has not yet been fully elucidated. The most widely supported theory to date is that the immune response to the drug induces viral reactivation, leading to lymphocyte stimulation, rather than being a triggering event in the etiopathogenesis of this syndrome [9].

In addition, various hypotheses have been proposed regarding how drugs may induce this reaction [10]. Specifically, in the anticonvulsants most closely associated with DRESS syndrome—such as phenytoin, phenobarbital, and carbamazepine—a common mechanism has been identified that is due to the presence of an aromatic ring in their chemical structure. Upon metabolism, this ring is converted into arenoxides, which are highly electrophilic compounds; consequently, they can covalently bind to macromolecules, leading to cytotoxicity and activation of the immune system [7,10].

Clinically, it is important to note that this condition can be highly mimetic, as the skin manifestations can be diverse, including pustules, vesicles, blisters, and target-shaped lesions, among others [6,11]. The most common skin manifestation is a morbilliform rash, that is, diffuse pruritic macules. In addition, it is associated with systemic symptoms, primarily affecting the lymphatic, hematologic, and hepatic systems; however, it can also involve other systems — including the gastrointestinal, renal, neurological, cardiovascular, endocrine, and pulmonary systems — which can lead to more severe clinical presentations. Thus, when evaluating a patient with suspected DRESS, multi-organ involvement must be ruled out [5].

Diagnosis requires a high degree of clinical suspicion due to its varied presentation, especially in pediatric patients, where exanthematous diseases are common. A key diagnostic clue is the recent onset (within the last two to eight weeks) of a medication, particularly if accompanied by a skin rash, hematologic abnormalities, abnormal liver function tests, lymphadenopathy, or involvement of a target organ. Because of this, diagnosing DRESS is considered challenging; consequently, in 2007, Kaun et al., as part of the European Registry of Severe Cutaneous Adverse Reactions (SCAR), developed criteria based on clinical and laboratory data for recognizing the condition, known as RegiSCAR. This is a scoring system that classifies the condition as "definite" when the score is greater than five points, "probable" for four or five points, "possible" for two to three points, and "no" when the score is less than two points [12,13]. The patient's RegiSCAR score was five points, which corresponds to probable DRESS syndrome. This is an accepted and recognized score; however, the original criteria were those proposed by Bocquet et al., and other criteria have also been proposed by the Japanese Research Committee on Severe Cutaneous Adverse Reactions (J-SCAR). These latter two have been classified as less useful and applicable due to their inflexibility and the limited availability of the respective laboratory tests required [14].

To date, there are no prospective treatment-based clinical trials; therefore, current management recommendations are based on expert opinions and case reports [9]. Ultimately, the most important step will always be to discontinue the causative agent as quickly as possible; if this is not possible, all potentially causative medications should be discontinued. This measure, in addition to improving the prognosis, may be the only step necessary to achieve remission.

In milder cases, such as the one presented by the patient, treatment is supportive, consisting primarily of managing symptoms with topical steroids, antihistamines, and emollients. There is no indication for systemic steroids in the absence of systemic involvement. In moderate-to-severe cases, immunosuppressants, intravenous immunoglobulin, and plasmapheresis have also been used [12].

The significance of the case presented lies in the fact that DRESS is not commonly reported in association with lithium. Although lithium frequently causes dermatological adverse effects such as acne, psoriasis, or alopecia, it is uncommon for it to trigger DRESS [15,16]. It is noteworthy that the patient was being treated with other psychotropic medications, including sertraline, quetiapine, and trazodone. Bradford Hill's criteria for causality—such as temporality, consistency, and plausibility—could be established [17]. Symptoms began to appear three days after starting lithium; clinical and paraclinical improvement was observed only after discontinuation of lithium, and not of the other psychotropic medications. From a pharmacovigilance perspective, the patient was also evaluated using the Naranjo Algorithm, with a score of eight points, classifying the reaction as probable [18].

A review of the literature revealed that multiple drugs can cause DRESS, but lithium is not included. In a systematic review published in 2020, which included 82 articles involving 148 patients under 18 years of age with a final diagnosis of DRESS, the majority of triggering medications were anticonvulsants and antibiotics, accounting for 52.6% and 33.6% in each case, respectively, with no mention of lithium [19]. Case reports specifically involving lithium are scarce; the majority of which involve adults, and only one was found in the pediatric population: a 16-year-old female adolescent with a history of bipolar disorder who developed DRESS syndrome three weeks after starting treatment with lithium carbonate. In this case, the reason for presentation was nausea and multiple episodes of vomiting, in contrast to our patient, for whom the skin rash was the initial complaint [20].

4 Conclusion

With regard to the case presented, it can be concluded that DRESS, although a rare condition, should be considered as a differential diagnosis, especially in the pediatric population, given the similarity of its skin manifestations to those of childhood exanthematous diseases. It is also important to bear in mind that, although it is not typically associated with anticonvulsants and antibiotics, lithium should be included on the list of potential causative medications.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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