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Case Report

Reversible Myocarditis Associated with Carbamazepine-Included Dress Syndrome

Fatma Essafi[1,2], Khaoula Ben Ismail[1,2]*, Najla Ben Slimene[1,2], Sana Dorgham[1,2], Imen Talik[1,2], Moez Kaddour[1] and Takoua Merhbene[1,2]

[1]University of Tunis EI Manar, Faculty of Medicine, Medical Intensive Care Unit, Regional Hospital of Zaghouan, Tunisia

[2]Research Unit for Respiratory Failure and Mechanical Ventilation UR22SP01, Abderrahmen Mami Hospital, Ministry of Higher Education and Scientific Research, Ariana, Tunisia

***Corresponding Author**: Khaoula Ben Ismail, University of Tunis EI Manar, Faculty of Medicine, Medical Intensive Care Unit, Regional Hospital of Zaghouan, Tunisia, Research Unit for Respiratory Failure and Mechanical Ventilation UR22SP01, Abderrahmen Mami Hospital, Ministry of Higher Education and Scientific Research, Ariana, Tunisia.

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Abstract

Introduction: DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is a severe toxidermia that combines skin manifestations with systemic involvement. Cardiac involvement has been rarely reported. Nevertheless, its occurrence is often a poor prognostic factor.

Case Description: This was a 44-year-old man with a history of bipolar disorder who was recently diagnosed, and put on carbamazepine. He was admitted to the medical ward with fever, extensive maculo-papular skin lesions with acute renal failure with preserved diuresis that had been evolving for 7 days. The diagnosis of a severe toxidermia type DRESS syndrome was evoked at this stage (probable according to the RegiSCAR score).

Carbamazepine was stopped and the patient received corticosteroids and antihistamines. Two days later, he developed acute respiratory failure and was transferred to the ICU. Examination showed a conscious, febrile patient in respiratory distress, hemodynamically stable, a generalized maculopapular and desquamative rash, facial oedema, aphthous ulceration on the inside of the cheeks and on the palate, and bilateral axillary and cervical lymphadenopathies. Electrocardiogram showed a sinus tachycardia with negative T waves.

Laboratory investigations revealed: eosinophil count at 253 el/mm^3, creatinine level at 110 µmol/l, C-reactive protein (CRP) was found as 125 mg/l, troponin-hs level of 570 ng/ml and N-terminal pro-hormone of basic natriuretic peptide (NT-proBNP) at 4594 pg/l. An echocardiogram showed a moderately impaired left ventricular ejection fraction at 43% with homogeneous kinetics and elevated left ventricular filling pressures. A chest CT scan showed perihilar flaky alveolar opacities and bilateral pleural effusion. Viral serologies: EBV, CMV, Herpes virus 6 showed previous immunity. Hepatitis serology was negative as well as the immunological assessment. The skin biopsy showed typical lesions of toxidermia. A DRESS syndrome complicated by myocarditis and acute lung oedema was considered. The patient was treated with non-invasive ventilation, diuretics and corticosteroids with improvement after 48 hours.

Conclusion: Dress syndrome can become complicated even after withdrawal of the presumed culprit treatment. Close monitoring is necessary to ensure early diagnosis.

Keywords: *Drug Reaction with Eosinophilia and Systemic Symptoms; Myocarditis; Carbamazepine*

Abbreviations

ANCA: Anti-Neutrophil Cytoplasmic Antibody; BAL: Bronchoalveolar Lavage; CBZ: Carbamazepine; CRP: C-Reactive Protein; CBZ: Carbamazepine; DRESS: Drug Rash with Eosinophilia and Systemic Symptoms; ICU: Intensive Care Unit; LVEF: Left Ventricular Ejection Fraction; SCAR: Severe Cutaneous Adverse Reaction; WBC: White Blood Cells

Introduction

Dress syndrome or Drug Rash with Eosinophilia and Systemic Symptoms syndrome is an unexpected, serious form of adverse cutaneous drug reaction. It is a potentially life-threatening syndrome characterized by skin rash, fever, facial edema, lymphadenopathy, haematological abnormalities and multivisceral involvement. Liver is the most common organ involvement [1] Cardiac involvement was rarely reported but was potentially fatal complication of DRESS [1,2]. It typically occurs within 2 to 8 weeks of initiation of therapy. The most common culprit medications are anticonvulsants, antibiotics, and allopurinol [3]. We report a case of a young man who presented with a diffuse skin rash and acute renal failure, after starting carbamazepine and secondary myocarditis. We aimed through this case report to emphasize on the interest of early diagnosis.

Case Report

A 44 -year-old man was admitted to intensive care unit with an acute respiratory failure associated with pruritic skin rash, facial oedema and fever of 7 days' duration. On further history, he had recently diagnosis with bipolar disorder and had been started on carbamazepine, Risperidone and Prazepam four weeks prior to the onset of symptoms. Seven days before his admission, he presented a pruritic skin rash that started on the face and hands and became progressively generalized (Figure 1), associated with systemic symptoms of fever and asthenia.

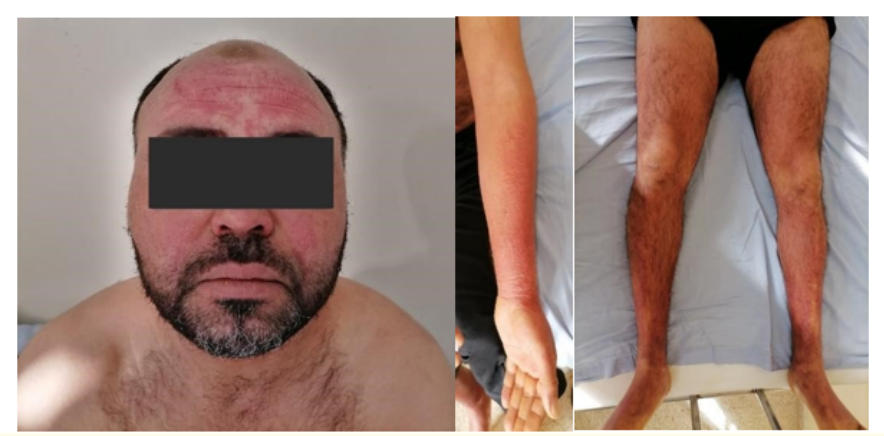

Figure 1: *Skin rash at admission.*

He was treated with amoxicillin/clavulanic acid and paracetamol.

At the second day of treatment, he invokes the emergency department for a worsening of cutaneous involvement and persistent fever. His examination showed confluent macular rash with erythema and vesicles on the face, neck, trunk, back, lower limbs and abdomen.

Carbamazepine induced-DRESS syndrome was suspected. Assessment of causality using the RegiSCAR scoring system established a probable relationship with CBZ.

Carbamazepine was discontinued and the patient received intravenous corticosteroids and antihistaminic medication, with progressive improvement. Two days after admission, he developed acute respiratory failure and agitation prompting his transfer to the intensive care unit.

On the day of ICU admission, clinical examination revealed an apathetic, dehydrated patient. He was conscious but restless. His respiratory rate was 28 breaths/minute with intercostal draught. He did not have chest pain. His peripheral oxygen saturation was 95% under 15 l/min of O_2. His heart beat was 106/min. His blood pressure was measured as 110/60 mm Hg. His body temperature was 38.4°C.

Specific skin findings included generalized erythematous, maculopapular and desquamative eruption on the entire body with pustules on the face and the neck, facial oedema, aphthous ulceration on the inside of the cheeks and on the palate. Nikolsky test was negative. Painless bilateral axillary and cervical lymphadenopathy. Laboratory tests showed: hemoglobin: 11.4 g/dL, white blood cells (WBC): 12660/mm^3 (9875/mm^3 neutrophils, 253/mm^3 eosinophils), platelet count: 151000/mm^3, urea = 6.5 mmol/l, creatinine = 110 µmol/l, prothrombin level: 55%. aspartate amino transferase (ASAT = 48), alanine aminotransferase (ALAT = 53), serum electrolytes, bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase and creatinine kinase (CK)-MB were found to be normal. C-reactive protein was found as 125 mg/L. lactate dehydrogenase (LDH = 578 UI/L) ferritin 2136 ng/ml. Cardiac biomarkers showed troponin-hs level of 57 ng/ml (normal range: 0 - 50 ng/ml), and N-terminal pro-hormone of basic natriuretic peptide (NT-proBNP) of 4594 pg/l (normal range: NT-proBNP < 125 pg/mL). Sinus tachycardia with ST-T changes was detected by an electrocardiography (ECG) (Figure 2).

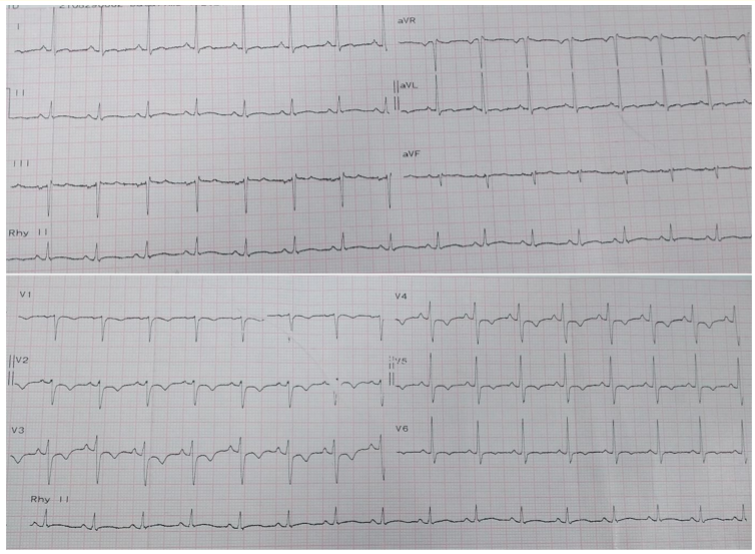

Figure 2: *ECG showing sinus tachycardia with negative ST-T wave changes (V1-V6).*

An echocardiogram revealed global hypokinesis with reduced left ventricular ejection fraction (LVEF) 46% (Figure 3), and grade 1 diastolic dysfunction with an increase in filling pressure with e/e =16. Cytomegalovirus, Epstein-Barr virus and human herpes virus 6 serologic tests showed that the patient had prior immunity. Hepatitis A, B and C tests were found to be negative. The patient's urine was

negative for pneumococcal and *Legionella pneumophila* serotype 1 antigens. Serologic data revealed no abnormal findings suggestive of collagen vascular diseases, including anti-neutrophil cytoplasmic antibody (ANCA), and no microorganisms grew on a sputum culture. RT-PCR for SARS-CoV-2 was negative. An incisional skin biopsy showed various degrees basal vacuolar alteration, dyskeratosis, lymphocyte and eosinophilic polynuclears exocytosis, dermal edema, superficial perivascular inflammation by mixed cells (mainly eosinophils but not atypical cells), thus diagnosed as toxiderma (Figure 3).

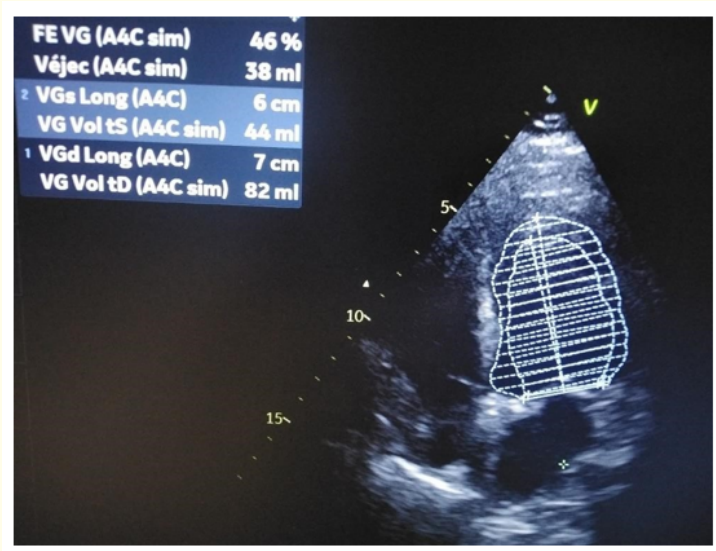

Figure 3: *Echocardiography showing systolic dysfunction.*

Thoracic CT scan showed perihilar consolidative and ground glass opacities with air bronchograms significantly affecting all lobs and bilateral pleural effusion.

Fiberoptic bronchoscopy revealed normal airways and the bronchoalveolar lavage (BAL) cellular analysis demonstrated a predominance macrophages (81%) with 17% neutrophils, 2% lymphocytes, and 0% eosinophil. No microorganisms grew on a BAL fluid culture. Head Computed tomography scan was normal. The lumbar puncture was normal. Cardiac and cerebral MRI were normal. The patient was diagnosed with DRESS syndrome and secondary myocarditis complicated by acute heart failure, according to both the biopsy results and the RegiSCAR study group scoring system criteria in table 1 and 2. He was made under CPAP and diuretics. Antibiotics (cefotaxime, ciprofloxacin) were started while waiting for bacteriological results. 48h after initiating this treatment the patient presented a worsening of skin lesions and continuous fever at 40°C. Dress syndrome worsened by antibiotics was suspected. Blood and BAL fluid cultures came back negative and procalcitonin was found as 0.06. Antibiotics were immediately interrupted and patient's evolution was marked by a spectacular improvement with total disappearance of all skin lesions. Troponin and N-terminal pro-B-type natriuretic peptide (BNP) levels decreased (4,8 ng/ml and 2,230 pg/ml). Repeat echocardiogram showed improvement in ejection fraction (EF) 55%. The Patient was discharged after ten days of hospitalization.

Discussion

Dress syndrome is a rare, severe and potentially life-threatening adverse drug reaction that includes a severe skin eruption, fever, hematologic abnormalities, and systemic involvement such as hepatitis, nephritis, interstitial pneumonitis, or myocarditis with eosinophilia

[4,5]. However, the relationship between the causative drug and the skin reaction is not clearly established in all cases. There is no reliable laboratory test to determine the culprit drug specially if polypharmacy.

It usually occurs within 2 to 8 weeks after the initiation of drug therapy [6,7]. Our patient was within the same range, he developed the first clinical signs 3 weeks after initiation of carbamazepine. The latency time in some reports was shorter especially with antibiotics. Some cases with chronic intake were described [8].

Various groups of drugs are known as inducers of this syndrome [9,10]. Aromatic anticonvulsants including carbamazepine are the most common offending drugs [11,12]. As reported in a series of 27 patients with DRESS syndrome in which Carbamazepine was the causative agent in 29.6% [13]. Other series described few cases of DRESS syndrome associated with Carbamazepine [7,14-16]. Herein was the most likely to be the causative agent. Reoccurrence of a generalized pruritic skin rash and fever two days after levofloxacin prescription may suggest a fluoroquinolone-induced DRESS syndrome. Various diagnostic criteria were developed to identify dress syndrome such as Borquet., *et al.* RegiSCAR study group and Japanese consensus group.

The RegiSCAR (European registry of severe cutaneous adverse effects) constitutes a European registry of severe cutaneous adverse reaction (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS have established different probability to diagnosis as certain, probable, possible or excluded [17] (Table 1).

Score	-1	0	1	2	Min	Max
Fever ≥38.5°C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia Eosinophils Eosinophils, if leucocytes < 4.0 x $10^9.L^{-1}$		No/U	0.7-1.499x$10^9.L^{-1}$ 10-19.9%	≥ 1.5x$10^9.L^{-1}$ ≥ 20%	0	2
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Skin rash extent (% body surface area) Skin rash suggesting DRESS Biopsy suggesting DRESS	 No No	No/U U Yes/U	> 50% Yes			
Organ involvement[a] Liver Kidney Lung Muscle/heart Pancreas Other organ		 No/U No/U No/U No/U No/U No/U	 Yes Yes Yes Yes Yes Yes		0	2

Resolution ≥15 days	No/U	Yes			-1	0
Evaluation of other potential causes						
Antinuclear antibody Blood culture Serology for HAV/HBV/HCV/ Chlamydia/mycoplasma If none positive and ≥ 3 of above negative			Yes		0	1
Total score					-4	9

Table 1: *Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case [17].*

U: Unknown/unclassifiable.

HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

a: After exclusion of other explanations.

1: One organ; 2: Two or more organs.

Final score < 2 =no case; final score 2–3=possible case; final score 4–5=probable case; final score > 5=definite case.

Our patient met six of seven RegiSCAR criteria as detailed in the table 2 and the diagnosis of DRESS syndrome was certain. He had organ involvement: myocarditis, renal failure but no hyper-eosinophilia. In our case the skin biopsy shows the typical histological description found in this syndrome.

Its etiology is still unknown. Some pathologic mechanisms are at increased risk of developing DRESS, including altered cellular immune reaction [9], genetic predisposition to develop drug reactions reactivation of some virus and association with HLA alleles. Even if some drugs were described as causal agent of DRESS syndrome, it is important to eliminate other associated factors such as viral infection (herpes, CMV, EBV) [7,18].

Myocarditis is infrequently reported in dress syndrome whereas it is a potentially fatal complication. It has been reported with varying incidences from one study to another 4% to 21% of cases of DRESS. It has been described in both children and adults [19,20]. Several clinical signs can be seen including: Tachycardia chest pain, dyspnea, hypotension, cardiogenic shock. The electrocardiogram may show ST segment changes, tachycardia, arrhythmia cardiomegaly and pleural effusions can be seen on the chest radiograph. In some cases, cardiac enzymes may be elevated. Left ventricular dysfunction decreased ejection fraction as well as segmental kinetic disorders can be found in echocardiography and be suggestive of the diagnosis but the certain diagnosis is made by a cardiac biopsy [21]. It is a very intriguing fact that there are two described forms of myocarditis in DRESS: hypersensitivity and acute necrotizing eosinophilic myocarditis (ANEM). ANEM is associated with more than 50% mortality, which is one of the reasons why this topic is important [22]. Treatment of DRESS syndrome is based on supportive care and corticosteroids, whereas initial management of patients with DRESS syndrome is to withdraw all medication immediately [23,24]. In most cases, DRESS syndrome resolved without sequelae after drug discontinuation. In some cases it may progress despite drug discontinuation. Mortality is estimated at 10% but increases with the number and severity of visceral failures [14]. Early recognition and treatment with corticosteroids may improve clinical outcomes. Our patient had rapid clinical response under

Score	-1	0	1
Fever ≥38.5°C		Yes	
Enlarged lymph nodes			Yes
Eosinophilia		No/U	
Atypical lymphocytes		No/U	
Skin involvement			
Skin rash extent (% body surface area) Skin rash suggesting DRESS Biopsy suggesting DRESS	No	Yes/U	> 50%
Organ involvement[a] Liver Kidney Lung Muscle/heart Pancreas Other organ		 No/U No/U No/U	 Yes Yes Yes

Table 2: *The clinical characteristics and variables of our case.*

corticosteroid therapy and adequate symptomatic treatment after discontinuing carbamazepine. Patients with anticonvulsant-induced DRESS syndrome should not be treated with carbamazepine, phenytoin, or phenobarbital because of the risk of cross-reactivity amongst anticonvulsants [7,12,24]. Patient should be informed of his or her illness and the avoidance of any further exposure. All patients with dress syndrome should be monitored and reported to pharmacovigilance centers for further follow-up and to identify the causative drug.

Conclusion

DRESS is a severe cutaneous eruption that typically presents within 2 to 8 weeks after of drug initiation. CBZ is a common psychotropic medication that have been implicated in this reaction. It is difficult to prevent drug adverse reactions but an early diagnosis allows to adequately treat and prevent complications.

Conflict of Interest

This is to certify that I Khaoula Ben Ismail and the author of the article: Reversible myocarditis associated with carbamazepine-included Dress syndrome certify that there is no conflict of interest regarding the publication of this manuscript.

Consent

Written informed consent was obtained from the patient for both photographs and publication of this case.

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