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Carbamazepine-induced DRESS syndrome: a case report

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening, idiosyncratic, acute adverse drug reaction. Fever, morbilliform cutaneous eruption, and eosinophilia are essential features for the diagnosis of this syndrome, along with significant multisystem involvement, hepatitis being the most common, followed by nephritis. The pathogenesis of DRESS syndrome is not yet fully understood. Several hypotheses have been proposed which support the involvement of an intricate interplay of multiple factors. We report a clinical case of DRESS syndrome with renal injury, induced by carbamazepine, in a patient with alcohol abstinence syndrome. In order to define the case, the RegiSCAR score and the Japanese Group score, used in the diagnosis of drug-induced hypersensitivity, were applied. DRESS syndrome is a potentially fatal disease, with a mortality that can reach up to 40% of cases. This condition endangers the patient's life by affecting the internal organs, mainly the liver, kidneys, heart, and lungs. Our case attempts to increase awareness among physicians about this serious disease and the importance of early diagnosis, especially since carbamazepine is a commonly used anticonvulsant drug.

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening, idiosyncratic, acute adverse drug reaction [1]. The incidence of this syndrome is estimated to range from 1:1000 to 1:10000 of drug exposures [2]. The overall mortality rate of this disease is 10-20% [3], but there are studies that present higher mortality rates, up to 40% if organ failure is present [4]. Fever, morbilliform cutaneous eruption, and eosinophilia are essential features for the diagnosis of this syndrome, along with significant multisystem involvement, hepatitis being the most common, followed by nephritis [3]. Highly suggestive of this condition is latency between initial drug administration and specific symptom onset [5]. The pathogenesis of DRESS syndrome is not yet fully understood. Several hypotheses have been proposed which support the involvement of an intricate interplay of multiple factors such as: mutations in genes encoding drug detoxification enzymes leading to the accumulation of drug reactive metabolites, reactivation of human herpes virus 6 and 7, Epstein-Barr virus (EBV), cytomegalovirus (CMV), genetic predisposition associated with certain human leukocyte antigens (HLA), and immunological phenomena [6]. Common drugs associated with DRESS syndrome are anticonvulsants (such as carbamazepine, phenytoin) [7]. The first step in treating the disease is prompt recognition and early discontinuation of the drug involved [8]. Systemic glucocorticoid therapy, intravenous immunoglobulin, antiviral drugs, plasmapheresis, cyclosporine, and symptomatic treatment are part of the appropriate management of this pathology [3]. In DRESS syndrome patients, careful long-term follow-up is crucial and monitoring for autoimmune diseases is required [5].

Case Presentation

A 46-year-old man was admitted to the Department of Internal Medicine with a history of high fever (40.1°C), diffuse pruritic morbilliform cutaneous eruption which had

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been continuing over the last ten days. Two days before hospitalization, the patient's condition worsened, with edema affecting his face and hands. Approximately 6 weeks before, treatment with carbamazepine and vitamin B supplements for his alcohol abstinence syndrome was initiated. The patient's medical history was notable for alcohol abuse, alcoholic steatosis, mitral valve regurgitation, and pulmonary tuberculosis. It is also important to mention that, prior to hospitalization, the patient underwent antibiotic treatment with ampicillin.

On physical examination, his consciousness was clear and his general status was moderate, with a body temperature of 39.3°C, a heart rate of 100 beats per minute, a blood pressure of 100/70 mmHg, and an oxygen saturation of 99%. The patient had important edema of his face and hands, and a diffuse maculopapular erythematous eruption. He also had purpuric lesions on the lower extremities. There was no conjunctival involvement. At the time of admission, no palpable lymph nodes were identified. Apart from tachycardia, cardiovascular examination was normal. The respiratory system was clear bilaterally, without rhonchi or crackles. Digestive system examination revealed the presence of hepatomegaly. There were no signs of focal neurological deficits.

On the day of the admission to our hospital, the patient was referred to an infectious disease specialist, who diagnosed him with acute pharyngitis, interstitial pneumonia, and polymorphous erythema, and prescribed treatment with antibiotics (macrolides: Azithromycin 500 mg/day for 5 days or Clarithromycin 2x500 mg/day for 7 days), antihistamines, and antipyretic drugs. He also recommended a chest X-ray and serological tests for Chlamydia, Mycoplasma, hepatitis B and C, HIV, and syphilis.

Laboratory findings at the time of admission revealed neutrophilia and lymphopenia, a low red blood cell count, a low hematocrit, macrocytosis, and a normal erythrocyte sedimentation rate. The coagulation workup showed a prolonged prothrombin time. The patient's biochemical tests evidenced an aspartate aminotransferase (ALT) level slightly above the upper limit, increased gamma-glutamyl transferase, a low plasma iron level, hypoproteinemia, and elevated C-reactive protein. Urinalysis showed a low urine density and the presence of urobilinogen in the sample. Blood samples for hemocultures were also collected and came back negative.

Abdominal sonography showed hepatomegaly. Chest radiography revealed a 2/2 cm cavity in the right lung, suggestive of an old TB lesion, and also raised the suspicion of interstitial pneumonia. Electrocardiography evidenced sinus tachycardia. The transthoracic echocardiogram results raised the suspicion of mitral valve vegetation, so we referred the patient for a transesophageal echocardiogram. The echocardiogram also revealed pulmonary valve, mitral valve, and tricuspid valve regurgitations. Neck ultrasound showed the presence of round and hypoechoic lymphadenopathy.

The suspicion of DRESS syndrome caused by carbamazepine was raised based on clinical examination, laboratory tests, and imaging investigations, and the patient was referred to a dermatologist. During physical examination, besides the rash, the doctor also identified enlarged lymph nodes in the inguinal area. The dermatologist confirmed our suspicion of DRESS syndrome and recommended treatment with prednisone 1 mg/kg, emollient cream, and a number of laboratory tests including hepatitis C antibodies, HBs antigen, and also tests for Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. The doctor also recommended cessation of carbamazepine administration and monitoring of renal function and blood cell count.

Carbamazepine was immediately withdrawn and no other anticonvulsants were administered. Treatment with peroral prednisone 1 mg/kg and symptomatic medication was administered. We also monitored our patient's blood cell count, renal function, blood pressure, heart rate, body temperature, and oxygen saturation.

During the following weeks, the patient's maculopapular exanthema progressed towards exfoliative erythroderma, with marked exfoliative facial dermatitis (Figure 1).

Figure 1. Exfoliative facial dermatitis: marked erythema and fissures of the facial skin

The laboratory tests improved until the third week of hospitalization, when new complete blood count alterations with leukocytosis (14.02x109 /L) and extensive eosinophilia (3.93x109 /L) were found. The biochemical tests revealed low total proteins and the urine tests showed

proteinuria. It was also observed that CK-MB levels were slightly above the upper limit. Taking into consideration the high eosinophil count, we performed a parasitological stool examination, which detected no parasite eggs or cysts. The eosinophil levels remained high for approximately one week. We continued the treatment recommended by the dermatologist, and the patient's health and laboratory tests improved.

After 4 weeks of hospitalization, our patient was released with no symptoms and improved laboratory tests, and we prescribed prednisone 25 mg/day (with gradually decreasing doses by 5 mg per week), and emollients for his face, thorax and hands. We also recommended avoiding anticonvulsants such as carbamazepine, phenytoin, phenobarbital, or other medications associated with DRESS syndrome.

Discussions

DRESS syndrome is a severe, potentially fatal, idiosyncratic adverse drug reaction [1]. Classical diagnosis is based on skin lesions, fever, and eosinophilia. Rash is the most common feature of this disease and is present in 73-100% of patients. The pattern of the lesions varies from one patient to another. Typically, they involve more than 50% of the body surface and have a polymorphic presentation such as infiltrative papules, plaques which resemble urticarial, target-like or eczema-like lesions [7, 8]. Facial edema is present in 76% of cases. Regarding organ damage, the liver (75%), kidneys (37%), and lungs (32%) are frequently affected [9]. There are atypical presentations of DRESS syndrome with cardiac, neurologic, gastrointestinal, and endocrine manifestations [1]. Our patient presented all the classic clinical features of this syndrome, with important facial edema that disfigured his physiognomy. In addition, the patient had mucosal involvement with pharyngeal erythema. Mucosal membranes are often affected by this disease [5].

Enlarged lymph nodes are also present in 54% of the patients. They can be a clinical finding or revealed by imaging [7]. In our patient, lymph node involvement was identified both by physical examination and neck ultrasonography.

Risk factors for renal involvement in DRESS syndrome include old age and a medical history of kidney disease or cardiovascular diseases [7]. In our patient, the kidney injury manifested as proteinuria, but his renal function recovered completely. Kidney involvement is most commonly seen in DRESS syndrome caused by administration of allopurinol, followed by carbamazepine [1].

Pulmonary involvement in DRESS syndrome is not only defined by clinical findings (cough, dyspnea), but also by chest X-ray. The most common imaging sign of lung injury is interstitial pneumonitis [10]. Our patient's chest radiography raised the suspicion of interstitial lung injury, but without any clinical signs of respiratory symptoms.

Eosinophilia was absent in the first 3 weeks of hospitalization and registered high values only on the 23rd day after admission. It is well known that eosinophilia is often absent initially in DRESS syndrome [5]. The white blood cell count tests in the reported patient are presented in Table I.

Table I. White blood cell count tests in the reported patient

Laboratory parameter	Day 1	Day 2	Day 4	Day 8	Day 23	Day 28
WBC (10Λ3/ul)	5.21	6.75	9.40	16.51	14.02	14.36
EO%	0.0	0.0	1.1	0.4	28.0	18.7
EO# (10Λ3/ul)	0.00	0.00	0.10	-	3.93	2.69

WBC white blood cell count, EO eosinophils

In our case, the culprit drug was carbamazepine. Aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital) are metabolized by cytochrome P450 with the formation of toxic reactive metabolites, which under physiological conditions are converted by epoxide hydroxylase or glutathione transferase to non-toxic components. If these pathways are deficient, the accumulation of toxic metabolites results in altered immune responses and cellular damage [11]. Ampicillin, another drug known to cause DRESS syndrome, was administered to the patient [7]. The relationship between the antibiotic and the pathogenesis of this idiosyncratic reaction was excluded by the short time interval between drug administration and symptom onset.

For the diagnosis of DRESS syndrome, we applied the RegiSCAR criteria for hospitalized patients and the Japanese Group score, used in the diagnosis of drug-induced hypersensitivity. Thus, the case was categorized as definite DRESS syndrome with a score of 7, atypical DRESS syndrome, respectively [12]. The RegiSCAR scoring and the Japanese Group scoring for diagnosis of DRESS syndrome and our case estimations are presented in Table II and Table III.

Table II. RegiSCAR scoring system for diagnosis of DRESS syndrome and our case estimation [12].

CRITERIA	SCORE			
	NO	**YES**	**UNKNOWN**	**CASE SCORE**
Fever ≥38.5°c	-1	0	-1	0
Enlarged lymph nodes ≥2 sites and >1cm	0	1	0	1
Peripheral eosinophilia				
• 0.7-1.5x10^9/l or 10-19.9%	0	1	0	
• ≥1.5x10^9/l or ≥20%		2		2
Atypical lymphocytes	0	1	0	0
Skin involvement				
• Extent of cutaneous eruption ≥50%	0	1	0	1
• Skin rash suggesting DRESS	-1	1	0	1
• Biopsy suggesting DRESS	-1	0	0	0
Organ involvement				
• One	0	1		1
• 2 or more		2		0
Resolution ≥15 days	-1	0	-1	0
Laboratory results negative for at least 3 of the following				
• ANA, blood culture, HAV/HBV/HCV serology, Chlamydia/Mycoplasma serology	0	1	0	1
Total score <2 no case; 2-3 possible case; 4-5 probable case; >5 definite				**7**

Table III. Japanese Group scoring system for diagnosis of DRESS syndrome and our case estimation [12].

CRITERIA	CASE SCORE
Maculopapular rash developing >3 weeks after drug initiation	1
Clinical symptoms continuing >2 weeks after stopping therapy	1
Fever >38°C	1
Liver abnormalities (ALT>100 IU/L) or other organ involvement	1
Hematological abnormalities	
• Leukocytosis	1
• Atypical lymphocytes	
• Eosinophilia	
Lymphadenopathy	1
Human herpes 6 reactivation	0
7=typical DRESS syndrome; 5=atypical DRESS syndrome; <5 consider other diagnosis	**6**

ALT Alanine transaminase

The diagnosis of DRESS syndrome requires a high level of suspicion, and differential diagnosis includes a large number of maladies such as infectious diseases (especially viral exanthema, particularly EBV infectious mononucleosis) [7], graft versus host disease [13], autoimmune diseases (Still's disease, Kawasaki disease), and neoplastic diseases [14]. The presence of neoplasia, infections, or collagenosis in our patient was excluded following imaging investigations and clinical consultations [3].

The appropriate treatment of DRESS syndrome is mainly supportive and symptomatic. The first step in the management of this disease is prompt withdrawal of the culprit drug. In case of organ involvement, the use of systemic corticosteroids (1 mg/kg/day) is recommended. If there is renal or lung injury, systemic glucocorticoid therapy is necessary until the clinical signs and the laboratory investigations normalize. Sometimes, pulsed methylprednisolone therapy is required [3]. If organ involvement is severe and life-threatening, intravenous immunoglobulin therapy should be associated with systemic corticosteroids [5]. In resistant cases, plasmapheresis could be a therapeutic option [15]. If corticotherapy is not efficient, cyclosporine can be used as a second line option in DRESS syndrome cases with severe organ involvement [3]. When virus reactivation is demonstrated, ganciclovir may be given in addition to intravenous globulin and systemic corticosteroids, but the efficiency of antiviral drugs in DRESS syndrome is not well documented [5]. In patients with exfoliative dermatitis, maintaining the skin barrier and proper hydration are essential to adequate management. Symptomatic treatment consists of emollients, topical corticosteroids, and antihistamines. After DRESS syndrome diagnosis, in our case, the first therapeutic step was to stop the administration of carbamazepine. The treatment we gave to our patient consisted of oral corticosteroids (prednisone 1 mg/kg), intravenous fluids, and symptomatic medication (H1-antihistamines for relief of pruritus).

Recovery of DRESS syndrome patients occurs gradually and takes weeks or even months [3]. Our patient fully recovered after 4 weeks of hospitalization. The evolution of these patients is marked by flare-ups even after using structurally different drugs. In case of reoccurrence, the most frequent findings are skin rashes and cell blood count abnormalities with eosinophilia [7]. The long-term sequelae of DRESS syndrome include autoimmune phenomena (autoimmune thyroid disease, type 1 diabetes mellitus, systemic sclerosis, and systemic lupus erythematosus) [16]. Taking into consideration the morbidity of these patients, careful follow-up is essential in order to identify recurrences or the development of autoimmune diseases. In our patient's case, during follow-up until now, there have been no recurrences of DRESS syndrome or manifestations of autoimmunity.

Conclusions

In patients with DRESS syndrome, early diagnosis and prompt intervention may improve outcomes. The diagnosis of this syndrome is often delayed due to polymorphic manifestations and to the long time period between administration of the culprit drug and symptom onset. Physicians should always keep in mind that the basic step in the disease management is immediate discontinuation of the suspected drug. Our case represents a DRESS syndrome induced by carbamazepine, an aromatic anticonvulsant. Our patient exhibited common signs and symptoms: morbilliform rash, fever, and eosinophilia. Apart from cutaneous manifestations, organ involvement was present with renal and pulmonary injury. Our case attempts to increase awareness of DRESS syndrome among physicians and to emphasize the importance of early diagnosis and treatment. We also aim to highlight the value of a multidisciplinary approach and proper follow up, which is crucial for the long-term prognosis of DRESS syndrome patients.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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