

Phenytoin Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Case Report

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Abstract

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and potentially life-threatening condition. It presents a long prodromal period, extensive rash, fever, lymphadenopathy, hematologic abnormalities (eosinophilia with or without atypical lymphocytosis), and internal organ involvement. **Purpose:** To describe a case of phenytoin induced DRESS syndrome, presenting diagnostic and management challenges of clinical interest. **Methods:** The Consensus-based Clinical Case Reporting Guideline Development (CARE) was observed for data analysis in case reports. **Case Report:** A 22-year-old man, using phenytoin for 60 days, sought medical attention due to fever and maculopapular cutaneous lesions. He presented lymphocytosis with eosinophilia and severe acute hepatitis 24 hours after admission day. Hepatic transaminases returned to reference levels after phenytoin withdrawal, and eosinophilia and cutaneous manifestations did not respond well to systemic steroids. A forearm biopsy showed findings suggestive of severe cutaneous adverse reaction. The patient's microscopic and clinical characteristics meet all criteria in the scoring systems of Bocquet *et al.*, Registry of Severe Cutaneous Adverse Reaction (RegiSCAR), and Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR), being highly suggestive of DRESS syndrome very probably caused by phenytoin. The complete remission of symptoms was achieved weeks after admission. **Conclusions:** DRESS syndrome is a defiant reaction. Clinicians must be aware of potential causative drugs and perform a complete clinical examination using the available resources, including laboratory tests and histopathological assessment. The clinical remission relies on the withdrawal of the culprit drug. Particular attention should be given to the involvement of internal organs.

Keywords

Drug Hypersensitivity Syndrome, Eosinophilia, Anticonvulsants

1. Introduction

The drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome belongs to the pathological group of severe cutaneous adverse reactions (SCARs) [1] [2]. The actual comprehension of this pathological entity is mostly based on Asian and European registries [3] [4] [5]. The reported prevalence of DRESS syndrome in the general population is 2.18 to 9.63/100,000. It would cause long-term sequelae (11.5% of cases) and a high death rate that can reach 10% of affected individuals [6] [7] [8] [9].

Several drugs represent potential etiological factors for DRESS syndrome. Still, exposure to antiepileptics, allopurinol, and sulfonamides are considered the most significant culprits [4]. The physiopathology is not fully understood but seems multifactorial, particularly in cases with long clinical courses and flare-ups [1] [5]. The clinical features include a long latency period, skin involvement, hematological abnormalities, and impairment of internal organs [3] [4] [5] [10].

The definitive diagnosis of DRESS would be challenging, and this reaction is rare enough that its recognition may be difficult for medical students or general practice doctors [11]. Therefore, herein is presented a case report of DRESS syndrome associated with phenytoin use and the discussion of relevant clinical aspects that might help diagnose and manage affected patients.

2. Case Report

This manuscript was submitted for publication after obtention of the patient's informed verbal agreement and signing an informed consent form. The Institutional Review Board granted ethical approval (Protocol 37219020.7.0000.5339). For completeness, transparency, and data analysis in case reports, the Consensus-based Clinical Case Reporting Guideline Development (CARE) was observed [12] [13]. The case report timeline is presented in **Figure 1**.

A 22-year-old man, with a known case of epilepsy, was under a six-week-long therapeutic regimen with phenytoin 100 mg. He searched for medical attention due to a skin rash of acute onset and fever lasting several days. His past medical history had not been remarkable, except for the neurological condition and long term use of fluoxetine 20 mg, and previous use of other anticonvulsants.

The patient was conscious in the emergency department; there was no respiratory distress (respiratory rate 18 breaths/min and oxygen saturation 99.6%). Arterial pressure (120/70 Hg mm) and cardiac frequency (103 beats/min) were within normal parameters, but the body temperature was high (39°C). The cutaneous surface was covered by pruritic, erythematous maculopapular rashes without vesiculation or blistering (**Figure 2**). No mucosal involvement was observed.

The altered laboratory parameters are shown in **Table 1**, indicating marked leukocytosis with eosinophilia and severe acute hepatitis, 24 hours after admission day (16.03.19). Urinalysis, erythron and platelets, glucose, lipid panel, urea,

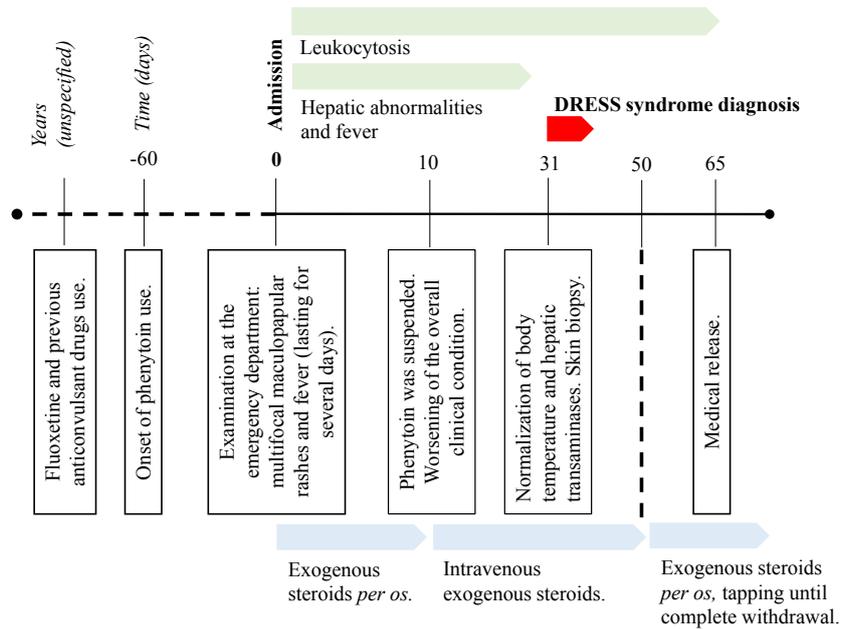


Figure 1. Case report timeline in accordance with the consensus-based clinical case reporting guideline development [13].



Figure 2. Initial clinical aspect of trunk erythematous macular morbilliform rash, without blistering or vesiculation, presented on the day of admission.

Table 1. Clinical characteristics during hospitalization.

| Laboratory parameters | Results | | | Reference values |
|------------------------------------|-------------|-------------|-------------|------------------|
| | 16.03.19 | 06.04.19 | 10.05.19 | |
| Leukocytes (cell/mm ³) | 40,701 | 28,100 | 17,520 | 3600 - 11,000 |
| • Neutrophils | 18,315 | 10,678 | 6132 | 1700 - 7800 |
| • Lymphocytes | 12,210 | 9554 | 6658 | 1000 - 4500 |
| • Monocytes | 1628 | 1405 | 1051 | 100 - 1000 |
| • Eosinophils | 8547 | 4215 | 3679 | 20 - 500 |
| • Basophiles | 0 | 0 | 0 | 0 - 200 |
| AST (U/L) | 179 | 29 | 13 | <37 |
| ALT (U/L) | 529 | 42 | 11 | <42 |
| ALP (U/L) | 138 | 67 | 42 | 30 - 120 |

AST—aspartate transaminase, ALT—alanine transaminase, ALP—alkaline phosphatase.

creatinine, sodium, potassium, reactive C protein, lactic acid, and bilirubin were not altered. Based on these findings, the patient was admitted to the department of internal medicine.

The diagnostic hypothesis included DRESS syndrome, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and vasculitis associated with human immunodeficiency virus (HIV) or B and C hepatitis virus (HBV, HCV).

During the first week after admission, occurred a notorious worsening of the overall clinical condition with periorbital and perioral edema, severe dissemination of cutaneous rash, and exfoliative dermatitis affecting 100% of the body surface. Clinical and tomographic evidence of lymphadenitis was seen in axillary, inguinal, and iliac fossa bilateral regions. Serologies were negative for syphilis, HIV, HBV, and HCV, and considering the rarity of vasculitis associated with these infectious diseases, this hypothesis was promptly excluded.

Phenytoin was suspended since it is a known risk factor for SCARs, intravenous methylprednisolone was started empirically (26.03.2019), and after that, the patient was kept in isolation. The normalization of body temperature and hepatic transaminases suggested a positive response to medical interventions. However, the patient still presented leukocytosis with neutrophilia and eosinophilia (Table 1, 06.04.2019, and 10.05.2019). There was a reduction of the erythematous rash, the persistence of skin desquamation, and progressive onset of alopecia (Figure 3). The steroid dose was adjusted several times following the patient's response (0.5 to 1.0 mg/kg/day).

A skin biopsy of the forearm was performed, and the histopathological analysis exhibited features considered suggestive of SCARs. The findings corroborated a definitive diagnosis of DRESS syndrome probably due to phenytoin use, meeting previously established diagnostic criteria, as shown in Table 2. Despite



Figure 3. Maculopapular rash and discrete exfoliative dermatitis (A), severe skin desquamation, periorbital and perioral edema (B), alopecia (C), cutaneous aspect of the thorax and left upper member (D), left inferior member (E), and right upper extremity (F).

Table 2. Available predefined criteria for DRESS syndrome diagnosis and patient's related findings [3] [4] [5].

| | Bocquet <i>et al.</i> | RegiSCAR | J-SCAR ^d |
|---------------------------------------------|-----------------------|------------------------------------------------------------|-------------------------------------------------------------------------|
| Cutaneous drug eruption ^a | Y | Acute rash ^b | Y |
| | | | Maculopapular rash developing 3 weeks after starting offending drug |
| Hematologic abnormalities ^a | | Reaction suspected to be drug-related ^b | Y |
| | | | Prolonged clinical symptoms after discontinuation of the causative drug |
| • Eosinophils $\geq 1.5 \times 10^9/L$ | Y | Hospitalization ^c | Y |
| | | | Fever $> 38^\circ C$ |
| • Atypical lymphocytes | N | Fever $> 38^\circ C$ | Y |
| | | | Systemic involvement |
| Systemic involvement ^a | | Enlarged lymph nodes involving ≥ 2 sites ^c | Y |
| | | | • Liver abnormalities (ALT > 100 U/L) or other organ involvement |
| • Lymph nodes ≥ 2 cm in diameter | Y | Involvement of ≥ 1 internal organ ^c | Y |
| | | | Leukocyte abnormalities (≥ 1) |
| • Liver transaminases ≥ 2 times normal | Y | Blood count abnormalities ^c | |
| | | | • Leukocytosis ($11 \times 10^9/L$) |
| • Interstitial nephritis | N | • Lymphocytes above or below normal limits | Y |
| | | | • Atypical lymphocytes (5%) |
| • Interstitial pneumonitis | N | • Eosinophils over laboratory limits | Y |
| | | | • Eosinophils $\geq 1.5 \times 10^9/L$ |
| • Carditis | N | • Platelets under laboratory limits | N |
| | | | Lymphadenopathy |
| | | | HHV-6 reactivation |

Y (yes) and N (no) indicate, respectively, the present and absent criteria in the reported case. ^aAll three criteria are required for diagnosis, including at least one hematological abnormality and one systemic involvement. ^bBoth are mandatory for diagnosis, plus ^cthree of these four criteria. ^dEight criteria are required for typical DRESS syndrome, while seven findings indicate atypical disease.

recommendations for DRESS syndrome screening, reactivation of herpes virus (HHV-6) infection would not be investigated. The echocardiogram was not altered, and the dimensions and general aspects of internal organs were normal in computed tomography scans.

The steroid dose was progressively reduced until the medication's complete withdrawal at release time (at week ten). The patient received neurological evaluation and was discharged using fluoxetine (20 mg) and valproic acid (250 mg) as a replacement drug for phenytoin. He was referred to the primary care unit for follow-up appointments; thus, recurrence and long term sequelae were not assessed.

3. Discussion

Regarding epidemiological aspects, DRESS syndrome is most commonly seen in adults (mean age, 51 years) and presents a marginal tendency to affect more women than men (1.3:1 female to male ratio) [14] [15]. The overall prevalence can be considered low in the general population (2.18 to 9.63/100,000). While its occurrence in hospital settings can be significantly higher, reaching a six months rate of 1/1000 to 1/10,000 [6] [7] [8] [16]. Thus, why medical students and general practitioners should be concerned about DRESS syndrome if it is a rare entity? The relevance of the subject is highlighted by two factors associated with this pathological late hypersensitivity reaction: 1) is potentially life-threatening; 2) its prompt recognition and removal of the culprit agent are imperative for resolu-

tion since the efficacy of universally used corticosteroids for SCARs treatment has not been established for DRESS syndrome [17] [18].

Regarding DRESS etiology, it is essential to underscore that aromatic anti-convulsants are among the most important culprits of this reaction, accounting for nearly 20% of cases [19]. In the present case, we described a detailed medical history of DRESS syndrome probably associated with phenytoin use. Therefore, comparisons with previous findings will be made considering this causative agent, when appropriate.

The pathophysiology of DRESS syndrome is not entirely elucidated. One theory suggests deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies aromatic amine anticonvulsants' metabolites. Phenytoin is metabolized by the hepatic cytochrome P450, which undergoes oxidation by aromatic hydroxylation, forming arene oxides. However, in individuals with genetic variations implied in this drug metabolism, there is inefficient detoxification. Therefore, the arene oxides would not be enzymatically converted by epoxide hydroxylase or glutathione transferase, remaining toxic and accumulating as metabolites that cause direct cellular toxicity or immune responses [20].

However, it is believed that in cases related to anticonvulsants use; two other factors should be contemplated: ethnic predisposition with particular human leukocyte antigen (HLA) alleles, and sequential reactivation of herpes virus [20]. Due to limitations of public health services in Brazil, neither the presence of a susceptible HLA allele nor HHV-6 infection, would be proved in this case.

The prodrome period is longer in DRESS syndrome than in other delayed-type hypersensitivity reactions, such as SJS/TEN, AGEP, and fixed drug eruptions [4] [15] [17]. The onset of clinical manifestations occurs between the second and sixth weeks after the offending drug first dose [17]. Pereira de Silva *et al.* [21], observed in epileptic patients with DRESS syndrome associated with phenytoin (75 mg/day to 300 mg/day dose), an exposure period between nine and 72 days until the onset of clinical manifestations. Also, in the study of Kano and Shiohara [22], a mean of 40.5 days-long therapeutic regimens with phenytoin was seen before skin rash. However, professionals must be aware that symptoms might occur earlier and be more severe in preexposure drug cases [3]. Nonetheless, a past medical history of previous adverse events associated with drugs is not a common finding reported in DRESS syndrome cases [21].

According to Husain *et al.* [17], pruritus and pyrexia are typical prodromal symptoms of DRESS syndrome. These features are not specific during the latency period and may lead professionals to fail to make an early diagnosis properly [23] [24]. Eventually, they can even be erroneously considered markers of systemic infection, especially when accompanied by early onset of lymphadenitis [20]. It is important to underscore that fever $\geq 38.5^{\circ}\text{C}$ and enlarged lymph nodes can be seen with frequency in phenytoin-associated DRESS syndrome cases, and high body temperatures might last several weeks [17] [21].

Our patient reported fever lasting for several days before the onset of a cutaneous rash that persisted until the administration of intravenous steroids ad-

ministration. He also exhibited axillary and inguinal lymph nodes larger than 2 cm, detected clinically and through computerized tomography. Both anatomical sites are frequently compromised in DRESS syndrome carriers; cervical lymph nodes can appear as well [17].

When there is a suspicion of this reaction, it must be considered that the clinical aspect of SCARs is variable and can mirror other clinical conditions. As proposed in the literature, DRESS can be considered a heterogeneous syndrome with some particular patterns associated with different drugs, constituting a diagnostic challenge [14]. One crucial characteristic is that clinical features should persist several weeks after discontinuation of the causal drug [17].

Skin eruptions cover more than 50% of the body surface in 73% to 100% of patients and are quite suggestive of DRESS syndrome [4] [21] [22] [23]. DRESS presents as a maculopapular inflammatory rash or erythroderma, with an exfoliative aspect and pruritic character that may be or not be present [4]. Blisters, pustules, target-like lesions, and lichenoid aspects are rarely found. The cutaneous lesions' duration lasts for more than fifteen days after drug removal, which is very characteristic of DRESS syndrome [4].

When the patient presents facial edema, especially in combination with fever and eruption, it constitutes a warning signal of SCARs. However, facial edema is mild in DRESS syndrome than in SJS/TEN, and should not be mistaken for angioedema [4] [17].

In this case, the maculopapular erythema accompanied by severe desquamative dermatitis covered 100% of the body surface and persisted for several weeks. The cutaneous lesions caused severe discomfort to the patient and increased risk for infectious disorders.

DRESS syndrome has been associated with alterations in hemoglobin, all subtypes of leukocytes, and platelets count [4] [23]. Eosinophilia has been described in 58% to 100% of phenytoin users and is the most frequent hematological abnormality, the presence of atypical lymphocytes, thrombocytopenia, and anemia are less prevalent [21] [22] [23]. In our patient, there was significant leukocytosis, marked neutrophilia, and persistent eosinophilia, which led us to the hypothesis of DRESS [4]. Bocquet *et al.* [3] pointed out that eosinophilia plays an important role in visceral manifestations since eosinophilic granules' proteins can cause toxic effects to several tissues.

When considering internal organ involvement, phenytoin has been strongly associated with liver impairment and less frequently with kidneys, heart, lungs, nervous system, or pancreas [6] [21] [22]. Assessment of hepatic enzymes levels, echocardiogram, and computed tomography are important complementary exams to evaluate overall patient condition [17]. Values of liver enzymes are abnormal in nearly 75% of DRESS syndrome cases [21]. The liver enzymes, especially alanine aminotransferases (ALT), can persist for days to months after the culprit drug's withdrawal [17]. In the present case, the ALT levels were more than ten times the upper limit of normal, indicating severe acute hepatitis. The patient was anicteric, and without cholangitis, as expected, and viral hepatitis

panels were negative. It is important to underscore that most deaths related to DRESS syndrome occur from hepatocellular necrosis, and underlying viral hepatitis infection can complicate the clinical picture [17] [23] [24].

There are no criterion standards for establishing the diagnosis of DRESS syndrome, thus clinical and laboratory abnormalities should be considered, and other potentially serious conditions (infections, neoplastic processes, autoimmune disorders, and connective tissue disease) must be excluded [9] [14] [17]. Histopathological evaluation of skin and internal organs can be helpful to confirm DRESS syndrome diagnosis. The microscopic findings present a not specific, but somehow a characteristic aspect comprising epidermal spongiosis, papillary dermis with perivascular lymphocytes infiltrate, and eosinophils [9] [14].

The scoring systems of Bocquet *et al.* [3], Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) [4], and Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) [5] are widely used and constitute a valuable tool for diagnosis. If the patient does not meet the standard criteria in all three scoring systems, the literature suggests following the criteria proposed by Bocquet *et al.* [3] [25]. Our patient meets criteria in all scoring systems. Thus the definitive diagnosis could be strongly suggested. Inclusively, meeting seven criteria of J-SCAR, which is the most rigorous because HHV-6 testing is not widely available [20].

There is no treatment consensus for DRESS syndrome, and the most critical step is the identification and withdrawal of the culprit drug, which can be difficult, mainly if the patient is under several medications. Treatment of symptoms and the use of exogenous steroids and histamine antagonists have been reported in the literature. However, their efficacy is still questionable, and systemic manifestations revert gradually between one and six months [21]. The prognosis is variable; however, in non-fatal cases, the duration of clinical symptoms shows a positive correlation with leukocyte, lymphocyte, and eosinophil counts. Increased creatinine and ferritin serum levels seemed to be related to fatal cases [25]. Long-term sequela could also be expected; younger patients tend to develop autoimmune conditions such as Graves' disease, hemolytic anemia, and type 1 diabetes [6]. However, those at more advanced ages should progress to end-organ failure [6].

In conclusion, DRESS syndrome is a defiant reaction, associated with high morbidity and can be terminal. The lack of a unified criterion and pathognomonic features can cause a diagnostic delay. To achieve a definitive diagnosis, clinicians must be aware of potential causative drugs and perform a complete clinical examination using laboratory tests and histopathological assessment. Particular attention should be given to the involvement of internal organs.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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