

Phenytoin-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome with Severe Hepatic Involvement in a Patient with Symptomatic Epilepsy: A Case Report

Seno Lamsir^{1,2)}, Muh. Eko Irwanto^{1,2)}, Triasari Oktavriana^{3,4)}

¹⁾Department of Dermatology, Venereology, and Aesthetics,
Faculty of Medicine, Universitas Sebelas Maret

²⁾Dr. Moewardi Regional General Hospital, Surakarta, Indonesia

³⁾Department of Dermatology, Venereology, and Aesthetics,
Faculty of Medicine, Universitas Sebelas Maret

⁴⁾Universitas Sebelas Maret Hospital, Surakarta, Indonesia

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ABSTRACT

Background: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe, life-threatening hypersensitivity reaction frequently caused by aromatic anticonvulsants like phenytoin. It is characterized by a long latency period, extensive rash, haematological abnormalities, and internal organ involvement. This case report explores the diagnostic challenges and management strategies for DRESS syndrome presenting as severe hepatitis and exfoliative erythroderma in an epilepsy patient.

Case presentation: A 47-year-old male with cerebral meningioma and symptomatic epilepsy presented with a 41°C fever and generalized erythematous rash following one month of phenytoin consumption. Physical examination revealed exfoliative erythroderma, facial oedema, cheilitis, and jaundice. Investigations confirmed significant eosinophilia (11.7%), monocytosis, and severe hepatitis with massive transaminase elevation and hyperbilirubinemia. Diagnosed with DRESS syndrome (RegiSCAR score: 5, probable) and Stevens-Johnson Syndrome as a differential, management included immediate phenytoin cessation. To prevent cross-reactivity, levetiracetam was substituted. Patient also received systemic corticosteroids (dexamethasone) and aggressive hepatoprotective therapy. The patient showed excellent clinical improvement, marked by normalized temperature, hemodynamic stability, and skin desquamation by the fifth day.

Discussion: DRESS syndrome carries significant mortality, primarily due to fulminant hepatic failure. The 4- to 6-week latency period is pathognomonic, distinguishing it from other exanthems. Its pathogenesis involves complex interactions among toxic metabolite accumulation, Th2-type immune activation triggering eosinophilia, and potential herpesvirus reactivation. Prompt discontinuation of the offending drug and selecting a non-aromatic anticonvulsant, such as levetiracetam, are essential steps in safely managing this patient's epilepsy.

Keywords: DRESS syndrome, phenytoin, eosinophilia, severe hepatitis, levetiracetam

Correspondence:

Seno Lamsir. Department of Dermatology, Venereology, and Aesthetics, Faculty of Medicine, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta, Central Java 57126, Indonesia. Email: kulkelest@gmail.com.

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BACKGROUND

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare but potentially life-threatening type of severe drug hypersensitivity reaction. This syndrome is characterized by a pathognomonic clinical triad of skin rash (cutaneous eruption), haematological abnormalities (particularly eosinophilia and atypical lymphocytes), and internal organ involvement. Aromatic anticonvulsant drugs such as phenytoin, carbamazepine, and phenobarbital are reported to be the most common causes of this condition. The mortality rate of DRESS is estimated to be 10%. DRESS syndrome is often caused by fulminant hepatic failure or massive liver necrosis, so early recognition and discontinuation of the causative drug are important for successful management (Bahçeci and Can, 2020).

The diagnosis of DRESS is based on a combination of clinical and laboratory findings using the RegiSCAR (Registry of Severe Cutaneous Adverse Reaction) scoring system as a widely used validation tool. Diagnostic criteria include acute fever, lymphadenopathy, hematological abnormalities (eosinophilia or atypical lymphocytosis), extensive skin involvement, and impaired organ function. Hepatitis is the most commonly found manifestation and serves as the primary prognostic indicator. Confirmation of the diagnosis is important to differentiate DRESS from other severe cutaneous drug reactions (SCAR) in order to determine the appropriate systemic corticosteroid therapy (Schunkert and Divito, 2021).

This case report discusses a 47-year-old male patient with a history of cerebral meningioma and symptomatic epilepsy who had been regularly taking phenytoin since July 2025. The patient presented with complaints of generalized erythematous rash accompanied by skin peeling, high

fever reaching 41°C, and signs of organ involvement in the form of icteric sclera and a significant increase in transaminase enzymes (AST/ALT). Based on the RegiSCAR criteria, the patient was classified as probable DRESS with a score of 5, which included eosinophilia, extensive skin rash, and liver dysfunction. This report aims to describe the clinical course, diagnostic process, and comprehensive management of DRESS syndrome due to phenytoin use.

CASE PRESENTATION

A 47-year-old male patient, Mr. H, was consulted from neurology department, presented with complaints of a red rash on his skin all over his body since 3 days ago. Initially, the rash appeared only on both arms, which then gradually spread to the rest of the body. The patient also complained of red lips followed by the appearance of extensive sores on the lips as well as thrush and severe rashes in the genital area. The patient acknowledged pain in the sores and pain when swallowing but denied any itching or pain when urinating. The sores had not been treated previously. These skin complaints were accompanied by a high fever that had started three days ago, which had subsided with paracetamol but then returned, and yellowing of the eyes since the onset of the skin complaints. The patient was admitted through the emergency room due to a whole-body seizure lasting less than 5 minutes approximately 6 hours before admission to the hospital. The patient denied a history of similar illnesses. Past medical history includes a brain tumor (meningioma) newly diagnosed in July 2025, symptomatic epilepsy, and weakness in the right limbs for the past 3 months. The patient denied a history of hypertension, diabetes mellitus, heart disease, stroke, or food or drug allergies. Regular medications taken since July 2025 included phenytoin,

mecobalamin, dexamethasone, piracetam, omeprazole, betahistine, and turmeric. The patient denied any history of similar diseases or other systemic diseases in the family.

Physical examination revealed that the patient appeared moderately ill with compos mentis consciousness. Vital signs showed blood pressure of 117/72 mmHg, pulse rate of 101 beats per minute, respiratory rate of 21 breaths per minute, and temperature of 41°C. The patient weighed 47 kg, was 167 cm tall, and had a body mass index of 16.85 kg/m² (underweight). Dermatological

status in the orbital region showed conjunctival injection, icteric sclera, and crusting. In the oral region, there were patches of erythema and mucosal erosion (Figure 1). In the anterior and posterior trunk regions, there were macules and multiple erythematous patches that were widely distributed with discrete lesions, some of which were confluent (Figure 2). Similar findings were observed in the upper and lower extremities in the form of macules and multiple erythematous patches that were widespread, discrete, and partially confluent (Figures 3 and 4).

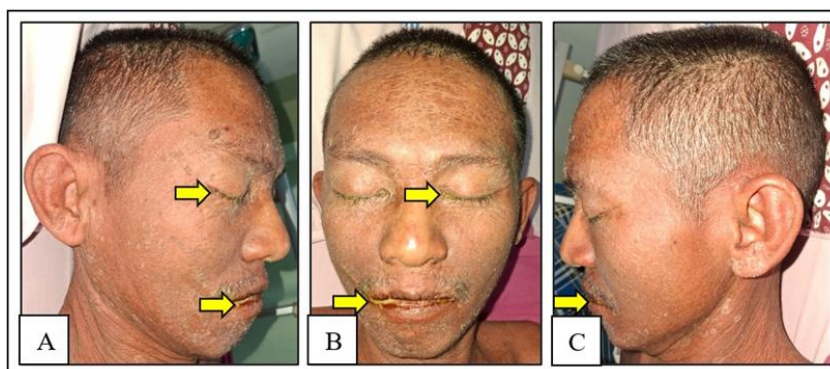


Figure 1. (A-C) Dermatological status in the orbital region shows conjunctival injection, icteric sclera, and crusting, while the oral region shows patches of erythema and erosion (yellow arrows).

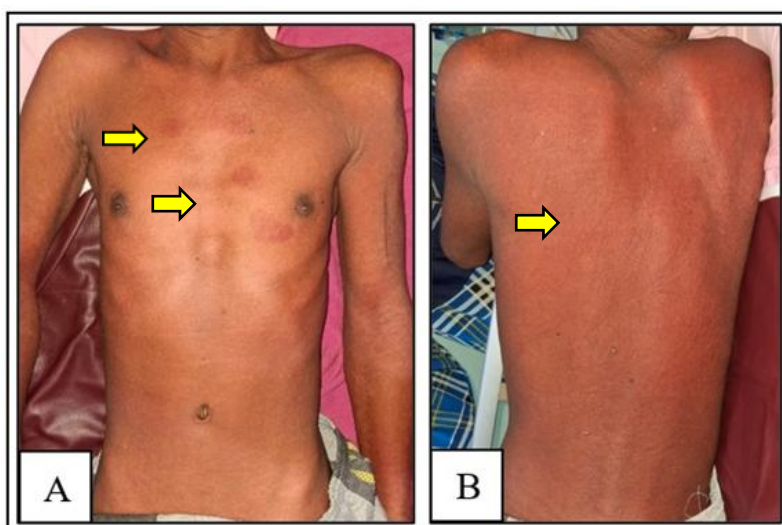


Figure 2. (A-B) Dermatological status of the anterior and posterior trunk regions show widespread macules and patches of erythema with discrete but partially confluent lesions (yellow arrows).

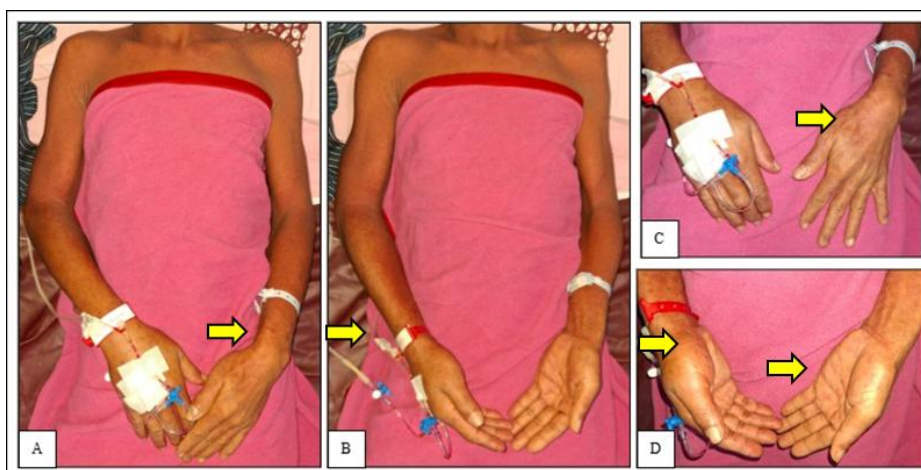


Figure 3. (A-D) Dermatological status in the upper-extremities region shows multiple macules and patches of erythema that are widespread, discrete, and partially confluent (yellow arrows)

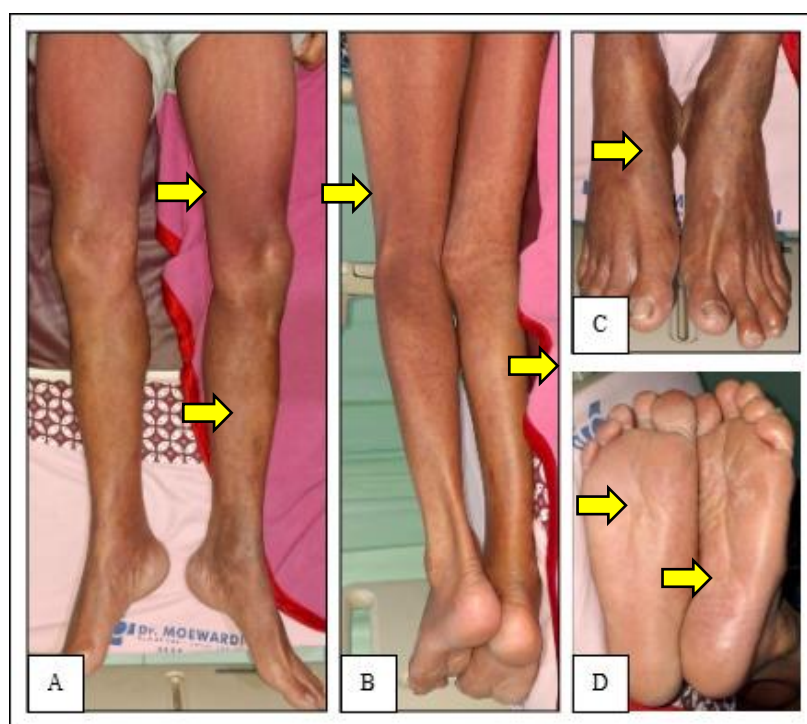


Figure 4. (A-D) Dermatological and venereological status in the lower extremity region shows widespread macules and multiple erythema patches that are discrete and partially confluent (yellow arrows).

The patient's general condition still appears to be moderately ill with compos mentis consciousness on the last day of treatment (August 19, 2025). Vital signs showed significant improvement compared to the initial consultation, with blood

pressure at 114/68 mmHg, pulse rate at 72 beats per minute, respiratory rate at 22 breaths per minute, and body temperature now normal at 36°C. The dermatological status shows resolution of skin lesions, with the red rash over the entire body now

accompanied by desquamation and the rash beginning to dry. In the orbital region, conjunctival injection and icteric sclera are still visible, while in the oral region, erythema patches and erosion are visible (Figure 5). Examination of the anterior and posterior trunk regions reveals macules and multiple discrete erythematous patches, some of

which are confluent, accompanied by desquamation (Figure 6). In the upper and lower extremities, similar lesions were found in the form of macules and multiple erythematous patches that were discrete and partially confluent, with signs of peeling and drying skin (Figures 7 and 8).

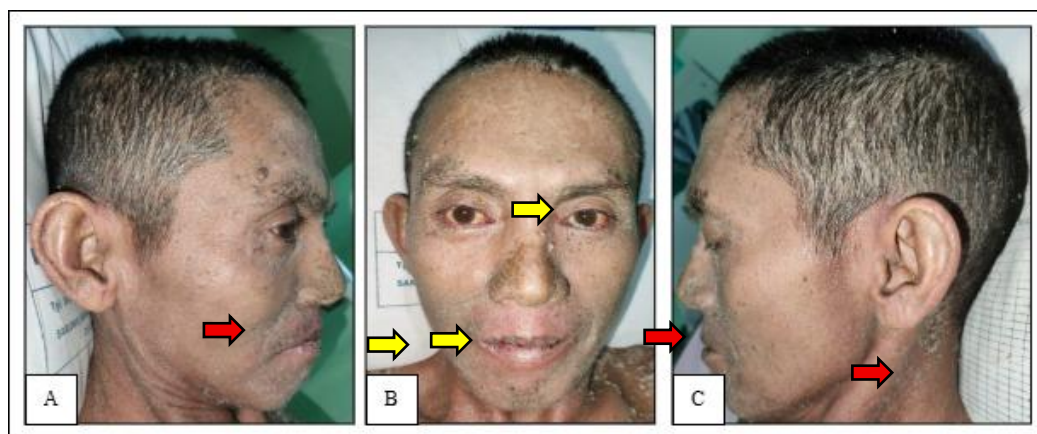


Figure 5. (A-C) Dermatological status in the orbital region still shows conjunctival injection and icteric sclera, while in the oral region there are patches of erythema and erosion (yellow arrows). There are dried erythematous lesions and desquamation (red arrows).

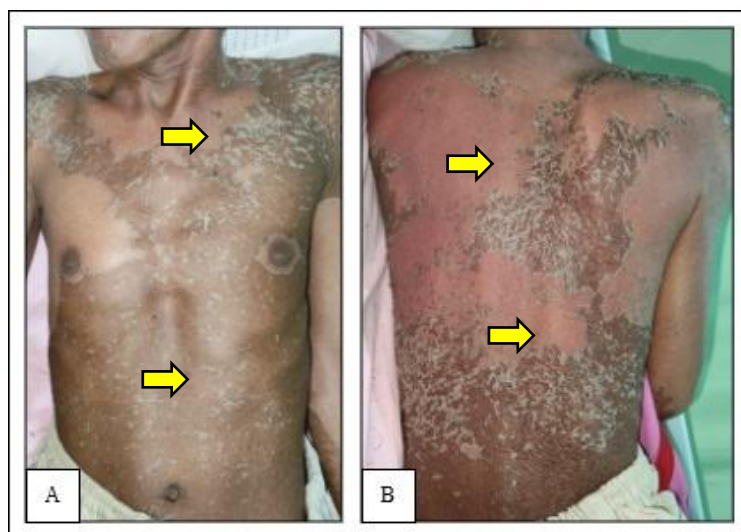


Figure 6. (A-B) Dermatological status in the anterior and posterior trunk regions shows macules and multiple discrete erythematous patches, some confluent, accompanied by desquamation (yellow arrows).



Figure 7. (A-D) Dermatological status in the upper-extremities region shows similar lesions in the form of macules and multiple erythematous patches that are discrete and partially confluent, with signs of peeling and drying skin (yellow arrows).

The patient in this case can be diagnosed with Stevens-Johnson Syndrome (SJS) and Exanthematous Drug Eruption (EDE) based on medical history and clinical findings. DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) is the primary consideration because the patient has a history of phenytoin use and exhibits a triad of symptoms consisting of extensive erythematous skin rash (erythroderma), hematological abnormalities in the form of eosinophilia, and internal organ involvement in the form of hepatitis (increased AST/ALT). Stevens-Johnson syndrome (SJS) was also considered as a differential diagnosis due to similar manifestations, namely high fever and mucosal involvement in the form of lip erosion and conjunctival injection, although the significant eosinophilia and predominance of visceral organ involvement in this patient were more

supportive of a diagnosis of DRESS than SJS, which is usually dominated by extensive epidermal necrosis. Exanthematous Drug Eruption was included as a differential diagnosis due to the appearance of multiple erythematous macular patches that appeared after drug exposure, but the nature of the lesions accompanied by severe systemic symptoms (40°C fever) and multiorgan involvement made it less typical of classic morbilliform drug eruptions, which are generally mild and limited to the skin. Therefore, it is necessary to calculate the RegiSCAR score, which in this patient was 5 (probable), and to perform complete blood count and serial liver function tests to confirm the diagnosis.

Microbiological tests performed on August 14, 2025, included Gram staining and KOH examination. Gram staining revealed polymorphonuclear (PMN)

inflammatory cells of 3-5/ LPF (Low Power Field) and gram-positive cocci bacteria of 10-20/LPF (Figure 9). KOH examination showed negative results for hyphae and spores (Figure 10). Hematology laboratory results on the same date showed leukocytosis (leukocytes 12,300/ul) accompanied by significant eosinophilia (11.7%) and monocytosis (9.00%) with a hemoglobin level of 15.5 g/dl, but lymphocytes were decreased (8.10%). Initial clinical chemistry tests showed severe liver dysfunction with a drastic increase in transaminase enzymes

(AST 512 u/l and ALT 807 u/l) and electrolyte imbalance in the form of hyponatremia (sodium 117 mmol/L) and hypocalcemia (calcium 1.07 mmol/L). Follow-up liver function monitoring on August 18, 2025 showed hyperbilirubinemia with total bilirubin 8.78 mg/dl, direct bilirubin 4.64 mg/dl, and indirect bilirubin 4.14 mg/dl, as well as hypoalbuminemia (albumin 2.7 g/dl). Serological test results showed the patient was nonreactive for HBsAg and Anti-HCV.

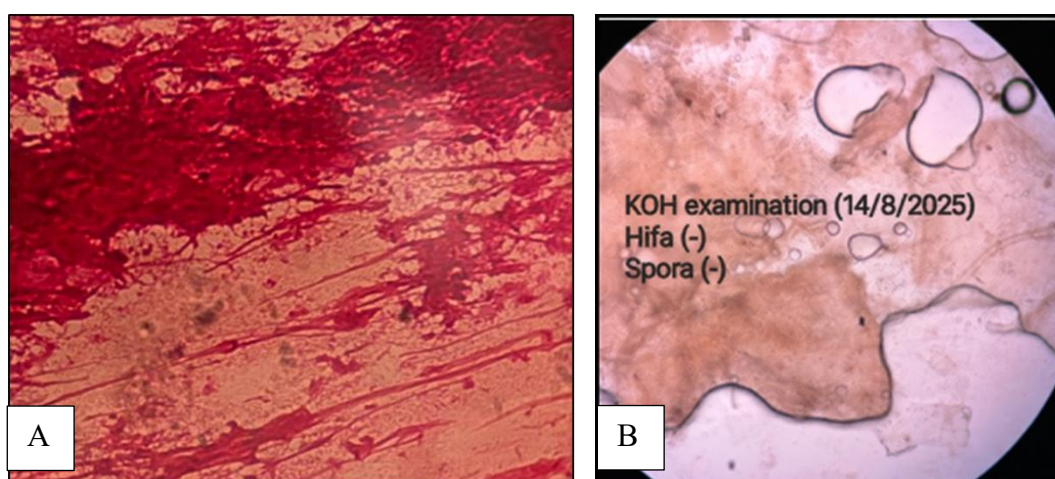


Figure 8 (A-B). Gram staining results showed 3-5 polymorphonuclear (PMN) inflammatory cells/LPF and 10-20 gram-positive cocci bacteria/LPF. KOH examination results were negative for hyphae and spores.

Based on the results of the medical history, physical examination, and supporting tests, the patient was diagnosed with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome caused by phenytoin based on the RegiSCAR criteria, which reached a score of 5 (probable). This diagnosis was based on strong clinical evidence, including a history of anticonvulsant use with a long latency period, persistent high fever, and the classic triad of widespread exfoliative erythroderma, hematological abnormalities (eosinophilia and atypical lymphocytosis), and internal organ involvement (severe hepatitis). The

differential diagnosis of Stevens-Johnson Syndrome (SJS), which was considered due to the presence of oral and ocular mucosal erosion, was ruled out because there was no massive epidermal necrosis or positive Nikolsky sign, and eosinophilia, which is rare in SJS, was the dominant manifestation. The working diagnosis of DRESS was further strengthened after infectious causes such as acute viral hepatitis were ruled out through non-reactive HBsAg and Anti-HCV serology results, as well as the clinical picture not matching that of Exanthematous Drug Eruption, which is generally mild without organ involvement.

Management includes non-pharmacological therapy focused on immediate discontinuation of the suspected causative drug, namely phenytoin, and providing education to the patient and family about the disease. Nutritional support is provided in the form of a high-calorie and high-protein diet to aid tissue healing. Skin lesions were treated topically by applying moisturizer (Soft U Derm®) twice daily to the entire body to maintain skin moisture, applying Kenalog® in Orabase twice daily to erosive lesions on the lips, and applying 0.1% mometasone furoate cream twice daily to the facial area. Oral and ocular hygiene is also maintained with the use of Betadine® gargle twice daily and Cendo Lyteers® eye drops 2-3 drops every 6 hours in both eyes. The main systemic drug therapy includes intravenous corticosteroids in the form of dexamethasone 5 mg injections every 12 hours (as instructed by a neurologist for cerebral edema and drug eruption treatment) and methylprednisolone 125 mg injections every 24 hours. Other supportive management is provided in a multidisciplinary manner, including switching anticonvulsants to levetiracetam 2 x 250 mg, 10 mg of diphenhydramine injection every 12 hours, and hepatoprotective therapy in the form of 2 flashes of SNMC injection in 100 cc of NaCl every 24 hours for 3 days, 3 x 1 tablet of turmeric, and 3 x 1 capsule of albumin supplementation to improve liver function and hypoalbuminemia. The patient also received electrolyte correction with 3% NaCl infusion to treat severe hyponatremia. The patient's condition showed significant clinical improvement after intensive care, marked by body temperature reaching normal limits and skin lesions beginning to dry and undergo desquamation on the last day of monitoring.

DISCUSSION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe cutaneous adverse reaction (SCAR) that is idiosyncratic and potentially life-threatening. This syndrome manifests with a clinical triad of skin rash, hematological abnormalities (eosinophilia and atypical lymphocytes), and internal organ involvement. Aromatic anticonvulsants such as phenytoin, carbamazepine, and phenobarbital are the most common causes of this condition (Pan and Wu, 2025). The main characteristic of DRESS syndrome is a long latency period between drug exposure and symptom onset. This latency period usually ranges from two to eight weeks (Abdelneam et al., 2025).

This case report discusses a 47-year-old male patient with a history of cerebral meningioma and symptomatic epilepsy who had been taking phenytoin since July 2025. The patient experienced complex clinical manifestations including high fever, exfoliative erythroderma, and acute hepatitis. This case highlights the importance of clinical vigilance for delayed-type drug reactions in patients receiving long-term anticonvulsant therapy, where early recognition is crucial to prevent mortality often caused by fulminant hepatic failure.

The clinical manifestations of DRESS syndrome in this patient began with severe prodromal symptoms. These prodromal symptoms were early signs of systemic immune system activation. The most prominent symptom was high-grade fever or hyperpyrexia. The patient's body temperature reached extreme levels of 40°C to 41°C. Fever in DRESS syndrome is persistent and often appears before the characteristic skin eruptions. This high body temperature indicates the presence of an acute cytokine storm. In this condition, there is a massive release of endogenous

pyrogens such as IL-1, IL-6, and TNF- α in response to drug hypersensitivity reactions (Arora et al., 2024).

The dermatological abnormalities in this patient show a characteristic chronological progression for DRESS. The skin eruption began as a diffuse morbilliform or maculopapular rash. As T cells and eosinophils progressively infiltrated the dermis, the lesions developed into erythroderma, defined as erythema involving more than 90% of the body surface area. A characteristic clinical sign in this case is the occurrence of desquamation or skin peeling in the subsequent days of treatment. This desquamation indicates the resolution phase of acute epidermal inflammation but also demonstrates the extent of skin barrier damage that has occurred. This peeling phenomenon distinguishes DRESS from mild drug exanthema (exanthematous drug eruption), which usually resolves without significant desquamation (Rotulo et al., 2024).

The patient in this case also experienced significant mucosal involvement. Physical examination revealed patches of erythema and erosion on the lips (cheilitis) and conjunctival injection in the eyes. Mucosal involvement occurs in approximately 50% of DRESS cases. It is important to note that despite the presence of erosion, the severity of mucosal involvement in this patient was not as severe as that found in Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). There was no massive epidermal detachment or extensive hemorrhagic bullae on the mucosa, which is an important point in clinical differential diagnosis (Pan and Wu, 2025; Mehsas et al., 2023).

Visceral organ involvement is a major prognostic factor in DRESS, with the liver being the most commonly affected organ. This patient experienced Drug Induced

Liver Injury (DILI) that manifested in two different patterns of damage. The dominant damage in the early phase was acute hepatocellular type, characterized by massive transaminase enzyme elevation (AST 512 u/L and ALT 807 u/L). This indicated extensive liver cell necrosis. The clinical manifestations in the subsequent evolutionary phase shifted towards bile excretion dysfunction (Thompson et al., 2024). This was evident from the patient's condition, which initially was anicteric but became icteric accompanied by significant hyperbilirubinemia with a total bilirubin level of 8.78 mg/dL. The shift from elevated transaminase enzymes to hyperbilirubinemia and clinical jaundice indicates persistent cholestatic impairment (cholestatic hepatitis) even though liver cell necrosis has begun to subside. This combination of hepatocellular and cholestatic damage places the patient at high risk of fulminant liver failure if not treated aggressively (Rahnama-Mogadham et al., 2025).

The diagnosis of DRESS syndrome was established based on the RegiSCAR criteria. These criteria include acute fever, lymphadenopathy, involvement of at least one internal organ, hematological abnormalities (eosinophilia or atypical lymphocytes), and widespread skin rash. This patient received a RegiSCAR score of 5 based on clinical assessment, classifying this case as probable DRESS. Points were obtained from the presence of fever, eosinophilia (11.7%), extensive skin rash (>50%), and liver involvement. Laboratory evaluation showed leukocytosis (12.3 thousand/ul) and monocytosis (9.00%), which may reflect the presence of atypical lymphocytes, as well as hypoalbuminemia (2.7 g/dL), consistent with systemic inflammation and impaired hepatic synthetic function (Houssini et al., 2024).

The main differential diagnosis considered in this case is SSJ due to significant mucosal involvement in the patient. The patient showed signs of painful erosion on the lips (cheilitis) and conjunctival injection, which are classic clinical manifestations of SSJ. There are fundamental pathophysiological and clinical differences between SSJ and DRESS. SSJ is characterized by a cytotoxic mechanism that causes widespread keratinocyte apoptosis, manifesting as epidermal necrosis and skin detachment (epidermal detachment) marked by blisters or a positive Nikolsky sign. In contrast, in this patient, the skin lesions were dominated by dermal oedema, diffuse erythema, and desquamation (peeling) without the presence of epidermal detachment in the form of extensive sheets of skin. SSJ is also rarely accompanied by marked eosinophilia (such as 11.7% in this patient) or visceral organ involvement (such as severe hepatitis) with the intensity found in DRESS cases (Cho and Hostoffer, 2023).

The main step in treating DRESS syndrome is early identification and immediate withdrawal of the suspected triggering drug. Delay in drug withdrawal has been shown to correlate directly with a worse prognosis and increased risk of mortality. Phenytoin was immediately discontinued in this case. The main clinical challenge in this patient was the presence of active epilepsy, so discontinuing the drug without substitution risked triggering status epilepticus. The selection of a replacement drug requires careful consideration of the phenomenon of cross-reactivity (Pisano et al., 2021). Aromatic anti-convulsants (phenytoin, carbamazepine, phenobarbital) have structural homology in the benzene ring, which causes a high level of immunological cross-reactivity (40-80%). Therefore, replacing phenytoin with

carbamazepine carries a high risk of triggering exacerbation of the DRESS reaction. The clinical decision to substitute phenytoin with levetiracetam 2 x 250 mg in this patient was an appropriate and evidence-based step. Levetiracetam has a pyrrolidine chemical structure that is different from the aromatic group and is not metabolized into arene oxide metabolites, so it is considered safe for patients with a history of hypersensitivity to classic anticonvulsants (Ak et al., 2022).

The first-line pharmacological therapy for DRESS syndrome, especially when accompanied by severe organ involvement, is systemic corticosteroids. The mechanism of action of corticosteroids in this case is through the inhibition of transcription of genes encoding pro-inflammatory cytokines (such as IL-5, IL-4, and TNF-alpha) and the induction of apoptosis in eosinophils infiltrating the tissue. This patient received initial therapy in the form of 5 mg dexamethasone injections every 12 hours. Dexamethasone is a high-potency glucocorticoid with strong anti-inflammatory effects and is expected to rapidly suppress systemic cytokine storms. The plan to convert to methylprednisolone 125 mg/24 hours is also in line with the protocol for treating severe cases, where high doses are required in the acute phase before slowly tapering off over 6-8 weeks to prevent rebound phenomena (Yang et al., 2021).

The patient in this case experienced severe Drug-Induced Liver Injury (DILI) with massive transaminase elevation and hyperbilirubinemia, necessitating aggressive hepatoprotective therapy. The patient received SNMC (Stronger Neo-Minophagen C) injections containing glycyrrhizin. Glycyrrhizin works by stabilizing hepatocyte cell membranes, inhibiting viral replication (if there is a viral component), and has a local anti-inflammatory effect on

the liver. The patient was also given Curcuma (curcumin) as an antioxidant to reduce oxidative stress on liver cells. This therapy aims to accelerate hepatocyte regeneration and prevent progression to fulminant liver failure (Wu et al., 2021).

Supportive therapy plays an important role in maintaining patient homeostasis during the critical phase. Patients with DRESS syndrome with erythroderma experience high insensible water loss through the skin and increased metabolic demands due to fever. These patients also experience severe hyponatremia (sodium 117 mmol/L), which is likely caused by the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) due to systemic inflammation. Electrolyte correction is performed with careful infusion of 3% NaCl to prevent neurological complications. High-calorie and high-protein nutritional management was provided to compensate for the high protein catabolic state. The use of topical moisturizers (Soft U Derm®) was dermatologically important during the desquamation phase to improve skin barrier function, reduce itching, and prevent secondary infections due to loss of skin integrity (Cabanias et al., 2020).

The prognosis for patients with DRESS syndrome varies. Generally, patients show improvement after discontinuation of the triggering drug and administration of corticosteroids. The patient showed a good clinical response on the last observation day (August 20, 2025), marked by stable body temperature within normal limits (36.1°C), improved hemodynamics, and skin lesions that began to dry and peel off, although jaundice persisted. This indicates the recovery phase from acute inflammatory reactions. Long-term education is necessary as the patient is at risk of developing autoimmune sequelae in the future, and phenytoin must be noted as a

drug contraindicated for life for this patient (Kanabaj et al., 2023).

For summary, a 47-year-old man with cerebral meningioma and symptomatic epilepsy who had been regularly taking phenytoin for the past month. Based on the medical history, he complained of a red rash that spread throughout his body, accompanied by a high fever reaching 41°C and mucosal involvement in the form of pain on the lips. Physical and supporting examinations showed signs of exfoliative erythroderma, conjunctival injection, and systemic abnormalities in the form of significant eosinophilia (11.7%), atypical lymphocytosis reflected in monocytosis, and severe hepatitis with massive transaminase enzyme elevation. These findings support the diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome based on a RegiSCAR score of 5 (probable) with SSJ as a differential diagnosis. The patient received comprehensive management, including immediate discontinuation of phenytoin, substitution of anticonvulsants with levetiracetam 2 x 250 mg, administration of dexamethasone 5 mg corticosteroid injections every 12 hours, and supportive hepatoprotective therapy. Monitoring during treatment showed a good clinical response on the fifth day, with body temperature returning to normal, hemodynamics stable, and skin lesions beginning to dry and desquamate.

AUTHORS CONTRIBUTION

All authors contributed equally to this work.

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None.

CONFLICT OF INTEREST

None.

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