Challenges in Managing Oral Manifestations of Anticonvulsant-Induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

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Received 24 October 2025; 1st revision 17 December 2025;2nd revision 18 December 2025; Accepted 30 December 2025; Published online 31 December 2025

Keywords:
DRESS Syndrome, oral manifestation, phenytoin, lamotrigine, temporal lobe epilepsy, affective bipolar

ABSTRACT

Background : *Antiepileptic drugs were common causative agents for DRESS syndrome, which was a severe, idiosyncratic drug hypersensitivity reaction characterized by a prolonged latency period, fever, rash, and marked eosinophilia. The oral manifestations present a diagnostic challenge due its similarity to other hypersensitivity reactions as well as its comprehensive management.*
Case: *A 19-year-old female inpatient was referred to Oral Medicine division, Dental and Oro-maxillofacial unit of Universitas Indonesia Hospital (RSUI) for severe oral sores after treated with phenytoin and lamotrigine for her temporal lobe epilepsy and bipolar affective disorder. Patient shows general weakness and clinical examination revealed multiple intra oral erosions, lips erosions with exfoliation and haemorrhagic crust, generalized maculopapular rash, facial oedema, tender lymphadenopathy, and. Laboratory findings confirmed a severe hyper-eosinophilia (32%) and lymphopenia (13.5%), while liver function was normal. A diagnosis of DRESS syndrome was finally established. Case management were immediate withdrawal of phenytoin and lamotrigine, followed by multidisciplinary care including intra vena and topical corticosteroids. The patient's condition significantly improved after collaborative comprehensive treatment.*
Conclusion: *Definitive diagnosis decisions requires careful consideration on the correlation of clinical findings, medication history, and hallmark laboratory results, especially in patients with complex comorbidities and intraoral clinical features with characteristics similar to other hypersensitivity reactions. Comprehensive collaborative management, including patient's and other healthcare professionals collaboration, is crucial for successful treatment.*

doi: http://dx.doi.org/10.30659/odj.12.332-345
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How to Cite: Fajrin, *et all*. Challenges in Managing Oral Manifestations of Anticonvulsant-Induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome. Odonto: Dental Journal, v.12, n.3, p.332-345, December 2025.

INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a distinct, severe, and potentially life-threatening idiosyncratic reaction to a drug. It is characterized by a prolonged latency period, typically 2 to 8 weeks, between drug initiation and the onset of symptoms.[1] **The reported incidence of DRESS is highly variable, influenced by the causative medication and the patient's immune status, and likely underreported due to undiagnosed cases. Estimates in the general population range from over 1 case per 10,000 medication exposures to between 0.9 and 10 cases per 100,000 to one million inhabitants.[2] Among hospitalized patients, incidence is higher, ranging from 2.18 to 40 per 100,000 inpatients. A higher incidence has been noted in the Black population and in women.[3] Despite treatment, the associated mortality rate is significant, typically ranging from 3.8% to 10%, though one prospective multinational study reported 1.7%.[4]** The essential clinical features include fever, an extensive skin rash, and significant haematological abnormalities, most notably eosinophilia. While the skin is the most commonly affected organ, DRESS is a systemic condition that can involve vital organs such as the liver, kidneys, lungs, and pancreas, leading to significant morbidity and mortality.[5] Aromatic antiepileptic drugs—including phenytoin, phenobarbital, carbamazepine, and lamotrigine—are among the most frequently implicated medications in inducing DRESS syndrome.[6] The clinical presentation can be highly variable, often mimicking other conditions and posing a significant diagnostic challenge.[7] This case report aims to describe the diagnosis and management of severe oral manifestations in a patient with DRESS syndrome, highlighting the clinical challenges in differentiating it from other mucocutaneous drug reactions and emphasizing the importance of a multidisciplinary approach.

Case Report

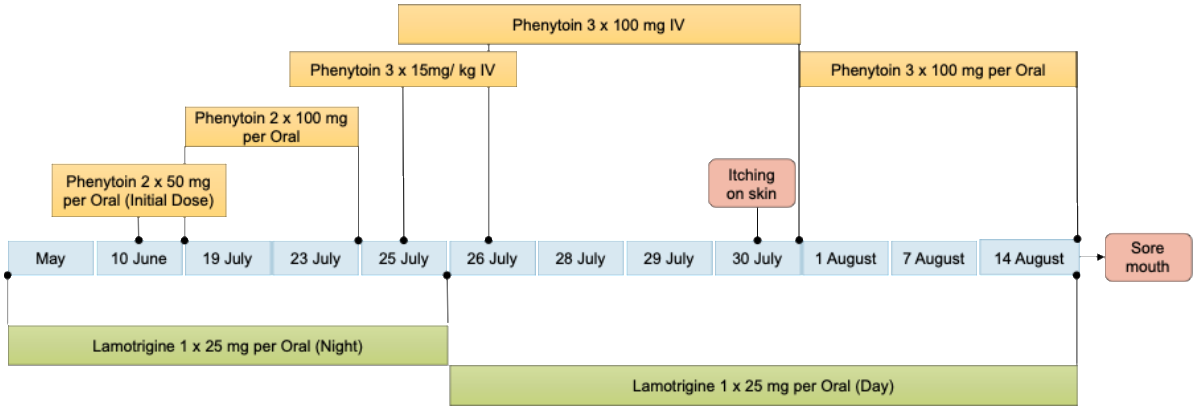
A 19-year-old female patient was admitted to the Emergency Room at the Universitas Indonesia Hospital two days prior the referral to Oral Medicine Division. Neurology department was admitted being the main in charge division since the chief complaint when submitted to ER was recurrent seizures (four episodes, each <5 minutes), nausea, coughing, fever, headache, as well as generalized body itching accompanied by mouth sores. A referral was made to the Oral Medicine clinic by the Internal Medicine department. The chief complaint was a severe sore mouth that had persisted for the past 10 days. Constant burning pain in the lips and mouth was reported, rated 7/10 on the Numeric Rating Scale (NRS), accompanied by a fever of 37.2°C. Notably, the oral ulcers began without any preceding blisters or vesicles**. The oral complaints were preceded by systemic symptoms; generalized itching throughout her body was experienced by the patient, which appeared approximately 17 days earlier, shortly after her previous hospital discharge for seizures**. The ulcerations were limited to the oral cavity, with no other lesions present and no history of recurrence. Treatments were attempted to alleviate the oral pain, such as using honey, an over-the-counter herbal solution, and a Nystatin drop smeared on the lips, but these provided only temporary relief.

The patient's medical history is complex. The history of measles was reported a month prior during a hospitalization at another hospital. The history of recurrent seizures began seven years ago, without treatment being administered. Additionally, there has been a decline in mental health and loss of motivation that started five years ago during junior high school. Psychiatric symptoms, including

mood swings and auditory/visual hallucinations, worsened significantly in 2022, leading to the patient stopping study at school in early 2024. Formal psychiatric treatment began six months before the admission, at which point the patient was diagnosed with bipolar affective disorder. Seizure activity frequently coincided with episodes of depression or periods of fear, prompting a referral for a neurological evaluation. This evaluation resulted in a new diagnosis of temporal lobe epilepsy, made two months prior to the current admission. Following this diagnosis, treatment was initiated at Universitas Indonesia Hospital.

The diagnoses established by the primary neurology team upon admission included: cluster seizures in symptomatic epilepsy (focal to bilateral onset, secondary to suspected temporal lobe epilepsy (TLE) or psychogenic non-epileptic seizures (PNES)); bipolar affective disorder; suspected delayed hypersensitivity to phenytoin and lamotrigine (differential diagnosis: measles); upper respiratory tract infection (URTI) (differential diagnosis: allergic bronchitis); hyper-eosinophilia; microcytic hypochromic anemia secondary to suspected iron deficiency anemia; and reactive thrombocytosis.

At the time of admission, the patient's medication regimen consisted of phenytoin (3x100 mg), lamotrigine (2x25 mg), clobazam (2x10 mg), fluimucil (3x200 mg), sucralfate (3x15 mL), aripiprazole (1x2.5 mg), and N-acetylcysteine (NAC) (3x200 mg). The administration timeline for the suspected medications was considered a crucial component of the diagnostic process. A detailed history of the patient's phenytoin and lamotrigine use is presented in the diagram below **(Picture.1)**

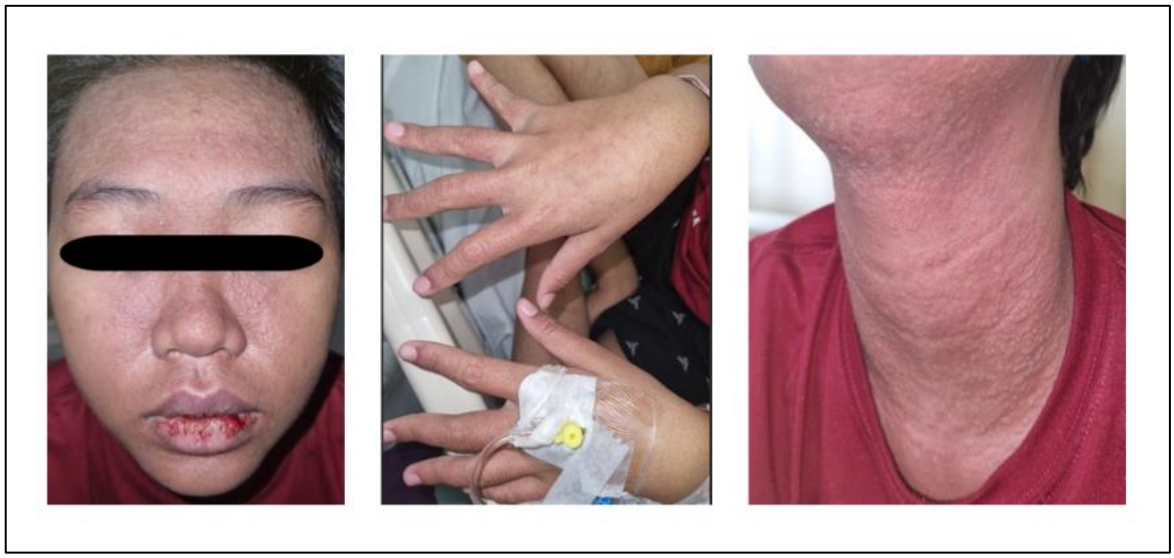


Picture 1. Timeline of Phenytoin and Lamotrigine Use

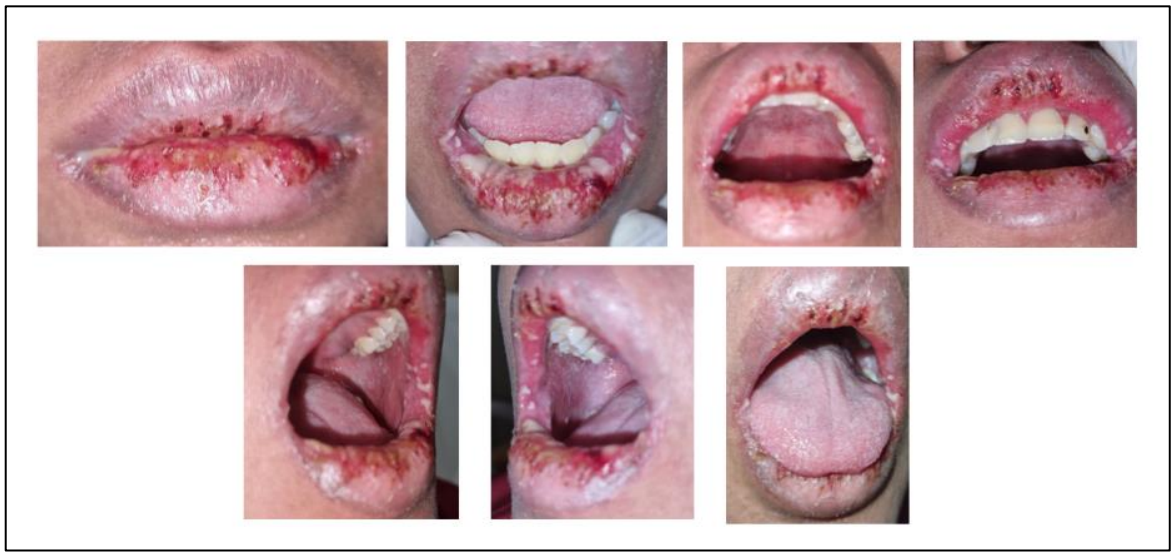
The clinical assessment was conducted following a recent episode of mania and agitation. Upon examination, the patient was found to be conscious. Gathering a detailed medical history was challenging. The interview process was interrupted by the patient's psychiatric condition, which included recent use of restraints and reports of auditory hallucinations that encouraged self-harm. Notable extraoral findings included a diffuse maculopapular rash on the face and extremities and bilateral, enlarged, soft, and tender submandibular lymph nodes. Severe involvement of the lips was observed, characterized by multiple irregular, well-defined erosions along the entire vermilion border. These lesions were covered with blackish-red, yellow, and brownish-black crusts and were tender upon palpation. The intraoral examination was constrained by the patient's limited mouth opening. Numerous

mucosal lesions were present. Several shallow, coalescing ulcers (ranging from 1 to 10 mm) with irregular borders and surrounded by diffuse erythema were observed on the labial mucosa. The buccal mucosa and hard palate exhibited multiple irregular erosions with indistinct borders. Additional findings included hyperemia of the anterior mandibular gingiva and a moderate white coating on the dorsum of the tongue. Oral hygiene was classified as moderate, with noted plaque, calculus, and dentin caries on tooth 11. The saliva appeared clear and runny.

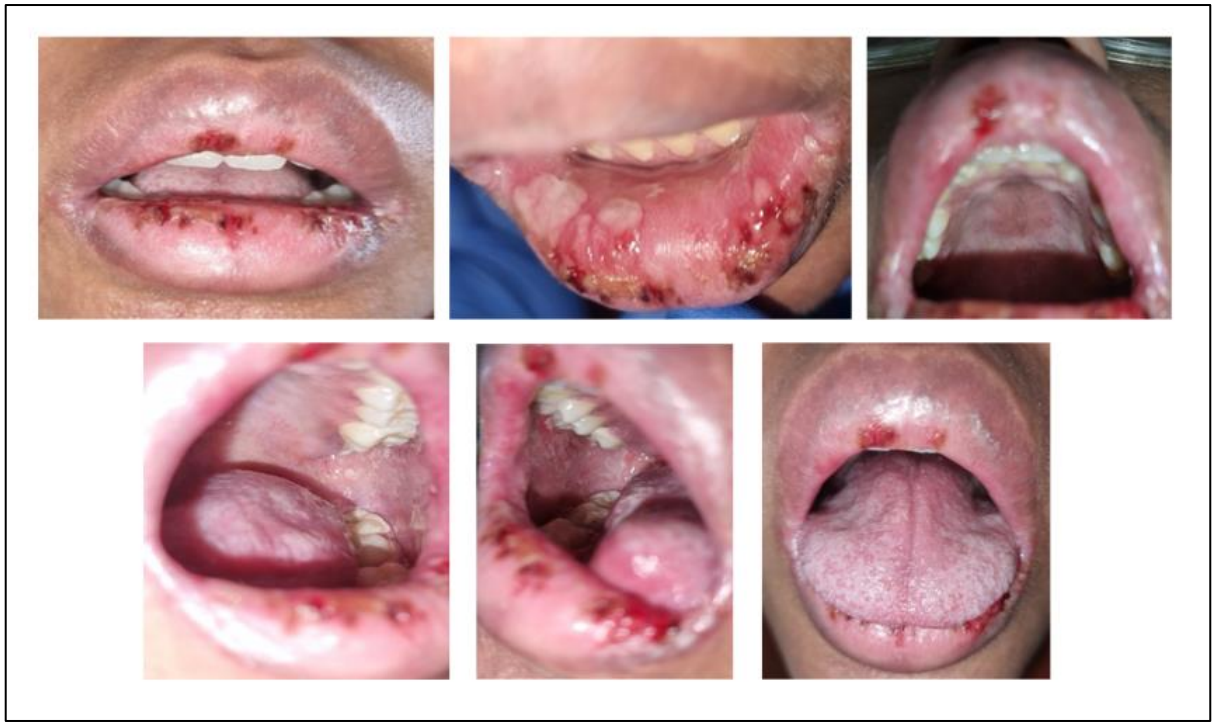
Picture 1. Clinical Extraoral Findings at Initial Presentation



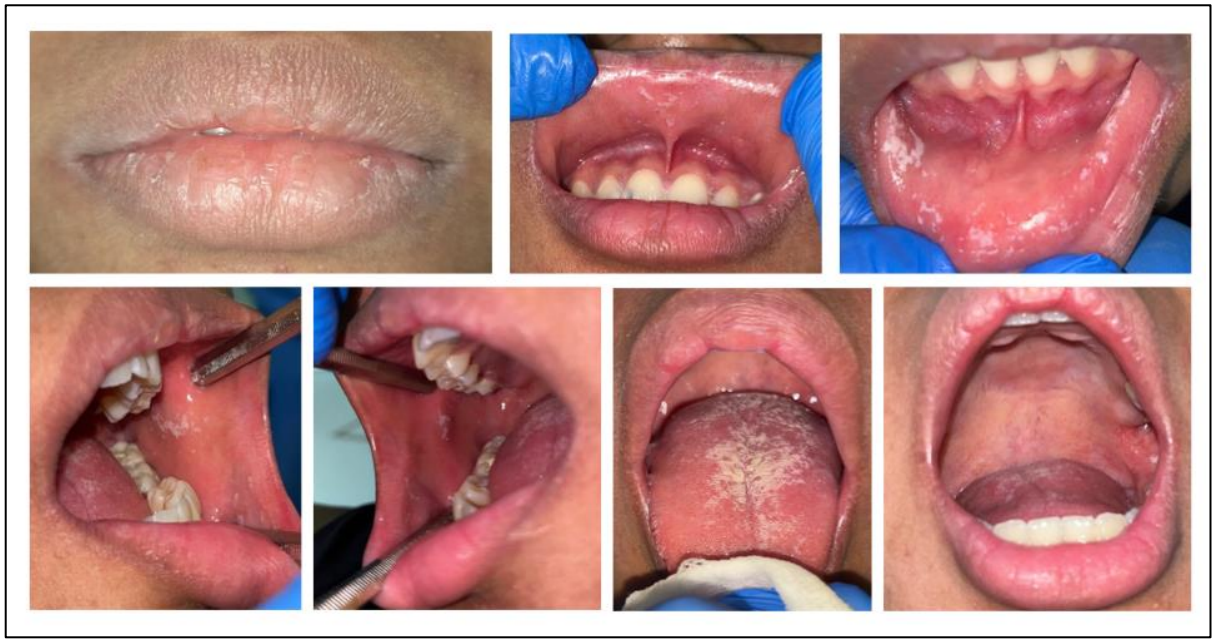
Picture 2. Intraoral view at the first visit.



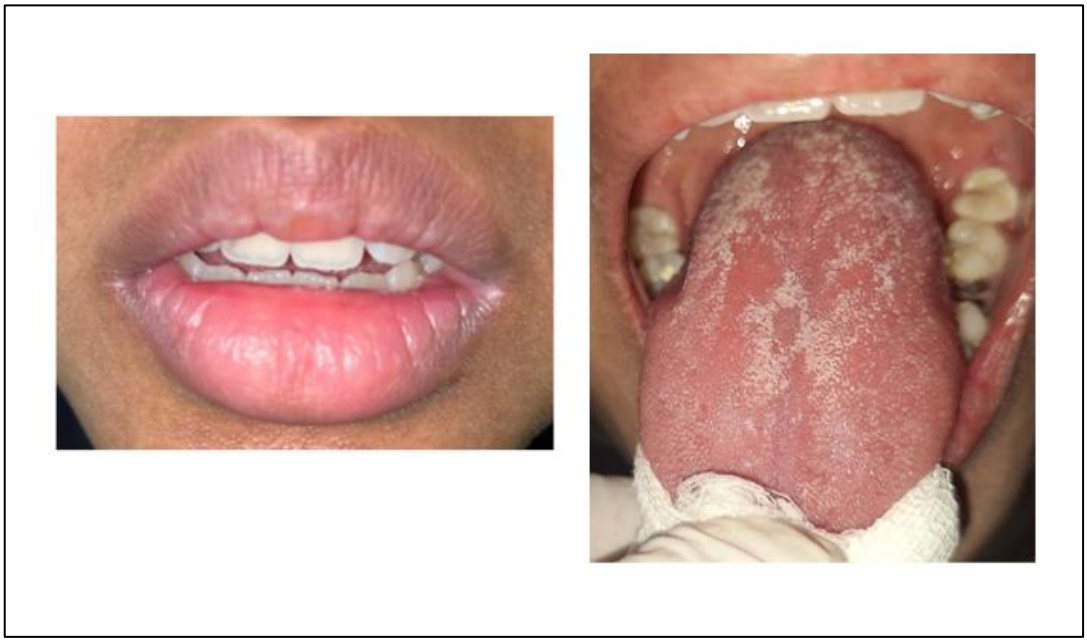
Picture 3. Intraoral view taken on the second visit (Day 2 post-first examination)



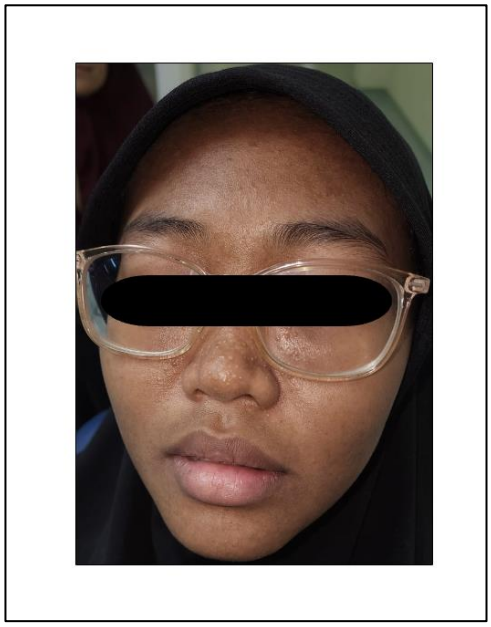
Picture 4. Intraoral view taken on the third visit (Day 15 post-first examination)



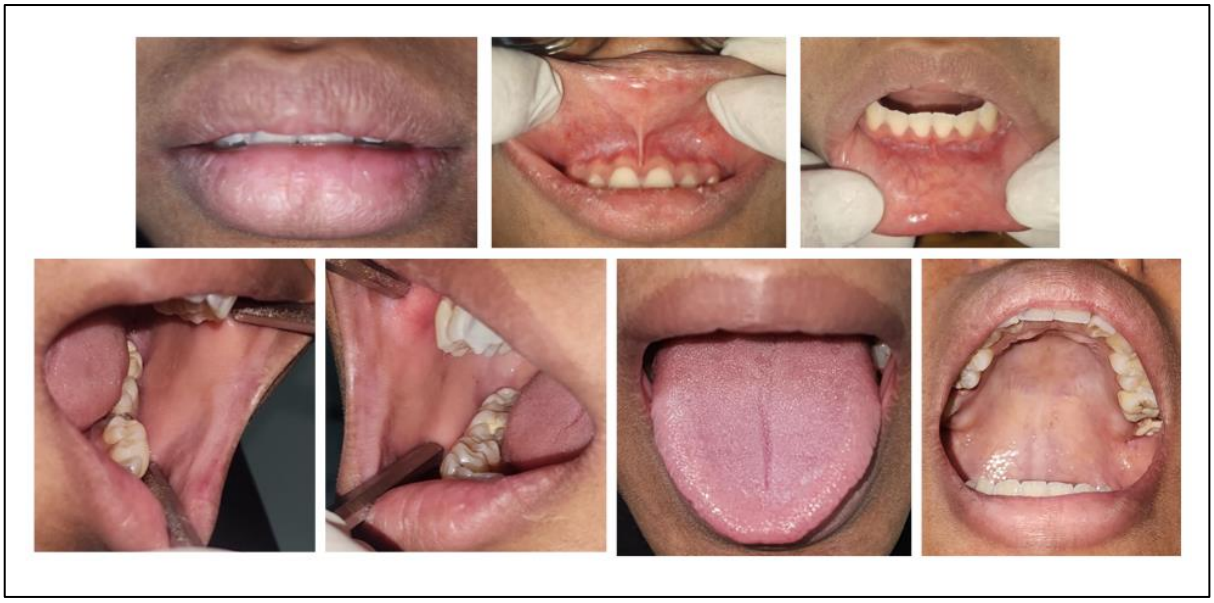
Picture 5. Intraoral view taken on the fourth visit (Day 21 post- first examination)



Picture 6. Clinical Extraoral Findings at fifth (Final) Presentation



Picture 7. Intraoral view taken on the fifth (final) visit (Day 29 post- first examination)



Several critical abnormalities were identified from the complete blood count results, including severe hyper-eosinophilia, lymphopenia, mild anemia, and reactive thrombocytosis (Table 3).

Table 3. Lab Test Result

Parameter	Result	Reference Range	Interpretation
Hemoglobin	10.7 g/dL	12.0–15.0 g/dL	Low
Hematocrit	32.40%	36.0–46.0%	Low
Erythrocytes	4.07million/µL	3.80–4.80million/µL	Normal
MCV	79.6 fL	83.0–101.0 fL	Low
MCH	26.3 pg	27.0–32.0 pg	Low
MCHC	33.0 g/dL	31.5–34.5 g/dL	Normal
Platelet Count	501,000/µL	150,000–410,000/µL	High
Leukocyte Count	9,090/µL	4,000–10,000/µL	Normal
Basophils	0.10%	0–2%	Normal
Eosinophils	32.00%	1–6%	Very High
Neutrophils	46.60%	52–76%	Low
Lymphocytes	13.50%	20–40%	Low
Monocytes	7.80%	2–10%	Normal
SGOT (AST)	30 U/L	5–34 U/L	Normal
SGPT (ALT)	31 U/L	0–55 U/L	Normal

To aid in standardizing the diagnosis, a validated scoring system, European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR), is performed. Through this system, cases are classified as "no," "possible," "probable," or "definite" DRESS based on a composite score derived from clinical and laboratory findings. The application of the RegiSCAR criteria to this patient was essential for diagnostic confirmation, particularly given the presence of atypical features such as the absence of liver involvement.[10] The patient's presentation was systematically evaluated against the RegiSCAR scoring criteria as outlined in Table 5

Table 4. RegiSCAR DRESS Validation Score for the Presented Case

RegiSCAR Criterion	Patient Finding	Points Awarded
Fever >38.5°C	Yes (38.2°C)	0
Eosinophilia	Yes, severe (32%)	+2
Lymphadenopathy	Yes (bilateral, tender submandibular)	+1
Skin Rash Extent >50%	Yes (generalized maculopapular rash)	+1
Rash Suggestive of DRESS	Yes (facial edema)	+1
Internal Organ Involvement	No (normal liver function, no other specified)	0
Resolution ≥15 days	Yes (prolonged course)	0
Total Score		5

A total score of 5 was calculated, which categorizes this presentation as a "probable" case of DRESS according to the RegiSCAR classification. Therefore, despite the absence of hepatitis—the most common visceral manifestation of DRESS—the patient's constellation of severe eosinophilia, characteristic rash with facial edema, and lymphadenopathy was sufficient to establish a confident diagnosis of probable DRESS syndrome. This highlights the robustness of the scoring system and underscores that a diagnosis can be made even when a classic feature is absent, preventing misdiagnosis in atypical presentations.

A diagnosis of Oral Manifestations of DRESS Syndrome was established based on the clinical findings, in conjunction with a history of exposure to high-risk drugs. Due to the severe mucosal involvement, Drug-Induced Erythema Multiforme was considered the primary differential diagnosis. A crucial distinction lies in the latency period and cause. A key differentiating factor is the onset **EM is an acute condition that often appears suddenly, while DRESS syndrome is characterized by a prolonged latency period, typically 2 to 8 weeks. Additionally, in 70% of EM cases, the condition is preceded by a viral infection, most commonly Herpes Simplex Virus (HSV), leading to a diagnosis of Herpes-Associated Erythema Multiforme (HAEM).[8] Furthermore, DIEM/HAEM is generally a self-limiting mucocutaneous reaction, whereas DRESS involves systemic symptoms, marked eosinophilia, and potential multi-organ involvement. The patient's 17-day latency period , severe hyper-eosinophilia (32%) , and systemic features strongly favored the DRESS diagnosis over DIEM/HAEM[5,8,9]**

A multidisciplinary approach to management was employed. The cornerstone of therapy was the immediate withdrawal of the suspected causative agent, phenytoin. This medication was subsequently replaced with a non-aromatic anticonvulsant (topiramate) by the neurology unit. The cutaneous manifestations were managed by the dermatology team with a tapering course of oral methylprednisolone (initially 32 mg in the morning and 16 mg in the evening for 4 days, followed by 16 mg in the morning and 8 mg in the evening for one week). Additional systemic treatment included cetirizine (10 mg once daily).

For the oral lesions, initial treatment consisted of a topical dexamethasone swish-and-spit rinse (4 mg in the morning, 2 mg in the evening). At the two-day follow-up, a slight improvement in the oral lesions was observed, and the topical dexamethasone dosage was tapered to 3 mg in the morning and 1 mg in the evening. In preparation for discharge two days later, the regimen was further tapered to 2 mg once daily in the morning. A follow-up appointment was scheduled for one week later at the Oral Medicine Clinic, Universitas Indonesia Hospital.

By the third visit, healing of the initial oral erosions associated with DRESS syndrome was observed. However, a new clinical manifestation of acute pseudomembranous candidiasis was present on the tongue, buccal mucosa, and labial mucosa, which was considered an iatrogenic complication of the topical steroid use. **No adjunctive diagnostic tests like mycological examination were performed for the candidiasis, as the clinical signs were pathognomonic and sufficient for diagnosis.** Further examination revealed a decreased salivary flow rate, confirmed by an unstimulated salivary flow rate (USFR) of 0.16 ml/min. No salivary secretion was yielded upon bimanual palpation of the parotid glands, although secretion remained present from the submandibular and sublingual glands. A Clinical Oral Dryness Score (CODS) of 5 was recorded, indicating moderate oral dryness, and the Summated Xerostomia Inventory-Indonesia Version (SXI-ID) score was 11, consistent with mild xerostomia.

Consequently, the topical steroid therapy was discontinued and replaced with a regimen of nystatin oral suspension (1 ml, four times daily, swish and swallow) and saline rinses to improve oral moisture. At a subsequent follow-up visit, complete resolution of the secondary candidiasis was achieved. Furthermore, an improvement in xerostomia was noted, with the SXI-ID score having decreased to 9, which still indicated mild xerostomia.

Discussion

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a life-threatening, delayed-type hypersensitivity reaction characterized by a latency period of 2 to 8 weeks. It manifests as a widespread rash, fever, marked eosinophilia, and multi-organ involvement, particularly of the liver.[10] The syndrome carries a mortality rate of up to 10%, often due to fulminant hepatitis.[5] The pathogenesis of DRESS syndrome is multifactorial, involving a complex interplay of drug metabolism, host genetics, and viral-immune interactions. Among antiepileptic drugs, those that most frequently trigger DRESS syndrome are drugs with an aromatic ring structure, including phenytoin, lamotrigine, carbamazepine, oxcarbazepine, and phenobarbital.[6] In susceptible individuals, deficient detoxification of reactive drug metabolites, often due to genetic mutations in the epoxide hydroxylase enzyme, leads

to their accumulation.[11] These metabolites can elicit a Type IVb hypersensitivity reaction, characterized by the activation of T-helper 2 (Th2) cells and the release of Interleukin-5 (IL-5), which drives the syndrome's hallmark eosinophilia.[12]

Type IVb corresponds to the Th2-type immune response in which Th2 cells secrete IL-4, IL-13 and IL-5, thereby promoting B-cell production of IgE and IgG4, macrophage deactivation and mast-cell and eosinophil responses. The high production of the Th2 cytokine IL-5 leads to an eosinophilic inflammation, which is the characteristic inflammatory cell type in many drug hypersensitivity reactions. In addition, there is a link to type I reactions, as Th2 cells boost IgE production by IL-4/IL-13 secretion. An in vivo correlate might be an eosinophil-rich maculopapular rash. [13] Upon reaching the target tissue, eosinophils are activated and degranulate, releasing toxic proteins like major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein (ECP), which are cytotoxic to the gastrointestinal epithelium and secrete cytokines that enhance the inflammatory responses.[14]

The same underlying immune cascade is responsible for the systemic and cutaneous damage and is implicated in the development of oral lesions. The accumulation of reactive drug metabolites and their subsequent presentation by HLA molecules to T-cells lead to a cytotoxic attack that targets the basal layer of the stratified squamous epithelium. The resulting inflammation, driven by inflammatory cytokines like IL-6 and IFN-γ, culminates in the painful ulceration and erosions commonly observed in the oral mucosa.[15]

Host susceptibility is strongly linked to specific Human Leukocyte Antigen (HLA) alleles, which vary by ethnicity. For example, HLA-B15:02 is a known risk factor for phenytoin-induced severe cutaneous adverse reactions (SCARs) in Southeast Asian populations, while other alleles have been associated with lamotrigine-induced reactions in Thai patients.[11,16] These HLA molecules are thought to present the drug or its metabolites directly to T-cells, triggering a robust immune response.[17] Polymorphisms in other genes, such as CYP2C93, can also increase risk by altering drug metabolism. Furthermore, reactivation of human herpesviruses, particularly HHV-6 (detected in 60–80% of cases), is a key pathogenic feature and is included in some diagnostic criteria.[18]

Upon initial consultation, a working diagnosis of Drug-Induced Erythema Multiforme was made, prompted by severe oral manifestations that included haemorrhagic crusting of the lips, ulceration on the ventral tongue, and widespread erosions on the buccal mucosa and hard palate. Concurrently, the cutaneous findings were evaluated by the Dermatology service, and a diagnosis of a maculopapular type of Drug-Induced Hypersensitivity Syndrome (DIHS)/DRESS was made. The reaction was suspected by the Internal Medicine team to be induced by phenytoin and lamotrigine. A definitive diagnosis was ultimately established through a multidisciplinary discussion involving consulting experts from Dermatology and Internal Medicine. Following a careful correlation of the oral, cutaneous, and systemic findings, a consensus was reached that the patient's overall clinical picture was most consistent with DRESS syndrome induced by phenytoin and lamotrigine.

Table 5. The Difference Between DRESS and Drug Induced Erythema Multiforme

Drug Induced Erythema Multiforme[9]	DRESS

Onset	Signs and symptoms appear quickly (within 24-72 hours) after first-time drug consumption.	Latency period of 2-8 weeks.
Systemic Findings	Pathognomonic target lesions (<3 cm) on skin.	Pruriginous morbilliform rash involving >50% BSA. Lymphadenopathies.
Oral Findings	Widespread erosion, edema, crusting, and bleeding on lips. Irregular erosions on all oral mucosa.	May involve a single site (cheilitis, pharyngitis) and can progress to erosions.
Lab Findings	May show moderate leukocytosis, eosinophilia, neutropenia, mild anemia, thrombocytopenia. ESR may be elevated.	Leukocytosis (preceded by leukopenia, lymphopenia), atypical lymphocytes, thrombocytopenia, anemia, and significant Eosinophilia. Liver and renal function tests may be abnormal.

The non-negotiable first step in managing DRESS syndrome is the immediate and permanent withdrawal of all potential causative agents.[1] In the presented case, this necessitated the cessation of both phenytoin and lamotrigine. The consulting neurologist successfully achieved this by substituting the offending agents with a non-aromatic anticonvulsant, topiramate, to maintain seizure control. Systemic corticosteroids are the established first-line treatment for ameliorating the clinical symptoms of DRESS during the acute phase, with rapid resolution of rash and fever typically occurring within days of initiation.[19] Accordingly, a tapering course of oral methylprednisolone was prescribed by the dermatology team. The regimen commenced with a dosage of 32 mg in the morning and 16 mg in the evening for four days, which was subsequently reduced to 16 mg in the morning and 8 mg in the evening for one week.

The oral medicine management strategy was twofold, focusing on treating the primary mucosal lesions and managing the subsequent iatrogenic complications. Severe and painful oral erosions are a prominent manifestation of DRESS syndrome. This is consistent with existing literature, such as the case reported by Wahbi Ben Salha et al., of an allopurinol-induced DRESS presenting initially with erosive cheilitis, which resolved with systemic and topical corticosteroid therapy.[20] To manage these lesions, a targeted topical corticosteroid regimen was implemented.

For the widespread intraoral erosions, an extemporaneously prepared dexamethasone swish-and-spit rinse was prescribed. The formulation of effective topical agents for oral application faces numerous obstacles, including dilution by saliva, enzymatic degradation, and potential for accidental swallowing leading to systemic absorption. A common clinical practice, particularly for conditions like oral lichen planus (OLP), involves using crushed 0.5 mg dexamethasone tablets mixed with water as a rinse, which has shown clinical efficacy.[21] The rationale for using dexamethasone is supported by *in vivo* and *in vitro* studies demonstrating the buccal mucosa's ability to act as a reservoir for the glucocorticoid after topical application. Critically, it has been found that only 1% of the topically applied dexamethasone is delivered across the mucosa, significantly mitigating the risk of systemic

absorption.[22] This permeability profile is ideal for treating multiple intraoral erosions, as it optimizes medication retention at the site of action for maximum therapeutic effect.

A different approach was necessary for the labial lesions, as a liquid rinse would be ineffective due to its inability to adhere to the lip surface. Consequently, a mometasone cream was prescribed. The cream's texture ensures excellent adherence to the mucocutaneous tissue of the lips, providing prolonged contact between the medication and the lesions to resolve inflammation and promote healing.[23] Upon clinical improvement of the lesions, a gradual tapering of the topical dexamethasone was initiated. Gradual dose reduction of topical steroids is the standard of care after successful treatment of oral mucosal diseases to prevent rebound symptoms and minimize local side effects.[24] The tapering schedule involved reducing the frequency of application based on the clinical response before complete cessation.

Close follow-up was essential for managing iatrogenic complications. The development of acute pseudomembranous candidiasis was observed, a condition considered to be a foreseeable consequence of the dual corticosteroid therapy. Both systemic corticosteroids, which cause general immunosuppression, and topical corticosteroids, which alter the local oral microflora, are major triggers. This is supported by Lian et al., who demonstrated that DRESS patients receiving systemic corticosteroids had significantly higher rates of infective complications than those on topical therapy (32.1% vs. 12.2%, $p = 0.02$).[25] As confirmed by Lopes and Lionakis, such iatrogenic immunosuppression enables *Candida albicans* to transition from a commensal to an opportunistic pathogen.[26] **Administration of polyene antifungal drugs, such as Nystatin, is typically recommended for mild cases of oral candidiasis. Polyenes, which are fungicidal drugs, work by binding directly to ergosterol in the fungal cell membrane, causing leakage of cytoplasmic contents which causes fungal cell death.[27]**

This suggests that in our patient, the development of acute pseudomembranous candidiasis was likely driven more profoundly by the interplay of systemic factors, primarily the steroid-induced immunosuppression and the presence of medication-induced xerostomia.[28] A history of psychotropic medication use is known to induce xerostomia, which leads to a reduction in saliva's natural antimicrobial function. Furthermore, it is possible that mucosal epithelial integrity was compromised by the patient's anemic condition. As identified by Nuncă et al., psychotropic medication and hematologic disorders create favorable conditions for *Candida* proliferation.[29] Thus, the combination of steroid-induced immunosuppression, decreased salivary flow, and systemic anemia created a highly conducive environment for opportunistic infection.

A third focus of oral management was addressing medication-induced xerostomia, as the patient was prescribed two medications known to contribute to this condition. The first was topiramate, a second-generation antiepileptic drug (AED) characterized by a non-aromatic sugar (pyranose) ring structure. While not its most frequent adverse effect, dry mouth is a recognized side effect of topiramate.[23] The second agent was aripiprazole, an atypical antipsychotic. Its mechanism of action involves partial agonism at dopamine D_2 and serotonin 5-HT_1A receptors, with antagonism at serotonin 5-HT_2A receptors. This unique profile stabilizes dopamine and serotonin activity to reduce symptoms of psychosis, mania, and depression. Despite its efficacy, meta-analyses of randomized controlled trials have reported higher rates of dry mouth in patients taking aripiprazole compared to placebo. [24]

Conclusion

This case demonstrates that successful outcomes in complex DRESS syndrome hinge on expert multidisciplinary collaboration. While neurology/psychiatry managed high-risk medication changes and dermatology led systemic therapy, oral medicine was pivotal in diagnosing severe oral lesions, managing local therapy, and treating iatrogenic complications.

Acknowledgement

The authors are grateful to the patient and her family for providing consent for publication. We wish to acknowledge the valuable collaboration of the specialists at Universitas Indonesia Hospital (RSUI) from the Departments of Neurology, Internal Medicine, and Dermatology and Venereology, as well as the support from the Oral Medicine Department, Faculty of Dentistry, Universitas Indonesia. The authors declare no funding sources or conflicts of interest.

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