International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 04 Issue 11 November 2024

Page No: 2011-2019

DOI: https://doi.org/10.47191/ijmscrs/v4-i11-25, Impact Factor: 7.949

A Rare and Complex Overlap of Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Case Report and Review of the Literature

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ABSTRACT

Toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are both life-threatening hypersensitivity reactions characterized by widespread cutaneous involvement and multiorgan damage. While these syndromes are distinct, overlapping cases are exceptionally rare and represent a diagnostic and therapeutic challenge due to their shared and divergent pathophysiological features. In this case report, we describe a 21-year-old male patient who developed overlapping TEN and DRESS following treatment with phenytoin, risperidone, and levofloxacin. The patient presented with widespread epidermal detachment, facial edema, lymphadenopathy, eosinophilia, and liver dysfunction. Clinical management required a multidisciplinary approach including prompt withdrawal of the offending drug, initiation of systemic corticosteroids and supportive care. This case highlights the critical importance of early diagnosis and tailored management in preventing severe outcomes. A review of the current literature on TEN-DRESS overlap syndrome is also provided, discussing potential immunological mechanisms, diagnostic criteria, and therapeutic strategies.

ARTICLE DETAILS

Published On:
19 November 2024

KEYWORDS: Toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, hypersensitivity reaction, overlap syndrome, cutaneous drug reaction, systemic corticosteroids

Available on:
https://ijmscr.org/

INTRODUCTION

Toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are severe, idiosyncratic, drug-induced hypersensitivity syndromes. TEN, often considered a continuum of Stevens-Johnson Syndrome (SJS), is characterized by extensive epidermal detachment and mucosal involvement, with mortality rates ranging from 25% to 35% depending on the extent of skin loss and systemic complications. DRESS, on the other hand, presents with diffuse skin eruption, eosinophilia, lymphadenopathy, and multiorgan involvement, typically affecting the liver, kidneys, and lungs. Despite these differences, both conditions share an immunological basis driven by a delayed-type hypersensitivity reaction to certain drugs, including anticonvulsants, antibiotics, and allopurinol.

Cases of overlap between TEN and DRESS are exceedingly rare but represent a formidable diagnostic challenge. The coexistence of these syndromes complicates clinical presentation, prognosis, and management. Overlapping features such as fever, extensive skin involvement, eosinophilia, and internal organ dysfunction can delay accurate diagnosis and complicate therapeutic decisions. Early recognition and timely intervention are critical to prevent severe systemic complications and improve patient outcomes.2,3

This report describes a unique case of a 21-year-old male who developed overlapping TEN and DRESS syndrome following treatment with phenytoin, risperidone, levofloxacin and celecoxib.The simultaneous presence of widespread cutaneous necrosis, systemic eosinophilia required urgent medical attention and a coordinated therapeutic strategy.

Through this case, we aim to highlight the clinical complexity of TEN-DRESS overlap syndrome, discuss the immunopathological mechanisms underpinning this condition, and review the existing literature on management strategies for these rare but severe drug reactions.3,4

Toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are both severe drug-induced hypersensitivity reactions, each associated with significant morbidity and mortality. While they are typically distinct clinical entities, overlapping cases have been sporadically reported, presenting diagnostic challenges due to their shared characteristics and divergent pathophysiological processes. Both conditions are part of the spectrum of severe cutaneous adverse reactions (SCARs), characterized by systemic involvement and profound cutaneous manifestations.4,5

TEN is primarily characterized by extensive keratinocyte apoptosis leading to full-thickness epidermal detachment, with severe mucosal involvement in over 90% of cases. The syndrome represents the extreme end of a spectrum that includes Stevens-Johnson Syndrome (SJS), differentiated mainly by the extent of skin detachment, with TEN involving >30% of total body surface area (TBSA). DRESS, on the other hand, manifests with a more varied clinical presentation, including a maculopapular exanthema, fever, lymphadenopathy, eosinophilia, and multiorgan involvement, particularly hepatotoxicity.4,5. Figure 1.

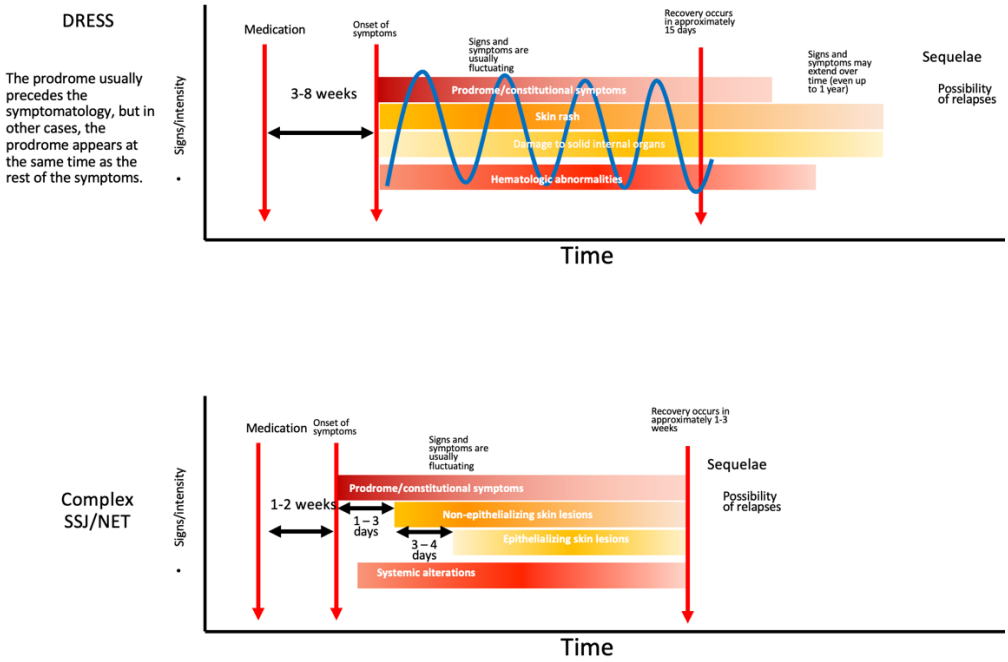

Figure 1. DRESS and SSJ/NET timeline.

While distinct in their classical presentations, TEN and DRESS can overlap, resulting in a syndrome that combines the systemic inflammatory features of DRESS with the widespread epidermal necrosis typical of TEN. This overlap poses significant therapeutic and diagnostic challenges, often requiring urgent and aggressive medical intervention to prevent fatal outcomes.6,7

Pathophysiology of TEN-DRESS Overlap

The pathophysiology of both TEN and DRESS is rooted in immune-mediated hypersensitivity reactions, most commonly triggered by medications. However, the underlying immunological mechanisms differ between the two entities.

In TEN, the immune response is dominated by cytotoxic CD8+ T cells, which induce keratinocyte apoptosis through the Fas-Fas ligand interaction and the release of cytotoxic molecules such as granzyme B and perforin. There is also evidence of a significant role for granulysin, a cytotoxic protein that is massively upregulated in TEN and directly implicated in widespread keratinocyte death.8

DRESS, by contrast, involves a more complex immunological response characterized by the activation of CD4+ T helper cells, leading to the release of pro-inflammatory cytokines such as interleukin-5 (IL-5), which drives eosinophilia. Additionally, regulatory T cells (Tregs) and monocytes are thought to play a role in modulating the immune response in DRESS, contributing to its prolonged clinical course and multiorgan involvement.8

In cases of TEN-DRESS overlap, the pathophysiological mechanisms of both conditions appear to converge, with simultaneous activation of cytotoxic T cells, eosinophils, and inflammatory cytokines, leading to a combination of systemic inflammation and epidermal destruction. Genetic susceptibility, particularly involving polymorphisms in the HLA system, is thought to play a critical role in predisposing certain individuals to these reactions. HLA-B*58:01, for example, is strongly associated with both allopurinol-induced

TEN and DRESS, highlighting the overlap in their genetic underpinnings.8

Clinical Presentation

The clinical presentation of TEN-DRESS overlap is variable, with patients typically exhibiting features of both conditions. The hallmark of TEN-widespread epidermal detachment-often dominates the cutaneous findings, with large areas of full-thickness epidermal necrosis and mucosal erosions. Nikolsky's sign, wherein gentle pressure causes sloughing of the epidermis, is usually positive. Additionally, patients may present with painful skin and fever.9

At the same time, systemic manifestations typical of DRESS, including facial edema, lymphadenopathy, eosinophilia, and multiorgan involvement (e.g., liver, kidneys, lungs), are commonly observed. Hepatitis, interstitial nephritis, and pneumonitis are frequent complications in DRESS and can also occur in overlap cases. The clinical overlap may present as a rapidly progressing illness with significant systemic toxicity, complicating diagnosis and leading to delayed treatment initiation, further increasing morbidity and mortality risks.9

Diagnostic Considerations

The diagnosis of TEN-DRESS overlap is clinical and relies on recognizing the features of both syndromes. Skin biopsy is a crucial tool in distinguishing between these conditions, though its findings in overlap cases may show features of both TEN and DRESS. In TEN, histopathology typically reveals full-thickness epidermal necrosis with minimal dermal inflammation. In contrast, DRESS is characterized by interface dermatitis with vacuolar alteration of the basal layer, spongiosis, and a prominent perivascular lymphocytic infiltrate often containing eosinophils.10

Laboratory investigations can further support the diagnosis. Blood tests often reveal eosinophilia, leukocytosis, and elevated liver enzymes, consistent with DRESS. The presence of eosinophils is a key feature distinguishing DRESS from TEN, where such peripheral eosinophilia is generally absent. Given the multisystem involvement in DRESS, it is also important to assess renal and hepatic function regularly.11

Therapeutic Approaches

The management of TEN-DRESS overlap requires an urgent, multidisciplinary approach due to the life-threatening nature of these conditions. The cornerstone of treatment is immediate withdrawal of the offending drug, followed by supportive care in an intensive care or burn unit, particularly for cases with significant skin detachment.11

Systemic corticosteroids are commonly used in the management of DRESS due to their ability to suppress the excessive immune response. Their use in TEN remains controversial due to concerns about increasing the risk of infection and delaying re-epithelialization, though they may be warranted in overlapping cases where systemic inflammation is prominent. In such cases, careful dosing and duration of corticosteroid therapy are critical, with a gradual taper to prevent rebound inflammation.11

Intravenous immunoglobulin (IVIG) has been shown to benefit patients with TEN by neutralizing granulysin and other cytotoxic molecules, thereby halting keratinocyte apoptosis. IVIG may also have a role in treating TEN-DRESS overlap cases, particularly when there is significant skin detachment. The combination of IVIG with systemic corticosteroids has been proposed as an effective strategy in treating overlap syndromes, though the evidence remains limited.12

In more refractory cases, other immunosuppressive agents such as cyclosporine or tumor necrosis factor (TNF)-alpha inhibitors (e.g., etanercept) may be considered. Plasmapheresis has also been explored as an adjunct therapy in severe TEN and DRESS cases, aimed at rapidly removing circulating immune complexes and pro-inflammatory mediators.13

Prognosis and Outcomes

The prognosis for patients with TEN-DRESS overlap is generally poor due to the combined systemic and cutaneous involvement. Mortality in TEN is primarily driven by the extent of skin loss and subsequent infections, as well as by multiorgan failure. In contrast, mortality in DRESS is more often associated with severe internal organ involvement, particularly liver failure.14

Given the severity of both conditions, early recognition and treatment are critical to improving patient outcomes. Long-term sequelae are common, particularly in survivors of TEN who may experience extensive scarring, mucosal damage, and visual impairment. Chronic organ dysfunction, particularly involving the liver or kidneys, may also occur following DRESS.14

Table 1. DRESS syndrome and SJS/TEN complex comparison.

Characteristic	**SSJ/TEN Complex/Spectrum**	**DRESS Syndrome**
Terminology/Nomenclature	• Toxic Epidermal Necrolysis (TEN) or Lyell's syndrome • Stevens-Johnson Syndrome (SSJ)	DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms
Hypersensitivity	Type IV or delayed	

Etiology	Mainly drug-induced and typically in association with an underlying diseases like acute type IV graft-versus-host disease, Mycoplasma pneumoniae infection, viral infections, or immune disorders (HIV, SLE, IBD, hematologic malignancies)	The most important cause are drugs. Associated with herpes virus reactivation, with HHV-6 being the most prevalent
Classification	According to SCT detachment: • SSJ < 10% SCT • SSJ and TEN overlap 10 – 30% • TEN > 30%	Controversial classification ranks severity from "mini-DRESS" (mild DRESS) to severe DRESS
Interval Between Exposure and Clinical Presentation	1 – 3 weeks after starting the drug.	3 - 8 weeks after starting the drug.
Prodrome	Flu-like symptoms in one-third of patients; precede skin lesions by 1 – 4 days	fever, malaise, dysphagia, pruritus, pain, lymphadenopathy, and even liver damage.
Skin Lesion Morphology	• On-detached lesions: erythematous macules, purpuric or atypical target lesions; erythematous papules. • Detached lesions: appears 3 – 4 days later, with vesicles, flaccid bullae, crusts, sheets/areas of necrotic epidermis (denuded), erosions, ulcers	Usually begins as a pruritic, morbilliform rash, that becomes diffuse and infiltrative. Despite the above, skin lesions often appear polymorphic; may evolve into erythroderma. Facial edema, affects half of the face and periorbital region.
Nikolsky Sign	Positive (3 – 4 days after onset)	Negative
Lesion Distribution/Topography	Axial and symmetrical: face, trunk, and proximal limbs. Sometimes lesions are more intense in photoexposed. Palmoplantar involvement.	Usually begins on the face, then progresses to the upper trunk, then the upper limbs, and finally the lower limbs. The rash affecting > 50% of SCT
Re-epithelialization/ Healing	Re-epithelialization begins in 7 – 10 days; complete healing occurs in 2 to 3 weeks	Duration averages 15 days, with fluctuations. Some symptoms may last up to 3 months or even 1 year
Histology (light microscopy)	Predominant keratinocyte necrosis over sparse dermoepidermal inflammatory infiltrate. Histology changes depending on the disease stage	Not specific. Interface dermatitis (vacuolization) is the most common histopathologic presentation. Perivascular lymphocytic, eosinophilic, neutrophilic, or atypical lymphocytic infiltration is a universal feature

Mucous Membranes	Frequently affected. Most affected is the oral cavity. Eyes affection is common and may be severe.	Frequently affected. Oral cavity and lips most commonly involved; usually mild. Rarely affects the eyes
Viscera/Systemic	Frequently involved but not essential. Constitutional symptoms as prodrome or during the disease	At least one internal organ is always affected, with liver involvement being most frequent. Constitutional symptoms as prodrome or during the disease
Hematological Involvement	Almost constant: multifactorial anemia and lymphopenia. Neutropenia indicates poor prognosis, eosinophilia rare	Eosinophilia most common. Atypical lymphocytes, Leukopenia and lymphopenia followed by leukocytosis, reactive neutrophilia, lymphocytosis, thrombocytopenia, and anemia
Diagnosis	Primarily clinical, but biopsy supports confirmation. Differential diagnosis is important. SCORTEN scale assesses TEN severity	RegiSCAR group criteria are most used. DiHS criteria used by the Japanese
Treatment	SCT detachment < 10 without severe visceral involvement: outpatient symptomatic management SCT detachment > 10 and/or severe visceral involvement: admission to a burn unit Close monitoring, supportive care, general measures, fluid therapy, nutrition, analgesia, antibiotics, IVIg, Systemic corticosteroids	Systemic and/or topic corticosteroids. Immunomodulators: most used is cyclophosphamide, plasma exchange, IVIg, monoclonal antibodies, etc.

CASE REPORT

A 21-year-old man with no personal or family history of atopy was involved in a motorcycle accident on 06/18/2023, resulting in severe traumatic brain injury (TBI) and a left tibial fracture. He was hospitalized and received treatment; upon discharge, he was prescribed phenytoin (as seizure prophylaxis for severe TBI), risperidone (due to a history of suicide attempt), levofloxacin, paracetamol, celecoxib, and omeprazole.

After three weeks of using the prescribed medication, the patient reported experiencing flu-like symptoms, including rhinorrhea, general malaise, and a fever of 38.2°C. Eight days later, he developed a maculopapular rash on his trunk, face, and extremities, which was associated with pruritus and pain. One week after the appearance of skin lesions, the patient went to the emergency room due to worsening skin and mucosal lesions and general malaise. He was referred to internal medicine, which detected the following:

Physical Examination Findings:

Neurological: Intact, no abnormalities.

Mucocutaneous: Facial edema and skin lesions including crusts, scales, erosions, erythematous macules, vesicles, swollen lips with blood-stained crusts (Figure 2), conjunctival erythema and discharge (Figure 3); on the trunk (Figure 4), back, extremities (Figure 5), and hands with scales, crusts, erosions, erythematous macules, blisters, and positive Nikolsky sign; lesions were confluent and in different stages of evolution. The scalp showed a scarring alopecia area in the right temporal region secondary to TBI. Oral cavity with stomatitis and ulcers; lesions on genital mucosa, eyes with conjunctival hyperemia, discharge, eye pain, and photophobia. The total de-epithelialized body surface area (denuded) was estimated at 32%, represented by blisters, crusts, erosions, and areas of denuded epidermis. Additionally, skin involvement was estimated at over 54%, with non-denuded lesions presented as morbilliform

maculopapular rash and desquamation. Others: Lymphadenopathy in the mandibular and cervical regions.

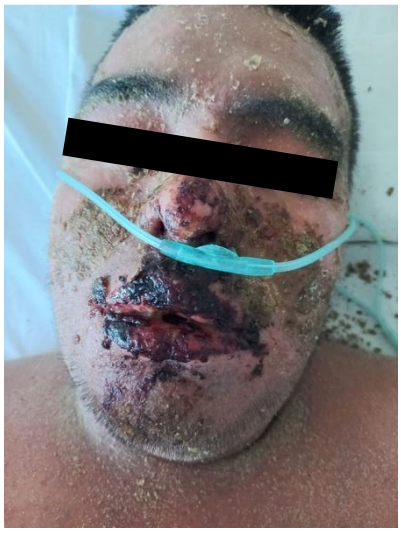

Figure 2

Figure 3

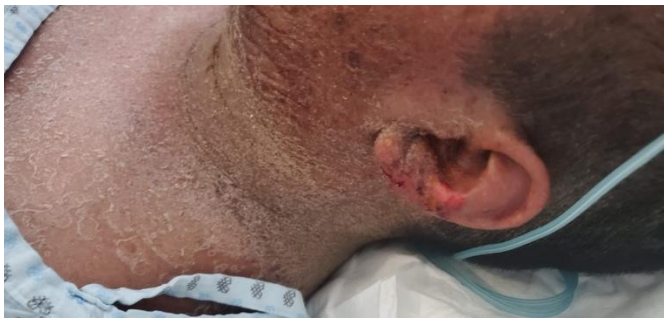

Figure 4

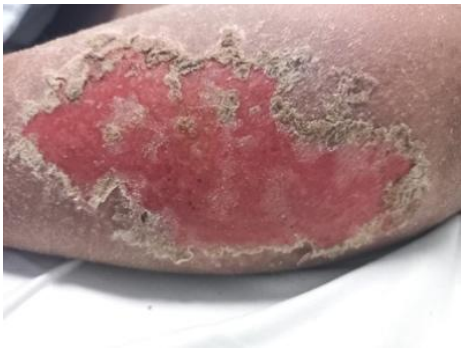

Figure 5

The laboratory results highlight the following:
Complete blood count: WBC 16,140/µL, monocytes 1,030/µL, eosinophils 7,110/µL, hemoglobin 10.10, MCV 90.50, MCH 30.0, platelets 339,000/µL.

Liver function tests: LDH 561, alkaline phosphatase 370, albumin 2.4, total proteins 4.50, GGT 219, AST 76, ALT 153. (An R-value of 3 indicates a mixed pattern.)
Renal function preserved, and glucose normal.
Blood culture: Positive for S. haemolyticus.

Given the previously described history, drugs used, duration of drug exposure, clinical findings, and laboratory results, toxic epidermal necrolysis versus DRESS syndrome was suspected. The RegiSCAR scale was applied, resulting in a score of 6, which indicates a definitive diagnosis of DRESS syndrome. However, the patient also exhibited features of toxic epidermal necrolysis, with a SCORTEN score of 1. The patient was admitted to internal medicine, where all previously used medications were discontinued. Analgesia with buprenorphine was initiated, along with linezolid based on the culture results, antibiotics, intravenous immunoglobulin, systemic corticosteroids**,** lubricating eye drops and ophthalmic antibiotic**.** A nasogastric tube was placed, and daily wound care was provided. Consultations with dermatology and allergy specialists were carried out, who recommended adding topical steroids and antihistamines to the ongoing treatment. The patient showed significant improvement with the treatment. During the hospital stay, the patient remained hemodynamically stable, did not require vasopressor support, had preserved renal function with normal urine output, and received supplemental oxygen via nasal cannula.

A skin biopsy was performed, with the following results (Figure 4):

Altered cutaneous histoarchitecture, with areas of hyperkeratosis with parakeratosis, spongiosis, vesicular lesions containing melanophages, lymphocytes, and sparse eosinophils. Additionally, there were areas with extensive keratinocyte necrosis. The superficial dermis showed fibroblastic reaction and lymphocyte, melanophage, and eosinophil infiltration. A perivascular infiltrate of lymphocytes and eosinophils was also observed.

Diagnostic Impression: Epidermal necrosis, perivascular infiltrate and dermis involvement, dermoepidermal lesions compatible with DRESS syndrome and SJS/TEN.

Based on the previous findings, an overlap diagnosis of DRESS syndrome and TEN was made. After three weeks, and given the patient's significant improvement, he was discharged (Figure 5), and advised to avoid using the previously prescribed drugs, as well as other aromatic antiepileptics, and to follow up in internal medicine consultations.

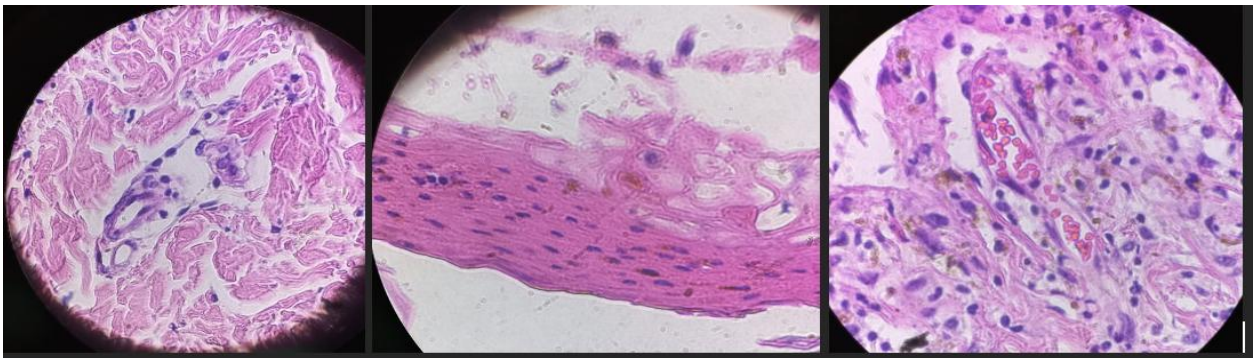

Figure 6

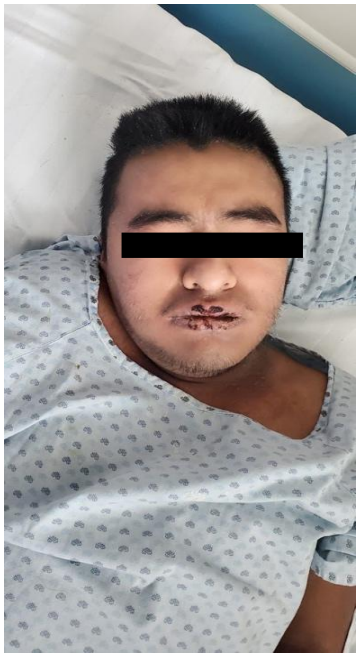

Figure 7

CONCLUSION

This case of overlapping Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) underscores the complexity and severity of drug-induced hypersensitivity reactions. The simultaneous presentation of widespread epidermal necrosis characteristic of TEN, alongside the systemic inflammatory response, eosinophilia, and multiorgan involvement typical of DRESS, posed significant diagnostic and therapeutic challenges. As demonstrated in this case, early recognition of the overlapping features is paramount for initiating prompt and appropriate management, as both conditions carry substantial morbidity and mortality risks when left untreated or mismanaged.

The pathophysiology of TEN-DRESS overlap suggests a convergence of immune-mediated mechanisms, primarily involving cytotoxic T cell-driven keratinocyte apoptosis in TEN and eosinophilic infiltration along with cytokine-mediated systemic inflammation in DRESS. This dual immune activation amplifies the risk of severe cutaneous and internal organ damage. The genetic predisposition involving HLA alleles, particularly HLA-B*58:01, further complicates the clinical picture, underscoring the need for genetic screening in populations at risk for these drug reactions.

Management in overlap syndromes, as illustrated in this case, requires a multidisciplinary approach. The prompt cessation of the offending drug, supportive care in a specialized unit, and the use of systemic corticosteroids combined with intravenous immunoglobulin (IVIG) were instrumental in stabilizing the patient and preventing further deterioration. The decision to use immunosuppressive therapy must balance the risks of immunosuppression, particularly in the context of TEN's vulnerability to infections, against the need to suppress the exaggerated immune response seen in DRESS.

This case also highlights the limitations of current therapeutic options and the ongoing need for individualized treatment strategies. While corticosteroids and IVIG have demonstrated benefit in overlapping cases, further research is necessary to establish optimal dosing regimens and to explore adjunct therapies, such as cyclosporine or biologics, for more refractory cases. The role of emerging therapies like tumor necrosis factor (TNF)-alpha inhibitors also merits consideration, particularly in severe overlap syndromes where conventional therapies may fall short.

The long-term prognosis for patients with TEN-DRESS overlap remains guarded, with the risk of chronic sequelae including persistent skin abnormalities, scarring, and organ dysfunction. Survivors of TEN often experience extensive cutaneous and mucosal complications, while patients with DRESS may suffer from chronic hepatitis, nephritis, or pulmonary fibrosis. As such, long-term follow-up and multidisciplinary care are essential to monitor for complications and manage any residual effects. The most common cause of NET/DRESS overlap is anticonvulsants, as was the case in our patient who used phenytoin.

In conclusion, this case of TEN-DRESS overlap highlights the need for heightened clinical awareness and swift, coordinated medical intervention. Despite the challenges posed by overlapping hypersensitivity reactions, early diagnosis, tailored immunosuppressive treatment, and vigilant supportive care can significantly reduce the risk of fatal outcomes. Future advancements in the understanding of the immunological pathways involved in TEN and DRESS will be crucial in developing more targeted therapies and improving the prognosis for patients afflicted with these severe drug reactions. This case serves as a reminder of the critical importance of recognizing drug hypersensitivity syndromes in their varied presentations and reinforces the necessity for continued research and innovation in the management of these complex conditions.

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