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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Associated With Iodinated Contrast Media: A Case Report with Fatal Outcome and Literature Review

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ABSTRACT

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any harmful and undesired response to a drug that occurs at doses normally used in humans for prophylaxis, diagnosis, treatment of a disease, or to modify a physiological function (1). Cutaneous adverse drug reactions (CADRs), or pharmacodermias, are a type of ADR that manifest in the skin, mucous membranes, and/or appendages (1). Their broad clinical presentation can pose a diagnostic challenge. Currently, with the constant development of new diagnostic and therapeutic options, exposure to various types of medications has increased, necessitating a high index of suspicion and the ability to detect any manifestation of a potential ADR. Furthermore, there is limited information on ADRs related to iodinated contrast media, as non-immediate hypersensitivity reactions are estimated to occur in only 0.5% to 3% of exposed patients, with even fewer reported cases of severe, potentially life-threatening reactions. We present the case of a patient with chronic exposure to medications for managing comorbidities, who developed a drug reaction with eosinophilia and systemic symptoms (DRESS) following exposure to iodinated contrast media as part of his diagnostic and therapeutic workup, ultimately leading to his death.

KEYWORDS: Drug Reaction with Eosinophilia and Systemic Symptoms iodinated contrast media

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INTRODUCTION

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any harmful and undesired response to a drug that occurs at doses normally used in humans for prophylaxis, diagnosis, treatment of a disease, or to modify a physiological function (1). Cutaneous adverse drug reactions (CADRs), or pharmacodermias, are a type of ADR that manifest in the skin, mucous membranes, and/or appendages (1). Their broad clinical presentation can pose a diagnostic challenge. Currently, with the constant development of new diagnostic and therapeutic options, exposure to various types of medications has increased, necessitating a high index of suspicion and the ability to detect any manifestation of a potential ADR. Furthermore, there is limited information on ADRs related to iodinated contrast media, as non-immediate hypersensitivity reactions are estimated to occur in only 0.5% to 3% of exposed patients, with even fewer reported cases of severe, potentially life-threatening reactions. We present the case of a patient with chronic exposure to medications for managing comorbidities, who developed a drug reaction with eosinophilia and systemic symptoms (DRESS) following exposure to iodinated contrast media as part of his diagnostic and therapeutic workup, ultimately leading to his death.

CLINICAL CASE

A 60-year-old male with no known allergies, diagnosed with systemic arterial hypertension, type 2 diabetes, and a history of acute myocardial infarction two months prior to the onset of his condition, presented with reduced ejection fraction heart failure. He was admitted due to edema and erythema of the lower extremities, along with biochemical evidence of acute kidney injury. It was noted that he had been exposed to iodinated contrast media for a CT angiography as part of the diagnostic workup for the infarction. Two weeks later, he developed general malaise, fever, generalized pruritus, and a dermatosis on the lower extremities, which progressed to a disseminated rash characterized by violaceous macules that did not blanch on pressure, polymorphic lesions (Image 1), disseminated scaling (Image 2), negative Nikolsky sign, erythema in the lower extremities, hands (Image 3), chest, involvement of the oral mucosa (Image 4), nasal, anal mucosa, and loss of epidermis in the scrotum and inguinal folds (Image 5), integrating a definitive case of drug reaction with eosinophilia and systemic symptoms according to a RegiSCAR score of 6 points. Laboratory studies revealed leukocytosis with neutrophilia, monocytosis, and eosinophilia of up to 2,320. Additionally, there was evidence of acute kidney injury KDIGO 3, increased acute-phase reactants, and shock requiring vasopressors from admission. A diagnostic approach was taken, with negative serology and rheumatological profile, ruling out other possible causes. Four days later, he experienced an episode of atrial fibrillation leading to pulmonary edema and decompensated heart failure, requiring pharmacological treatment and CPAP placement. He also presented with laryngeal stridor likely due to edema. However, due to acute multiorgan failure, the family decided to sign a denial of invasive procedures and initiated palliative sedation, resulting in a fatal outcome two days later.

LITERATURE REVIEW

Drug reaction with eosinophilia and systemic symptoms, known as DRESS, is a severe adverse drug reaction characterized by cutaneous involvement, eosinophilia, and systemic symptoms. However, eosinophilia is not considered an essential diagnostic criterion, which is why it is also known as drug-induced hypersensitivity syndrome (DIHS). Although rare, this reaction can be fatal, as patients may progress to multiorgan failure (2).

It is challenging to establish the incidence of DRESS, as it is an underdiagnosed condition. Variations may also exist due to factors such as the type of medication or the immune status of each patient. Overall, the incidence is estimated at 1 case per 10,000 medication exposures, with a higher incidence in African American populations and women. Other data suggest an incidence of 0.9 per 100,000 inhabitants and 10 cases per million in the general population. In hospitalized patients, the incidence ranges between 2.18 and 40 per 100,000 patients (4).

DRESS typically presents late, between two and eight weeks after drug exposure (3). Initially, it manifests with nonspecific symptoms such as pruritus, malaise, and fever, followed by cutaneous involvement with diffuse scaling, facial edema, and a morbilliform erythematous maculopapular rash (88-90%), which usually affects the face, trunk, and extremities. A rash is considered suggestive of DRESS when it affects more than 50% of the total body surface area (4). Less frequently, vesicles and bullae (10%), target lesions (9%), purpuric lesions (6%), sterile pustules in follicular and non-follicular distribution (3%), and erythroderma may also be observed, along with mucosal involvement such as cheilitis and xerostomia (5). As the condition progresses, the skin may take on a violaceous appearance associated with diffuse scaling, potentially progressing to erythroderma in 20-30% of patients (4), and cutaneous manifestations may persist for weeks (5). Although cutaneous manifestations are the most evident, a comprehensive evaluation is crucial, as the syndrome can affect virtually all organs and systems. (Table 1)

Lymphadenopathy is usually localized in the cervical, axillary, and inguinal regions, presenting as soft and measuring between 1 and 2 cm. However, not all patients develop lymphadenopathy, as it is present in only 75% of cases (5). Organ involvement is observed in 88% of cases (2), with the liver being the most frequently affected organ, with an incidence of 60-80% (4). This involvement may manifest as elevated liver enzymes in 59% of cases, typically exceeding twice the normal value of alanine aminotransferase (ALT) and a value greater than 1.5 times that of alkaline phosphatase (4). Hepatomegaly (12%), cholestasis, or even fulminant hepatitis may also occur (2).

On the other hand, renal involvement occurs in approximately 30% of patients, including alterations ranging from a moderate increase in creatinine and blood urea nitrogen (BUN), proteinuria, and urinary sediment abnormalities with eosinophils, to severe interstitial nephritis that may progress to acute kidney injury (4). Laboratory studies may reveal leukopenia or lymphopenia in the early stages. Once the condition is established, leukocytosis is observed in 30-70% of patients, predominantly neutrophils, followed by monocytosis and eosinophilia (5), the latter reported in 60-70% of cases and typically appearing between 1 and 2 weeks later (4). Other findings include lymphopenia (51.9%), atypical lymphocytosis (18.5%), and thrombocytopenia (3.7%), and less frequently, hemophagocytic syndrome (4).

Establishing a diagnosis can be challenging due to the varied and nonspecific manifestations. Over the years, attempts have been made to unify diagnostic criteria. The first were established in 1996 by Bocquet. However, in 2006, the Japanese Committee for Severe Cutaneous Adverse Reactions proposed the J-SCAR criteria, which include

Human Herpesvirus type 6 and allow classification of the condition as typical or atypical. Finally, in 2007, the European Registry of Severe Cutaneous Adverse Reactions introduced the RegiSCAR criteria, which define the condition as possible (2-3 points), probable (4-5 points), definitive (>6 points), or exclude it (<2 points) (1,4) (Table 2).

In these cases, biopsy is not definitive, as histological findings in DRESS are nonspecific but may guide the diagnosis. Spongiosis, acanthosis, vacuolization, lymphocytic infiltrate in the papillary dermis with perivascular predominance, eosinophils, atypical lymphocytes, or granulomas may be observed (4). Different histopathological patterns may also be present, with interface dermatitis involving the follicular annex being the most common, followed by eczematous, erythema multiforme-like, acute generalized exanthematous pustulosis (AGEP)-like pustulosis, or even a multicomponent pattern (two or more histopathological patterns in the same biopsy) (5). It is important to consider other alternatives as part of the differential diagnosis, especially other potentially fatal drug-induced cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and erythroderma, as well as infectious diseases or connective tissue disorders (2).

In most cases, the responsible drug can be identified through a detailed clinical history. It is essential to specifically ask about the patient's current pathologies, their current treatment, sporadic use of any medication, the time of onset, and the interval between this and the appearance of manifestations. However, in up to 20% of cases, the causative agent cannot be identified, and tests such as patch testing or lymphocyte transformation testing may be useful (5). These tests are recommended to be performed between 4 and 6 weeks after the reaction, ensuring that the patient does not receive immunosuppressive therapy or systemic corticosteroids for at least 4 weeks to reduce the rate of false negatives (4).

Various drugs have been associated with DRESS syndrome, with aromatic anticonvulsants, sulfonamides, sulfones, nonsteroidal anti-inflammatory drugs, beta-lactam antibiotics, vancomycin, allopurinol, minocycline, and antiretrovirals being the most common (4). Genetic susceptibility has been reported based on the presence of certain haplotypes (HLA-B*58:01 associated with allopurinol, HLA-A*31:01 with carbamazepine, and HLA-B*13:01 with dapsone) (3). Additionally, with the increasing use of biologic drugs and targeted therapies, associated cases have been observed (5) (Table 3). Regarding iodinated contrast media, non-immediate hypersensitivity reactions have been described in 0.5% to 3% of exposed patients, with maculopapular rashes and delayed urticaria being the most common, although severe, potentially fatal reactions have also been reported. In 2021, Soria et al. documented a series of DRESS cases associated with iodinated contrast media (6). Certain risk factors have been identified that increase the likelihood of adverse reactions to contrast media, such as a history of severe allergic reactions to foods and medications, asthma, bronchospasm, heart failure, or renal disease. However, the American College of Radiology does not recommend premedication or contraindication of its use in these situations, as the increased risk is not significant (7). The manifestations of DRESS syndrome usually resolve gradually over 6 to 9 weeks, although in 20% of cases, the disease may persist for several months with relapses. Factors related to a prolonged course include severe hepatic involvement and the presence of atypical lymphocytes. Poor prognostic factors reported include eosinophil counts greater than 6000 × 10^3/µL, thrombocytopenia, pancytopenia, leukocytosis, coagulopathy, comorbidities such as chronic kidney disease, and the use of medications such as minocycline and allopurinol, with an estimated mortality rate of 3.8%, primarily due to fulminant hepatitis and hepatic necrosis (4).

DISCUSSION

The presented case of a 60-year-old man who developed drug reaction with eosinophilia and systemic symptoms (DRESS) following exposure to iodinated contrast media highlights the complexity and severity of this condition. DRESS is a rare but potentially fatal adverse reaction characterized by systemic and cutaneous symptoms, eosinophilia, and, in many cases, multiorgan involvement. In this patient, exposure to iodinated contrast media for a CT angiography was followed by typical DRESS symptoms, including fever, pruritus, and an extensive cutaneous rash, underscoring the importance of considering this condition in patients presenting with systemic and cutaneous symptoms following exposure to drugs or contrast agents.

The literature review indicates that although eosinophilia is a common marker, it is not essential for diagnosis, which can complicate early identification of DRESS. Additionally, organ involvement, particularly hepatic and renal, is common and can be severe, as observed in this case with progression to acute renal failure and cardiac decompensation. Identifying the causative agent is crucial but can be challenging, and in some cases, such as the one presented, the suspected agent is iodinated contrast media, which, although rarely, can trigger severe hypersensitivity reactions.

CONCLUSION

This case underscores the need for a high index of suspicion for the diagnosis of DRESS, particularly in patients with recent exposure to drugs or iodinated contrast media who present with systemic and cutaneous symptoms. Early identification and withdrawal of the causative agent are essential to improve prognosis. However, as observed in this

case, the progression can be rapid and severe, leading to a fatal outcome despite medical interventions. The literature review highlights the importance of a multidisciplinary approach to managing DRESS, including comprehensive evaluation of organ involvement and the use of standardized diagnostic criteria such as the RegiSCAR score to guide diagnosis and treatment.

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Table 1. Clinical, biochemical, and histopathological manifestations of DRESS.
Taken and adapted from Echeverría et al 4 and Calle et al 3

Manifestations of DRESS	
Clinical	
Nonspecific	Pruritus, general malaise, fever (38-40ºC), lymphadenopathy (75%)
Mucocutaneous	Diffuse scaling, periorbital and facial edema, morbilliform erythematous maculopapular rash, erythroderma, vesicles, bullae, target lesions, purpuric lesions, sterile pustules in follicular and non-follicular distribution, cheilitis, and xerostomia.
Respiratory system	Acute respiratory distress syndrome, acute interstitial pneumonitis.
Thyroid	Autoimmune thyroiditis, hypo- and hyperthyroidism.
Cardiovascular	Acute eosinophilic myocarditis.
Gastrointestinal	Hemorrhage, esophagitis, cholecystitis, pancreatitis, hepatomegaly, fulminant hepatitis.
Renal	Acute kidney injury, proteinuria, interstitial nephritis.
Atypical	Cicatricial conjunctivitis, oral ulcers, dysphagia, myositis, polyneuritis, and uveitis.
Biochemical	
Liver biochemistry	Cholestatic or mixed pattern.
Hematologic	Eosinophilia, atypical lymphocytes, lymphopenia, thrombocytopenia, hemophagocytic syndrome.
Histopathological	
Findings	Spongiosis, acanthosis, vacuolization, lymphocytic infiltrate in the papillary dermis with perivascular predominance, eosinophils, atypical lymphocytes, or granulomas.
Histopathological patterns	Interface dermatitis with follicular adnexal involvement, eczematous, erythema multiforme, pustulosis resembling acute generalized exanthematous pustulosis (AGEP), or multicomponent pattern.

Table 2. Diagnostic criteria for DRESS. Taken and adapted from Echeverría et al 4

Bocquet	**J-SCAR**	**RegiSCAR**
	Fever>38 ºC	Fever >38ºC
Skin rash	Development of a maculopapular rash > 3 weeks after starting a drug	• Involvement >50% of body surface area • At least two of: edema, induration, purpura, or scaling • Suggestive biopsy findings

Adenomegaly ≥2cm	Lymph nodes > 1 cm in more than 2 sites	Lymphadenopathy
Hematological alterations • Eosinophilia≥ 1.5 x 10^9/ L • Atypical lymphocytes	Hematological alterations (at least one present): • Lymphocytosis or lymphopenia • Thrombocytopenia • Eosinophilia	Hematological alterations (at least one present): • Leukocytosis >11 x10^9/L • Atypical lymphocytosis >5% • Eosinophilia >1.5 x10^9/L
Systemic involvement • Hepatitis with transaminase elevation x2 • Interstitial nephritis • Interstitial pneumonitis • Myocarditis	Involvement of internal organs (≥1)	Hepatic involvement: • ALT > 100 U/L
	Resolution of the clinical picture >15 days	Prolonged clinical symptoms after discontinuation of the causative drug
	Rule out other possible causes: blood cultures, HIV, HBV, HCV	HHV-6 reactivation
One clinical criterion and one hematological criterion	<2 points: DRESS is ruled out 2-3 points: Possible case 4-5 points: Probable case >6 points: Definitive case	7 criteria = Typical DRESS 5 criteria = Atypical DRESS
A skin rash suggestive of DRESS is considered when it affects >50% of the total body surface area (TBSA); however, all previously described manifestations may still occur.		

Table 3. Drugs associated with DRESS. Taken and adapted from Calle et al 3

Drug class	**Drugs**
Antiepileptics	**Carbamazepine, lamotrigine, phenobarbital, phenytoin, oxcarbazepine**
Antibiotics	**Amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, trimethoprim-sulfamethoxazole, vancomycin**
Antituberculosis agents	**Ethambutol, isoniazid, pyrazinamide, rifampicin**
Antivirals	**Abacavir, nevirapine, efavirenz, zalcitabine**
Antihypertensives	**Amlodipine, Captopril**
Antidepressant	**Bupropion, fluoxetine, olanzapine**
NSAIDS	**Celecoxib, aspirin, diclofenac, dbuprofen, piroxicam**
Others	**Allopurinol, amitriptyline, dapsone, hydroxychloroquine, omeprazole, sulfasalazine, erythropoietin**

Immunotherapies	**Imatinib, vemurafenib, ipilimumab, nivolumab, pembrolizumab, cetuximab, erlotinib, sorafenib, sunitinib, rituximab, ibrutinib, bortezomib, daclizumab**

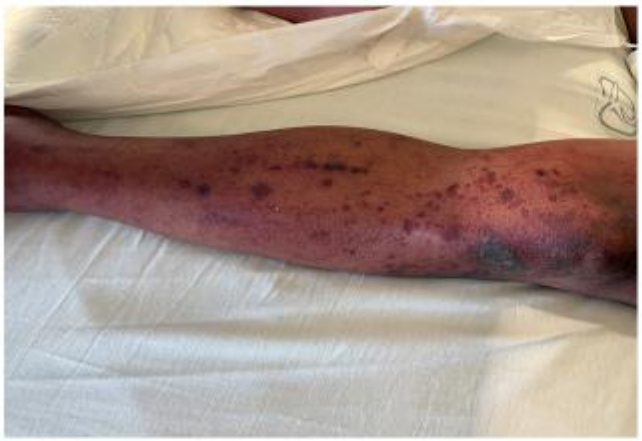

Image 1. Lesions on the lower extremities characterized by erythema and polymorphic, violaceous macules that did not blanch with pressure (non-blanching), with a negative Nikolsky sign.

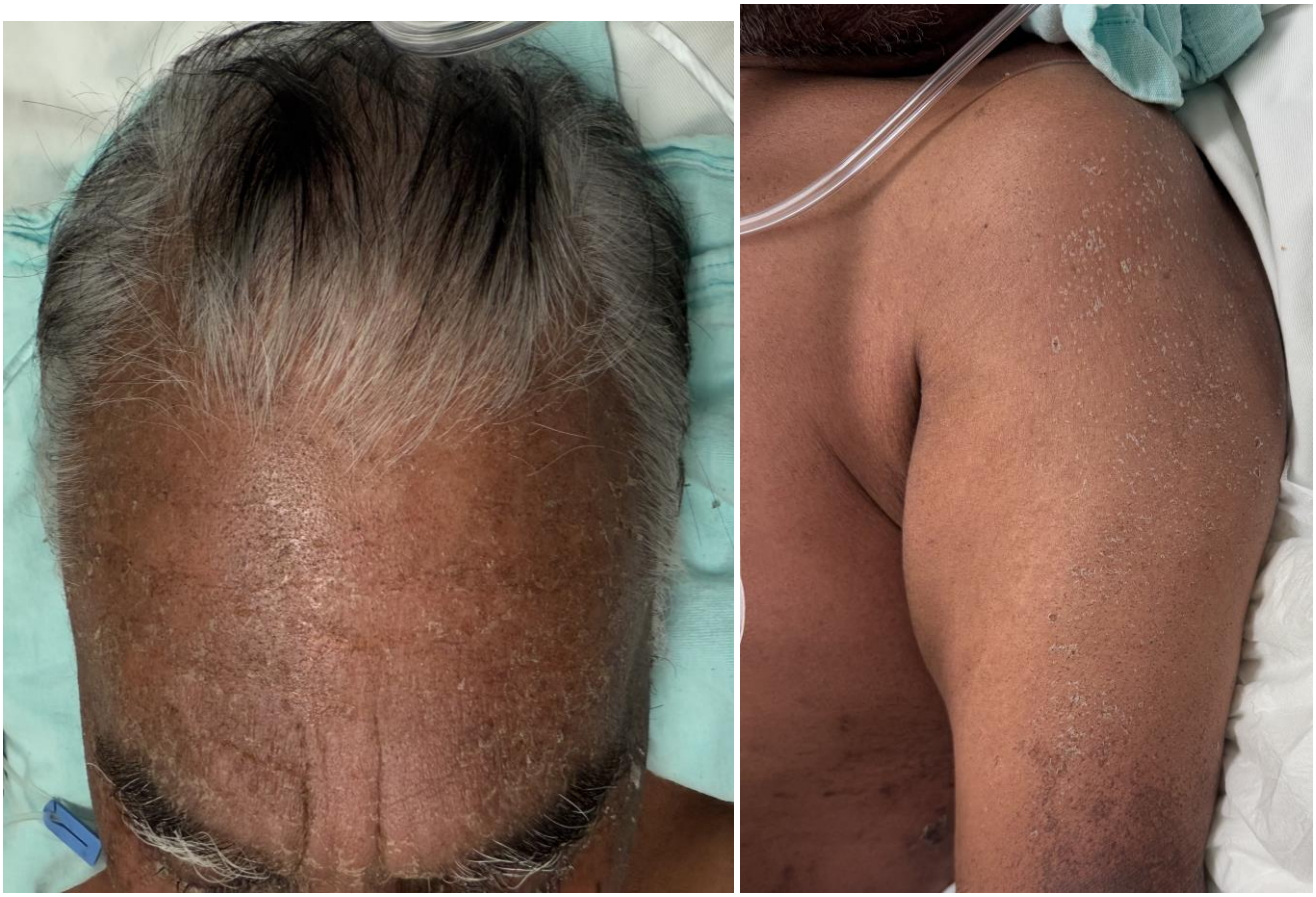

Image 2. Disseminated scaling located on the arms and face

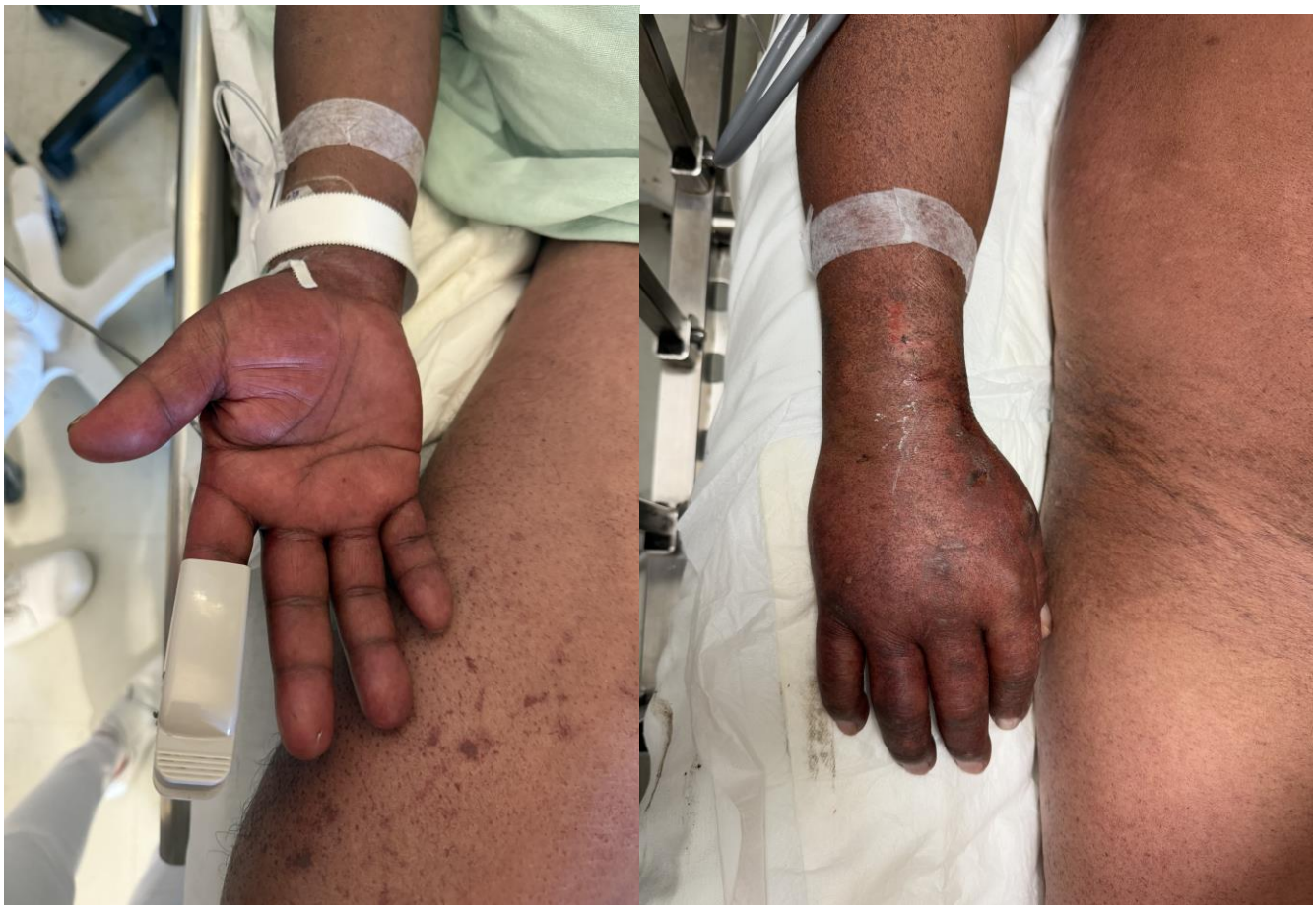

Imagen 3. Edema y eritema localizado en extremidades superiores

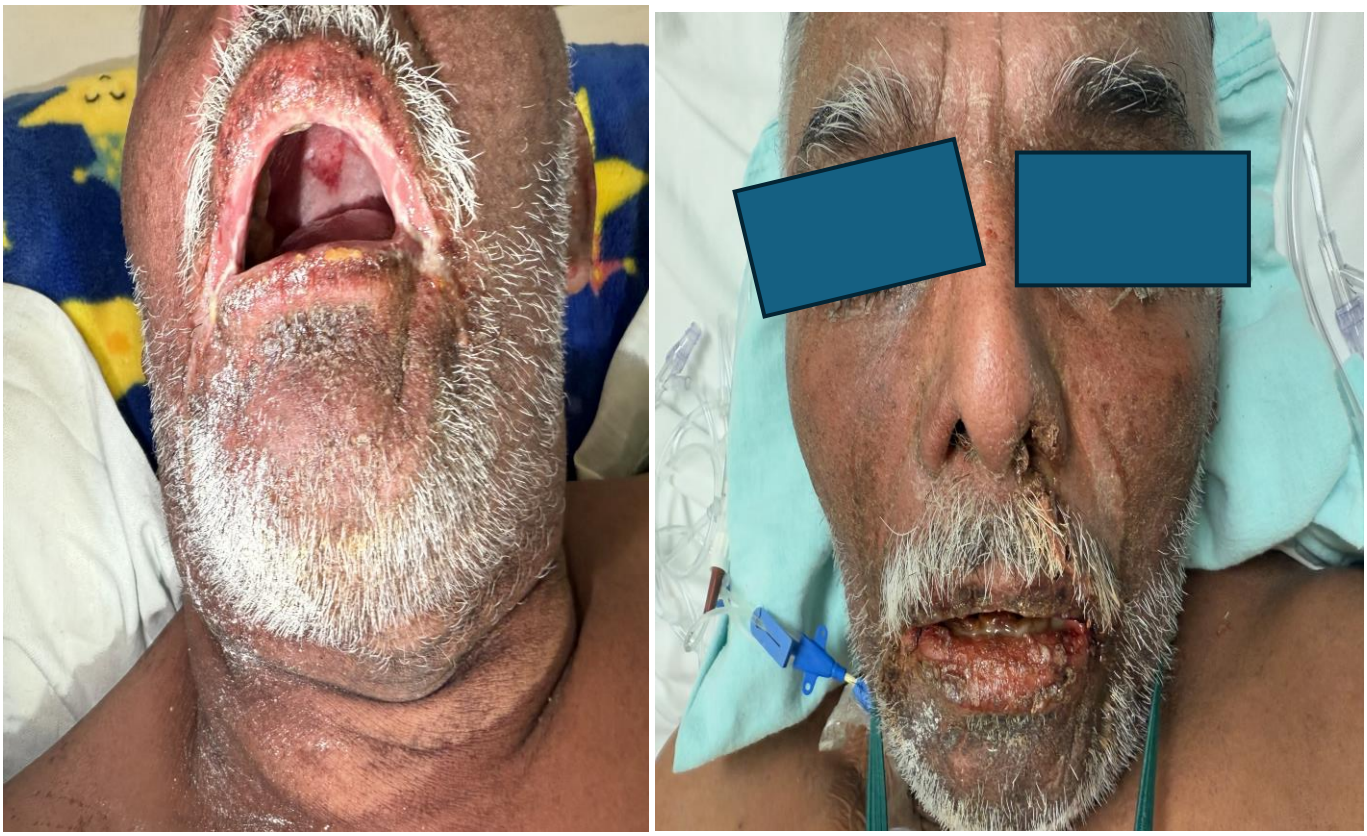

Image 4. Involvement of the oral mucosa. Initial lesions characterized by purpura and erythema on the palate, which progressed to loss of the oral mucosa and lip epithelium with multiple hemorrhagic crusts

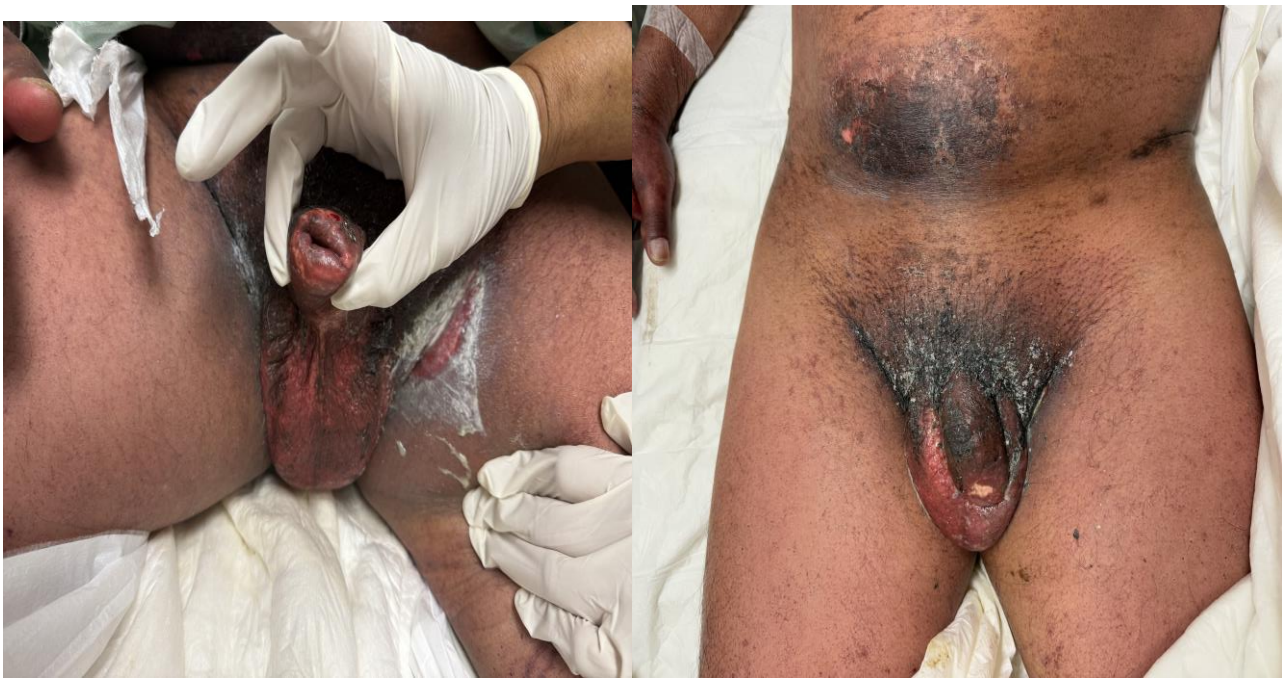

Image 5. Loss of epidermal continuity in the bilateral inguinal region, along with significant edema and loss of the epidermis on the prepuce and scrotum