Erosive cheilitis as an early manifestation in DRESS syndrome

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is part of Severe cutaneous adverse reactions. Allopurinol, an uric acid-lowering drug, had been incriminated in several cases of Allopurinol-induced Dress syndrome.Through this paper, we present a case of Allopurinol-induced DRESS syndrome with initial oral mucosal involvement.

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Patient consent:

I confirm that written patient consent has been signed and collected in accordance with the journal's patient consent policy.

Author contribution:

Ben salha wahbi: data collection and interpretation

Eya moussaoui : aquisation and analysis of data and drafting the manuscript

Ouaha lamia: revising the manuscript for important intellectual content

Anoun jihed: collection and interpretation of data

Nabiha douki: conception and design and revising the manuscript

Key clinical message: In DRESS syndrome, drug history and the timing of apparition of muco-cutaneous lesions are the keys to diagnosis. Systemic symptoms and negative Nikolsky's sign are two clinical indicators differenciating DRESS from other maculopapular drug eruptions.

Abstract:

Drug reaction with eosinophilia and systemic symptoms (DRESS) is part of Severe cutaneous adverse reactions. Allopurinol, an uric acid-lowering drug, had been incriminated in several cases of Allopurinol-induced Dress syndrome.Through this paper, we present a case of Allopurinol-induced DRESS syndrome with initial oral mucosal involvement.

Keywords: DRESS syndrome, erosive cheilitis, drug-induced hypersensitivity syndrome, Allupirinol, maculopapular drug eruptions. eosinophilic infiltrate, oral mucosa, erosions

Abbreviations:

DRESS: drug reaction with eosinophilia and systemic symptoms

DIHS: drug-induced hypersensitivity syndrome

SCARs: severe cutaneous adverse reactions

RegiSCAR: The Registry of Severe Cutaneous Adverse Reaction

SJS: Stevens-Johnson syndrome

TEN: Toxic epidermal necrolysis

AGEP: acute generalized exanthematous pustulosis

HHV-6: human herpes virus 6

AST: Aspartate transaminase

ALT: alanine aminotransferase

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Introduction:

Adverse cutaneous drug reactions involve a variety of clinical manifestations, ranging from minor skin rashes to fatal hypersensitivity reactions. Drug reaction with eosinophilia and systemic symptoms (DRESS), also

known as drug-induced hypersensitivity syndrome (DIHS), is one of these manifestations. This pathology, which can lead to death in 10% of cases [1][2], is commonly overlooked and misdiagnosed [3].

Through this paper, a case of Allopurinol-induced DRESS syndrome with initial oral mucosal involvement is presented while emphasizing the importance of early diagnosis to achieve the appropriate management.

CASE REPORT:

A 69-year-old female patient was referred to our department by the internal medicine department for lesions of the oral mucosa. The patient was a housewife living with her husband in an urban setting, mother of 6 daughters, and had no prior travel history. She had no history of smoking, alcohol consumption, or illicit drug use. No allergies were identified.

Her medical history revealed type-2 diabetes for 17 years, hypertension for 10 years, dyslipidemia, and Gout disease. She had a surgical history of coronary artery bypass surgery 11 years earlier and cholecystectomy 17 years earlier. Medications involved metformin (Glucophage®), Glibenclamide (Diabenil®), Captopril (Tensopril®), Isosorbide dinitrate (Pensordil®), Propranolol (Normocardil®), Fluvastatin (Lescol®), Aspirin®, and Colchicine® . She started taking Allopurinol® 6 weeks before hospitalization. No history of drug hypersensitivity reactions was identified.

A week before her hospitalization, the patient developed chills with unrecorded fever. The following day, the patient noticed bluish spots on the lower limbs with a very important edema on the lips. She consulted the emergency department where she had an unspecified symptomatic treatment, without improvement. Then, the patient consulted a dermatologist who prescribed Corticosteroid (Solupred® 20mg) as a mouthwash and referred the patient to the internal medicine department where she was hospitalized.

On the first day of admission to the internal medicine department, the patient was conscious and well-oriented. The initial recorded temperature was 38.7°C, blood pressure was 120/70 mmHg, pulse was 67 beats/minutes, and weight was 72 kg. Physical examination showed the presence of a confluent erythematous maculopapular rash, diffused all over the body (feet, legs, stomach, chest, back), and sparing the face, scalp, palms, and soles. (Figure 1, 2). Nikolsky's sign was negative. No lymphadenopathy was present. On auscultation, the chest was clear on both sides. The patient's heart had a regular rate and rhythm. The remainder of the examination was without abnormalities. In the department of dental medicine, oral examination showed the presence of a painful erosive cheilitis, crusty lesions on both lips, and confluent ulcerations across the labial mucosa (Figure 3). These aspects were reminiscent of those seen in some bullous drug eruption (Erythema multiforme, Stevens-Johnson syndrome...) but Nikolsky's sign was negative. Antibodies (Amoxicillin 2g per days) were prescribed to avoid infection of the lesions. Local corticosteroid therapy (Solupred as a mouthwash), antalgic, and chlorhexidine-based mouthwash were also prescribed. Oral biopsy was scheduled.

Complete blood count (CBC) showed a normal number of white blood cells (WBCs) of 10.28*10ˆ3/mm3 with 9.4% lymphocytes, 11.3% monocytes, and16.1% (1.65*10ˆ3/mm3) eosinophils, corresponding to a moderate eosinophilia. C -reactive protein was elevated at 13 mg/L. Results of tests for serum electrolytes, hemoglobin, hematocrit, and sedimentation rate were normal.

Serology for hepatitis B and hepatitis C was negative. Urine and blood cultures were also negative. Uric acid level was high. Similarly, high levels of Serum glucose and triglyceride were noted.

Skin biopsy was performed and it showed necrotic keratinocytes and a subepidermal perivascular inflammatory infiltrate, consisting of lymphocytes and eosinophils (Fig 4). This histological aspect was in accordance with drug eruption (toxiderma).

Based on the patient's history, clinical presentation, and biological tests, diagnosis of cutaneous adverse drug reaction was made. Systemic corticosteroid therapy (Solupred 20mg) was therefore started. The most likely etiology was allergic response to Allopurinol. Infectious and immunological etiologies were eliminated.

On the seventh day of admission, the patient had an alteration in her renal function and decompensation of diabetes, with blood glucose level rising from 7.0 (mmol/l) to 9.8. Creatinine level increased to 116 µmol/l. Liver function tests showed a low albumin level (31 g/l), an abnormal coagulation panel with an international normalized ratio (INR) of 1.3, and transaminitis (AST: 47 IU/L; ALT: 43 IU/L), all indicating an alteration in hepatic function.

Diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) was therefore made.

Five days after corticosteroid therapy, an improvement in both cutaneous and oral lesions was noted (Fig 5).Three years later, the patient was rehospitalized with similar mucocutaneous lesions after automedication using Allopurinol.

Discussion:

Severe cutaneous adverse reactions (SCARs) are a class of life-threatening adverse drug responses affecting the skin and the mucosal surfaces (oral, genital, ocular etc). They can cause severe damages to internal organs in more critical cases. [4]

Drug reaction with eosinophilia and systemic symptoms (DRESS) is part of SCARs and it constitutes a challenge with regard to diagnosis, management, and treatment. [4]

The pathophysiology of DRESS is not yet fully understood. It has been suggested that certain drugs may cause hypersensitivity reactions in patients with genetic or acquired mutations in the drug metabolism pathways, due to abnormal production and detoxification of their active metabolites. Allopurinol was introduced in 1963 as a uric acid-lowering drug. Its mechanism of action involves its conversion to oxypurinol after being absorbed. It is speculated that excessive oxypurinol can cause tissue damage, trigger immune response, and produce antibodies against tissue components. Others have invoked cell-mediated immunity [5] [6]. Virus reactivation, especially human herpes virus 6 (HHV-6), has been considered an important factor in the pathogenesis of DRESS syndrome [7]

Several diagnostic criteria have been utilized to standardize DRESS diagnosis. Bocquet et al. were the first to propose criteria for the diagnosis of DRESS in 1996 [8] [Table 1].In 2007 [Table 1], the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) group added criteria to diagnose DRESS syndrome and a scoring system to provide a more precise definition. [Table 2,3] [9]. This system tends to be the most widely used and accepted tool. Another set of diagnostic criteria was proposed by a Japanese group[10] [Table 4, 5]. The use of this Japanese model is limited because it requires laboratory measurement of Ig G anti HHV6, which is not routinely available. Using the RegiSCAR scoring system, our patient's score was 6, indicating that it was a definite case of DRESS syndrome.

Drug history was the key to diagnosis in our case as Allopurinol had been incriminated in several cases of Allopurinol-induced Dress syndrome. [11]

Diagnosis of (DRESS) is still challenging on multiple levels despite the presence of well-defined criteria. Dermatological involvement presents a notable overlap among the other SCARs, such as Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). No pathognomonic skin rash pattern for DRESS is available. [12] Systemic symptoms and negative Nikolsky's sign are two clinical indicators differenciating DRESS from other maculopapular drug eruptions. Skin biopsy is the gold standard for diagnosis. Subepidermal bullae are present in SJS/TEN; however, eosinophilic infiltrate is present in DRESS.

The timing of cutaneous manifestations is also challenging in terms of diagnosis because DRESS and SJS/TEN overlap. Indeed, SJS usually occurs within 1 to 3 weeks while DRESS occurs within 6 weeks of the drug administration [13] as observed in our patient.

Other differential diagnoses for DRESS syndrome include acute infections (viral exanthemas, streptococcal, and staphylococcal shock syndrome), autoimmune diseases (hypereosinophilic syndrome, and Kawasaki disease), and neoplastic diseases (lymphomas) [14].

Involvement of the oral mucosa and the vermillion border in DRESS syndrome is frequent. The usually encountered manifestations are nonspecific, including cheilitis [15], erosions [16], crusting lips [17], and edema [3] as observed in the reported case.

There are no specific treatment guidelines for DRESS syndrome management. The only definitive treatment is to identify and eliminate the culprit drug. [18] In our case, Allopurinol cessation led to healing in 15 days.

For patients with internal organ involvement, systemic corticosteroids are the main treatment. It is recommended to use medium to high doses of systemic corticosteroids until clinical improvement and laboratory normalization are obtained [19].

Conclusion:

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a life-threatening condition that should always be suspected in patients with fever, rash, and in those with a history of high-risk drug use taken within the past 8 weeks. Oral mucosa lesions are frequently present. Early diagnosis and withdrawal of the culprit medication are the cornerstone of the appropriate management.

Table 1: **Diagnostic criteria for DRESS as proposed by Bocquet et al.**
1-Cutaneous drug eruption 2-Adenopathy > 2cm in diameter *****Hepatitis (liver transaminases >2times of normal) *Interstiti

Table 2: **Registry of severe cutaneous adverse reaction criteria for diagnosis of DRESS**
1-Hospitalization* 2-Reaction suspected to be drug-related* 3- Acute rash* 4-Fever >38 °C — 5- Enlarged lymph nodes at

Table 3: **Registry of severe cutaneous adverse reaction diagnosis score for DRESS:**
Features No Yes Unknown
-Fever >38.5 °C -1 0 -1 **-** Enlarged lymph nodes (>2 sites, >1cm) 0 1 0 **-**Atypical lymphocytes 0 1 0 -Eosinophilia 700-1499

Table **4: Japanese group's criteria for diagnosis of DRESS / DIHS**
Developing maculopapular rash >3 weeks starting with the suspected drug. Prolonged clinical symptoms 2 weeks after disc

Table 5: the patient's score using the RegiSCAR scoring system:
Features No Yes Unknown
-Fever >38.5 °C 0 **-** Enlarged lymph nodes (>2 sites, >1cm) 0 **-**Atypical lymphocytes 0 -Eosinophilia 700-1499 or 10%-19.9%
Final score=6 >>>> Definite case

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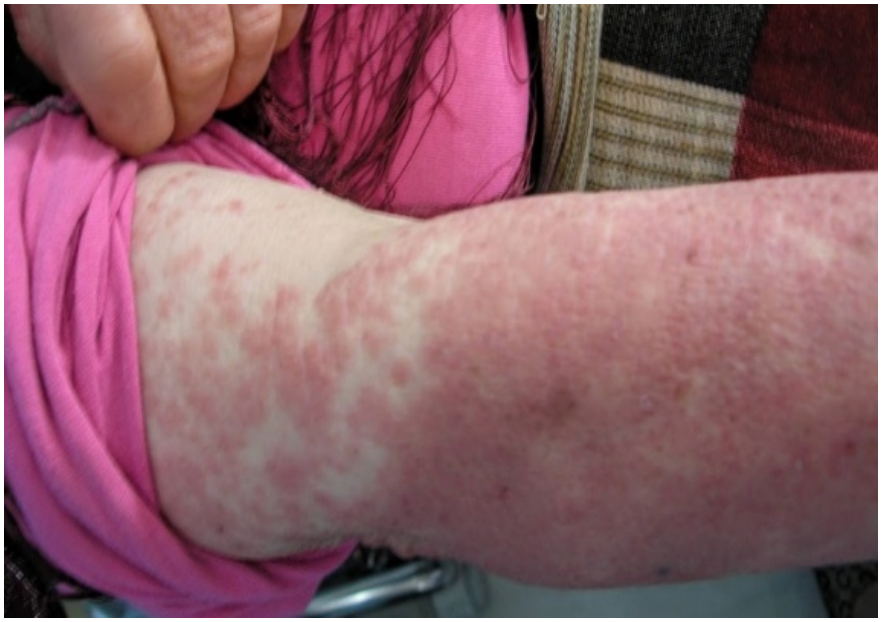

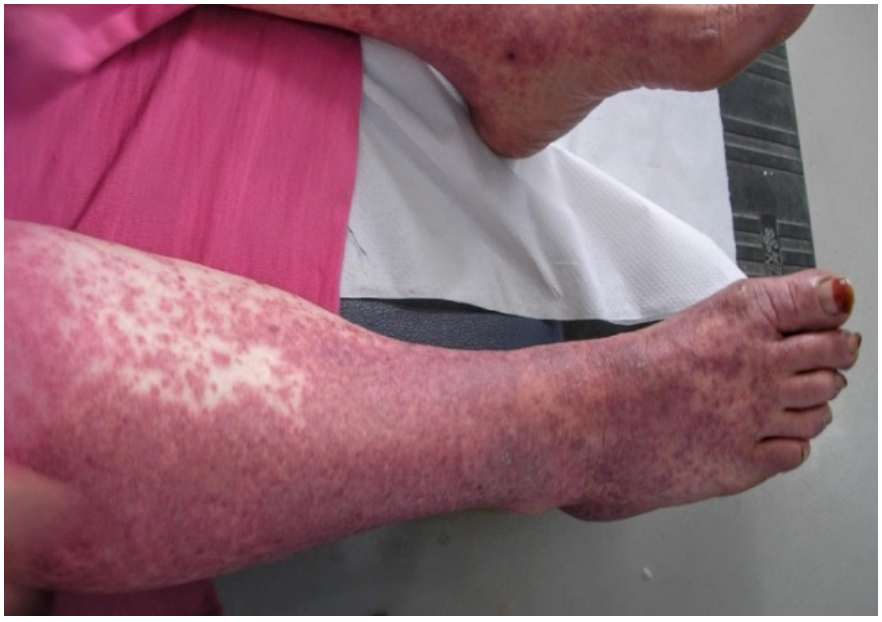

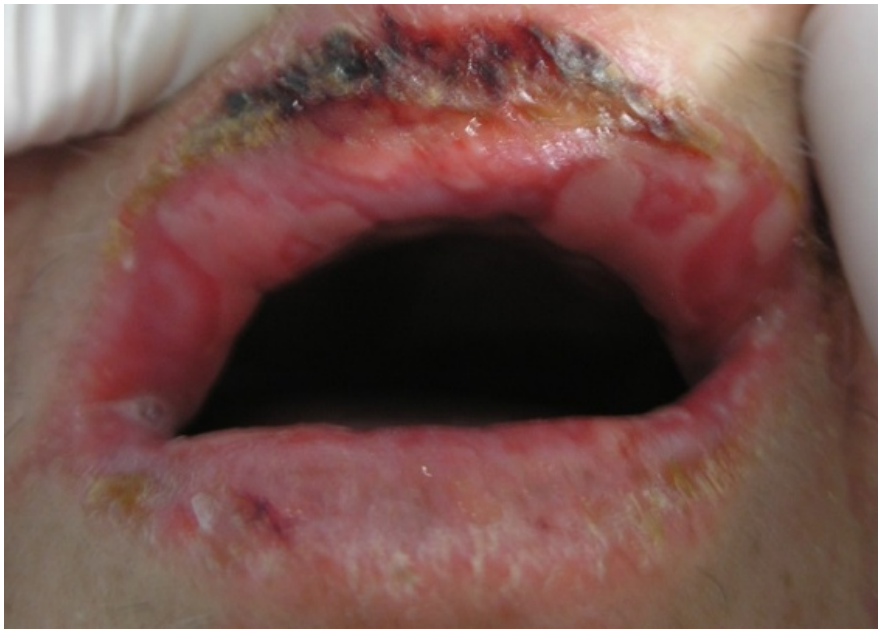

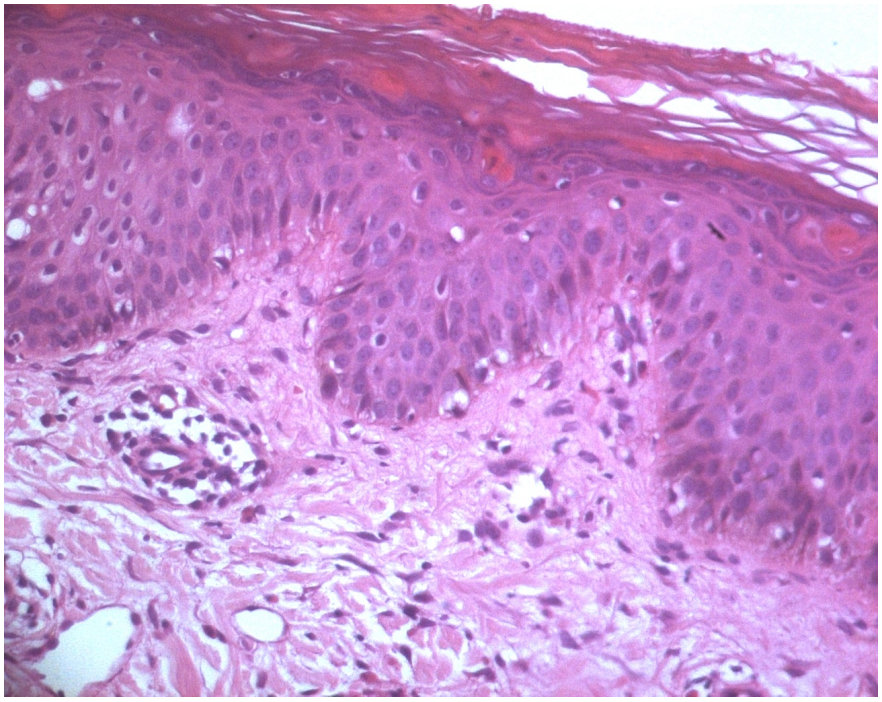

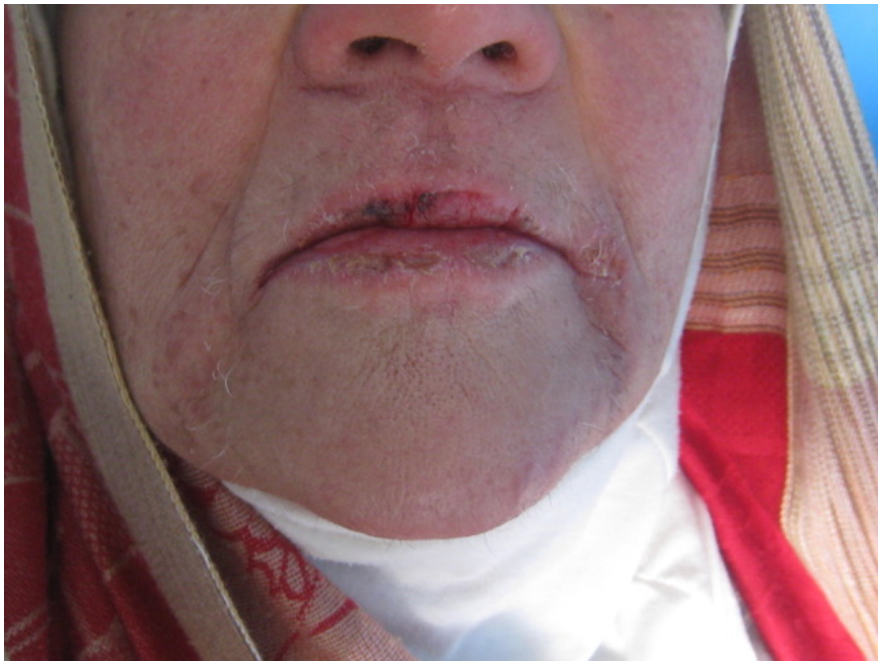

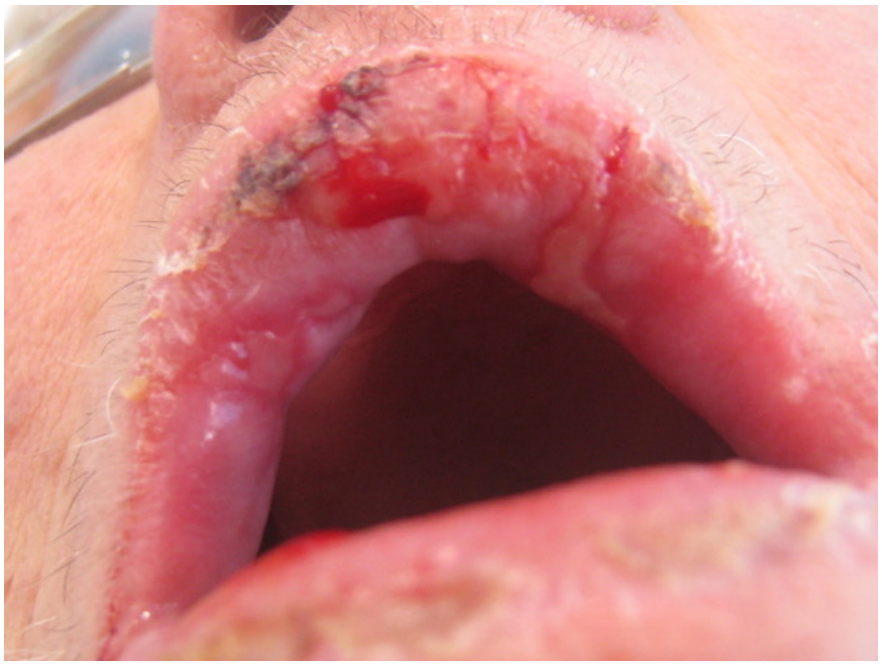

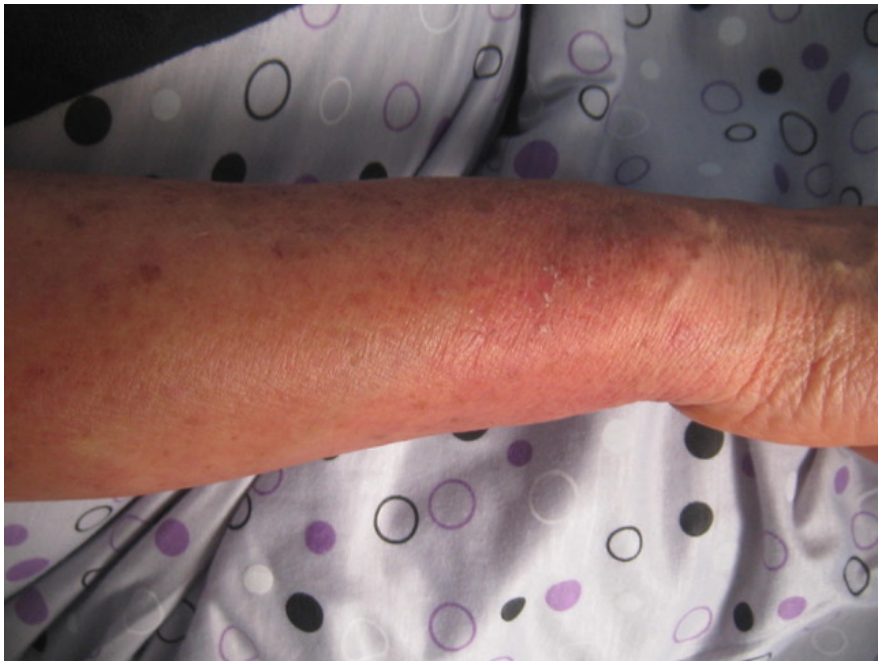

Conflicts of interest:

All the authors declare not having any conflicts of interest.

Ethics statement:

Data from the patient included in this case report were treated anonymously and a statement of informed consent was signed to allow the use of her medical and dental records and photos.

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