Drug reaction with eosinophilia and systemic symptoms (DRESS) with anti-tuberculosis drugs, a rare and serious complication

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Abstract

Drug hypersensitivity syndrome or DRESS (drug reaction with eosinophilia and systemic symptoms) is a severe reaction with an estimated mortality of 10%. Antibacillary drugs are rarely incriminated. A 28-year-old patient with tubercular miliaria who developed antibacillary-induced DRESS is presented. The dermatological lesions appeared four weeks after the beginning of the antitubercular treatment. The diagnosis of DRESS was made when all the Registry of Severe Toxidermia (RegiSCAR) criteria were present. The treatment was stopped and the patient was put on symptomatic treatment under supervision in the intensive care unit, with progressive improvement. Substitution with second-line antituberculosis drugs was necessary and was done with caution. DRESS with antituberculosis drugs is rare and its management is not codified.

Keywords: antibacillary, DRESS, drug reaction, eosinophilia, reintroduction, toxidermia

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as drug hypersensitivity syndrome, represents a severe and potentially life-threatening systemic adverse reaction primarily triggered by anticonvulsants, sulfonamides, or non-steroidal anti-inflammatory drugs [1]. In this report, we present a rare case of DRESS induced by anti-tuberculosis medications.

Case Synopsis

A 28-year-old man with no prior underlying disease was diagnosed with miliary tuberculosis, for which he was started on an antituberculosis treatment based on rifampicin, isoniazid, pyrazinamide and ethambutol, in combined form. At first treatment was well tolerated. Four weeks later, the patient developed a fever of 39.5°C associated with general malaise and the appearance of submandibular adenopathy. Two days later, he developed severe conjunctival jaundice, with an erythematous skin rash. The evolution was marked by the extension of skin lesions, which led to consultation. A thoracic CT scan was performed, showing tuberculous miliaria with mediastinal and left hilar adenopathies.

Dermatological examination revealed periorbital edema, diffuse purpuric maculopapular exanthema more marked on the lower limbs, with palmoplantar involvement, petechial purpura on the hard palate, and conjunctival icterus. There was no involvement of the oral or genital mucosa (**Figure 1**). Pleuropulmonary examination was normal. There was no hepatomegaly or splenomegaly. Examination of the lymph nodes revealed centimetric cervical and inguinal adenopathies. The rest of the somatic examination was unremarkable.

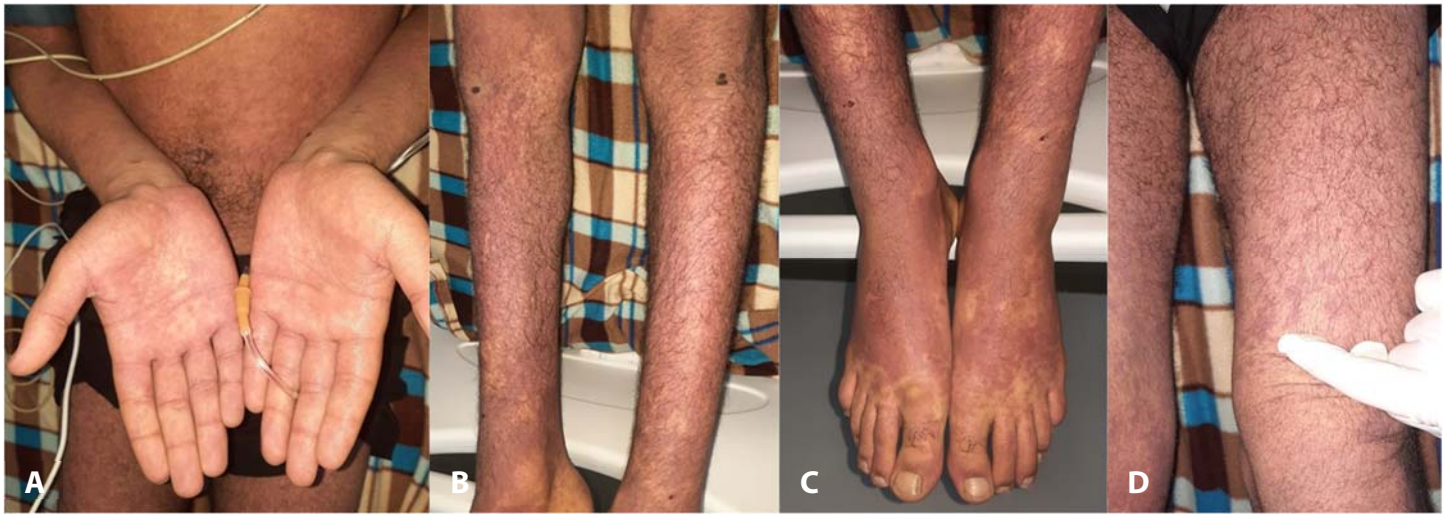

Figure 1. ***A)*** *Petechial purpura locally confluent with purpuric macules on the hands, mild edema.* ***B)*** *Petechial purpura confluent with purpuric macules on legs.* ***C)*** *Petechial purpura confluent with purpuric macules on feet, mild edema.* ***D)*** *Petechial purpura confluent with purpuric macules on thighs.*

The blood count showed a leukocytosis of 15,820/mm^3 with hypereosinophilia of 1,120/mm^3, monocytosis of 1,930/mm^3 and a normal lymphocyte count of 3,630/mm^3. Liver function tests showed aspartate amino transferase at 805IU/l (16 times normal) and alanine amino transferase at 967IU/l (19 times normal), thyroid stimulating hormone was normal. Renal function was normal, with negative 24h proteinuria. Hepatitis B and C, and HIV viral serologies were negative, but serologies for other viruses (Epstein–Barr virus, cytomegalovirus, human herpesvirus 6) were not performed. A skin biopsy was taken and showed epidermal vacuolar changes. The dermis was infiltrated by lymphocytes and a few eosinophils (**Figure 2**).

The diagnosis of DRESS was based on the following criteria: the onset of lesions four weeks after the start of anti-bacillary treatment, a diffuse cutaneous eruption, fever, adenopathy, hypereosinophilia, liver damage, and biological worsening even after discontinuation of the drug. The eosinophil count rose to 6,480/mm^3, lymphocytosis to 12,430/mm^3, monocytosis to 1,080/mm^3, aspartate amino transferase to 903IU/l (18 times normal), and alanine amino transferase to 1,505IU/l (30 times normal). The patient was monitored closely in the intensive care unit, but treated symptomatically.

After ten days, the laboratory check-up showed normalization of the white blood cell count to 8,650/mm^3, a drop in the eosinophil count to 980/mm^3, monocytes to 750/mm^3, aspartate amino transferase to 441IU/l, i.e., 8 times normal, and alanine amino transferase to 709IU/l, i.e., 14 times normal.

Although rifampicin and isoniazid are the most incriminated of the four drugs in the literature, the severity of our patient's reaction justified avoiding all four. He was treated with second-line therapy, bedaquiline, linezolid and levofloxacin with good clinical tolerance. Six months later, the patient showed marked clinical and radiological improvement, with a weight gain of 13kg.

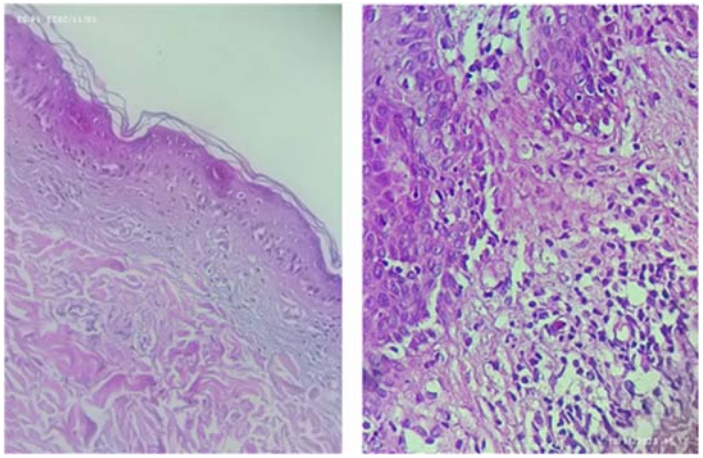

Figure 2. *Histological section of skin tissue bordered by regular epidermis with scattered keratinocyte necrosis and vacuolar basal lesions. The dermis is infiltrated by lymphocytes and few eosinophilic polymorphs. H&E, 100×, 200×.*

Case Discussion

DRESS, also known as drug-induced hypersensitivity syndrome, was introduced by Bocquet et al. [2] and is based on the observation of Callot et al. [3], who reported a series of 24 patients in 1996. It is a serious drug reaction, with an estimated mortality rate of 10% [4,5]. It is characterized by a long latency period, from two to 8 weeks after taking the offending drug. In our case, the latency period was four weeks. This syndrome gives rise to a series of clinical manifestations. The initial clinical picture may mimic a viral infection, with high fever, malaise, polyadenopathy, macular exanthema and often facial edema. Skin involvement is present in the majority of cases of DRESS. The rash is macular, erythematous, and often pruritic. It frequently progresses to erythroderma, as in our patient's case. Other types of skin involvement have also been described, such as pustular lesions, purpura, and vesiculobullous lesions. Mucous membrane involvement may be present, mainly in the oral cavity and pharynx (oral rash and pharyngitis). The most frequently observed visceral involvement is hepatic, in the form of hepatocellular necrosis. However, depending on the drug involved, other organs may also be affected, sometimes leading to multivisceral failure [6,7].

Biologically, the first signs are most often lymphopenia, followed by a mononucleosis-like syndrome with circulating monocytosis (a sequence similar to that seen in severe viral infection). This is followed by eosinophilia (present in 70% of cases), and biological abnormalities indicative of visceral involvement (hemophagocytosis syndrome, hepatic cytolysis, renal failure), [6]. Skin biopsy is often necessary to exclude other diagnoses but does not confirm the diagnosis of DRESS.

Virus-drug interaction associated with viral reactivation is one of the associations of DRESS [4]. This phenomenon has already been observed with herpes viruses (notably Epstein Barr virus). Shiohara et al. [8] observed that sequential reactivations of several herpes viruses (human herpesvirus 6, human herpesvirus 7, Epstein Barr virus, and cytomegalovirus) can be detected at the same time as the clinical symptoms of drug hypersensitivity reactions. Our patient was not tested for these serologies.

The drugs most frequently incriminated in DRESS are aromatic antiepileptics, allopurinol, sulfonamides, antiretrovirals (abacavir, nevirapine), and minocycline. The incrimination of anti-tuberculosis drugs is rarely reported in the literature, with a frequency of around 3%. A retrospective study over 10 years (1998-2008) showed that two of the 60 cases of DRESS reported (3%) were associated with antituberculosis drugs [9].

Our patient was taking anti-tuberculosis drugs in the combined form of four molecules. Patch testing, delayed interpretation of the intradermal test and the lymphocyte transformation test have proved useful in identifying the drug responsible for the DRESS in some cases. However, the validity of these results warrants further study of sensitivity and specificity. Nevertheless, skin tests have higher positivity rates in the assessment of delayed hypersensitivity than intradermal tests and lymphocyte transformation test. Several cases of positive patch tests to anti-tuberculosis drugs have been documented [5,10]. Rifampicin and isoniazid appear to be the most frequently implicated molecules, identified as causative agents in the literature. Pyrazinamide and ethambutol appear to be less frequently implicated.

There are several consensus statements on the diagnostic criteria for DRESS, including that of the European Registry of Severe Toxidermia (RegiSCAR). This group has proposed criteria for the diagnosis of DRESS syndrome in hospitalized patients presenting with drug-induced rash. Our patient's diagnosis was based on the presence of the five RegiSCAR criteria, suggestive skin involvement, fever, polyadenopathy, and hypereosinophilia. In addition there was the timing link between the clinical symptomatology and the incriminating drug. A Japanese consensus group then proposed the term drug-induced hypersensitivity syndrome (DIHS). Today, the two terms (DRESS and DIHS) are used synonymously. This group proposed a further set of diagnostic criteria, including human herpesvirus 6 activation, fever >38°C, maculopapular rash appearing more than three weeks after the start of treatment with the

incriminating drug, lymphadenopathies, leukocyte abnormalities, altered liver function (alanine transaminase >100lU/l), and persistence of symptoms two weeks after discontinuation of treatment with the incriminating drug [11].

The management of DRESS consists of discontinuation of the incriminating drug, close monitoring and supportive care, and corticosteroids. The French Society of Dermatology [12] recommends the use of systemic corticosteroids at a dose of one mg/kg/day prednisone in patients with signs of severity: transaminases greater than five times normal, renal, pulmonary or cardiac involvement, or macrophagic activation syndrome. Intravenous immunoglobulins and/or antivirals (ganciclovir) may be required [13]. Despite these recommendations, our patient had not received corticosteroid therapy because of concerns for exacerbating the miliary TB.

Reintroduction of potentially causative agents in patients with DRESS is generally not recommended, owing to the risk of recurrence. Management of hypersensitivity reactions to anti-tuberculosis drug combinations may involve desensitization, permanent exclusion or substitution with second-line anti-tuberculosis drugs. However, given the dose-dependent T cell response in DRESS, desensitization may result in a milder reaction or induce tolerance. Thus, a desensitization protocol could be considered as an alternative to the reintroduction of anti-tuberculosis drugs, including those potentially responsible [5]. Nevertheless, there is currently no standardized protocol or guideline for desensitization and its mechanism of tolerance induction remains uncertain, particularly for cases of DRESS.

In the study of 29 patients by Hyun Oh and colleagues [5], of the 27 patients who resumed anti-tuberculosis treatment, 13 underwent successful desensitization in 84.6% of cases. However, of the 9 patients for whom the treatment regimen was modified to include second-line anti-tuberculosis drugs, only one tolerated these new regimen without developing hypersensitivity reactions. Our patient received second-line antituberculosis drugs based on bedaquiline, linezolid and levofloxacin, with good tolerability and clear clinical and radiological improvement on reassessment at the end of treatment.

Conclusion

The onset of DRESS during anti-tuberculosis treatment remains a rare complication. Its diagnosis should not be delayed at the risk of compromising the prognosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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