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Sildenafil-induced drug reaction with eosinophilia and systemic symptoms

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) is a life-threatening, multi-organ adverse drug reaction with a mortality rate of approximately 10 %–20 %. The most common culprit drugs are anticonvulsants, some antibiotics such as dapsone and minocycline, salazosulfapyridine, allopurinol and some antiretroviral molecules such as abacavir and nevirapine. Only one case of DRESS induced by sildenafil has been reported in the literature. Here we report a new case.

1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) is a life-threatening, multi-organ adverse drug reaction with a mortality rate of approximately 10 %–20 %.[1] The most common culprit drugs are anticonvulsants, some antibiotics such as dapsone and minocycline, salazosulfapyridine, allopurinol and some antiretroviral molecules such as abacavir and nevirapine. Only one case of DRESS induced by sildenafil has been reported in the literature.[2] Here we report a new case.

2. Case report

A 50-year-old male with no known medical history, presented with a three-day widespread rash associated with a high fever and asthenia. Physical examination showed fever (38,9 °C), a generalized maculopapular rash affecting 70 % of the body surface (Figs. 1–2) with urticarial and purpuric lesions, a facial edema and erosive cheilitis. No cervical lymphadenopathy was found on examination. Laboratory examinations showed hypereosinophilia (1080/mm3), lymphopenia (400/mm3), cytolysis [ASAT and ALAT: 4 times upper limit of normal (ULN)] and cholestasis (PAL ang GGT: 3*ULN), elevated CPK (1.5*ULN) and LDH (2*ULN). There was no sign of liver failure or impaired renal function (CREATININE: 60µmol/L). Hepatite B and C markers were negative. Serological results of cytomegalovirus, Epstein Barr virus (EBV), and human herpesvirus type 6 (HHV6) were consistent with a viral reactivation of EBV. A nasopharyngeal swab was performed for SARS-CoV-2 detection and it was negative. Screening for atypical lymphocytes was not performed. A skin biopsy was performed. It showed polymorphic inflammatory dermal infiltrate. Hemocultures, as well, were negative. The diagnosis of DRESS syndrome was made according to the validation criteria of the RegiSCAR group with a final score of 5.

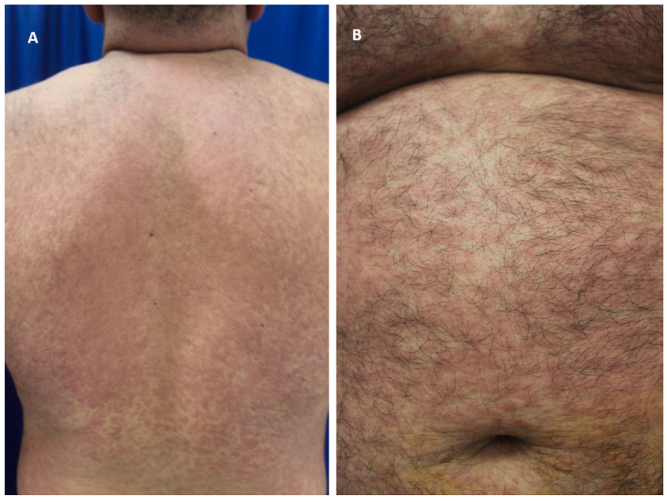

Fig. 1 (A, B). maculopapular rash of the trunk.

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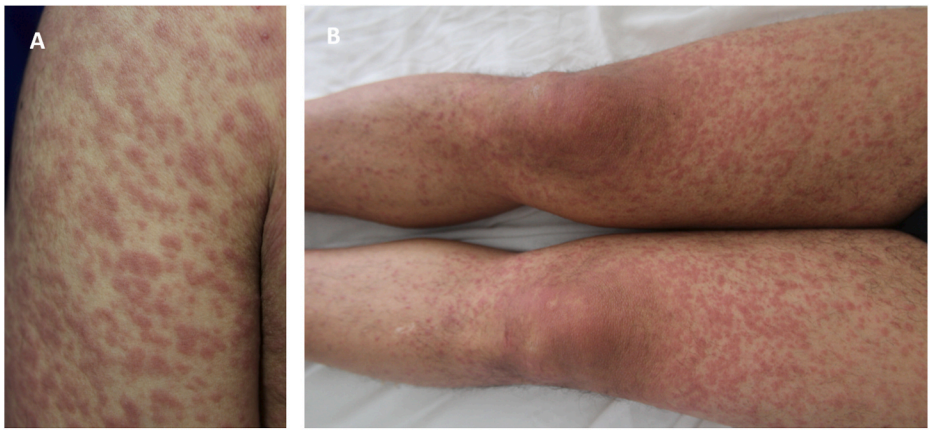

Fig. 2 (A, B). maculopapular rash of the upper and the lower limb.

Patient history revealed no drug-intake three months before the onset of the rash except sildenafil [Viagra®] which was taken once one month earlier. He received a dose of 100mg of sildenafil, without any medical prescription, to improve erectile function. He didn't use any herbal products either. The patient was treated with dermocorticoids with close monitoring. The evolution was marked by a whitening of the lesions after three weeks and a return to normal of the biological anomalies. This case has been reported to the national pharmacovigilance center on April 15, 2022 and registered under number 1260/2022.

3. Discussion

Sildenafil was the first approved phosphodiesterase 5 (PDE5) inhibitor and was approved by the U.S. Food and Drug Administration for erectile dysfunction on March 27, 1998.[3] Sildenafil is also FDA-approved for the treatment of World Health Organization Group I human pulmonary hypertension to improve exercise tolerance and delay clinical deterioration.[4] The most common side effects are headache, flushing, dyspepsia, nasal congestion, back pain, myalgia, nausea and dizziness.[5]

DRESS syndrome develops 2–6 weeks after drug initiation, later than most other immunologically mediated skin reactions.[6] The most frequent manifestations are fever, rash, lymphadenopathy, eosinophilia, and visceral involvement.[1] Following the RegiSCAR study group criteria, a validation scoring system for DRESS was subsequently suggested.[7,8] The pathogenic mechanisms of DRESS are not clear. Various factors are involved.[1] The initial event is viral reactivation, which leads to expansion of the T cell population through cross-reactivity with drugs. Antigen-targeted activated $CD8^+$ cytotoxic lymphocytes subsequently cause tissue damage upon activation.[1]

In our case, no inflammatory or infectious disease explained the symptoms and the biological abnormalities. The diagnosis of DRESS syndrome was certain based on RegiSCAR criteria. Sildenafil was the only drug taken in the last three months and the delay was consistent with the diagnosis of DRESS.[9] No patch testing has been performed in the case reported in the literature as well in our case. No recurrence was noted.

Cutaneous adverse reactions to sildenafil are uncommon. A few cases have been documented in the literature: lichenoid eruption (two cases), fixed drug eruption (two cases), erythema multiforme (one case), toxic epidermal necrolysis (one case).[2] The risk of melanoma with sildenafil is also reported.[10] Only one case of DRESS induced by sildenafil has been reported in 2020.[2] To the best of our knowledge, our case is the second case. The number may be underestimated and this rarity may be explained by the difficulty to prove their imputability due to the irregular and intermittent use of this drug, its availability without medical prescription and non-disclosure of use in some cases.[11] Finally, special attention should be attributed to sildenafil because of its wide use.[12]

Competing interest

The authors declare that they have no competing interest.

Conflict of interest disclosure

None Declared.

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CRediT authorship contribution statement

Amel Chabbouh: Writing – original draft. **Faten Rebhi:** Supervision. **Malek Ben Slimene:** Supervision. **Kahena Jaber:** Validation. **Abderaouf Dhaoui:** Validation.

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