



Dapsone Induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome - A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

A 50-year-old male Sudanese patient presented with a three-week history of jaundice, high-grade fever, and mucocutaneous eruption. For last months he was on compound therapy for leprosy, which had been confirmed recently. The patient's face was prominent, along with the erythematous dusky morbilliform rash covering all the body. On examination, we detected hepatosplenomegaly and generalized lymphadenopathy. Laboratory investigations revealed hepatorenal impairment, and hematological analysis revealed leukocytosis mainly due to eosinophilia. The clinical and laboratory findings interpretation ranked DRESS or Drug-Induced Hypersensitivity Syndrome (DIHS) on top of possible causes before Dapsone Hypersensitivity Syndrome (DHS) and lepra reactions. We promptly discontinued MDT, admitted him to the dermatological ward. Two skin biopsies were sent to two different histopathologists, MF was suggested by one and Sezary syndrome by the other one. Besides the general conservative measures and vital functions monitoring, he received systemic and topical steroids. However, unfortunately, within the next three weeks, his condition deteriorated, and passed away from multi-systems failure.

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1. INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also referred to as Drug-Induced Hypersensitivity Syndrome (DIHS) is a distinct, potentially life-threatening adverse reaction. It is seen in children and adults most often as a morbilliform cutaneous eruption with fever, lymphadenopathy, hematologic abnormalities, and multiorgan manifestations [1,2]. Many drugs have been implicated. Aromatic anticonvulsants, especially phenytoin, carbamazepine, phenobarbital, and sulfonamides, such as dapsone and sulfasalazine, are the most common causes of DRESS. We report a case of fatal DRESS caused by dapsone (dapsone hypersensitivity syndrome) in a 50-year-old Sudanese male patient.

2. CASE REPORT

A 50-year-old Sudanese male, was referred to the Dermatology Military Hospital, in June 2014,

with generalized erythematous skin rash, fever, and jaundice, for 2-3 weeks. The patient had a history of skin rash one year before presentation, which was diagnosed as leprosy and treated with Novartis Multidrug Therapy® (rifampicin, clofazimine, and dapsone). No significant previous history, family history, social history, or drug allergy. Clinical examination revealed a very ill, toxic, febrile, and jaundiced patient. The skin was dusky, showed growth morbilliform rash, scaling, crusting, nodules, and plaques all over his body. The face was severely disfigured, edematous, swollen, infiltrated with large nodules and tumors. (Figs. 1, 2, and 3). The palms and soles were affected (Figs. 4). The oral mucous membrane was affected. There was generalized lymphadenopathy (cervical, axillary, and inguinal), with sizes of 3x3 cm, and hepatosplenomegaly. The sensorial exam was normal and there was no nerve thickening. Their hearing was impaired and he had a cataract in the right eye.



Fig. 1 Disfigured face



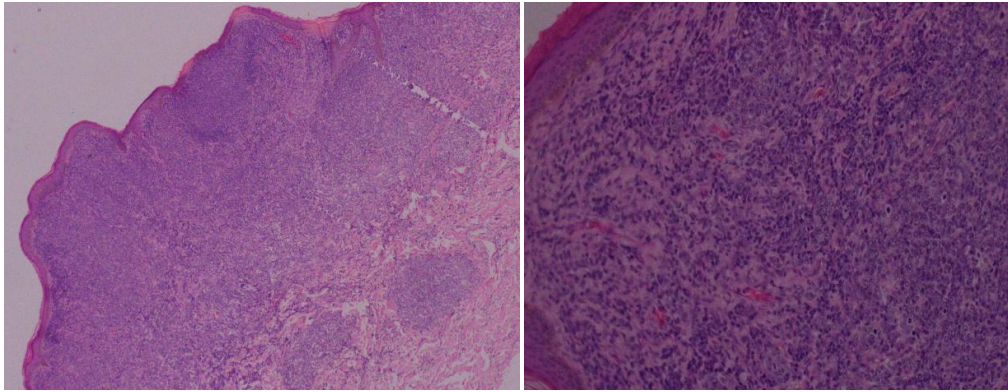
Fig. 2 Scales, edema and crusts



Fig. 3 Dusky skin



Fig. 4 Palms affected



Figs. 5 and 6. Skin histopathology The hematoxylin/eosin staining showed nodular infiltration of the superficial and deep dermis, mainly lymphocytic with atypical features of irregularly folded cribriform nuclei

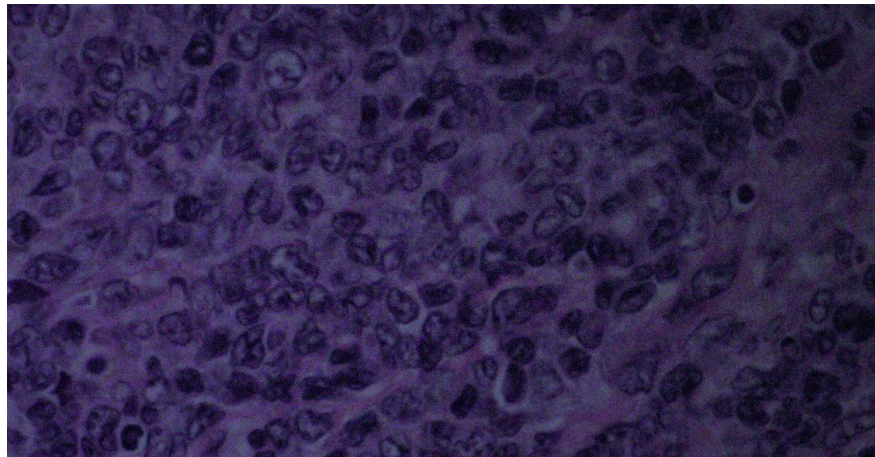


Fig. 7. Skin histopathology. The hematoxylin/eosin staining showed lymphocytic infiltrate with atypical features of irregularly folded cribriform nuclei. Features suggestive of primary skin lymphoma/Sezary syndrome

Investigations showed: hemoglobin: 11.0 g/dL, total white blood cell count: 41900 cell/ μ L, with monocytes 2500 cell/ μ L, lymphocytes 9500 cell/ μ L, eosinophils 4700 cell/ μ L and basophils 100 cell/ μ L, urea 7.8 mmol/L (normal range 3-8.5 mmol/L), creatinine 85 μ mol/L (normal range 50-110 μ mol/L) alkaline phosphatase 255 u/L (normal range 40-150 u/L) alanine aminotransferase 125 u/L (normal 0-56 u/L) , aspartate aminotransferase 100 (normal range 4-35 u/L) , and total bilirubin 80 μ mol/L (normal 2.5-25.5 μ mol/L) at presentation, but rapidly become 8.000 cell/ μ L, hemoglobin 8.7g/dL, and platelets 108.000 units/ μ L. Sezary cells were negative. There was liver and renal impairment. The viral screening was negative. Abdominal ultrasound showed hepatosplenomegaly without esophageal varicose veins. Repeated skin smears for lepra bacilli were negative. Skin biopsy showed

atypical lymphocytes and suggested mycosis fungoides in one report and Sezary syndrome in another specimen (different pathologists). (The two pathologists belonged to two different private laboratories and didn't involve in the study but as routine we asked for histopathology images to be attached with the descriptive reports) (Figs. 5, 6 and 7). Bone marrow aspirate showed atypical lymphocytes and suggested lymphoproliferative disease. Diagnosis of DRESS was considered along with lepra reaction type 2, mycosis fungoides, lymphocytic lymphoma, Kaposi sarcoma, and toxic epidermal necrolysis as other differential diagnoses. Dapsone was the possible etiologic factor in this condition. Patient failed treatment with topical and systemic corticosteroids; rapidly deteriorated and finally died of multi-organ failure.

3. DISCUSSION

In this case report, we present a patient who was referred to the dermatology clinic, severely ill with fever, generalized skin rash, jaundice, generalized lymphadenopathy, and cough. Clinical examination and laboratory tests proved liver and renal impairment, and complex hematological disturbances.

The patient reported the use of dapsone as part of multidrug therapy (MDT). These clinical features suggested drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome as the first differential diagnosis. DRESS is a potentially life-threatening adverse drug-induced reaction, with an estimated mortality of 10%, manifests as fever, skin rash, eosinophilia, and lymphadenopathy, pulmonary, hepatic, and renal manifestations [2]. The clinical features of our patient were highly indicative of DRESS syndrome [1,2,4,5 and13]. Features of erythema multiforme, exfoliative dermatitis, acute generalized exanthematous pustular dermatosis-like eruption, and erythroderma may exist in the same patient. In some cases, bullous lesions are found on the forearm, which is also characteristic features of DIHS/DRESS [13].

The liver is the most frequently affected visceral organ and the most dangerous manifestation is hepatic necrosis, which may be extensive and can lead to liver failure, coagulopathy, and sepsis. It is the primary cause of mortality in DRESS syndrome [1,2,4,5,8]. Recent advances in laboratory diagnostic features demonstrated that 75-95% has leukocytosis There can be marked leukocytosis (up to 50.00 leukocytes/ μ L), 18.2-90% show atypical lymphocytes, 52-95% have eosinophilia, and 75-100% has hepatic abnormalities [2]. The laboratory findings in our patient were typical and suggestive of DRESS [2,4,5, and14].

In reference to the RegiSCAR DRESS validation score our patient fulfilled the criteria of definite case with a final score of >5 (fever -0, Lymphadenopathy- 1, Peripheral blood: Eosinophilia- 2, atypical lymphocytes-0, Skin reaction: extent > 50%-1, morphology -1, histology: compatible with DRESS-1, internal organ involvement-2) [2,14]. Saltzstein et al (1959) described this cutaneous drug reaction as pseudolymphoma because of its clinical and histologic similarities to malignant lymphoma [3]. This is typical in our patient as the histopathology reported features of primary cutaneous T cell lymphoma.

Characterized by a prolonged latency period [5], the most common clinical manifestation of DRESS syndrome is an erythematous morbilliform rash mainly on the face, upper trunk, and upper and lower extremities, but it may involve the entire surface of the skin as observed in our patient [1,2,4,5,13].

Skin histopathology of cutaneous lesions in DRESS syndrome highlights various associated inflammatory patterns in a single biopsy [6]. It reveals a perivascular lymphocytic infiltrate in the papillary dermis, with eosinophils, atypical lymphocytes, and spongiosis, interface dermatitis [7]. The histology of affected lymph nodes in DRESS syndrome may show either benign lymphoid hyperplasia or a pseudolymphoma pattern, which must be carefully distinguished from lymphoma [2,3,4,5]. Clinico-pathological correlation is needed to make a diagnosis of DRESS with a reliable margin of certainty [7].

Diagnostic criteria according to the "Registry of severe cutaneous adverse reactions" RegiSCAR DRESS validation score, Fever $\geq 38.5^{\circ}$ C, Enlarged lymph nodes, Eosinophilia (eosinophil count 700-1499/ μ L, atypical lymphocytes, skin involvement and internal organ involvement (liver, kidney, lung, muscle/heart) (8, 9). Other diagnostic criteria involves Bocquet (1996), and Shiohara (2007) criteria. These 3 different sets of criteria can impede a proper diagnosis and assessment of DRESS syndrome (10). Patch testing has been helpful in confirming its cause [11,12]. Histologically, eosinophils were observed less frequently than we expected (20%) [13].

Dapsone, a major implicated drug in DRESS can cause several adverse effects, the most serious being dapsone hypersensitivity syndrome (DHS), which is potentially fatal [13,15]. DHS manifests as fever, skin rash, eosinophilia, and lymphadenopathy, pulmonary, hepatic and renal manifestations, all these features were reported in the patient we present [2,4,13,15 and 16]. Colonic involvement and secondary bacterial and fungal infection were additional risk factors in DHS [15]. The prevalence of DHS among Chinese patients was 1.5% and 2% in Nepal, with a fatality rate of 9.6%. HLA-B*13:01 allele was considered an important genetic marker among high-risk populations [13,16,17]. It was most surprising that HLA-B13:01 exhibited a strong association with DIHS attributable to dapsone (dapsone hypersensitivity) but HLA-B13:02 did not [13]. In one report from Nepal (2017), 94.44% of the affected with DHS were of

multibacillary and 5.56% were of paucibacillary type [18,19 and 20].

It is evident that our patient had fulfilled the criteria of severe DHS/DRESS, presented with acute symptoms of fever, extensive rash, jaundice, renal impairment, hematological disturbances and cough. He had history of taking dapsone for months before the development of this condition. His investigations including: the blood counts showed leukocytosis; eosinophilia, and atypical lymphocytes. Blood chemistry showed liver, renal impairment and negative viral screening. Histopathology suggested signs of lymphoma; bone marrow showed atypical lymphocytes and suggested lymphoproliferative disease. The clinical and laboratory criteria were typical of DRESS syndrome “Dapsone hypersensitivity syndrome” as proposed in 3 of the diagnostic criteria: Bocquet (1996) [4], RegiSCAR [2,3], and the J-SACR (2, 21, 22, 23, 24 and 25). Dapsone-induced DRESS rate is 0.2–0.5% and it has the longest latency period between antibiotics that induced DRESS. In many reported cases the latency period for dapsone was around 4 months in our case it was 12 months [26].

4. CONCLUSIONS

dapsone is the backbone in the treatment several infections and inflammatory conditions including leprosy. DHS/DRESS, although a rare condition, but could be fatal as in the patient we presented.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline patients consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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