Case Report

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Sulfone Syndrome: A Unique Delayed Type of Drug Hypersensitivity from Dapsone

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Abstract:

Nowadays, dapsone is more commonly used in some dermatologic and inflammatory conditions other than leprosy. Even though it has excellent therapeutic efficacy, its side effects are of common concern. Although immune mediated drug hypersensitivity is less common, it can be fatal. Sulfone syndrome is a unique presentation that occurs in dapsone hypersensitivity syndrome (DHR). Here, we report on a 22-year-old female who was prescribed one month of dapsone for dermatitis. She developed a generalized maculopapular rash and low-grade fever and observed that her sclera had a yellowish discoloration. This case report demonstrates a unique character of delay-type drug hypersensitivity from dapsone, with the aim of increasing physician awareness when prescribing dapsone.

Keywords: dapsone allergy, dapsone hypersensitivity syndrome, Sulfone syndrome

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Introduction

Dapsone (4, 4'-diaminodiphenyl sulfones, DDS) has a dual mechanism as an antibiotic and anti-inflammatory drug to treat infections such as leprosy, Pneumocystis jirovecii pneumonia as well as to treat various autoimmune and dermatological diseases. Over the last century, since Dapsone was developed, it has been found to have many side effects; however, the overall prevalence has been low[1,2]. Dapsone hypersensitivity syndrome (DHS) has been one of the most serious, independent dose-related adverse drug reactions. Presenting clinical conditions can vary from mild to severe severity. If clinicians are unaware and prompt treatment is not undertaken, it can lead to a poor outcome. Herein, we demonstrate a case of DHS including a review of this condition. This study was approved by the Human Research Ethics Committee (REC. 66-191-14-1), and patient informed consent was obtained.

Case report

A 22-year-old Thai female without underlying diseases presented with a fever for five days. One month before her hospitalization, she was diagnosed with dermatitis and was prescribed dapsone 100 mg daily, and prednisolone for treating dermatitis. One month later, she developed a new generalized skin rash and low-grade fever. She immediately discontinued the medication herself and sought a doctor at a private hospital after developing symptoms; however, the skin rash persisted. Five days before admission, she had a high-grade fever and jaundice in combination with persistent skin rashes. On admission, she was jaundiced and had mild tachypnea. Her vital signs revealed a temperature of 39.3 °C, respiratory rate of 26 breaths per minute, heart rate of 100 beats per minute, blood pressure of 100/52 mmHg, and an oxygen saturation of 97% on room air. She had a marked icteric sclera, mild facial edema, and a generalized confluent maculopapular rash. The liver was just palpable without tenderness, with its span being 12 cm. She had no mucositis or lymphadenopathy. Other physical examinations were within normal limits (Figure 1). The laboratory revealed mild anemia (Hb 10 g/dL), with an elevated reticulocyte count (3.35%), leukocytosis (white blood cell 14,780/mcL) with atypical lymphocytes (10%), and her total eosinophil count was 414 (2.8%). A peripheral blood smear showed normochromic normocytic 2+, micro spherocyte 1+, reticulocyte1+, and atypical lymphocytes. Methemoglobinemia was not detected: glucose-6-phosphate dehydrogenase (G6PD) enzyme was normal. The liver function tests showed cholestatic hepatitis by elevation of alanine aminotransferase (572 U/L), aspartate transaminase (309 U/L), direct bilirubin (12.98 mg/dL), total bilirubin (17.65 mg/dL), and elevated alkaline phosphatase (538 IU/l). The results of the coagulation tests, renal function tests, and urine analyses were all normal. Additional negative tests included: anti-HIV, antinuclear antibody (ANA), and viral hepatitis profiles (A, B, C, and E). Diagnostic imaging tests; including an ultrasound of the liver and a chest X-ray, revealed no abnormalities. Additionally, her blood cultures came back negative as well: Table 1 summarizes the laboratory assessment.

According to the patient's medical history of dapsone usage, and its current clinical symptoms; such as fever, skin rash, hepatitis, and jaundice, Dapsone hypersensitivity syndrome or "Sulfone syndrome" was the most likely diagnosis. Ceftriaxone was administered intravenously until a negative blood culture was obtained. She received dexamethasone intravenously on the second day of admission and continued this for three days. Her symptoms improved, with a gradual subsiding of fever, rash, jaundice, and abnormal laboratory tests (Table 1). She was discharged with oral prednisolone (1 mg/kg/day), which subsequently gradually decreased over the six weeks. At the end of treatment, her condition was completely normal.

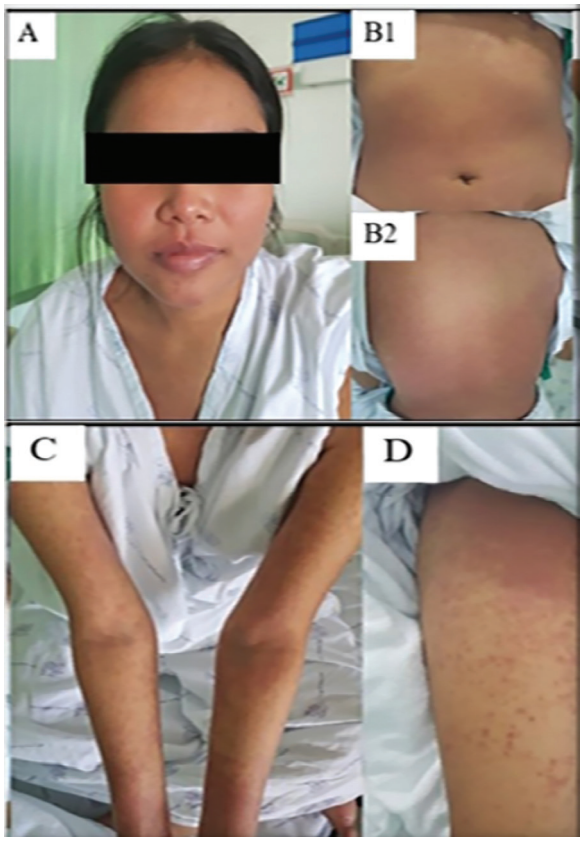

Figure 1 Physical findings of the patient: (A) Facial erythroderma with icteric sclera; (B1, B2, C, D); skin maculopapular rash at abdomen, back, both arm and right leg, respectively

Table 1 Laboratory assessment of dapsone hypersensitivity syndrome at diagnosis and after treatment initiation

Investigation	Before treatment	Day 3 post-treatment	Day 14 post-treatment	Day 30 post-treatment
White blood cell (mcL)	14,780	17,410	15,700	14,380
Neutrophil (%)	47.0	56.0	76.0	67.8
Lymphocyte (%)	38.0	29.0	18.0	26.7
Atypical lymphocyte (%)	10.0	0.0	0.0	0.0
Eosinophil (%)	2.8	0.0	0.0	0.0
Hemoglobin (g/dL)	10.0	12.0	14.1	15.4
Hematocrit (%)	30.5	35.3	42.2	48.4
Platelet (mcL)	261,000	395,000	296,000	224,000
Alanine aminotransferase (U/L)	572	421	108	23
Aspartate transaminase (U/L)	309	119	25	20
Total bilirubin (mg/dL)	17.65	5.95	1.96	0.48
Direct bilirubin (mg/dL)	12.98	4.98	1.24	0.24
Alkaline phosphatase (U/L)	538	467	132	54
Albumin (g/dL)	3.4	3.5	3.8	3.7

Discussion

DHS, also known as sulfone syndrome or dapsone syndrome (D.A.D.P.S. syndrome), was originated name by Allday and Barnes[1]. Dapsone has been widely prescribed in non-leprosy diseases and because of this, physicians have become aware of this complication; thus, the incidence of DHS has increased. Currently, the overall incidence of DHS is uncertain and appears to depend on the population of the study reports; however, a low incidence has been reported: incidence in all populations was 0.6-3.6%[2], while in non-leprosy this was about 1.66%[3]. DHS is commonly found in males and young patients[4,5]. The average age is 35.2 years, which ranges between 5 to 83 years. Most cases were found in the Asian population[5]. One study in Thailand showed that dapsone was the fifth most common cause of drug-induced hypersensitivity syndrome[6]. DHS occurred 1 to 6 weeks after initiating dapsone[1,3-5,7], with the classic clinical symptoms of DHS being fever, a rash on the skin, lymphadenopathy, and hepatic involvement; however, not all classic symptoms present simultaneously. In 61- 63.7% of patients, complete DHS was noted[5], additionally, fever and skin rashes are always found (96-100%) in patients with DHS[2,3,5,8,9].

Our patient was a young, Asian, non-leprosy woman. Clinical symptoms occurred four weeks after being prescribed Dapsone, which was similar to previous reports; however, she was younger than the average age. The dose of dapsone (100 mg) used in our patients is quite similar to other previous DHS reports[2-5,9]. In this case, the patient did not exhibit all the classic symptoms. Specifically, she displayed three out of four classic symptoms; including fever, maculopapular rash, and hepatic involvement, but did not have lymphadenopathy. Although our patient had a maculopapular skin rash, which is mostly indicated in many reports[2], the report from Agrawal et al., revealed a maculopapular eruption in 19.2% of cases[4]. Liver injury is one of the most commonly occurring side effects in DHS[3-5, 8]. Our patient had mix-pattern hepatitis using the Roussel-Uclaff causality assessment method (RUCAM)[10]. This liver pattern, which resembled the study conducted by Devarbhavi et al., was predominantly detected[11]. Although the mechanism behind liver injury in DHS is presently undefined, hydroxylated dapsone, a metabolized form of dapsone, is believed to be the leading cause of liver injury and other hematologic complications such as hemolysis and methemoglobinemia. It directly causes hepatocyte injury due to its oxidative stress function and induced hemolysis, which leads to iron accumulation in the liver, thereby enhancing hepatitis, and injury to the bile duct, leading to cholestasis. Hemolysis and anemia in DHS commonly occurs; particularly in G6PD deficiency patients. The G6PD enzyme reduces the oxidative stress effects of hydroxylated dapsone; thereby, increasing the risk of hemolysis and, subsequently, anemia[7,12]. Fortunately, our patient had the G6PD enzyme, which resulted in mild anemia and hemolysis. The hematologic disorder in this current case is often similar to those described in previous reports[3-5,8]. Anemia has often been found in studies, such as performed by Lorenz et al. five and Wang et al.[8]. Many patients were reported as having leukocytosis by Agrawal et al. and Lorenz et al.[4,5]. Our patient presented signs and symptoms similar to those reported in non-leprosy studies conducted in Thailand. Most of these patients were female, and had a fever, maculopapular rash, hepatic involvement, and mild anemia[13,14]. However, eosinophilia, which is a characteristic of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), was not demonstrated in our patient. This may be explained by the effect of a previous corticosteroid prescription for dermatitis and rapidly initiated high-dose corticosteroids for her symptoms. In addition, the number of peripheral eosinophilia in DHS is variably enriched and associated with pulmonary symptoms.

DHS typically presents with a triad of fever, skin eruptions, and internal organ (lung, liver, neurological and other systems) involvement, occurring several weeks to as late as six months after the initial administration of the drug. In this sense, it may resemble DRESS syndrome. DHS must be promptly identified, as untreated, the disorder can be fatal. Moreover, the pulmonary/systemic manifestations may be mistaken for other disorders. Eosinophilic infiltrations, pneumonitis, pleural effusions, and interstitial lung disease may be seen.

In all DHS cases, dapsone was discontinued immediately. Typically, systemic corticosteroids were provided to DHS patients. Lorenz et al. showed that 82% of studies used systemic steroids as therapy[5]. Although, controlled trials of systemic steroid treatment in DHS have not been conducted, retrospective studies and case reports suggest that the use of systemic steroids could accelerate patient recovery. Many studies reported using similar dosages of systemic steroids, at a dosage of approximately 1 mg/kg/day, with a gradual tapering medication throughout 4 to 6 weeks to discontinue the medication safely[3-5,8]. In this present study, the patient also received a systemic steroid prescription at a dose of 1 mg/kg/day, which gradually decreased over six weeks. Her improvement was consistent with previous reports. The mortality rate of DHS is 9-10%[4,5,8]. In patients with leprosy and DHS, the mortality rate is higher, and the prognosis was generally poor compared to non-leprosy patients. However, due to the limited number of studies on non-leprosy patients with DHS, it is not certain that this group has a lower mortality rate or better prognosis. Our non-leprosy patient had a favorable prognosis, comparable to what Sheen et al. reported[3].

DHS is a life-threatening disease, for which the only effective preventive strategies are counseling for complications and early recognition. Previous studies have investigated the associated between HLA-B13:01 and DHS, with the aim to develop new approaches for preventing and reducing the incidence of DHS. This is done by genetic testing of HLA-B13:01 as a screening tool for high-risk patients with or without leprosy. The pharmacogenomics studies in Thai and Taiwanese populations showed that HLA-B13:01 had a sensitivity of 76.5 -85.5% and specificity of 85.7-92.3% in predicting dapsone-induce severe cutaneous adverse reaction irrelevant with underlying leprosy[8,14]. In addition, a highly negative predictive value (99.6%) of HLA-B13:01, with a 12.37% positive predictive value, has been reported[14].

However, a limitation of screening for HLA-B13:01 has been that this allele's detection varied among populations worldwide. HLA-B*13:01 was mostly found in the Asian population, but was rare in Europe and Africa[8].

Conclusion

DHS is an infrequent but serious condition that can be fatal. The typical symptoms of DHS comprised of: fever, skin rash, lymph node swelling, and liver complications; especially profound hyperbilirubinemia. However, not all these symptoms may manifest simultaneously. When dapsone is prescribed, patient counselling regarding drug allergy is essential for all health care providers. Early recognition and timely treatment are crucial strategies in determining the prognosis of patients. HLA-B*13:01 can be used for screening before starting dapsone to prevent the development of DHS.

Conflict of interest

The authors have no conflicts of interest to declare.

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