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Case Report Open Access

Dapsone Hypersensitivity Syndrome- A Fatal Adverse Drug Reaction

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Abstract

Dapsone (4,4'-Diaminodiphenylsulphone) is simplest, oldest, cheapest, most active antibacterial agent belongs to sulphone family. It is used to treat various infections such as Hansen's disease, cutaneous mycetoma, *Pnemocystis carinii* etc. It is also employed in many immune and hypersensitivity disorders like dermatitis herpetiformis, vasculitis, polyartritis nodosa etc. Dapsone can cause several adverse reactions ranging from simple rashes to multiorgan involvement. Here we are reporting a rare case so called dapsone syndrome or DHS (Dapsone Hypersensitivity Syndrome), which include skin eruption (rash), fever and internal organ involvement like hepatobiliary, pulmonary, hematological and neurological and others. Our patient presented with fever, skin eruption, jaundice, and anaemia which responded to withdrawn of dapsone and intravenous steroids.

Keywords: Dapsone Hypersensitivity Syndrome (DHS); Rash; Hepatitis; Cholangitis

Introduction

Dapsone (4,4,-diaminodiphenylsuphone) compound is related to sulphone drug group family first synthesized by Fromm and Wittmann in 1908. Dapsone is used as a first line drug for leprosy since long time, and also been used for other dermatological condition like dermatitis herpetiformis and infection such as *Pnemocystis carinii* in patient with AIDS.

In 1950, Lowe reported the first case of Dapsone Hypersensity, later on Allday and barnes coined the term DHS (Dapsone Hypersensitivity Syndrome). The incidence of DHS ranges from 0.2% to 0.5% [1]. The symptoms can occur as early as 2-6 hrs in previously sensitized patients to as late as 6 months.

DHS typically constitute a triad of fever; skin lesions and internal organ involvement include hematological, hepatobiliary, pulmonary, neurological and others. Cutaneous lesion range from erythematous papules to plaque, pustules and eczematous lesions, which usually resolve within 2 weeks after discontinuation of dapsone, rarely some patients may develop Steven Johnson syndrome or toxic epidermal necrolysis. Pulmonary manifestation are very common in a patient of DHS, among them infiltrative lung disease such as hypersensitivity pneumonitis, pulmonary eosinophilia and pleural effusion are common. Hematological manifestation characterized by hemolysis, methemoglobinemia and bone marrow suppression, and in gastrointestinal system it can cause hepatitis, cholangitis, hepato-splenomegaly and pancreatitis. DHS can also involve nervous system (psychosis and peripheral neuropathy) and kidney (nephrotic syndrome and papillary necrosis) and endrocrine (hypothyroidism).

Case Report

A 35 year old male presented with history of high grade fever since 5 days with dry cough and loss of appetite. After 4 days of symptoms he started to develop generalized body rashes with swelling over face and lip and yellowish discoloration of sclera & urine. The patient also complained of right hypochondral pain.

Two months prior to presentation he consulted a dermatologist for a skin lesion on his left shin of tibia, and diagnosed as lichen planus for that dapsone was started (100 mg per day) along with antihistaminic and local steroidal cream. And he was taking all these medications for 2 days prior to visit to the hospital. At the time of admission to hospital, he was febrile (temperature 101°F), toxic and dyspnoeic. The vitals were as follows respiratory rate 26/min, pulse rate 110/min and blood pressure was 118/78 mmHg. On examination he was having icterus and erythematous maculopapular, distributed more over face, upper part of trunk and extremities along with swelling around eyes and face, but there was no mucosal involvement. On systemic examination he was having enlarged liver 7 cm below the costal margin and just palpable spleen. On auscultation of chest he was having bilateral rhonchi and creptations mainly in the lower part of chest.

In laboratory investigation we found that Hb was 12.1 gm/dl, TLC was 20,700/mm^3, DLC neutrophil 51%, lymphocyte 36%, eosinophil 11%, monocyte 2%, platelet count was 1.64l ac/mm^3 and ESR was 45 mm in 1st hr, peripheral blood film showed leukocytosis with eosinophilia and no parasite was found. His random blood sugar was 140 mg/dl, blood urea 43.0 mg/dl, serum creatinine 1.34 mg/dl, serum electrolyte was within normal limit, in urine examination 3+ bilirubin was present, total bilirubin 5.47 mg/dl out of which 2.89 mg/dl was direct, AL/AST was 279.0/251.0, PT was 12.54 and INR was 1.1, serum LDH was 758.0, serological marker for Hepatitis A, Hepatitis B, Hepatitis C, EB virus, ricketsia and leptospira were negative, rapid card test (hrp2) for malaria was also negative. ANA was which was negative, and G6PD level was also normal. The blood and urine culture were also negative for any bacterial growth which were sent on first day. His skiagram of chest was normal and ultrasound abdomen suggested enlarged liver with mild increased ecotexture with splenomegaly.

As our patient presented with high grade continuous fever and raised TLC, so we empirically started broad spectrum antibiotics and supportive measures on the first day. On third day we found that patient was not responding to treatment and fever didn't subside and on serial investigation we found that his total bilirubin was now raised to 12.4 mg/dl (direct-8.2 mg/dl) and AST/ALT was 900/906, PT was 17.9 secs (INR 1.57) and TLC was still higher 18200/mm^3. After all these findings and unresponsiveness to empirical treatment, we suspected this to be a

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Day	On admission	3rd day(steroid started)	5th day	10th day	15th day
Temperature	101 F	101.1 F	No fever	No fever	No fever
Hb	12.1 g/dl	10.4 g/dl	10.8 g/dl	11.5 g/dl	12.9 g/dl
TLC	20700/mm^3	18200/mm^3	11300/mm^3	8100/mm^3	6700/mm^3
DLC	N51%, L36%, E10% , M2%	N64%, L32%, E2%, M2%	N73%, L21%, E3%, M3%	N62%, L32%, E3%, M3%	N64%, L31%, E3%, M2%
Bilirubin (total) mg/dl	5.47	12.4	11.3	4.5	2.1
Bilirubin (direct) mg/dl	2.89	8.2	7.1	2.1	0.8
Alkaline phosphate (U/L)	306	830	400	320	230
ALT/AST (IU/L)	279/251	900/960	230/150	65/69	25/34
Prothrombin time in secs	12.54	17.9	11.7	11.6	11.6
INR	1.1	1.54	1.0	1.0	1.0

Table 1: Biochemical improvement as fever subsided within 24 hrs.

case of dapsone syndrome and we started intravenous hydrocortisone. A dramatic improvement was noted as fever subsided within 24 hr and also there was biochemical improvement as shown in (Table 1), we continued the systemic steroid for next 10 days followed by tapering the over 2 weeks with oral steroids at home. And after 2 weeks patients came to us with normal biochemical investigations.

Discussion

DHS is a rare but potentially fatal hypersentitivity reaction. It is considered as part of syndrome so called Drug Rash with Easinophilia and Systemic Symptoms (DRESS). DRESS is also an adverse reaction that can be seen with the use of many drugs such as dapsone, sulfonamides, allopurinol, cyclosporine, azathioprine, minocycline, antiviral drugs, anticonvulsant and gold salt [2]. DHS differs from other drug reactions because it can occur after prolonged exposure of offending drug and even upto 6 months after exposure.

The main toxicity of dapsone is hematological includes methemoglobinemia, hemolysis (dose related and especially in G6PD deficiency), pancytopenia due to marrow suppression and rarely agranulocytosis. Our patent had high LDH suggestive of hemolysis which may be dose related because G6PD level was normal. Liver involvement displays a mixed hepatocellular and cholestatic pattern [3].

Jaundice present in DHS is partly due to hemolysis and partly due to hepatotoxicity. In hepatotoxicity both hepatocellular injury and cholistatic pattern has been found. Cholistatic pattern has less severe course, it presents with high alkaline phosphatase and moderately elevated ALT/AST levels; while hepatocellular toxicity can be fatal and characterized by markedly elevated AST/ALT levels. As in our case there was marked elevation of transaminase levels as well as alkaline phosphatase levels suggestive of mixed injury to the liver.

Our case having classical presentation of dapsone syndrome fulfilling all the criteria suggested by Richardus and Smith [4], which are as follows-

1. The symptoms appear within 8 weeks after commencement of dapsone and disappear after the discontinuation of the drug.
2. The symptoms cannot be ascribed to any other drug given simultaneously with dapsone.
3. The symptoms are not attributable to lepra reaction.
4. No other disease liable to cause similar symptoms is diagnosed.
5. Two of the following signs, symptoms are present - fever, skin eruption, lymphadenopathy, liver pathology (hepatomegaly, jaundice and/or abnormal LFTs.

DHS is a multisystem illness and thus it should be differentiated from disease such as: DRESS syndrome and its variants, infectious mononucleosis, viral exenthematous fever, hypereosinophilic syndrome, TENS(Toxic epidermal necrolysis syndrome), Steven Johnson Syndrome, Hematological malignancies (leukemia and lymphoma), Still's disease, vasculitis like Churg Strauss syndrome and connective tissue disorders.

The exact mechanism behind DHS is not known however few hypotheses have been proposed. Among these, it might be combination of type I and type IV, and perhaps type III hypersensitivity reactions [5], some said DHS could be a modified graft versus host disease mediated by activated T-lymphocytes [5].

According to Prussick and Shear [3], there is some evidence suggesting that the metabolic differences in the production and detoxification of reactive metabolites are an important factor in sulfonamide hypersensitivity reactions. After absorption dapsone metabolized in liver via N-acetylation and N-hydroxylation. It is presumed that hydroxylated metabolites are important in the pathogenesis of DHS.

DHS are generally self limiting reaction and respond well after withdrawn of dapsone and by starting oral or parenteral glucocorticoids (depending upon severity). Since dapsone can persist in the body up to 35 days due to its high protein binding property, tapering of steroids required for a period of one month. Nutritional support, fluid and electrolyte balance, control and prevention of infections (cellulitis, sepsis) and skin care are also required. Vitamin E supplement found to be beneficial in dapsone induced hemolysis.

Conclusion

DHS, although a rare condition, but could prove fatal if not treated promptly. The physician's high suspicion is decisive for the betterment of the patient. As in the reported case of DHS with hepatic manifestation, the withdrawal of dapsone and administration of steroid render improvement in patient's condition. So every physician must be aware about this unusual rare fatal adverse effect of dapsone.

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