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CASE REPORT

Dapsone hypersensitivity syndrome in a lepromatous leprosy patient – A Case Report

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Summary Dapsone hypersensitivity syndrome (DHS) can be classified as a 'drug reaction with eosinophilia and systemic symptoms' (DRESS). It has a variable course, it is not dose dependent and may present with different clinical and laboratory abnormalities. In some cases it may be fatal. We describe a 31 year old man with lepromatous leprosy in whom DHS developed 4 weeks after initiation of World Health Organization multibacillary multidrug therapy (dapsone, clofazimine and rifampin). He had fever, dehydration, diffuse rash, pain on abdominal palpation and inguinal painless lymph nodes. Severe anaemia, abnormal liver function and hyperbilirubinaemia were also found. The patient was treated with prednisone 50 mg daily. There was gradual improvement in the clinical and laboratory signs. We encourage health professionals to be aware of the risk of DHS and to have in mind the development of investigative studies related to HLA and MHC in these patients.

Case Report

A 31-year-old white married man, born in Japeri, Rio de Janeiro, Brazil, was diagnosed with lepromatous leprosy and admitted 4 weeks after the start of World Health Organization (WHO), multidrug therapy (MDT). He presented at the Out Patient Department with prostration, fever, nausea and vomiting. On physical examination there was dehydration, pallor, jaundice, facial and lower limb edema, pain on abdominal palpation at the right upper quadrant and painless cervical plus inguinal lymph nodes. Skin evaluation revealed generalized exanthema that later progressed to an exfoliative dermatitis. Signs of erythema nodosum leprosum (ENL) were not detected and no enlarged or painful nerves were found. Dapsone Hypersensitivity Syndrome (DHS) was diagnosed. MDT was withdrawn and prednisone 50 mg /day prescribed. On admission severe anaemia and abnormal liver

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functions as well as hyperbilirubinaemia were found. The main laboratory data are summarized in Table 1.

Significant eosinophilia and atypical lymphocytes were not observed. Abdominal ultrasonography showed mild hepatomegaly, steatosis, splenomegaly, thickened gallbladder wall and normal bile ducts. Eighteen days after admission the patient showed clinical and laboratory improvement and was discharged. Prednisone dose was decreased gradually. He was seen weekly until he was medically stable. Thereafter treatment for leprosy was restarted with supervised monthly ofloxacin 400 mg, clofazimine 300 mg and rifampin 600 mg, and daily 400 mg ofloxacin and 50 mg clofazimine.

Discussion

While the global reported prevalence of leprosy has decreased, endemicity in Brazil remains high, second only to India.[1] For multibacillary patients like our patient, the WHO recommends MDT with supervised doses of 600 mg rifampin and 300 mg clofazimine once monthly, and unsupervised clofazimine 50 mg/day and dapsone 100 mg/day for 12 months. Dapsone acts as a bactericidal agent against *M. leprae*. It may trigger different adverse effects, which are related to individual genetic susceptibility, intolerance, idiosyncrasy and hypersensitivity. The most common adverse effect is mild haemolysis. The average haemoglobin in leprosy patients who receive daily dapsone falls by almost 2 gr/dL before reaching a nadir, whereas in 16% of patients the haemoglobin falls at least 3 gr/dL.[2,3] Peripheral neuropathy, methaemoglobinemia, nausea, vomiting, fatigue and headache can also occur.[4,5] Dapsone may also lead to life-threatening reactions like Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/NET) and DHS.[6]

Table 1. Laboratory Data

	Before Treatment	Admission	7 days after admission	30 days after discharge
Erythrocytes (million/mm3)	4·69	3·18	3·44	4·88
Hemoglobin (g/dl)	13·7	8·7	9·6	12·8
Hematocrit (%)	40·0	25·1	28·3	42·0
Leukocytes (/mm3)	10 900	16 460	7 970	11 500
Eosinophils (%)	7	3	1	5
Bands (%)	3	12	8	2
Polymorphs (%)	70	67	60	47
Lymphocytes (%)	17	15	23	46
Platelets (/mm3)	220,000	210,000	412,000	197,000
Aspartate aminotransferase (uds/mL)	–––	55	120	17
Alanine aminotransferase (uds/mL)	–––	124	310	25
Alkaline Phosphatase (U/L)	–––	684	1152	121
Gamma Glutamyl Transferase (U/L)	–––	822	1110	136
Total Bilirubin (mg/dL)	–––	10·3	6·04	0·5
Direct Bilirubin (mg/dL)	–––	6·3	3·06	0·4
Indirect Bilirubin (mg/dL)	–––	4·0	2·98	0·1

–––: Data not available.

Our patient presented with severe anaemia and besides withdrawal of dapsone he received treatment with prednisolone leading to clinical and laboratory improvement. He did not need a transfusion nor iron supplementation.

Over time, different terminologies have been used for DHS; Lowe and Allday first described it in 1950 under the name of DDS syndrome or sulfone syndrome. Later, investigations revealed its relationship with a hypersensitivity reaction so it was termed dapsone hypersensitivity syndrome. Currently DHS is considered an example of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), which is also known to some authors as DiHS (Drug induced Hypersensitivity Syndrome) since not all patients have eosinophilia.[6] Even though the terminology seems to have changed, it is the same DDS Syndrome earlier described.

DHS occurs more commonly between the fourth and sixth week after the initiation of dapsone with remission when interrupted. Although considered a rare event with controversial pathophysiological mechanisms, three hypotheses have been suggested: an immune humoral response, a delayed hypersensitivity reaction and altered hepatic metabolism including acetylation and hydroxylation with secondary toxic metabolite production.[2,3,5–7] Recent studies have demonstrated an association between DHS and the presence of HLA B * 13:01, and the existence of one locus within the MHC as a risk factor and predictor of DHS in in the Chinese population.[8–11] Leta *et al.* classified DHS into complete and incomplete.[7] The complete form is characterized by the presence of rash, fever, lymphadenopathy, hepatomegaly and clinical or laboratory evidence of hepatic dysfunction. When one of these findings is absent, it is classified as incomplete.

Most patients have a complete DHS and are often paucibacillary.[7,8] We emphasize that our case fits in the group of complete DHS but it occurred in a multibacillary patient. Additionally, we found no significant eosinophilia; atypical lymphocytosis or thrombocytopenia although these are widely described in the literature. DHS is not dose dependent and its course is variable. It may be fatal with a mortality rate ranging from 11 to 13 %.[2,3,7,8] This has been associated with liver involvement but none of the studies have demonstrated significant statistical association.[7] Another observation is that more severe hepatic involvement is observed in young people. This could be attributed to their greater enzyme activity, and therefore increased production of toxic metabolites.[5] In the literature the dermatosis is not well defined, some authors describe it as a rash while others refer to it as a morbiliform rash or even as an exfoliative dermatitis.[7,8] Criado *et al.* described skin involvement in DRESS as variable and therefore the 'R' in DRESS was subsequently changed from 'rash' to 'reaction'.[6] Our patient initially presented with generalized exanthema, which progressed to a diffuse exfoliative dermatitis.

As well as dapsone, the rifampin included in MDT can also cause significant liver and cutaneous disorders. These last ones are rare and self-limiting. Hepatitis caused by rifampin is usually associated with ethionamide use.[12] Since 1980 there has been an increase in the incidence of DHS in the treatment of leprosy.[9] Some relate this to a possible interaction between rifampin and dapsone with the development of DHS as consequence.[7,8]

Successful treatments of DHS have been reported with empirical use of oral prednisone in a 30 to 60 mg /day doses. Nevertheless, there are no double-blind studies to evaluate its true effectiveness.[2,5,8] The recommendation is to perform a gradual reduction of the prednisone dose due to the fact that dapsone persists on average 35 days in the body since it binds to proteins and suffers entero-hepatic circulation.[5] The use of antioxidants such as vitamins C and E for the prevention of haemolytic anaemia has been studied, but there is insufficient

Table 2. Monitoring Guidelines According Zhu et al.

Baseline	Clinical evaluation	Careful history and physical Examination
	Laboratory evaluation	CBC with differential WBC count and reticulocyte count Serum chemistry including liver function test and renal function tests Urinalysis G6PD level
Follow up	Clinical Evaluation	Careful history and physical Examination
	Laboratory evaluation	***Hemolysis***: Especially in G6PD-deficient patients; CBC count with differential WBC count and reticulocyte count every 2 wk. for first 3 mo, then every 3 mo.
		Methemoglobinemia: Monitor methemoglobin levels in patients with cardiopulmonary disease, hemoglobinopathy, or methemoglobin reductase deficiency
		Agranulocytosis: Monitor CBC count 4–10 wk after initiation of therapy; stop therapy when WBC count $<4000/mm3$
		Peripheral neuropathy: Periodic neurologic screening examination by dermatologist; any suspected abnormality needs referral for full neurologic examination and electromyogram with nerve conduction studies
		Psychosis: Manifested by insomnia, irritation, excitability, and even violence; reversible on stopping dapsone

CBC count, Complete blood cell count; Hb, hemoglobin; WBC count, white blood cell count, G6PD Glucose-6-phosphate dehydrogenase.

evidence to recommend it. On the other hand, use of a metabolic inhibitor such as cimetidine to reduce hepatic oxidation has successfully decreased dapsone's adverse effects.[2]

Although rare, the DHS is still under-diagnosed and does not always present with the classical manifestations. Therefore, it is important for health professionals to be aware of it, especially in endemic areas.

Dapsone is metabolized in the liver via acetylation or N-hydroxylation. About 85% is excreted in the urine and about 10% in the bile. It is distributed to all body organs including skin and erythrocytes. Orally ingested dapsone (100 mg) in adults reaches its peak serum concentration of between 1·10 and 2·33 mg/L within 0·5 to 4 hours. Serum levels stabilize after 8 to 10 days of therapy.[2] Monitoring guidelines for its use have been proposed by Zhu *et al.* which are summarized in Table 2.

He suggests laboratory investigations to be done at baseline and every 2 weeks after the beginning of therapy.[2] We agree with his proposal, but we would suggest for it to be every week during the first 6 weeks of therapy since dapsone serum levels stabilise after 8 to 10 days of oral treatment. If done more frequently, these laboratory investigations may predict possible onset of DHS, allowing prompt withdrawal of the drug, and thus preventing a greater number of cases of DHS. In addition, investigation related to HLA and MHC may be considered in the Brazilian population.

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References

[1] Saunderson PR. Leprosy elimination: not as straightforward as it seemed. *Public Health Rep*, 2008; **123**: 213–216.

[2] Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol*, 2001; **45**: 420–434.

[3] Evangelista M, Prada DB, Piola JC, Tomasini R. Síndrome de hipersensibilidad a la dapsona, Internet 2013 [cited 2013 Dec 10]; Available from: URL: http://www.sertox.com.ar/img/item_full/publicaciondapsona.pdf.

[4] Ensina LF, Rodrigues FF, Di Gesu J *et al.* Reações de hipersensibilidade a medicamentos. *Rev. bras. alerg. imunopatol*, 2009; **32**: 42–47.

[5] Prussick R, Shear NH. Dapsone hypersensitivity syndrome. *J Am Acad Dermatol*, 1996; **35**: 346–349.

[6] Criado PR, Criado RFJ, Avancini JM *et al.* Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Drug-Induced Hypersensitivity Syndrome (DIHS): a review of current concepts. *An Bras Dermatol*, 2012; **87**: 427–441.

[7] Leta GC, Simas MEP, Oliveira MLW *et al.* Síndrome de hipersensibilidade à dapsona: revisão sistemática dos critérios diagnósticos. *Hansen. Int*, 2003; **28**: 79–84.

[8] Bucaretchi F, Vicente DC, Pereira RM *et al.* Dapsone hypersensitivity syndrome in an adolescent during treatment of leprosy. *Rev Inst Med trop S Paulo*, 2004; **46**: 331–334.

[9] Zhang FR, Liu H, Irwanto A *et al.* HLA-B*13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med*, 2013; **369**: 1620–1628.

[10] Liu H, Zhang F. Establishment and application of risk prediction test for dapsone hypersensitivity syndrome: preliminary report. In: *2013 Eighteenth International Leprosy Congress*, 2013 Sept 16–19; Brussels.

[11] Wang H, Tian W. HLA-B*1301 Association with dapsone hypersensitivity syndrome among leprosy patients in China. In: *2013 Eighteenth International Leprosy Congress*, 2013 Sept; 16–19; Brussels.

[12] Andrade ZMV, França ER, Teixeira MA *et al.* Síndrome sulfônica: relato de um caso. *An Bras Dermatol*, 1999; **74**: 59–61.