

Case Report

# A Case Report of Fatal Dapsone-Induced Agranulocytosis in an Indian Tuberculoid Leprosy Patient

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## ABSTRACT

**Introduction:** Being one of the oldest diseases known to mankind, leprosy continues to be a public health challenge. Dapsone continues to be the drug used against this since time immemorial. The most common side effects of dapsone are hemolytic anaemia, methemoglobinemia and agranulocytosis. We report a case of dapsone-induced agranulocytosis in a patient being initiated with leprosy therapy.

**History:** A 56 year old female presented with fever and non productive cough with no other known co-morbidities. Examination revealed enlarged erythematous tonsils and cervical lymphadenopathy in a pale female. After three days of hospital care, attenders confessed about the treatment taken for Hansen's disease since 2 weeks and her present complaints started after starting the treatment. Her WBC counts were low and absolute neutrophil count was 780cells/mm<sup>3</sup>. She was managed with antibiotics, and G-CSF. Dapsone was stopped and the WBC counts increased, patient improved clinically.

**Conclusion:** Sound knowledge of the drugs that can cause agranulocytosis is essential. Identifying the offending drug by meticulous history taking and clinical examination to look for sites of skin biopsy/skin lesions might help in identifying the offending drug. Stopping the use of the offending drug, careful monitoring of blood counts, isolation of the patient to avoid contact of infections, hand hygiene, use of Granulocyte colony stimulating factors till white blood counts recover to more than 10,000/microL are all integral part of patient management and to prevent impending sepsis and death.

**Key words:** Dapsone, agranulocytosis, Leprosy, G-CSF

## INTRODUCTION

Being one of the oldest diseases known to mankind, leprosy continues to be a public health challenge. The WHO launched a 5-year "Global leprosy strategy 2016-2020" in April 2016 titled 'Accelerating towards a leprosy-free world'.<sup>[1]</sup> The latest update from the WHO titled "Global leprosy update, 2016: accelerating reduction of disease burden: states that - although there has been a significant reduction in the prevalence of the disease worldwide since the mid-1980s to

elimination levels, new cases continue to arise indicating continued transmission.<sup>[2]</sup>

The global prevalence at the end of 2016 was 171,948 with a registered prevalence rate of 0.23 per 10,000 population, a decrease from that in 2015.

In India, the National Leprosy Eradication Programme (NLEP) is the centrally sponsored health scheme of the Ministry of Health and Family Welfare, Government of India. The programme is also supported by WHO, ILEP, and few other nongovernmental organizations (NGOs).

Due to their efforts, from a prevalence rate of 57.8/10,000 in 1983, India has succeeded with the implementation of MDT in bringing the national prevalence down to “elimination as a public health problem” of less than 1/10,000 in December 2005 and even further down to 0.66/10,000 in 2016. In addition to achieving the national elimination target by the end of 2005, India by the end of March 2011–2012 succeeded in achieving elimination at the state level in 34 states/UTs out of the total of 36 states/UTs. Only the state of Chhattisgarh and the UT of Dadra & Nagar Haveli were yet to achieve elimination. By the end of March 2016, 551 districts (82.36%), out of the total 669 in districts, in India had a prevalence of <1/10,000 population which is the target of elimination as a public health problem. The number of districts with prevalence between 1 and 2/10,000 was 76, the number of districts with prevalence between >2 and 5/10,000 was 39, and those between 5 and 10 were 2.<sup>[3]</sup>

From its introduction in 1982 to till date, the same three drugs constitute MDT for leprosy. Dapsone, rifampicin and clofazimine still continue to be the drugs in the repertoire of treating leprosy. As the patient usually hides of being treated with these drugs, clinical manifestations of adverse effects of these drugs pose a clinical challenge for clinicians. The first case of dapsone-induced agranulocytosis in a leprosy patient was reported in 1986 in a young Melanesian male receiving unsupervised treatment with 100mg dapsone daily for indeterminate leprosy.<sup>[4]</sup> It has been reported to occur in 0.2-0.4% of patients treated with dapsone.<sup>[5]</sup> We report a case of dapsone-induced agranulocytosis in a patient being initiated with leprosy therapy.

## CASE HISTORY

A 56year old female presented to us with the history of a cough and fever for 2 weeks. She had a non-productive cough without any diurnal or positional variation. Fever was sudden onset high-grade intermittent fever with chills. There was no history of rashes, joint pain, wheeze, dyspnea. She was not a known case of hypertension, diabetes, coronary artery disease, bronchial asthma, pulmonary tuberculosis. Family history and personal didn't reveal significant data.

On examination, she was a moderately built and nourished female, afebrile with the pulse of 90/min and regular. Blood pressure of 100/60mmHg. She was pale and had level II right cervical lymphadenopathy with erythematous anterior faucial pillars. Tonsils were also reddened with few yellowish follicles.(figure 1) There was no skin rash or organomegaly. Systemic examination was within normal limits. Routine Blood investigations revealed a total count of 780/mm<sup>3</sup>. (Table 1) Differential count and peripheral smear showed a drastic reduction in neutrophils (156cells/mm<sup>3</sup>).



Figure 1: Enlarged erythematous tonsils

Table 1: Blood investigations of the patient during the hospital course

Date/ Investigation	3/9/18	4/9/18	5/9/18	6/9/18	7/9/18	9/9/18	12/9/18
Hemoglobin(g/dL)	10.5		9.2	8.8	8.6	8.9	9.2
Total count (cells/mm <sup>3</sup> )	780	800	1090	1000	1430	17000	10850
Neutrophils (%)	20.6	19.9	21.1	20	19.6	69.7	66.4
Platelet count (cells/mm <sup>3</sup> )	263000			274000		401000	429000

ECG was found to be in normal limits. A diagnosis of Febrile neutropenia was made

and further investigations as to the cause were followed. The patient was shifted to

ICU for further management. She was treated with cefoperazone sulbactam and other supportive care. After 3 days of intensive care management, total count continued to be on the lower side with the total count of 1000/mm<sup>3</sup>.

On day 4, a new patient attender confessed about the treatment taken at another tertiary care centre for some skin disease and that skin biopsy was done. The biopsy report and previous prescription revealed that the patient was diagnosed to have tuberculoid leprosy and was started with dapsone 2 weeks back. But the patient had discontinued Dapsone a week back. As she was a dark-skinned female, further targeted examination revealed few hypopigmented macules over the malar region of the face.(Figure 2)



Figure 2: Skin lesion below the left ear pinna (within marked area)

Due to low haemoglobin and systemic symptoms, dapsone was not restarted. Instead, clofazimine was added. Also, filgrastim was given for 3 days and rise in total count and improvement in the absolute neutrophil count was seen. She improved gradually and was discharged. Due to reduced hemoglobin and systemic symptoms, dapsone couldn't be restarted and hence clofazimine was started. Follow up after a month and two showed normal neutrophil count and total count.

## DISCUSSION

Dapsone (diamino-diphenyl sulfone) is both an antibiotic and an anti-inflammatory agent. It is primarily used in the treatment of leprosy. It has also been

used successfully to treat actinomycetoma, in prophylaxis and treatment of *Pneumocystis carinii* pneumonia and for malaria.<sup>[6]</sup>

As an anti-inflammatory agent, dapsone has been used to treat many skin diseases characterized by the abnormal infiltration of neutrophils or eosinophils, such as erythema elevatum diutinum, dermatitis herpetiformis, Sneddon Wilkinson disease, linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum and Sweet's syndrome.<sup>[6]</sup> It is also used as an anti-neutrophilic agent in the treatment of brown recluse spider bites.<sup>[7]</sup> The most common side effects of dapsone are hemolytic anaemia, methemoglobinemia and agranulocytosis. Hemolytic anaemia is a dose dependant side-effect which usually develops three to four weeks after initiation of dapsone therapy if the dose is >300mg/day.<sup>[8]</sup> Methemoglobinemia is also a dose-dependent side effect of Dapsone, symptoms of which include headache, dyspnea and tachycardia. The fundamental treatment of methemoglobinemia is careful observation. In severe cases of methemoglobinemia, treatment with methylene blue 1-2mg/kg is advised. In a well-known study, a report on 16 soldiers in Vietnam who developed agranulocytosis while on treatment with dapsone as malaria prophylaxis is documented.<sup>[9]</sup> The initial symptoms include fever, throat pain, ulcers and lymphadenopathy. Once agranulocytosis develops, the patient's susceptibility for sepsis and death increases. However, unlike methemoglobinemia, agranulocytosis is not a dose-dependent side effect of dapsone. Clofazimine is well tolerated in the standard dose of 50 mg daily used for leprosy. The major effect seen is pigmentation of the skin (especially within skin lesions), since the drug is lipophilic and accumulates in the lipid-rich cell wall of *M. leprae*.

Diagnosis of dapsone-induced agranulocytosis is confirmed when all of the following are present- low to absent absolute neutrophil count, absence of

anemia and thrombocytopenia, hypocellular bone marrow that shows normal erythropoiesis and megakaryocytopoiesis but few if any granulocytic precursors, return of the neutrophils count to normal when the offending agent is stopped, with or without concomitant use of G-CSF. There are two basic mechanisms by which drugs cause neutropenia and/or agranulocytosis-immune-mediated destruction of circulating neutrophils by drug dependent or drug-induced antibodies or due to direct toxic effects upon marrow granulocytic precursors. Both mechanisms appear to be mediated by reactive metabolites.<sup>[10]</sup> Dapsone is metabolized to highly reactive hydroxylamine which is toxic to bone marrow myeloid cells.<sup>[11]</sup> There is no effective way to detect the rare patient with high risk for drug-induced agranulocytosis. Monitoring the white blood cell count and white cell differential in order to permit early detection has been used.

Sound knowledge of the drugs that can cause agranulocytosis is essential. Meticulous history taking is of utmost importance for the early detection of drug-induced agranulocytosis. In our case, for the first three days, the patient and attenders had concealed from us about the Hansen's disease and dapsone treatment, probably due to social stigma. This led to the clinical dilemma as to what was the cause for agranulocytosis in our patient. Unless the patient reveals the history of drug intake prior to the onset of symptoms, it was not possible for us to identify the offending agent. In our case, the patient was taking only dapsone; however some patients will be taking multiple drugs and identifying the possible offending agent may be difficult. Neutropenia usually resolves within one to three weeks after cessation of the offending drug but studies have shown that median recovery time of 15 days with a range of 5 to 31 days.<sup>[12]</sup> Older age, sepsis, shock and renal failure are poor prognostic factors. A number of non-randomized studies have reported excellent results with the use of granulocyte-colony stimulating factors (G-

CSF) in patients with drug-induced agranulocytosis and secondary infection. The results have generally been characterized as shorter recovery time, less antibiotic use and shorter hospital stay. G-CSF can be given subcutaneously, empirically, at the recommended dose of 5mcg/kg per day, to patients with significant drug-induced agranulocytosis. Treatment with G-CSF can be discontinued when the total white blood cell count exceeds 10,000/microL. In our case, it took 3 days of G-CSF to bring total white cell count back to normal. Dapsone was not continued in view of anemia and systemic symptoms. Clofazimine was started instead of dapsone and the patient tolerated this well.

## CONCLUSION

We report a case of dapsone-induced agranulocytosis in an Indian tuberculoid leprosy patient. Identifying the offending drug by meticulous history taking and clinical examination to look for sites of skin biopsy/ skin lesions might help in identifying the offending drug. Stopping the use of the offending drug, careful monitoring of blood counts, isolation of the patient to avoid contact of infections, hand hygiene, use of Granulocyte colony stimulating factors till white blood counts recover to more than 10,000/microL are all integral part of patient management and to prevent impending sepsis and death.

**Conflicts Of Interest:** The author does not have any conflict of interest regarding research, authorship and publication of this article.

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