Agranulocytosis Induced by Multidrug Therapy in Leprosy Treatment: A Case Report

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Multidrug therapy (WHO/MDT) in multibacillary leprosy consists of treatment with rifampicin, dapsone and clofazimine. However, adverse effects can cause the patient to abandon treatment. We report on a patient who presented agranulocytosis and hemolytic anemia associated with this treatment regime. We also examined the importance of laboratory exams for diagnosis and follow-up of the patient, and for early detection of adverse effects, with a view to improving adhesion to treatment and contributing to the eradication of Hansen's disease as a public health issue.

Key-Words: Hansen's disease, multidrug therapy, neutropenia, hemolytic anemia.

Hanseniasis is a long evolution disease that is transmitted from human to human by close and prolonged contact with patients that have had no treatment and who have the contagious form of the disease (virchow's or dimorphous leprosy). The incubation period normally varies from two to five years [1]. Hansen's disease is normally treated quite effectively with a multidrug regimen of dapsone + clofazimine + rifampicin. This regimen has been officially adopted by the Brazilian Ministry of Health [2,3].

It is well known that there is no primary prevention for leprosy; so multidrug therapy is the only intervention available to break the chains of transmission of *M. leprae* [4]. However, this drug regimen can provoke undesirable side effects, which may require further attention. It is quite important to be familiar with these adverse effects of multidrug therapy, so that we may prevent them, establish a prompt diagnosis, and increase adherence to treatment [5].

The following syndromes and reactions have been reported in patients on dapsone: hemolysis, metheglobinemia, gastrointestinal problems, neuropsychic complications, peripheral neuropathy, cutaneous disorders, dapsone (sulfone) syndrome, agranulocytosis. The main adverse effects of clofamizine are cutaneous pigmentation, xeroderma, photosensitivity, gastrointestinal problems, and lower limb edema. The principal side effects of rifampicin are icterus, painful hepatomegaly, altered liver function tests, intra-hepatic cholesthasis, gastrointestinal symptoms, cutaneous manifestations, general hypersensibility signs, acne lesions, eosinophilia, leucopenia, hemolysis, anemia, thrombocytopenia, agranulocytosis and a flu-like syndrome. [1]

The causal relationship between hematological alterations and multidrug therapy (MDT) is not as clear cut as it seems. This is because it is not easily identified, in that it may occur immediately after the medication is taken or several days afterwards. One may be completely sure of an adverse side effect only if the patient is intentionally re-exposed to the same drug, which is unfeasible [5]. This is even more unlikely when the side effect is neutropenia.

In severely neutropenic patients, the signs and symptoms of infection are usually very unpronounced; often the site of infection is not found. Fifty per cent of these patients will have a well-established or occult infection, and at least 20% of the patients with <100/mm³ neutrophils are found to have bacteremia [6]. Once the site of infection is established, it is imperative to start treatment with a broad-spectrum antibiotic and supportive therapy [7]. Healthcare personnel should be made aware of the need for diagnosis and management of adverse effects of these drugs [5].

Case Report

EMTS, 28 years old, a female mullato, was born in João Pessoa and is a resident of the city of Bayeux, Paraiba. When she came to the outpatient clinic in our hospital, she had been having headaches and a sore throat for three days, with progressive decline of her condition, which included fever, chills and growing dysphagia. She consulted a doctor in a Bayeux hospital 24 hours after the beginning of her symptoms. She was treated for a presumed diagnosis of acute tonsillitis with a single dose of benzathine penicillin.

The disease progressed with deterioration of her general condition, and she no longer could swallow solids; later, she presented a syncope. At this time, she consulted a doctor in our outpatient clinic. She was treated symptomatically and with IV saline hydration therapy. Then she was evaluated with laboratory exams and put under observation.

Her complete blood count showed the following results: Red blood cell count: 2,810,000/mm³; hemoglobin: 8.28 g%; hematocrit: 25.4%; WBC: 626/mm³; segmented neutrophils: 4%; lymphocytes: 92%; monocytes: 4%; basophils: 0%; eosinophils: 0%; myelocytes: 0%; metamyelocytes: 0%; platelets: 152,000/mm3; BUN: 28 mg/dL; creatine: 0.8 mg/dL; AST: 13U/L; ALT: 20 U/L.

She was admitted to the University Hospital in João Pessoa (Paraíba) for treatment and follow-up. A salient factor

Received on 13 November 2008; revised 9 January 2009.
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The Brazilian Journal of Infectious Diseases 2009;13(1):158-160.

in her previous history was the fact that she was on the 35th day of treatment of Hansen's disease with MDT. The leprosy diagnosis was established at the Hospital Clementino Fraga with a dermatological examination; she had multiple erythematous infiltrated plaques all over her skin, with alteration of sensibility to pain. Her disease was classified as a multibacillary, dimorphous type of leprosy. Baciloscopy: right elbow: +++; left elbow: ++; right ear: negative; left ear: +; bacteriological index: 1.25%; morphological index: 0.25%.

On physical examination, she was moderately pale (++/4), dehydrated (+/4), feverish (axillary temperature 37.8º C) and with a pulse of 120 bpm. The oropharynx showed hypertrophied tonsils (+++/4) and was covered with plaques. Detailed examination of her skin showed no blemishes or signs of leprosy.

Lung auscultation showed vesicular murmur in both lungs, with no crackles or wheezes. Her heart sounds were normal, with two tones and a systolic murmur. Her abdomen was flat, flacid and sensitive to the touch on the right hypochondrium and hypogastrium; there was no evidence of visceromegaly.

Several lab exams were ordered to better define the diagnosis, including blood and urine culture, blood coagulogram, ionogram, renal and liver function tests, total protein and protein fractions, serology for CMV, Epstein-Barr, HIV I and II, baciloscopy for *M. leprae*, chest X-ray, echocardiogram, myelogram and abdominal USG. Both blood and urine cultures did not produce bacterial growth, even after five-days incubation. Prothrombin activity was 40%; fibrinogen: 840 mg/dL; the other coagulation parameters showed normal values; prothrombin: 4.8 g/dL; albumin: 2.4 g/dL; globulin: 4.7 g/dL. Serology for CMV, Epstein-Barr, HIV-1 and 2 was negative. Baciloscopy for *M. leprae* was positive. Chest X-ray, echocardiogram and abdominal USG were normal.

Hematology Department opinion: Patient with Hansen's disease developed anemia, with leukopenia and neutropenia. The myelogram showed severe hypoplasia of the bone marrow granulocytic component and hyperplasia of the red bone marrow, which were probably related to the medications prescribed for her original pathology. Prompt suspension of the drugs was recommended, with treatment of neutropenia with one ampoule sc/day of 300 ug filgastrim, and a broad spectrum antibiotic. Lab test follow-ups included a hemogram and a reticulocyte count. Conclusion: agranulocytosis and hemolytic anemia possibly induced by dapsone.

Dermatology Department opinion: absence of skin lesions typical of Hansen's disease (caused by agranulocytosis?). Immediate suspension of MDT, baciloscopy for *M. leprae*, treatment of febrile neutropenia, re-treatment of hanseniasis after hematological compensation of the patient with an alternative drug regimen for reaction to rifampicine and dapsone, consisting of ofloxacin + clofazimine + minociclin, in a hospital setting, given one drug at a time.

Discussion

Neutropenia was diagnosed in a patient as a laboratory finding, in the routine procedures of the University Hospital for patients that were seen at the outpatient clinic.

As a first step in the diagnosis, we focused our attention on the probable causes for febrile neutropenia.

As the lab results came in, the hypothesis of neutropenia due to MDT was strengthened. The myelogram showing an improvement of hemolytic anemia after suspension of MDT (in accordance with the Hematology Department opinion), the reversal of agranulocytosis after treatment with filgrastim, and the exclusion of several conditions responsible for agranulocytosis, were crucial for making the final diagnosis. The reappearance of the leprosy lesions after this treatment led us to believe that their disappearance was due to neutropenia. As expected, the skin lesions reappeared after the restoration of blood cells. Acid-fast bacilli were not searched for in the bone marrow smear.

We initiated treatment with cefepime, oxacillin, fluconazole and filgrastrim. Later, we introduced an alternative treatment for Hansen's disease, using one drug at a time, with a 30-day interval between them (ofloxacin + clofazimine + minociclin).

Conclusions

Agranulocytosis due to multidrug therapy (MDT) in Hansen's disease is a rare condition, and its diagnosis is quite a challenge for the accompanying physician. Its occurrence should always be kept in mind and patients on treatment should be monitored for hematological imbalances. The patient had a favorable outcome after the prescribed treatment, with total recovery of the granulocytic system.

The absence of significant lab exam results (total blood count, the usual biochemistry tests, hepatic and renal function tests, blood glucose) in a hospital or clinic where Hansen's disease is diagnosed and the almost immediate appearance of agranulocytosis post MDT, led us to implement a new laboratory protocol for the diagnosis and follow up of such patients.

We also suggest that the first follow up should be made 15 days after the beginning of treatment, so that adverse side effects can be detected as early as possible and proper measures taken to compensate for those such. This should contribute to the patient's safety and enhance motivation for treatment, and as an ultimate goal help eliminate Hansen's disease as a public health issue.

Acknowledgments

We thank our colleagues at the Department of Infectology of Lauro Wanderley University Hospital for their help and support, as well as Dr. Orlando Gomes Falcão, Coordinating Biochemist of the Clementino Fraga Hospital Laboratory, Pernambuco Health Department;/ Dr. Carlos Alberto Fernandes Ramos, Pathologist at Lauro Wanderley

University Hospital, UFPB; Dr. João Bruno de Oliveira, Nuclear Medicine Professor at Alagoas Federal University; Dr. Benedito Bruno de Oliveira, Medical residence coordinator for Infectology at the Lauro Wanderley University Hospital, UFPB; Dr. Dóris Amorim Pontes de Oliveira, Dermatologist at Lauro Wanderley University Hospital, UFPB; and Dr. Gilson Guedes, Haematologist at Lauro Wanderley University Hospital, UFPB.

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