CASE REPORT

Aplastic anaemia associated with multidrug therapy (dapsone, rifampicin and clofazimine) in a patient with lepromatous leprosy

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Introduction

Leprosy remains an important public health problem in Brazil, that ranks second in the world regarding incident and prevalent cases.1 Feared since ancient times for its stigmata, leprosy can now be treated and cured, leaving no disability if the disease is recognized early. Multidrug therapy (MDT) has had a major impact on leprosy worldwide, and made achievable the proposal of elimination of leprosy as a public health problem within the next few years.2 The enormous success that has been obtained with MDT has, nevertheless, a few drawbacks. The fixed combination of dapsone, rifampicin and clofazimine, the MDT components, has been associated with a series of adverse drug reactions (ADR) that are sometimes severe and even life-threatening. We report here a fatal case of MDT-associated aplastic anaemia, analyse the likelihood of a causal association, and discuss the validity and usefulness of preventable measures.

Case report

A 23-year-old Brazilian male sought the State Reference Center for Sanitary Dermatology and Leprosy outpatient clinic, in Uberlândia, in southwestern Minas Gerais State, Brazil, complaining of having noticed stains on his skin for 5 years and swelling and nasal obstruction and bleeding for 2 years. Two weeks before, he had injured a toe, which developed secondary infection and led him to seek medical help. When first seen, he had generalized infiltration of the skin, mainly in the face (ears and nose), facial nodules...
involving his ear lobes, and madarosis. The clinical diagnosis of lepromatous leprosy was confirmed by a skin slit smear, which had a bacterial index of 5.25. MDT was initiated in September 1999. A blood cell count was obtained only after the second rifampicin monthly dose, and revealed a haematocrit of 31.9%, white cell count (WBC) 3700 per mm$^3$ (48% neutrophils and 1% band forms), and platelets 272,000 per mm$^3$. In June 2000, under regular MDT, the patient had a severe episode of epistaxis. The blood cell count was repeated: the haematocrit was 8.3%; WBC count 1300 per mm$^3$ (28% neutrophils), and platelets 5000 per mm$^3$. The patient was then admitted to the hospital with a diagnosis of pancytopenia. A bone marrow aspirate suggested the diagnosis of aplastic anaemia, which was confirmed by a bone marrow biopsy. Alternative diagnoses such as infectious disease (hepatitis B, HIV and cytomegalovirus infections), paroxysmal nocturnal haemoglobinuria, and B$_12$ and folic acid deficiency were ruled out. Assessment of the likelihood that MDT was causally related to aplastic anaemia was made using the Naranjo adverse drug reaction (ADR) probability scale. The patient scored 6 points (previous conclusive reports of this reaction, 1 point; adverse event after the administration of the suspected drugs, 2 points; no likely alternative causes, 2 points; adverse reaction confirmed by objective evidence, 1 point), which indicates the relationship as ‘probable’.

After numerous platelet and packed red cell concentrate transfusions the patient died from bleeding and nosocomial infection.

Discussion

Aplastic anaemia is a rare and often fatal haematological disease. Up to 74% of cases reported in case series published in the literature are classified as idiopathic. Infections, drugs, solvents and other chemical agents have been associated with aplastic anaemia, but it is difficult to prove whether there is a causal relationship, given the absence of confirmatory cases. In this case, there was a probable association between the fatal case of aplastic anaemia and the use of MDT. Even if we were unable to detect a possible alternative cause, such as unreported exposure to a drug already associated with aplastic anaemia, the patient would still score 3 in the Naranjo scale, which would make the association rank as ‘possible’. As the three drugs were used concurrently, it is not possible simply by applying Naranjo’s scale to assess which one was responsible for the ADR, or if it was a consequence of an interaction between them. Nevertheless, from previous reports in the literature, it is more likely that the severe ADR observed in this patient was due to dapsone.

Dapsone is a drug that is known to be associated with serious haematological ADR, including agranulocytosis, haemolytic anaemia, and, more rarely, aplastic anaemia. A non-fatal case of dapsone-induced aplastic anaemia was reported in 1985 in a patient with lepromatous leprosy who was taking a daily 50 mg dose for about 24 days. Another case was a patient with bullous systemic lupus erythematosus taking a daily dose of dapsone that ranged from 25 to 200 mg over 4 months. Three other cases, all of them fatal, were reported to the Food and Drug Administration (FDA); two of these patients were treated for dermatitis herpetiformis and one for Pneumocystis carinii pneumonia.

We are unaware of reports of aplastic anaemia associated with rifampicin or clofazimine used alone. Haematological ADR that have been recognized to be associated with rifampicin are haemolytic anaemia, which is of allergic origin, and thrombocytopenia. There is a reported association between clofazimine and leucopenia, but a cause-effect relationship has not been shown.
It is of interest to note that aplastic anaemia was detected in our case only after 10 months of the initiation of MDT, that is much later than the two other cases we have information about. In other drug-associated bone marrow toxicity cases, there are two patterns that are recognized and that have implications for the prognosis. Early onset bone marrow toxicity is usually detected during or shortly after drug exposure, may be dose-related, and is usually reversible. Late onset aplastic anaemia does not depend on the dose and duration of exposure, and is irreversible.10,14 – 16

Could this case of aplastic anaemia have been prevented? If regular blood counts had been performed during the first months of therapy, and the results had been complied with, abnormalities could have been detected earlier. In cases of haemolytic anaemia or thrombocytopenia, early diagnosis would probably prevent the occurrence of severe manifestations. Arguably, the same can be said regarding aplastic anaemia. The fact is that regular blood counts will not prevent the occurrence of the ADR. They will only permit earlier recognition of their occurrence. Unfortunately, there is no clear evidence that the prognosis of patients with aplastic anaemia will change. Given the rarity of aplastic anaemia, it is debatable whether regular blood counts in patients under MDT can be recommended on these grounds. However, given that there are other more common MDT-associated hematological ADR, and that blood counts are not particularly complex or costly, it might be sensible to recommend to order these tests every few months perhaps during the first year of treatment. Instructions should be given to all patients under MDT about signs and symptoms that might suggest anaemia, thrombocytopenia and/or neutropenia. An alternative model aiming at early detection of bone marrow toxicity would be early referral for blood counts of patients with one or a set of signs and symptoms, instead of performing such tests in all patients.

References