



Leukopenia induced by anti-tuberculosis treatment

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Abstract

Poor compliance to anti-tuberculosis treatment is sometimes related to its adverse effects. By reporting any unusual or severe treatment related accident, we try to enlarge our background in order to manage better any similar case.

By writing this paper, up further evidence is provided for a better knowledge and management of ATT adverse events. Here we report a case of leukopenia induced by an anti-tuberculosis oral treatment.

Our 43 years old patient was diagnosed with pleural tuberculosis. Biological tests were ordered prior to the onset of the treatment and were all normal. After one month under treatment, he developed hematological and hepatic toxicity signs: Neutropenia, cytolysis and cholestasis. After an onward investigation, rifampicin was identified as neutropenia causal treatment and pyrazinamid was avoided to prevent its hepatotoxicity. The decision of the multidisciplinary staff was to introduce a combination of three drugs: Isoniazid, Ethambutol and Ciprofloxacin during eight months while stopping Rifampicin. Chest X ray exam showed no recurrence of the pleural effusion.

Despite our widened knowledge and long background, identification of the causal molecule is still a challenge in some patients. To restore a second therapeutic protocol with fewer risks of side effects, quinolons may provide a better option than aminosids.

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Keywords: Rifampicine; Side effects; Neutropenia

Abbreviations: TB: Tuberculosis; ATT: Anti-Tuberculosis Treatment; WBC: White Blood Cells; ULN: Upper Limit of Normal; G-CSF: Granulocyte-Colony Stimulating Factor

Background

Adverse effects under Anti Tuberculosis Treatment (ATT) are various, some of them are frequent and some others may become life threatening.

When they occur, the first challenge is to identify the causal agent among the association of ATT. Case report reviewing may help physicians to avoid drugs already known to induce a similar side effect. To deal with such case, the classic management usually suggested is to re-introduce one-by-one the ATT starting

with the less harmful ones. The second challenge after suppression of the causal molecule is to keep the patient on a treatment that guarantee a bactericidal effect and to minimize the therapeutic disruption.

By writing this paper, up further evidence is provided for a better knowledge and management of ATT adverse events. Here we report a case of leukopenia induced by an anti-tuberculosis oral treatment.



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Case report

A 43 years old man was diagnosed with pleural Tuberculosis (TB). The diagnosis was established using direct sputum smear microscopy and positive culture in the pleural liquid. Biological tests were ordered prior to the onset of the treatment and were all normal. Drug susceptibility test was performed for major anti TB medicines: Rifampicin, isoniazid, Ethambutol and Pyrazinamid. Bacilli were susceptible to all medicines. Our patient was put on a combination of Isoniasid 300 mg once a day, Rifampicin 600 mg once a day, Pyrazinamid 1500 mg once a day and Ethambutol 1200 mg once a day.

After one month he developed leukopenia (WBC=2700/mm³), neutropenia (720/mm³) with high levels of transaminases (10xULN) and cholestasis (10xULN). The patient was asymptomatic and the physical examination revealed only conjunctival jaundice. Blood tests were checked repeatedly every week until they normalized (20 days later). He was put on a non hepatotoxic background regimen while stopping Pyrazinamid.

Details of re-introduction regimen:

Day 1: Ethambutol was introduced and biological tests two days after were normal.

Day 4 onwards: Isoniazid was introduced according to the recommended dose of the acetylation test. Blood cell count was normal.

Day 10: Ciprofloxacin was introduced with normal blood cells count

Day 17: Rifampicin was introduced. Two days after, neutrophils dropped from 1600 to 600 cells/mm³

ATT was interrupted once more. Leukoneutropenia was related to Rifampicin as a causing agent. The decision of the multidisciplinary staff was to introduce a combination of three drugs: Isoniazid, Ethambutol and Ciprofloxacin for a duration of eight months while stopping Rifampicin. Chest X ray exam showed no recurrence of the pleural effusion.

Discussion

Drug-related neutropenia

Hematological disorders arise through a variety of mechanisms and etiologies. Drug-induced hematological disorders can span almost the entire spectrum of hematology, affecting red cells, white cells, platelets, and the coagulation system [1]. Drug-induced neutropenia can occur in association with various analgesics, psychotropics, anticonvulsants, antithyroid drugs, antihistaminics, non-steroidal anti-inflammatories, antimicrobials, cardiovascular drugs, and, as expected, with chemotherapy drugs. Immune-mediated mechanisms are associated with some drugs which act as haptens inducing antibody formation against neutrophils after the first systemic administrations. Soon or late after, a Gell-Coombs type II hypersensitivity reaction takes place leading to lysis of neutrophils.

Clozapine accelerates apoptosis of neutrophils, and propylthiouracil causes complement mediated destruction of neutrophils. Drugs such as β -lactam antibiotics, carbamazepine, and valproate have a dose-dependent inhibition of granulopoiesis. Drugs with direct toxic effects on myeloid precursors include ticlopidine, bulsufan, methimazole, ethosuximide, and chlorpromazine.

Imputability of anti-tuberculosis treatment in neutropenia

In a review of literature, authors reported that the incidence rate of agranulocytosis due to anti-tuberculosis drugs was estimated at 0.06% [2,3]. In the context of anti-tuberculosis therapy, neutropenia is recognized as being most frequently happening due to isoniazid [4-6], but it can be related to rifampicin [7-9], ethambutol [10,11] and streptomycin prescription [12]. In the vast majority of cases during anti-tuberculosis therapy, the occurrence of neutropenia is due to a single agent [13]. By re-challenging the patient with each antibiotic individually, the offending drug can be identified, subsequently omitted and therapy completed using an alternative first or second line antibiotic if necessary. The occurrence of neutropenia to more than one anti-tuberculosis antibiotic in the same individual has been described few times [2,3,13-15]. Usually, medical staff try to suppress the molecule causing the side effect and come up with a combination of first line or second line anti-tuberculosis molecules. This combination must guarantee a bactericidal anti-tuberculous action and prevent emerging drug-resistant strains. Managing cases with neutropenia related to more than one molecule is problematic since therapeutic options of efficient combinations get narrowing. Such cases were published. In several cases, medical teams maintained classic drugs and associated prednisolone or G-CSF treatment [13,15] to keep normal count of blood cells.

Difficulty of our case

After receiving only one month of anti-tuberculosis treatment, our patient showed an hepato-biliary toxicity and a severe haematological accident. We were forced to establish a well-tolerated treatment regimen that avoids hepato-toxic molecules (Pyrazinamid, Rifampicin) and potential neutropenia inducers (Rifampicin, Isoniazid and Ethambutol). But also, that therapeutic regimen must keep as much as possible the major bactericidal molecules, guarantee the eradication of quiescent intra-macrophage mycobacteria and prevent the development of multi-resistant strains of Mycobacterium Tuberculosis. We choose to stick to Tunisian National Guidelines of anti-TB treatment that recommend Pyrazinamid cessation after a severe hepatic cytolysis under quadruple anti-TB treatment. Ciprofloxacin is known as a second line anti-TB, as most quinolones. It was chosen because of its availability in Tunisia.

Severity

Severity of this accident and its repercussion on the treatment course is to clarify. Neutropenia and/or leukopenia can arise and keep mild to moderate even with no treatment cessation [16]. Lee's retrospective study described the frequency, the severity and the outcome of patients who were diagnosed with tuberculosis, whose count of blood cells showed leukopenia after administration of first-line anti-tuberculosis medication [17]. From a group of 825 patients with no anterior hematological disease, 185 patients developed leukopenia. The same medications were continued in 109 of these patients despite the development of leukopenia on a physician's decision. There was no statistical difference in the lowest leukocyte count between the two groups (cessation group VS continuation group). Out of these 109 patients who continued on their medication, leukopenia resolved spontaneously in 32 (29.4%) patients and persisted in 77 (70.6%) during medication, then remained to normal rates after completion of the treatment regimen [17]. The lowest leukocyte count was in the range of 2,000–2,999 cell/ μ l in 30 patients (16.2%) and 1,000–1,999 cell/ μ l in 3 patients (1.6%).

No clinically significant episode of infection developed in any of these 3 patients with the lowest leukocyte counts [17]. Authors concluded that the development of mild leukopenia during anti-tuberculosis treatment with first line drugs was relatively common. However, the physicians could safely continue administering the same drugs as long as the patient did not have any other underlying diseases, which might cause leukopenia.

Conclusion

Side effects related to ATT are various, unexpected and sometimes severe. Despite our widened knowledge and long background, identification of the causal molecule is still challenging in some patients. To restore a second therapeutic protocol with fewer risks of side effects, quinolons may provide a better option than aminosids.

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