

Agranulocytosis induced by anti-tubercular drugs, Isoniazid (INH) and Rifampicin (R) – A rare case report

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Abstract

Background: Tuberculosis is a chronic granulomatous infection that has caused a high morbidity and mortality over decades. Tuberculosis treatment has many side effects due to long duration and compliance problems that might require cessation of treatment. Agranulocytosis is a serious idiosyncratic drug reaction characterized by severe leukopenia and a very rare side effect of anti-tubercular treatment mainly due to first line drugs namely Isoniazid (INH) and Rifampicin (R). The current study presents the case of a patient with Isoniazid and Rifampicin induced agranulocytosis.

Conclusion: Isoniazid and Rifampicin are the first line anti-tubercular drugs. Agranulocytosis is most commonly due to drug toxicity but isoniazid and rifampicin are very rare causes of agranulocytosis. Pulmonologists and physicians must be aware of this complication induced by Rifampicin and Isoniazid. The distinction must be drawn between the small risk of neutropenia that seems on present evidence to be benign and agranulocytosis which is fatal if left untreated and unrecognized. Discontinuation of the offending drug can reverse the neutropenia.

Keywords: Isoniazid, Rifampicin, Agranulocytosis.

1. Introduction

Agranulocytosis is also known as agranulosis or granulopenia, is an acute condition involving a severe and dangerous leukopenia (lowered white blood count) most commonly of neutrophils causing a neutropenia in the circulating blood.[1] Agranulocytosis is a serious idiosyncratic drug reaction and very rare side effect of anti-tubercular treatment and mainly due to isoniazid (INH), Rifampicin (R). Isoniazid (INH) and Rifampicin (R) are the first line drugs to combat tuberculosis. Here we publish a case of Agranulocytosis due to Isoniazid (INH) and Rifampicin (R).

2. Case report

A 55 years old female patient with a known case of pulmonary tuberculosis on treatment, presented with dental pain. CT scan was done and revealed a multi-loculated thick walled collection in supraclavicular region and multiple conglomerate lymph nodes over para-tracheal region. Cervical biopsy of granulomatous lesions suggested tuberculous lymphadenitis.

Four drug regimen (Isoniazid (H): 300mg/day; Rifampicin (R): 450mg/day; Ethambutol (E): 1000mg/day; Pyrazinamide (Z): 1500mg/day) was continued according to patient's weight and national guidelines. After 6 weeks, patient developed new onset of fever associated with sore throat. Although blood profile were normal at start of therapy, white blood cell (WBC) of $5.40 \times 10^3/\mu\text{L}$, neutrophil count of 68%, Lymphocytes 20%, eosinophils 2%, hemoglobin of 10.7 g/dL, and platelet of $222 \times 10^3/\mu\text{L}$. After 6 weeks patients neutrophils counts began to decrease.

Report at 6 weeks (WBC: $2.6 \times 10^3/\mu\text{L}$, neutrophil: 2%, lymphocytes: 72%, eosinophils: 0%, hemoglobin 11.2 g/dL, and platelet of $297 \times 10^3/\mu\text{L}$) revealed agranulocytosis with neutropenia. After stop-start trial, Isoniazid and Rifampicin were identified as possible cause of neutropenia and were removed. Subsequently, patient was started on alternate regimen; (Ethambutol: 1000mg/day, Linezolid: 600mg/day, Streptomycin: 1gm/day, Ethionamide: 250mg/day). After 5 days of stopping the Isoniazid and Rifampicin and starting of above alternate regimen the neutrophil counts were increased (WBC: $9200/\mu\text{L}$, neutrophil: 72%, lymphocytes: 20%, eosinophils: 0%). After One month post-treatment, the sputum smear revealed no acid-fast bacilli. There were no clinical or laboratory abnormalities during follow up examination. The ATT present regimen was continued without further complications.

3. Discussion

Agranulocytosis is most commonly due to drug toxicity but Isoniazid and Rifampicin are very rare causes of agranulocytosis. Isoniazid is a prodrug which acts by inhibiting the synthesis of mycolic acid, a unique constituent of myobacterial cell wall. Rifampicin is a derivative of rifamycin B, isolated from *streptomyces mediteranei*. It acts by inhibiting bacterial DNA-dependent RNA polymerase thus inhibiting RNA synthesis.[2] Umeki et al[3] reported that the incidence rate of neutropenia and agranulocytosis due to antituberculosis drugs were observed in 10.9% and 3.96%, respectively. Shishido et al[4] reported that the incidence rate of agranulocytosis due to antituberculosis drugs was estimated at 0.06%. Therefore, it is important to detect neutropenia earlier and treat it in a patient taking antituberculosis drugs.

Our case is the agranulocytosis induced by isoniazid and rifampicin. According to the previous reports 4 and 5, neutropenia can be developed in a patient who is treated with antituberculosis drugs during a few months after starting administration. In administering antituberculosis drugs including isoniazid and rifampicin, as in our case, we should regularly make a close monitoring of the CBC to avoid serious events.

4. Conclusion

In most cases of drug-induced agranulocytosis, a spontaneous regeneration of the myeloid cells occurs after 5–9 d.³ In this case the patient recovered within 5 days after stopping rifampicin and isoniazid.

Pulmonologists and physicians must be aware of this complication induced by Rifampicin and Isoniazid. The distinction must be drawn between the small risk of neutropenia that seems on present evidence to be benign and agranulocytosis which is fatal if left untreated and unrecognized. Discontinuation of the offending drug can reverse the neutropenia.

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