

Treatment with High Dose Rifampicin in Tuberculous Meningitis: A Case Report

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Abstract

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Introduction : Tuberculous meningitis continues to be associated with considerable mortality and morbidity. A randomized comparison of higher-dose intravenous rifampicin (approximately 13 mg/kg per day) versus a standard oral dose in adults with tuberculous meningitis showed that mortality among patients who received higher intravenous dose was 50% lower than those who received the standard dose.¹ While there are other contradictory results regarding the use of high-dose rifampicin in patients with tuberculous meningitis.

Method : We hereby report a case of a 20-year-old female patient presented with a history of fever, palpable neck lymph nodes and headache since 1 month before admission. Neurological examination revealed nuchal rigidity without other neurological deficits. Head MRI with contrast showed meningitis with tuberculoma in the right parietal lobe +/- 0.4 cm and neck ultrasonography showed multiple lymphadenopathy with 1 cm in diameter. Cerebrospinal fluid examination revealed tuberculous meningitis. The patient had been treated with rifampicin 450 mg, other tuberculosis regimens, levofloxacin, and dexamethasone. After one week of treatment, the patient developed generalized seizure and deterioration of consciousness. Imaging re-evaluation showed multiple acute infarction in the cortical and subcortical left frontal lobe, bilateral insula, bilateral temporal lobe, right parietal lobe to the corpus callosum, more prominent leptomeningeal contrast, and communicating hydrocephalus. Ventriculoperitoneal shunt was done. The patient was then treated with a higher dose of Rifampicin (15 mg/kg ~ 900 mg) and showed improvement after 2 weeks of treatment without any abnormal laboratory findings.

Conclusion : The usage of high dose rifampicin is still controversial. From this case we can conclude that by giving high dose rifampicin, the patient has a better outcome without any significant side effects. Thus, we support the hypothesis of using high-dose rifampicin in patients with tuberculous meningitis that does not respond to the standard treatment.

Introduction

Tuberculous meningitis (TBM) is one of the most common form of central nervous system infection with with a high frequency of neurologic sequelae and mortality if not treated promptly. TBM is typically a subacute disease with symptoms that may persist for weeks before diagnosis. One-third of the world's population is infected with latent TB.^[1] These individuals are not clinically affected but carry a lifetime risk of 10% for developing active disease. There were an estimated 8.6 million incident cases of TB globally in 2012, with 1.3

million deaths. A total of 22 high-burden countries accounted for 81% of all estimated incident cases. TB is the leading cause of death in people living with HIV, accounting for approximately 1 in 5 deaths. The largest share of the global burden of TB is in the Southeast Asia, Western Pacific, and African regions.^[2]

This report describes a case of a 20-year-old female with a diagnosis of tuberculous meningitis. Owing to the complexity of the case, the patient was treated with a higher dose of Rifampicin to reach a therapeutic amount without any known complications.

Case Report

A 20-year-old female presented with intermittent headache since 1 month before admission. Fever, frequent vomiting, and palpable lymph node were noticed 3 weeks ago. No other systemic features were present. Her past medical history was unremarkable. On neurological examination, the patient was conscious and alert with a GCS of 15. Nuchal rigidity was positive with cranial nerve functions were intact without any motor deficits. General examination found multiple immobile cervical nodules with +/- 1 cm in size. No other neurological deficits was found. Brain MRI with contrast showed meningitis and tuberculoma with a

diameter of +/- 0.4 cm and neck ultrasonography revealed multiple lymphadenopathy of the neck with a diameter of +/- 1 cm, and colloid cyst of the right thyroid lobe. Laboratory investigations including full blood count, liver function, renal function, electrolytes, HIV and autoimmune were unremarkable except for positive IGRA spot TB, high CRP levels and ESR count of 65 mm/hours. Cerebrospinal fluid (CSF) examination revealed tuberculous meningitis (Figure 1). After diagnosis, the patient was then treated with Rifampicin 450 mg PO, Isoniazide 300 mg PO, Ethambutol 1000 mg PO, Pyrazinamide 1500 mg PO, Dexamethasone 5 mg IV, and Levofloxacin 750 mg IV.

| Test | Result | Reference Range |
|-------------------------------------------|------------------|------------------|
| Macroscopic | | |
| Color | Colorless | Colorless |
| Clarity | Clear | Clear |
| Clot | Negative | Negative |
| Sediment | Negative | Negative |
| Microscopic | | |
| Cell Count | 509 | < 10 |
| PMN | 3 % | |
| MN | 97 % | |
| Random Blood Glucose | 85 mg/dL | < 200 mg/dL |
| Chemicals | | |
| Nonne | Positive | Negative |
| Pandy | Positive | Negative |
| Glucose | 14 mg/dL | 40 – 76 mg/dL |
| Protein (Quantitative) | 1.92 g/dL | 0.15 – 0.45 g/dL |
| Microbiology | | |
| India ink direct smear | Cryptococcus (-) | |
| Bacteria gram stain | Negative | |
| Acid Fast Bacilli direct smear (ZN Stain) | Negative | |

Figure 1. Cerebrospinal fluid results showing tuberculous meningitis

After one week of treatment, the patient developed generalized seizure with deterioration of consciousness. Upon physical examination, we found GCS score E3M5V2 with anisocoric pupil 3 mm/5mm and nuchal rigidity. Imaging re-evaluation with MRI contrast was done and showed more prominent leptomenigeal contrast and hydrocephalus. Chest X-Ray was performed and revealed no abnormalities. Ventriculoperitoneal shunt was performed for the hydrocephalus and the dose of Rifampicin was increased to 900 mg (15 mg/kg) per oral. After 2 weeks of treatment, the patient showed improvement with full consciousness and no headache.

Laboratory evaluation after the higher dose was given showed no abnormalities.

Discussion

Patients with TBM develop typical symptoms and signs of meningitis including headache, fever, stiff neck, although meningeal signs may be absent in the early stages. The duration of symptoms before presentation ranges from several days to several months. Cranial nerve (CN) palsies, hemiparesis, paraparesis, and seizures are common and should raise the possibility of MTB as the etiology of meningitis.

Patients often present with multiple CN palsies, most commonly involving CN III, VI, and VII. Chest X-ray is suggestive of active or previous pulmonary TB in approximately 50% of cases.

Contrast-enhanced brain CT or MRI can help support a diagnosis of TBM because of the high frequency of abnormalities on initial presentation. The most common findings in descending order are meningeal enhancement, hydrocephalus, basal exudates, infarcts, and tuberculomas. Infarcts occur as a result of vasculitis affecting the vessels of the Circle of Willis, the perforating branches of the middle cerebral artery, and the vertebrobasilar circulation.^[4] In the discussed study, the disease progressed from stage 2 to stage 3 TBM. The condition of the patient deteriorated significantly proving the progression of the disease. CSF examination is the mainstay in the diagnosis of tuberculous meningitis. CSF lymphocytosis, elevated proteins and reduction of CSF glucose by 40% than the concentration in blood serum suggest the diagnosis. CSF sample is still the best standard diagnostic tool in tuberculous meningitis. Treatment of MTB begins with a four drug regimen including isoniazid, rifampicin, pyrazinamide, and ethambutol

which will be given for 2 months followed by rifampicin and isoniazid alone for about 6-9 months.

An Indonesian randomized controlled trial showed that oral administration of 750 mg and 900 mg rifampicin (17 and 20 mg/kg) daily resulted in geometric mean AUC₀₋₂₄ values in plasma that are approximately comparable with geometric mean exposure achieved after 600 mg (13 mg/kg) rifampicin IV during the first days of TBM treatment. Reversible liver function disturbance as reflected by increased plasma ALT values was common but was transient with continuation of treatment.^[5] After given the standard regimen of TBM, the patient showed a progression of the disease with deterioration of consciousness which leads us to the increase dose of rifampicin with caution and repeated liver function test to evaluate the common side effects of rifampicin to the liver. Early diagnosis and commencement of specific therapy determines survival of the patient. Although the usage of high dose rifampicin is still controversial, this case showed that giving increase dose of rifampicin might decrease mortality rate and increase survival rate in patients with MTB without significant side effects.

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