http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v11i2.06

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Multi Drug Hypersensitivity Syndrome (MDHS) in a Case of Tubercular Meningitis- A Case Report

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Abstract
Multi drug hypersensitivity syndrome (MDHS) is often challenging as it endangers patient compliance as well as treatment failure. It develops due to dysregulated cell mediated immunity that results in drug hypersensitivity reactions (DHR) and is characterized by severe exanthems or drug rash with eosinophilia &systemic symptoms (DRESS).
DHR is very common among patients on anti-tubercular therapy (ATT) for Pulmonary as well as Extra-Pulmonary Tuberculosis (EPTB), particularly with 1st line anti tubercular drugs like ethambutol, pyrazinamide, Rifampicin & Isoniazid. But reporting of MDHS has been low in India, despite having high burden of tuberculosis.
A 13-year-old female child, on ATT for Tubercular Meningitis (TBM), presented to us with DHR, was found out to have MDHS and was managed tactfully with an alternate regimen.
TB meningitis is a severeform of EPTB that needs aggressive treatment to avoid neurological complications & sequelae.
For these patients, it was crucial to identify the offending drug as soon as possible and restart a suitable alternate regimen in order to reduce morbidity and mortality.
Keywords: *MDHS, EPTB, TB-Meningitis, ATT.*

Introduction

Multiple-drug hypersensitivity syndrome (MDHS) is characterised by DHR to two or more chemically& pharmacologically unrelated drugs, where their involvement has been proven by skin tests or in vitro tests[1, 2]. It is a distinct entity with three varieties i.e. simultaneous, sequential and distant.

In simultaneous variety, sensitization to more than one drug is seen usually at the beginning of therapy, when being used concurrently. This is often due to therapy with fixed drug combinations like ATT. In sequential variety, a second, true DHR directed against the alternative drug may develop whereas in distant variety, the interval between 1st& 2nd DHR may range between 2-20years.[3]

Clinical studies of MDH[1,2,4,5,6] have shown that the initial manifestation can be exclusive severe exanthema or erythroderma rather than DRESS.

History of drug allergy[7], family history of drug allergy[8] & autoimmune disorders are often associated with MDHS.

This is a case report of multiple-drug hypersensitivity syndrome (MDHS) to multiple 1st-line anti-tubercular drugs like isoniazid (H), ethambutol (E), and pyrazinamide (Z) in a case of TB meningitis.

Patient information & History

A 13-year-old female child from Bargarh, Odisha, presented to the emergency department with complaints of generalized body rash, oral ulcer& myalgia for past 10 days.

The patient was being treated for clinically diagnosed TB-Meningitis at the VIMSAR Pediatric Department in Burla.ATT was started according to the pediatric weight band (30–39 kg) under National Tuberculosis Elimination Program. The drug regimen contained 2 tablets of 3-FDC-P, 2 tablets of Adult 4-FDC, and 2 tablets of Ethambutol 100 mg (rifampicin 450 mg, isoniazid 250 mg, pyrazinamide 1100 mg, and ethambutol 750 mg). After 3 weeks of anti-TB treatment, the patient developed generalized itching, erythematous patchy skin rash, and crack ulcers over the lips and mouth gradually over 8 days.

There was no past history of Pulmonary Tuberculosis or ATT intake, no known food or drug allergies and no history of drug allergy in family as well

On Examination

The vitals of the patient were stable. She was found to have multiple dusky erythematous skin lesions involving approximately 44% of total body surface area, oral ulceration with haemorrhagic crusting over both lips &multiple erythematous painful erosions with sloughing present in buccal mucosa. Other system examinations were unremarkable except for reduced visual acuity in both eyes ($VA_{6/14}^{6/12}$).

Laboratory Findings

Complete blood count showed a mild eosinophilia. Serum transaminases levels were mildly increased. Other blood parameters were normal. Anti Nuclear Antibody Profile revealed a borderline ds DNA and a higher anti-centromere antibody level.

Management

In concordance with dermatologist's opinion, ATT was kept on hold& patient was started with oral Prednisolone (0.5mg/kg/day), tab Levocetrizine, topical steroid & emollients.

After 5 days, when the skin lesions had subsided, the drug provocation test was triedwith individual anti-TB drugs in the H-R-Z-E sequence. Standard drug provocation test procedure was followed.

Drugs were tried at lowest possible dose and gradually the dose was increased in every 12 hour after monitoring the response. Whenever patient developed reaction, the procedure was called off till there was improvement in cutaneous symptoms. The patient developed exanthema to Isoniazid, Pyrazinamide & Ethambutol even at lowest possible doses. However she tolerated Rifampicin (R).

Then she was tried with Levofloxacin (Lfx) & Cycloserine (Cs) along with Rifampicin (R).The patient tolerated these three drugs well and was discharged with this modified regimen containing Rifampicin (R), Levofloxacin (Lfx) & Cycloserine (Cs) for a period of 1 year with advice of frequent follow ups.

Outcome

The patient did not develop further cutaneous complications, stayed compliant to therapy during the course. She clinically improved after completion of the therapy.

Discussion

MDHS influences the choice of drugs, resulting in a negative impact on the quality of medical care.

MDHS with multiple 1st line ATT is unusual.

TBM is a severe form of EPTB with high morbidity & mortality andthe use of steroids to manage severe skin reactions without ATT is not advisable as it may worsen the underlying disease. Among the 2nd line ATT, ethionamide (Eto) was not preferred as it is related to Isoniazid & Linezolid was not considered as the patient had poor visual acuity ($VA_{6/14}^{6/12}$).

Cycloserine was preferred because it is not chemically related to the drugs that caused skin reactions and has excellent CNS penetration.[9]

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10. Ethical Consideration: Informed consent was taken from guardian of patient regarding drug provocation test and publication of the data in journal.