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Maculopapular Rash in a Case of Sacroiliac Joint Tuberculosis, Induced by Pyrizinamide: A Rare Side Effect and a Concern of Compliance

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Abstract
Pyrazinamide is primarily used in the treatment of active tuberculosis as a first line agent. Gastric adverse effects due to Pyrazinamide have been commonly reported. On the contrary, skin rash and photosensitivity as a side effect are seldom observed. We reported a case of maculopapular rash due to Pyrazinamide in a patient on anti-tuberculosis treatment (ATT) for right sacroiliac joint tuberculosis, using three questionnaire systems. The patient developed maculopapular rash on receiving combination ATT. The rash disappeared after discontinuation of the suspected drug. The patient was rechallenged with pyrazinamide, which led to reappearance of rash. The causality and severity were assessed using the Naranjo algorithm, WHO-UMC causality assessment score and Hartwig scale. In developing countries, musculoskeletal tuberculosis has a high prevalence with pyrazinamide as the first line drug. Since rare adverse effects like skin manifestations may lead to non compliance of the patient to the therapy. Hence, awareness, early detection and timely management may hold prime importance.
Keywords: *Pyrazinamide, Maculopapular rash, sacro-iliac tuberculosis, Naranjo algorithm, WHO-UMC causality assessment scale, Hartwigs scale.*

Introduction

Pyrazinamide belongs to the antimycobacterial class of medications. It is among the first line anti-tubercular drugs, along with isoniazid, rifampicin, ethambutol and streptomycin for active tuberculosis.[1] It is not generally recommended for latent tuberculosis.[2] Common adverse effects include GI effects (nausea, vomiting, anorexia), mild arthralgia and myalgia, hyperuricemia and sider zoblastic anemia.[2] More serious side effects include gout and hepatotoxicity. Maculopapular rash and photosensitivity are rare due to pyrazinamide.[3] The term maculopapular rash typically implies an acute and generalized eruption.

The body's hypersensitivity to a drug or its metabolite most commonly manifests in the form of a maculopapular rash which is a type IV or delayed cell-mediated reaction.[4] Both CD4+ and CD8+ T cells producing type 1 and type 2

cytokines and endowed with cytotoxic properties are involved in non-immediate allergic drug reactions.[5] The maculopapular rash is suspected to be due to drugs when it appeared within 4-12 days on the start of administering the new medication. It may be confirmed when you discontinue the usage of the drug and the maculopapular rash disappears within a certain amount of time. It reappears once the drug that you have an adverse reaction to is being readministered.

Case Report

A 30 year old male residing at Tanda in himachal Pradesh belonging to the lower middle class family visited Guru Nanak Dev Hospital, Amritsar (tertiary care centre) with a complaint of lower backache since last six months along with loss of appetite , loss of weight over a period of past six months. Initially the patient was examined for lower backache, and xray was done (figure 1) and accordingly patient was managed conservatively on OPD basis. The patient revisited the OPD after one month with aggravated lower backache with the symptoms and pain just medial to the posterior superior iliac spine on right side. On clinical examination, sacro-iliac joint involvement was observed and a differential of musculoskeletal TB was made and patient was sent for sputum examination, chest x-ray & ESR/CRP. The sputum was examined as per Revised National Tuberculosis Control Programme (RNTCP) by Zeihl-Neelson (ZN) staining for acid-fast bacillus (AFB) and were found to be negative. Chest radiograph showed signs suggestive of previous tubercular involvement. The ESR and CRP values were markedly raised. The patient was then sent for MRI lumbo sacral spine and pelvis and MRI was suggestive of tubercular involvement of right sacro-iliac joint (figure 2). Based on the clinical and radiological findings observed, the patient was diagnosed as a new case of extra pulmonary tuberculosis and started on antitubercular regimen (Category 1) in intensive phase, according to his weight (61kg) on OPD basis. Category I antituberculosis therapy includes isoniazid 600 mg, rifampicin 450 mg, pyrazinamide 1500 mg and ethambutol 1200 mg. The patient returned to the OPD on Day 5 of starting ATT with generalized maculopapular rash predominantly on shoulders and trunk (figure 3). A diagnosis of antitubercular drug-induced maculopapular rash was made. The Anti Tuberculosis Treatment was withdrawn and the patient improved.

A rechallenge with the individual tuberculosis drugs one by one was conducted. When pyrazinamide was reintroduced, the patient experienced return of maculopapular rash on same regions of the body. Therefore, pyrazinamide was stopped and remaining Anti-Tuberculosis Treatment drugs were continued with the addition of oral anti-histaminics and the patient was kept under close observation for evaluation. On stopping pyrazinamide, rash started subsiding. Hence, suspected drug (pyrazinamide) was stopped as per the national RNTCP guidelines.[6] He tolerated isoniazid, rifampicin, and ethambutol but on addition of pyrazinamide, rashes reappeared in the same part of the body and on withholding the suspected drug, there was complete absence of rash all over the body. He is on regular follow-up with disappearance of rash as well as signs and symptoms of tuberculosis. We carried out the causality assessment according to Naranjo algorithm[7] and WHO-UMC[8] causality assessment scale and severity assessments according to Hartwig scale[9]. The causality assessment revealed a “probable” association (Naranjo score 7 & WHO-UMC Probable/likely) between the ADR and pyrazinamide. The severity was found to be moderate (Hartwig Level 3).

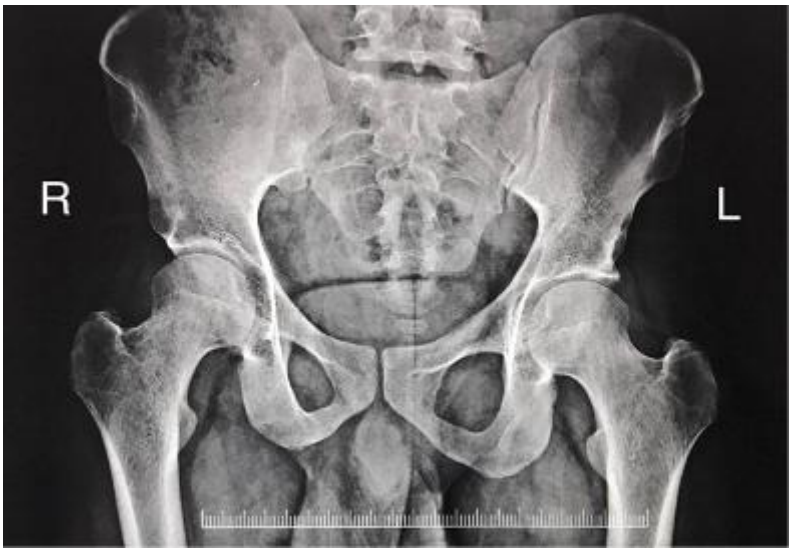

Figure 1 - X-ray pelvis with both hips showing right sacroiliac joint involvement

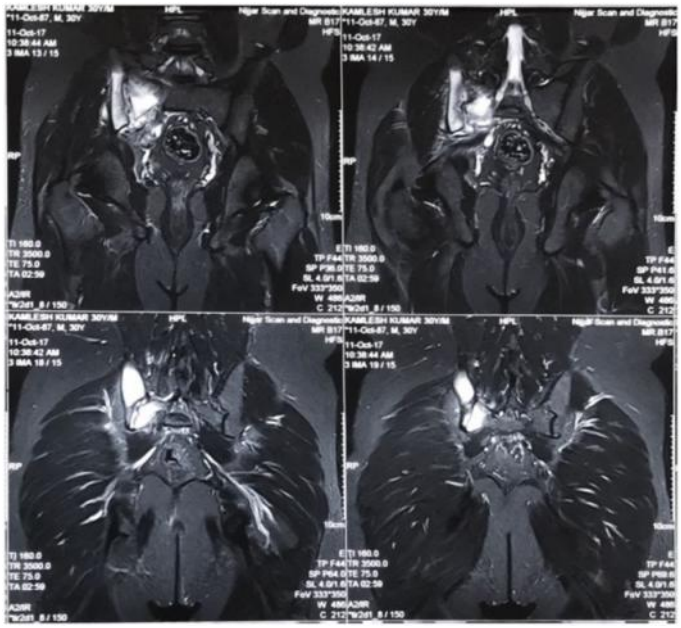

Figure 2 - MRI showing sacroiliac joint pathology

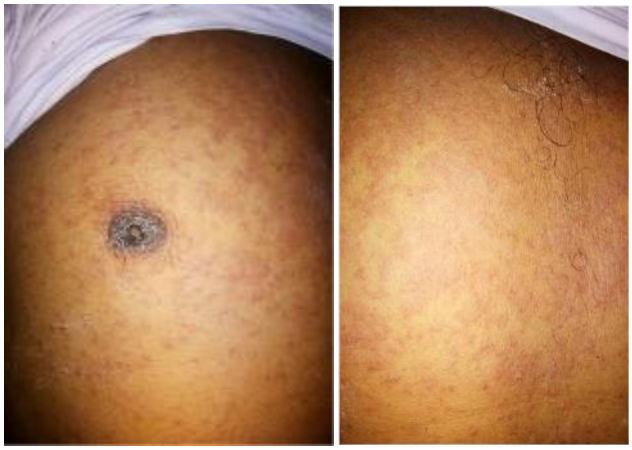

Figure 3 - Images showing maculopapular rash over trunk

Discussion

The term maculopapular rash implies a skin eruption of flat and raised lesions. The rash is usually bright red in color and the skin may feel hot with burning sensation or itch. The whole of the skin surface may be involved, though the face is often spared.[10] Histopathological examination shows a superficial, mainly perivascular, mononuclear infiltrate composed of CD3+ T cells, neutrophils and some eosinophils. CD4+ T cells are predominantly noted perivascularly in the dermis, whereas both CD4+ and CD8+ T cells are equally distributed at the dermoepidermal junction zone adjacent to basal keratinocytes.[5] Dermatological adverse effects due to pyrazinamide are rare. Another type of hypersensitivity seen with pyrazinamide is hypersensitivity hepatitis. Hypersensitivity side effects have been reported rarely. At least one case of hypersensitivity hepatitis has been reported, in addition to a case of erythema multiforme.[11] A 59-year-old female experienced hypersensitivity hepatitis coincident with pyrazinamide therapy. Drug-induced hepatitis was suspected. On day 1, her tuberculosis treatment was withdrawn and the patient improved. When pyrazinamide was reintroduced, the patient experienced acute malaise, fever, arthralgia, perioral paresthesia, and vomiting. Twelve hours later, laboratory tests showed elevated AST. In our case, the patient developed the rash on the 5th day after initiating antituberculosis therapy and disappeared after two days when the drug (pyrazinamide) was stopped. The rash again reappeared when pyrazinamide was restarted. The causal relationship between the drug and the ADR was found to be probable (WHO-UMC probable/likely). The management of such reactions needed discontinuation of the suspected drug and management of symptoms, if any.[6] In this study, the suspected drug was stopped immediately following the ADR and antihistamines were added to manage the symptoms. The severity assessment revealed the ADR to be moderate with Hartwigs Level 3, suggesting that the suspected drug should be withheld, discontinued, otherwise changed. According to the revised RNTCP Guidelines (2017) for extra pulmonary tuberculosis with bone and joint involvement, a person who comes to the outpatient with localized back pain for more than 6 weeks with tenderness on examination of the spinous processes, fever and weight loss, with or without signs of spinal cord compression is a presumptive case of spinal TB.[12] All cases should undergo chest X-ray, HIV test, MRI spine and Biopsy of the lesion. The treatment protocol includes- 2RHZE/10RHE. Duration of total treatment is 12 months (extendable to 18 months on a case-by case basis).

Conclusion

As we know Pyrazinamide is a commonly used drug in tuberculosis which is also the most common infection in India. The rare adverse reactions like maculopapular rash due to Pyrazinamide may be responsible for noncompliance which can lead to the anti tubercular treatment failure. The offending drug should be excluded from the regimen, without changing the dosage and timing of other drugs. The patients undergoing treatment on an outpatient basis should be counselled for the early recognition and reporting of adverse manifestations. The aim of this case report of rare adverse manifestations of pyrazinamide is to bring these ADRS in the knowledge of attending doctors and may lead to increase compliance of patients.

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