An Unusual Case of Pyrazinamide Induced Erythema Multiforme in A Patient of Tuberculous Meningitis: A Case Report

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Abstract: Erythema Multiforme (EM) is a skin condition having various aetiologies including drugs. Pyrazinamide, one of the 1st line Antitubercular drugs (AKT) is known to cause various adverse effects. However, reports of Pyrazinamide induced EM are rare. In the below mentioned case, the patient had presented to Dermatology Department with skin lesions after taking AKT for two months prescribed for Tuberculous Meningitis. These AKT drugs were withdrawn and reintroduced one by one. Rechallenge was performed with Pyrazinamide. The lesions had reappeared with reintroduction of Pyrazinamide. Thus the diagnosis of Pyrazinamide induced EM was confirmed. This adverse drug reaction (ADR) is also reported to the WHO-Uppsala Monitoring Centre via Vigiflow Base. Key Message: Skin hypersensitivity reactions to Pyrazinamide can be rare but serious. They usually begin after 4-6 weeks of treatment. They need to be recognized early and the physician shout be watchful once the patient commences AKT. [Haiya S NJIRM 2017; 8(3):153-155]

Key Words: Erythema Multiforme, AKT, Pyrazinamide, Rechallenge.

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Introduction: Pyrazinamide is a 1st line drug used for the treatment of tuberculosis, co-administered along with Isoniazid, Rifampicin, Ethambutol and Streptomycin. Pyrazinamide is known to cause various adverse effects involving different body systems. Photosensitivity, pellagra, and skin rashes have been reported on rare occasions[1]. These skin reactions appear to be prostaglandin-mediated[2].

Erythema Multiforme (EM) is an acute, self-limiting, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers[3]. Drug-induced EM is reported with many antimicrobial and antipyretic medications[4]. However, AKT induced EM has not been reported much in the literature. Thus, we present a case of Pyrazinamide, being the suspected drug from the AKT regimen to be responsible for EM.

Clinical Case Details: A sixty-five years old male, diagnosed with Tuberculous Meningitis and taking AKT since two months, presented to the Dermatology OPD of a Tertiary Care Teaching Hospital with chief complaints of skin lesions over the dorsal aspect of both feet, associated with itching since 5 days. These lesions were multiple, raised, reddish, gradually increasing in size and spreading towards the legs & buttocks (Fig. 1) along with swelling in both feet & ankle. He also had rashes in both arms (Fig. 2).

Fig. 1 Lower Limbs showing Targetoid Lesions at the time of admission.

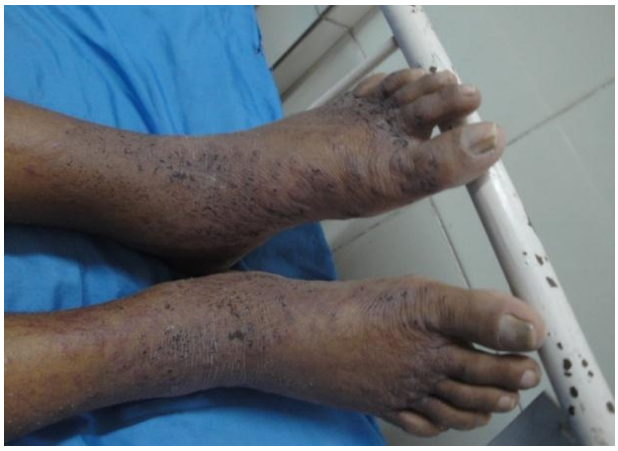
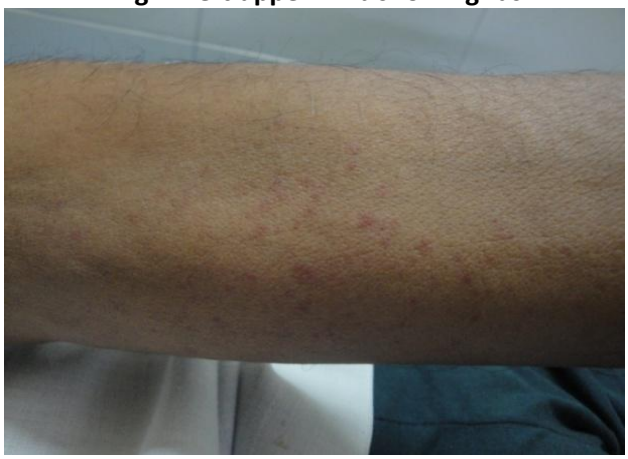


Fig. 2 Left upper limb showing rash



There was no significant past h/o allergic reaction or photosensitivity.

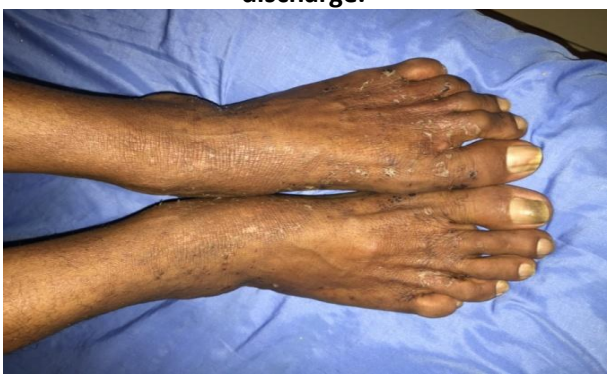
On examination of lower limbs; multiple, well defined, raised erythematous plaques with central necrotic area (targetoid lesions) were observed bilaterally. Petechia was present over buttocks and both arms. It was diagnosed as EM and suspicion of drug induced EM with one of the AKT drugs was raised.

No abnormality was detected on head, neck, scalp, chest, abdomen and back. No lymph node enlargement. Chest X-ray was normal.

Initially on day 1, AKT-4 was withdrawn. The ADR was treated with Dexamethasone 1 ml & Pheniramine maleate 2 ml. The complete blood count and serum electrolyte investigations were also normal.

One by one, AKT drugs were reintroduced. On day 2, Tab. Rifampicin 450 mg was restarted. On day 4, it was replaced with Tab. (Isoniazid 600mg + Rifampicin 450mg). The lesions were healing. On day 8, Tab. Pyrazinamide 750 mg was added. On day 12, these tablets were replaced with Tab. (Isoniazid 600mg +Rifampicin 450mg + Pyrazinamide 750mg +Ethambutol 800mg). On day 13, the patient complained of fresh lesions on his left lower limb & both arms which had actually reappeared since day 11. Thus, on day 13 Tab. (Isoniazid 600mg +Rifampicin 450mg + Pyrazinamide 750mg +Ethambutol 800mg) was withdrawn and treatment was changed to Tab. (Isoniazid 600mg + Rifampicin 450mg) and Tab. Pyrazinamide 750mg. On day 14, the patient's condition remained unchanged. Instead the lesions had aggravated overnight. Hence, on day 14 Tab. Pyrazinamide 750 mg was withdrawn while Tab. (Isoniazid 600mg + Rifampicin 450mg) was continued. No new lesions appeared. Thus the diagnosis of Pyrazinamide induced Erythema Multiforme was confirmed. The patient was in recovering phase at the time of discharge (Fig. 3).

Fig. 3 Patient's lesions were recovering at the time of discharge.



Discussion: In this case report, Pyrazinamide is the most likely agent for the above ADR. According to the study done by Gillani et al, AKT drugs account for almost 7.8% of cutaneous ADRs[5]. This cutaneous reaction in our case report occurred within 2 months of starting the offending drug. These findings are similar to a study done by Dua et al which reported the same duration[6]. However, incidence of Pyrazinamide induced EM is extremely rare.

EM is a skin condition with varying severity. As per the article by Dr. Oakley, the lesions are first seen on the backs of hands and/or tops of feet, and then spread along the limbs towards the trunk[7]. Here, the patient had lesions on his feet, gradually spreading towards the trunk. The initial lesions are sharply demarcated, round, red/pink and flat (macules), which become raised (papules/palpable) and gradually enlarge to form plaques (flat raised patches) up to several centimetres in diameter[7]. Here; multiple, well defined, raised erythematous plaques with central necrotic area (targetoid lesions) were observed bilaterally.

EM seems to be an immunological process of hypersensitive type IV[8]. Cell-mediated immunity appears to be responsible for the destruction of epithelial cells. Immunologically active cells like CD8+ T lymphocytes, macrophages, CD4 lymphocytes; infiltrate the epidermis and dermis respectively. There they release diffusible cytokines, which mediate the inflammatory reaction and resultant apoptosis of epithelial cells[3].

Here, the patient had presented with EM lesions after taking AKT therapy for 2 months. Inorder to identify the suspected drug, AKT drugs were withdrawn and reintroduced one by one. After reintroducing Pyrazinamide, the lesions had reappeared. Thus rechallenge was performed with Pyrazinamide being reintroduced on day 8. According to standard Causality Assessment criteria; WHO & Naranjo' criteria; both arrived at a consensus that the ADR because of Pyrazinamide was Certain/Definite, the major reason being rechallenge confirmation. This case was reported to the nearest ADR Monitoring Centre and uploaded via Vigiflow Base under Pharmacovigilance Programme of India (PvPI) with a unique id no. 2016-49011. The patient's written informed consent was also taken.

Since AKT drugs are one of the most common causes for cutaneous ADRs, awareness in this direction is an important concern. All the TB physicians need to be provided with the basic training of identifying and reporting cutaneous ADRs induced by AKT drugs. E-nikshya, an initiative of RNTCP in collaboration with PvPI is a stepping stone

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