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Lamotrigine Induced Erythema Multiforme: A Case Report

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Abstract
The prototypical lesion of Erythema Multiforme is a targetoid dusky erythematous patch, found predominantly on the extremities, although many different morphologies may be observed. Lamotrigine is an anti epileptic drug found to be effective to treat bi polar disorder, however it is reported to cause various hypersensitivity reactions ranging from a simple rash to life threatening reactions like Steven Johnsons Syndrome. A case of Lamotrigine induced Erythema Multiforme is discussed herewith.
Key words: *Erythema Multiforme, Lamotrigine, Anti-epileptic drugs*

INTRODUCTION

Erythema Multiforme is an acute mucocutaneous inflammatory and hypersensitivity reaction characterized by a skin eruption, with symmetric erythematous edematous or bullous lesions of the skin or mucous membranes[1] possibly mediated by deposition of immune complex (mostly IgM) in the superficial microvasculature of the skin and oral mucous membrane that usually follows an infection or drug exposure.[2]

Lamotrigine is a novel anti-epileptic drug that has been proven effective as an adjuvant medication in children and adults with refractory partial seizures, in Lennox-Gastaut syndrome and in tonic-clonic seizures that are not satisfactorily controlled by other anti-epileptic agents. Lamotrigine is also found to be effective in bipolar depression with minimal risk of inducing mania.[3] It mainly acts by prolonging the sodium channel inactivation and suppression of high frequency firing. In addition it also bocks the voltage sensitive sodium channels, thus stabilizing the presynaptic membrane and preventing release of the excitatory neurotransmitters, mainly glutamate and aspartate.[4]

Adverse effects reported with the use of Lamotrigine include angioedema, photosensitivity, diplopia, blurred vision,

conjunctivitis, dizziness, insomnia, headache, ataxia, tiredness, nausea, vomiting, aggression, tremor, confusion and Skin rashes. Rashes account for withdrawal from the therapy in about 2% of those given lamotrigine and serious skin reactions including Steven Johnson syndrome and toxic epidermal necrolysis occur in about 1 in 1000 adult patients. The main risk factors appear to be concomitant with use of valproate and exceeding the recommended initial dose of lamotrigine or the recommended rate of dose escalation (Sachs *et al.*, 1997).[5] These skin rashes reactions usually occur within 8 weeks of starting the therapy with Lamotrigine, but onset as early as the first day and as late as 2 years has been noted.[6]

The commonly seen severe forms of dermatologic reactions with lamotrigine therapy are erythema multiforme, Steven Johnson syndrome and toxic epidermal necrolysis. The pathogenesis of these severe cutaneous ADR's is unknown, although a metabolic basis has been hypothesized. Anticonvulsants like lamotrigine are metabolized to toxic metabolites which are subsequently detoxified in most individuals. However in predisposed patients with genetic defect, the metabolite may bind covalently to proteins. In some of these patients, the metabolite- protein adduct may trigger an immune response, which may lead to a cutaneous adverse reaction.[7]

Treatment of erythema multiforme, Steven Jhonson syndrome and Toxic epidermal necrolysis includes discontinuation of the drug and supportive measures, such as careful wound care, hydration and nutritional support.[7]

CASE REPORT

The patient was 34 year old male who was a known case of bipolar disorder and on lamotrigine 50 mg once daily (OD) along with magnesium valproate 200mg since month and a half. Apart from his psychiatric history, he was on tamsulosin hydrochloride since one year for benign prostrate hyperplasia and urinary incontinence,

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no known drug or food allergies were reported previously. Patient was admitted to hospital with fever and moderate degree rash (maculo papular) centrifugal in distribution, first noticed over arms and abdomen which then spread to face, extremities and scalp. Rashes were associated with itching and scaling of skin, bleeding of gums and skin was not reported. Patient was emotionally unstable and extremely uncomfortable with his new found problem, more so considering his psychiatric condition. Patient was isolated since he was not comfortable with the other people around. Hematological, Urine, Renal as well as Liver function tests were carried out which were normal, suggesting clearly that it was a hypersensitivity reaction induced by lamotrigine and valproate. The drugs lamotrigine and valproate were discontinued immediately. Treatment was done with Hydroxyzine (anti-histaminic agent) and prednisolone (steroid) prescribed to subside the itching and rashes of the skin. Escitalopram and Alprazolam were considered for psychiatric problem of the patient, however tamsulosin was continued.Apart from the pharmacotherapy, supportive care including proper skin care, fluid therapy, liquid paraffin were started. Patient was better after 3 days of admission with reduced itching and redness of skin and was discharged on 5th day of treatment with the same discharge medication as mentioned above.

DISCUSSION

Erythema Multiforme is caused by various insults from a drug, characterized by a dense dermal inflammatory cell infiltrate and keratinocyte necrosis. **Erythema Multiforme** minor which typically affects a single mucosa is the most common form and may be associated with symmetrical target lesions on the extremities. **Erythema Multiforme** major is more severe, typically involving 2 or more mucous membranes with more variable skin involvement. This feature is used to distinguish it from Stevens–Johnson syndrome, where there is extensive skin involvement, significant morbidity, and a mortality rate. Although it is more frequently seen in males, the incidence of drug-related **Erythema Multiforme** is similar in males and females.[8]

Many reports have mentioned that Lamotrigine and one of the other AED exhibited hypersensitivity with rashes indicating that LTG-induced rash is more likely to occur with polytherapy. The reason of the latter finding has not been known till date. In addition several researches pointed out that higher starting dose and rapid increment of dose are risk, factors for Lamotrigine induced rash.[9,10,11]

Hypersensitivity reaction with lamotrigine typically develops between 2 and 8 weeks after starting therapy but can occur after 12 weeks or longer. Although lamotrigine can be added to valproic acid with an acceptable incidence of side effects; reports suggest that 60% of the

Fig.1:

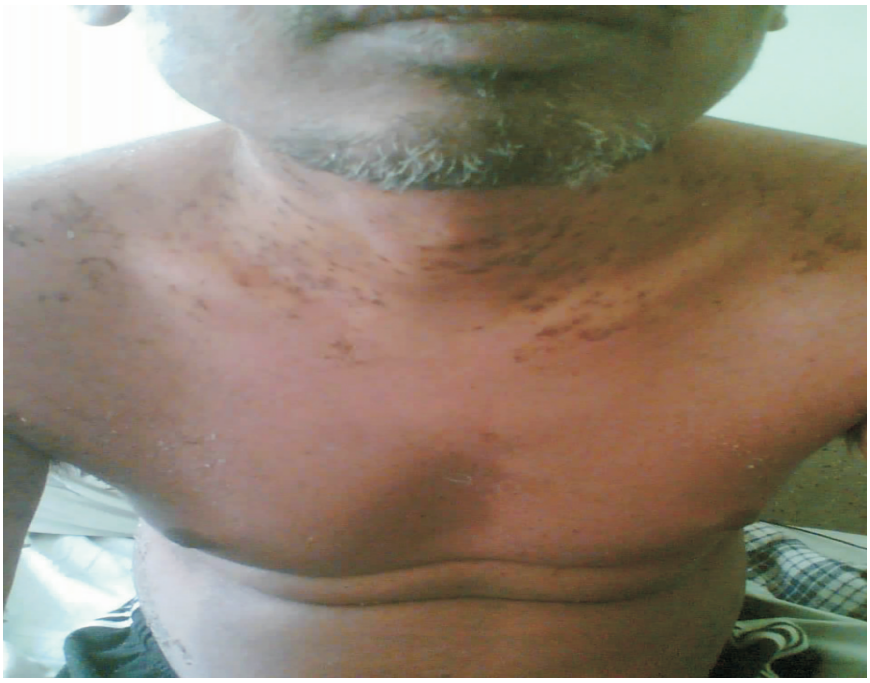


Fig.2:

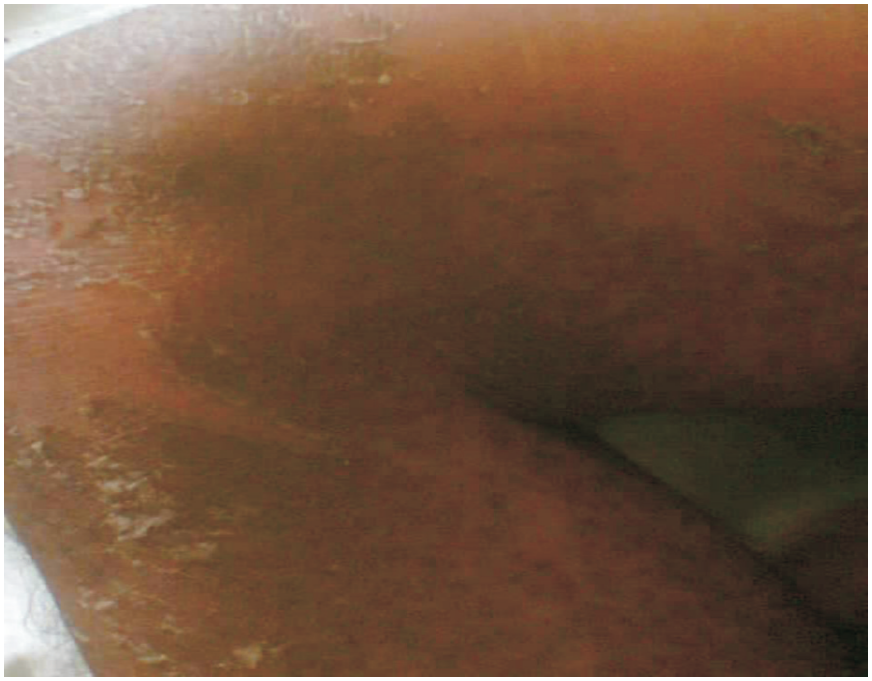
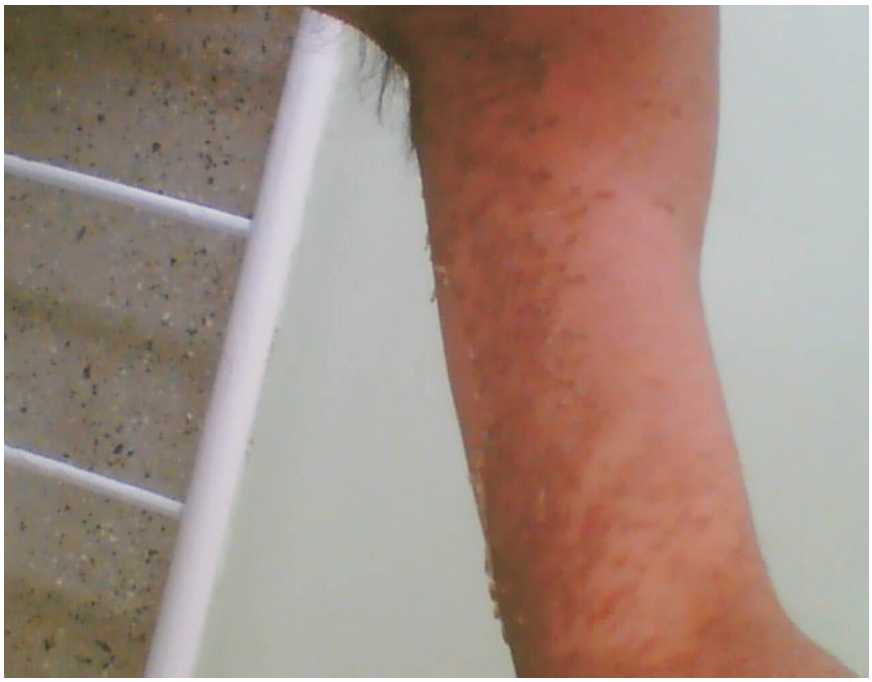


Fig.2:



patients with hypersensitivity related to lamotrigine were taking valproic acid. [12] Although prolonged symptoms and fatalities have been reported, early recognition and discontinuation of offending agents often result in rapid improvement, as with our patient.

After the hypersensitivity reaction is seen cessation of lamotrigine is essential, and the patient should be closely monitored over the next several weeks for the development of other systemic problems, such as hepatitis and renal failure, as residual symptoms can persist for weeks. Intravenous steroids may also have utility in slowing the progression of the syndrome.[13] With

the proper recognition of lamotrigine-associated hypersensitivity, the risk of morbidity and mortality of this rare condition can be reduced.

CONCLUSION

Since lamotrigine is known to cause hypersensitivity skin reactions, it must be used with care and in the appropriate dose recommended instead of using a higher dose at the outset. In our case the initial dose of lamotrigine was 50 mg/day, higher than the recommended starting dose of 25 mg/day for bipolar disorder which could be the possible reason to trigger the hypersensitivity reaction. Another major factor could be the concomitant use of magnesium valproate with lamotrigine suggestive of the reaction.

The risk can be minimized with appropriate use of drugs, it is recommended to inform all patients about skin complications that are not uncommon, especially in the initial two months and to avoid polytherapy as far as possible.

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