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Case Report

Acute generalized exanthematous pustulosis secondary to Valproate: An uncommon cutaneous reaction of a common drug

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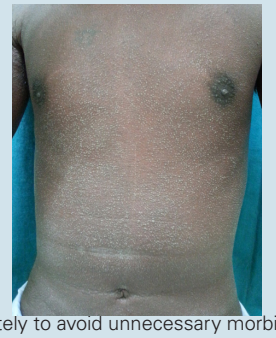
ABSTRACT

Objective: There are various adverse drug reaction (ADR) associated with pharmacological therapy that differ in clinical presentation, prognosis and therapy. Among these, cutaneous eruptions are the most common type of all ADRs.Theclinical presentation of cutaneous drug eruptions ranges from common transient and benign erythema to the most severe forms such as Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN). Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous drug reaction accounting for 1–5 cases/1,000,000 per year. Antibiotics like β-lactams and macrolides are the usual offending agents. Among anticonvulsants-carbamazepine, phenobarbital and phenytoin are commonly associated with AGEP. Sodium valproate is relatively free from cutaneous drug reaction. Thus, we hereby, report a rare case of AGEP in a 24 years old male, reaction following valproate intake used to control post traumatic seizure.

Key words: Acute generalized exanthematous pustulosis, Valproate, Adverse drug reaction.

Key message: Now-a-days valproate is being widely used in patients of neurosurgery, neurology and psychiatry. AGEP is a quite rare adverse drug reaction produced by valproate. Thus, patients taking valproate if develops fever along with non-follicular pustules then, AGEP should be kept as a differential diagnosis and the offending agent to be replaced with some safer drug immediately to avoid unnecessary morbidity.

PICTORIAL ABSTRACT



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INTRODUCTION

Acute generalised exanthematous pustulosis (AGEP) is usually characterized by acute erythematous skin eruptions, initially involving the face and intertriginous areas. Consequently, the erythematous areas become studded with pinhead-sized non-follicular pustules and involve other body surface area, which, if coalesce, may sometimes give a positive Nikolsky's sign.[1]This is followed by spontaneous resolution with post-pustular desquamation. This is frequently accompanied by fever, facial edema, pruritus and neutrophilia on differential blood count.[2] Organ involvement occurs in less than 20 % of cases and usually resolves rapidly. Though severe, the mortality rate is approximately 5%.[3]

Approximately in 87% of cases the etiological factor are the pharmaceutical drugs like beta lactams and macrolids.[2]In addition, there are few case reports, describing some viral infections like cytomegalovirus, parvovirus B19, chlamydia, mycoplasma pneumonia and hypersensitivity to mercury as the potential causes.[4]Although various drugs have been implicated in this condition, there are no reported cases of AGEP caused by valproate in the current literature. We report here a case of AGEP induced by valproate.

CASE REPORT

A 24-year-old male came with chief complaints of widespread skin eruption, fever and generalised body ache since 2 days. A week before he developed throat infection for which he was prescribed amoxicillin-clavulanic acid fixed dose combination along with diclofenac. He also had history of road side accident with moderate head injury 3 weeks back. Subsequently, he developed post traumatic epilepsy for which he was started on valproate since 1 week.

Clinical examination showed maculopapular eruptions involving chest and arms as well as pinhead-sized non-follicular pustules on patient's face and trunk covering about 30% of body surface area. Rest of general and systemic examination was unremarkable.

Laboratory investigations revealed a white blood cell count of 15.6×10^9/L with increased erythrocyte sedimentation rate (ESR). Rest biochemical and haematological investigation were within normal limits. Gram's stain of the pustule showed plenty of neutrophils. Bacterial and fungal cultures of the pustular lesions were negative. Histopathological examination was done with the differential diagnosis of AGEP, Subcorneal pustular dermatosis and Pustular psoriasis. Biopsy from the pustular lesion showed subcorneal spongiform pustules and scattered necrolytic keratinocyte. The superficial dermis was edematous, with mixed inflammatory infiltration, including neutrophils and eosinophils. With these clinical features and histopathological findings a diagnosis of AGEP was made.

Initially amoxicillin-clavulanic acid was thought to be the cause of AGEP and stopped immediately. In view of seizures, he was advised to continue tablet valproate as recommended by neurologist along with topical corti-

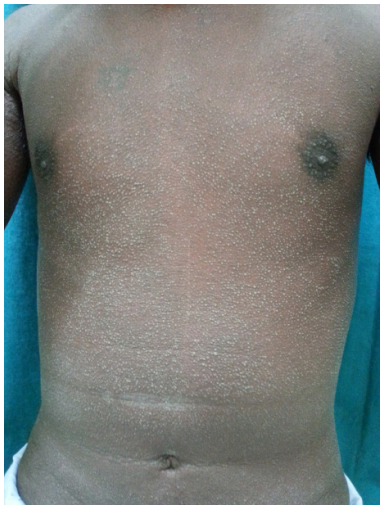

Figure 1: Widespread discrete pustules covering the whole abdomen.

costeroid and oral antihistaminic. He was advised to follow up after one week. However, the patient again presented to us in emergency with flare up of some old lesions and development of multiple itchy pustules with erythema all over the body. Dermatological examination revealed diffuse erythema with numerous follicular and non-follicular minute pustules of variable size (0.5×0.3 to 0.6×1 cm), covering almost 70% of the total body surface area (Figure 1-Widespread discrete pustules covering the whole abdomen). The scalp, palms, soles and mucous membranes were spared.

Thus, the doubt arises, that, valproate might be responsible for AGEP, as there was exacerbation of skin lesions. In suspicion valproate was stopped and was replaced with levetiracetam. The condition of AGEP was controlled within 48 hours with injectable hydrocortisone and the skin eruptions resolved within two weeks, followed by desquamation.

Unexpected flare of lesions on continuing valproate fortunately worked for us as an oral re-challenge test so, we did not feel any need to carry out any further test to establish valproate as the causative agent for AGEP. With these clinical features, histopathological findings and positive oral re-challenge test it was confirmed that this was a case of valproate induced AGEP.

The association of AGEP with sodium valproate in the present case was categorized as "Propable" (7), as per the Euro SCAR scoring system.[1]Similarly, according to World Health Organization-Uppsala Monitoring Centre causality assessment scale, it was found to be "Probable".[5]

DISCUSSION

AGEP was first described by Baker and Ryan in 1968.[6] It is also known as toxic pustuloderma and pustular drug reaction.[2] Depending on the duration from the ingestion of suspecting drug to the onset of the reaction, AGEP can be divided into two different reaction pattern: first one is rapid onset, developing within few hours to 2-3 days after drug administration, i.e. reported with antibiotics and second one is delayed type in which the rash develops after 1-3 weeks.[1] It is characterized by (1) multiple, small, non-follicular pustules arising on edematous erythema (2) Typical histopathological changes (3) Fever > 38°C (4) Leucocytosis (5) sudden eruption of skin lesions and spontaneous resolution with desquamation in less than 15 days.[1]Our patient satisfied all these criteria. A multinational case control study (Euro SCAR), a validation score has been developed to confirm the diagnosis. The scoring is done on the basis of morphology, course of disease and histopathology. It classifies each case as "definite", "probable", "possible" or "not a case".[1]

Though the exact pathogenesis is unknown,it is thought to be a type IV hypersensitivity delayed reaction involving both CD4and CD8 cells.[7] The most important differential diagnosis in these patients is pustular psoriasis. This can be differentiated from AGEP on the basis of evolution of skin lesion, history of drug intake and of course histopathology.[1]

Valproic acid (VPA) has been used in clinical practice predominantly in epilepsy and psychiatric disorder. VPA has good efficacy and relatively favourable safety profile. The most common adverse drug reactions are pancreatitis, hepatotoxicity and teratogenicity.[8] However, various types of cutaneous drug eruptions are reported, which include: Maculopapular rash, fixed drug eruption (FDE), erythema multiforme (EM), toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), urticaria, erythroderma and psoriasiform eruption.[2] On reviewing the English literature, AGEP caused by valproate has not been reported previously. Thus, patients on valproate developing high grade fever along with pustular lesion must prompt a physician to suspect about drug reaction besides infectious aetiology or pustular psoriasis.

CONCLUSION

Based on decades of therapeutic use, various types of drug reactions are reported. Though rare, but AGEP may be a serious adverse drug reaction associated with valproate. The physician must be aware of this uncommon cutaneous side effect of a commonly prescribed anti-epileptic drug. Hence, proper monitoring of adverse drug reactions associated with valproate can continue to improve the safety profile of this drug which is very common used in neurosurgery, neurology and psychiatry.

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SUMMARY

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ABBREVIATIONS USED

AGEP- Acute generalized exanthematouspustulosis, VPA- Valproic acid.

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