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Case Report *Medical research*

A case report on augmentin (amoxicillin/ potassium clavunate) induced acute generalized exanthematous pustulosis

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ABSTRACT

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare and severe cutaneous reaction whose etiology is most often drugs. Spontaneous resolution is observed in most patients. Augmentin [Amoxicillin/ potassium clavunate] is an uncommon cause of AGEP. A 42-year-old male patient presented with severe AGEP due to Augmentin [Amoxicillin/ potassium clavunate] treatment prescribed for common bacterial infections.

INTRODUCTION

Acute generalized erythematous pustulosis (AGEP) is a rare severe cutaneous reaction pattern that in the majority of cases is related to medication administration. The cutaneous reaction is manifested by an erythematous and often oedematous eruptions, which usually appears first in the intertriginous areas or on the face and then disseminates to other skin areas, accompanied by a burning or itching sensation. Soon thereafter, dozens to hundreds of small, pinhead sized, nonfollicular sterile pustules arise in the folds. Mucous membrane involvement may occur in about 20% of the cases. Pustules resolve spontaneously within a few days and are followed by a characteristic post pustular pinpoint desquamation [1]. The cutaneous manifestation of AGEP are usually associated with fever above 100^0F and leukocytosis, mostly due to blood neutrophil count above 7000/µl. Mild eosinophilia may be present in about one third of the patients [2]. Internal organ involvement is relatively rare and the mortality rate is approximately 5% [3]. Histologically, well developed lesions show spongiform subcorneal and or intraepidermal pustules, edema of the papillary

dermis, perivascular infiltrates with neutrophils and exocytosis of some eosinophils. Single cell necrosis of keratinocytes may be present [4]. A drug etiology is found in the vast majority (>90%) of cases. The main causative drugs are antibiotics (mostly beta lactam and cephalosporins). In a minority of cases additional triggers, such as acute viral infection and hypersensitivity to mercury have been implicated [5]. The etiopathogenesis of AGEP is still obscure. Viral causes have been reported by some authors, who reported a case of AGEP in a patient with positive serum diagnosis for cytomegalovirus. In some studies, serum conversions for enterovirus were observed, in particular for coxsackie A9 and echovirus 11 and 30 and positive serum diagnosis for hepatitis B and Epstein-Barr virus are also reported. Nevertheless data suggest that a viral etiology is responsible for no more than 25% of the cases [6]. Pharmaceutical drugs are the origin of some 87% of the cases, among which the most important are antibiotics, especially beta-lactam and macrolides. The chronological relationship with administration of the drug has its own characteristics. The cases due to antibiotics usually occur within a short span of time (less than 24 hours) after administration of the medication. This can be accounted for by the fact that people have been sensitized by the widespread use of pencillins. Other prescription drugs may take an average of 18 days to bring the patient to the clinical picture described. Hydroxychloroquine and norfloxacin are described as drugs that can lead to lesions located on photo exposed areas, and hydroxychloroquine has been described as an isolated agent [7, 8] or one associated with PUVA [9]. Mercury and ultraviolet radiation have also been held responsible for triggering AGEP [10-13]. AGEP has also been caused by tetrazepam [14], diltiazem [15]. And after exposure to sulfuric acid and bromic acid vapour [16]. The etiopathogenesis may be explained by the occasional existence of leukocytoclastic vasculitis, which evokes an Arthus-like hypersensitivity mechanism. This could account for the surrounding immune complexes introduced by the infection or drug [17]. Nevertheless, some authors reported that AGEP is often present in subjects with a psoriatic history (11 out of 63 cases), but this fact is argued by others [2]. In a study that comprised 104 cases of pustular psoriasis five cases were reported to be a transitory psoriasi form reaction, probably a toxidermal one. The authors were not convinced of the psoriatic etiology and described it as a psoriasiform reaction under the influence of infection and drugs, without a genetic predisposition. However, they reminded their readers that corticosteroids, acetylsalicylic acid and promethazine are all drugs that can induce pustular psoriasis [18]. AGEP, in some cases, may manifest as initial psoriasis, which is disregarded if here is no recurrence of the psoriasiform lesion within the two years following the clinical presention [19].

CASE REPORT

A 42-years old man was treated by with Augmentin (Amoxicillin/ potassium clavunate) 625mg twice a day and pantoprazole 40mg/day for common infections. On day two he developed erythema on face, neck trunk and upper limbs, rapidly spreading to the body surface. He was admitted on day-3 to Dermatology department with fever of 100^0F, edematous erythema and non-follicular pustules on his face, trunk and proximal limbs. His blood reports showed leukocytosis (14390/mm3) with neutrophilia (13600/mm3), normal eosinophil count (400/mm3) and elevated C-reactive protein (1.75 mg/dl). Liver and renal function tests were normal. Bacterial cultures from lesions and blood were negative. Skin biopsy showed sub corneal pustules with some epithelial cells, consisting with AGEP. He was treated with prednisolone 40 mg/day and from day-7 pustules start cleaning following desquamation: A complete resolution was achieved on day-14. AGEP is due to usage of Augmentin (Amoxicillin/ potassium clavunate) shown in **figure (1)**. One month later he was evaluated in our dermatology Out-patient Clinic. He denied previous personal history of autopsy, adverse drug reaction and skin disease. He referred to take Augmentin (Amoxicillin/ potassium clavunate) several times before the AGEP episode, last assumption one month before the reaction. Patch tests with a panel of beta lactam antibiotics (penicillin G, amoxicillin, cephazolin, cefuroxime, cephalexin at a concentration of 5% in petrolatum) was not performed. For better results performing of patch test is useful for further studies.

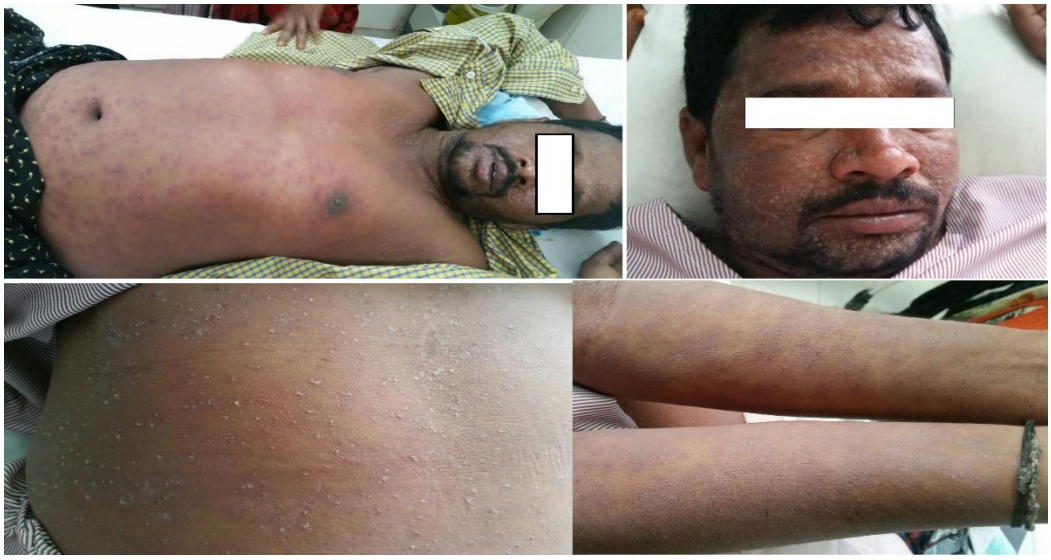

Figure 01: Augmentin (Amoxicillin/ potassium clavunate) induced AGEP

ADR Management

Generally, management of ADR includes withdrawal/suspension, dose reduction of suspected drug and administration of supportive therapy, he was treated with Prednisolone 40mg orally BD, CPM 4mg BD. And patient recovered in 7 days of treatment. Here in this case report the suspected drug Augmentin [Amoxicillin and potassium clavunate] was discontinued.

ADR analysis

Table 01: causality assessment of suspected ADRs

Suspected drug And Reaction(ADR)	Naranjos scale	WHO-probability scale	Karch& Lasagnas scale
Augmentin [Amoxicillin and potassium clavunate] inducedacute generalized exanthematous pustolosis.	Possible	Probable	Probable

Severity: -Moderate level- IV
Predictability: -unpredictable
Preventability: -Probably preventable

DISCUSSION

AGEP is a rare drug-induced disease from the inclusion rate in the Euro SCAR study the incidence rate was estimated to be in the range of 1 to 5 cases per million per year 20, AGEP diagnosis is based on clinical aspect, disease course and histological features of skin biopsy. The EuroSCAR study group developed an AGEP score system in which the achievement of 8-12 points represents a definite diagnosis [20], the case score was 9, Typically AGEP has a benign course and complications are rare[21], Systemic involvement in AGEP is not frequent and generally consisted of slight renal function reduction and mild hepatic enzymes elevation [22, 23]. Differential diagnosis of AGEP is mainly pustular psoriasis, but our patient had no previous history of psoriasis. Kokaji et al. suggested that a bacterial infection could be a condition leading to the cloning of drug-specific T-cells [24], but on the other hand the EuroSCAR case-control study showed that infections played no prominent role in causing AGEP[1].Although AGEP pathophysiology is not completely understood a IV- type allergic reaction has been proposed; T cells production of IL-8 and CXCR8 activate and recruit neutrophils which leads to sterile pustular eruption [25]. According to Pichler's new sub-classification of delayed IV- type hypersensitivity reactions (a-d), AGEP can be considered a type IV

d reaction [26]. In clinical practice patch testing to drugs in AGEP is used in differential diagnosis in ambiguous cases with a good sensitivity (50% rising to 80% for some antibiotics) [27]. Generally, patch testing with the specific drug is a safe procedure even if some cases of reactions not limited to the application site have been reported [28]. Little is known about cross-reactivity in Augmentin (Amoxicillin/ potassium clavunate) induced AGEP; a case of recurrent episodes of AGEP due to different betalactam antibiotics (penicillin G, amoxicillin, cephazolin, cefuroxime, cephalexin at a concentration of 5% in petrolatum) has been described [29], but patch testing was not performed. In case report we present a case of AGEP induced by Augmentin (Amoxicillin/ potassium clavunate) in which patch tests were helpful to identify better results. Some beta lactam antiboitics and cephalosporins to provide specific indications of avoidance.

CONCLUSION

Owing to its safety profile, tolerance, and efficacy, Augmentin (Amoxicillin/ potassium clavunate) is used extensively. Therefore awareness of this rare, yet severe adverse reaction induced by Augmentin (Amoxicillin/ potassium clavunate) is imperative. Early diagnosis of AGEP is vital to terminate the exposure to the causative agent and to avoid unnecessary testing and treatment. Obviously the causative drug has to be discontinued and antibiotics are not to be given unless there is a clear and well-documented associated infection.

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