ejpmr, 2020,7(4), 672-673

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS INDUCED BY ACETAZOLAMIDE

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Article Received on 16/02/2020 **Article Revised on 06/03/2020** **Article Accepted on 27/03/2020**

ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is mostly caused by drugs. The combination of high fever, leucocytosis and pustules is often misinterpreted as acute infectious disease. We report a case of AGEP caused by acetazolamide, a diuretic agent, rarely incriminate in adverse drug reactions.

KEYWORDS: Pustulosis, exanthematous, acute generalized, acetazolamide.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) involves numerous non follicular sterile pustular lesions, associated with fever above 38°Celsius, neutrophilic leukocytosis, an intensely pruritic rash, and in later stages, desquamation. A high proportion of cases are triggered by drugs, especially macrolides and aminopenicillins. We present a patient with a AGEP, induced by acetazolamide.

CASE PRESENTATION

A 44-year-old man, with a long history of hypertension and diabetes mellitus, was admitted to the hospital following exacerbation of a pruritic rash. Three days earlier, he had been treated for acute glaucoma, with oral acetazolamide, twice a day.

His medications included insuline, calcium, ferrous fumarate, acetazolamide and potassium. Two days after introduction of acetazolamide, he had presented an increasingly widespread pruritic and febrile eruption composed of erythematous macules, that were studded with flaccid, nonfollicular, 1-to 3- mm pustules, and involved more than 50% of his body surface area (Fig.1.). Lesions evolved to broad areas of desquamation.

There was no scalp scaling, nail pitting or other stigmata of psoriasis, and lesions evolves of one alone thrust.

He had a white blood cell count of $14,8x10^3$ /µL, with 81% neutrophils and 6% eosinophils. Otherwise, laboratory tests showed increased concentrations of Urea 1,12 g/L (reference range 0,15-0,39 g/L), and creatinine 42 mg/L (6-13 mg/L).

Histopathological examination revealed subcorneal pustules containing neutrophils, some of which were degenerated, and mild surrounding spongiosis (Fig.2.). The papillary dermis showed marked edema and vasodilatation with endothelial swelling, extravasation of erythrocytes, and perivascular and dermal accumulation of neutrophils and some eosinophils supporting a diagnosis of AGEP. Staining with periodic acid-Schiff and Gram stains revealed no microorganisms.

Upon admission to our department, the suspected offending drug was discounted, and the eruption resolved within 5 days without any medications.

Diagnosis of AGEP was definite with an EUROSCAR at 10.

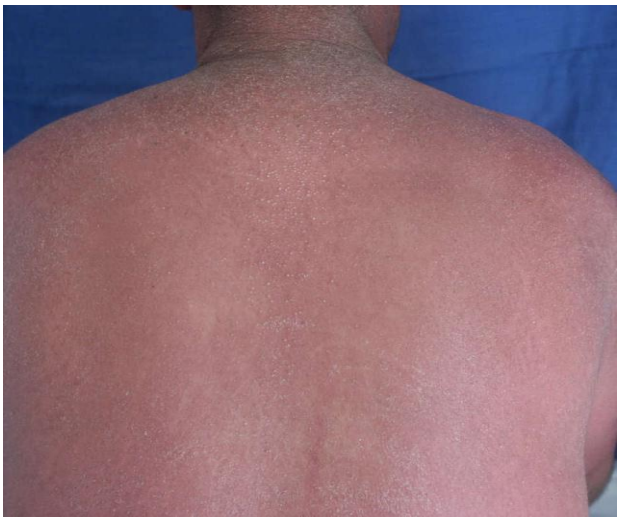

Figure 1: Wide speared pinhead pustules with erythema of the back.

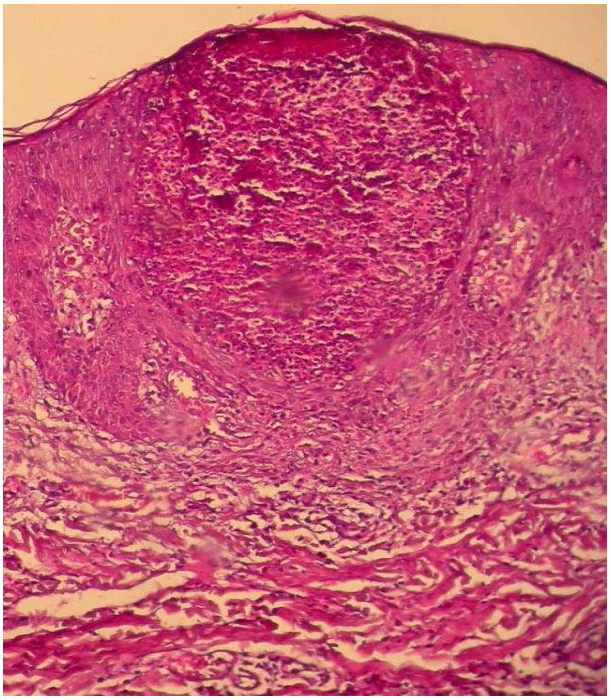

Figure 2: Intraepidermal pustule, edema of dermis and perivascular infiltrates. (HEx200)

DISCUSSION

A wide range of diseases or reactions can cause pustular eruptions of the skin. In this spectrum there seems to be a subgroup with characteristic clinical features and a typical course which is mostly caused by drugs for which the term acute generalized exanthematous pustulosis (AGEP) has been established. They have been regarded as uncommon manifestations of adverse drug reactions. Until now few confirmation studies have been carried out.

Mostly beginning in the intertriginous areas or in the face, a diffuse, often edematous erythema develops very acutely. Patients often describe a burning or itching sensation. On this– often widespread – erythema soon dozens to hundreds of small (pinhead sized <5 mm) non follicular, sterile pustules, arise mainly in the folds. Mucous membrane involvement may occur in about 20% of the cases but usually is mild and remains limited to one location (mostly oral). Skin symptoms are almost always accompanied by fever above 38°Celsius and leucocytosis mostly due to blood neutrophil counts above $7x10^3/\mu l$. A mild eosinophilia may be present in about one third of the patients. The combination of high fever, leucocytosis and pustules is often misinterpreted as acute infectious disease. Early diagnosis of AGEP is important to avoid unnecessary investigations and/or the administration of expensive and sometimes risky antibiotics.[1,2]

The typical histopathology of AGEP shows spongiform subcorneal and/or intraepidermal pustules, an often marked edema of the papillary dermis and perivascular infiltrates with neutrophils and exocytosis of some eosinophils. Vasculitis and/or some single cell necroses of keratinocytes may be present. Psoriatic changes like acanthosis and papillomatosis are usually absent.

In our case, only acetazolamide was recently introduced, suggesting its indictment in this pustular eruption. So, acetazolamide is a carbonic anhydrase inhibitor, and his chemical name is N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide. It is a nonbacteriostatic sulfonamide with a chemical structure and pharmacological activity that is different from the sulfonamide antimicrobials.[3] Acetazolamide, sold under the trade name Diamox, is used to treat glaucoma, epileptic seizures, benign intracranial hypertension, altitude sickness, cystinuria, and dural ectasia. Acetazolamide is available as a generic drug and is also used as a diuretic. His half life is about 3 to 9 hours. Acetazolamide is metabolised to 80% and excreted, unchanged in the urine in 10 hours.

An investigation of the common database of Medline, for spontaneously reported adverse drug reactions, revealed one case of AGEP induced by cefaclor and acetazolamide.[4]

In our case, the diagnosis of generalized drug eruption was based on the history of drug intake, the clinical and histopathological findings. The time relationship between drug administration and onset of the rash, and withdrawal tests manifested by rapid, spontaneous clearing after discontinuation of the drugs, provided additional evidence for a drug aetiology. In vivo tests such as patch tests and readministration were not applied in our patient because of the risk of severe allergic reaction. Alternatively, we can use two in vitro tests, namely MCD and MIF tests, to confirm the etiological role of the suspected drugs. The MCD test is known to reflect immediate type hypersensitivity. Otherwise, the MIF test, consist in measuring the release of the lymphokine MIF from sensitized T lymphocytes by the appropriate antigen.[5]

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