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Case Report

Acute generalized exanthematous pustulosis induced by meropenem: An unusual side effect and review of literature

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Abstract Extensive formation of non-follicular sterile pustules on erythematous background combined with fever and peripheral blood leukocytosis are the characteristics of acute generalized exanthematous pustulosis (AGEP). It is a rare skin rash, usually secondary to a drug reaction and shares several clinical and histological features in common with pustular psoriasis. Most reported cases have been triggered by ingestion of broad spectrum antibiotics, particularly betalactams and macrolides.

We report a 45-year-old male who developed AGEP shortly after commencing treatment with meropenem for chest infection. Skin biopsy revealed subcorneal pustules filled with neutrophils, mixed perivascular infiltrate as well as mild dermal edema. There was no evidence of vasculitis. The eruption improved after cessation of the offending drug and a short course of systemic corticosteroids. To our knowledge, this is the second case of meropenem-induced AGEP in English-language literature.

Key words
Acute generalized exanthematous pustulosis, meropenem, pustular eruption

Introduction

Acute generalized exanthematous 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 edematous eruption, 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 postpustular pinpoint desquamation.[1]

The cutaneous manifestation of AGEP are usually associated with fever above 38ºC 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]

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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 aminopenicillins or macrolides). 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 penicillins. Other prescription drugs may take an average of 18 days to bring the patient to the clinical picture described.[2]

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 vapor.[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 psoriasiform 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 there is no recurrence of the psoriasiform lesion within the two years following the clinical presention.[19]

Here, we report the second case of meropenem-induced-AGEP and highlight the importance of differential diagnosis.

Case report

A 45-year-male patient admitted to our hospital with chest infection and fever for which he received meropenem. Within 24 hours he developed diffuse exanthematous skin eruption. The patient had a history of hepatitis C, chronic renal insufficiency, insulin requiring diabetes mellitus, hypertension and dilated cardiomyopathy. He had been treated with aspirin, digoxin, isosorbide dinitrate, omeprazole, hydralazine, methyldopa, furosemide, calcium and vitamin D. The only drug which had been newly introduced was meropenem. Chest x-ray revealed right basal pneumonia.

Skin examination revealed bilateral symmetrical erythematous confluent patches on the trunk and extremities (**Figure 1**) with small, discrete non-follicular pustules (**Figure 2**). Purpuric lesions were observed on the lower trunk as well as the upper and lower extremities (**Figure** 3). The pustules were also present on the lower lip and ventral surface of the tongue (**Figure** 4). The patient was febrile.

A complete blood cell count (CBC) showed the following values: white blood cells, $18.1x10^9$/l (neutrophils, $14.45x10^9$/l), hemoglobin, 9.2 g/dl, MCV, 80 fL (79.4-94.8 fl) and ESR 70 mm/h.

Biochemical profile revealed the following values: alanine aminotransferase (ALT), 289 IU/l (0-35), aspartate aminotransferase (ALP), 98 IU/l (35-104), total protein, 57g/l (60-80), total bilirubin, 6.5 µmol/l (3-22), urea, 29 mmol/l (2.14-7.14), creatnine, 177 µmol/l (53-97), Na^+ 134 mmol/l (135-146), K^+ 5.7 mmol/l (3.8-5). Blood sugar was maintained within the normal range.

Antinuclear antibody (ANA), anti-neutrophil cytoplasmic antigen antibodies (ANCA), monospot screen and rheumatoid factor (RF) were negative. Bacterial and fungal culture of the pustular lesions were negative.

Histopathological examination revealed subcorneal neutrophil rich pustules, with extravasation of RBCs in the upper dermis (**Figure 5**), admixed with neutrophils. Perivascular infiltrate of lymphocytes, histiocytes neutrophils and eosinophils (**Figure 6**), as well as mild dermal edema was also evident. Fibrinoid necrosis and nuclear dust were not detected. No atypia or malignancy was regarded.

Management

After establishing the diagnosis of AGEP, we discontinued meropenem, and shifted to a combination of erythromycin and ciprofloxacin. The other medications were continued unchanged. Moreover, oral prednisolone 60 mg/day was started and tapered later on. The rash subsided and the skin returned to normal upon taking these measures.

Discussion

The skin is the most frequent target of reported drug reactions. The overall frequency of cutaneous drug reaction ranges from 1% to 8% and is higher for certain drugs. AGEP is a clinical reaction pattern,

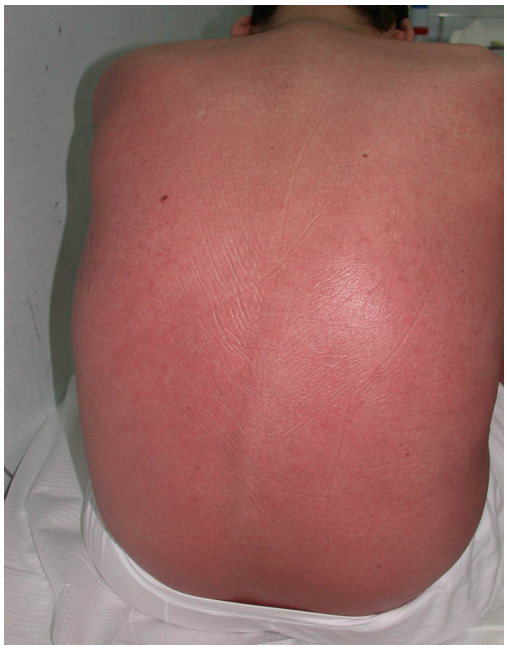

Figure 1 Erythematous confluent patches on the back.

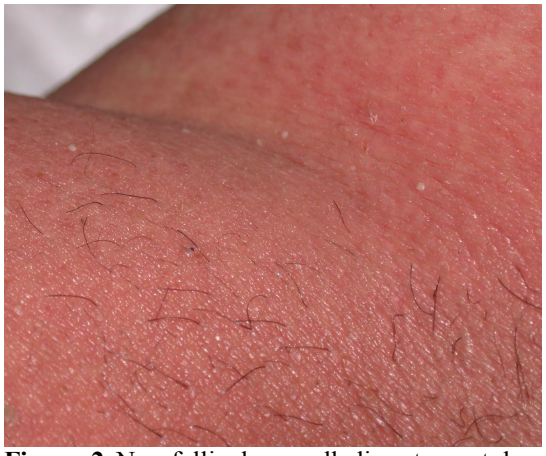

Figure 2 Non-follicular small discrete pustules on an erythematous base.

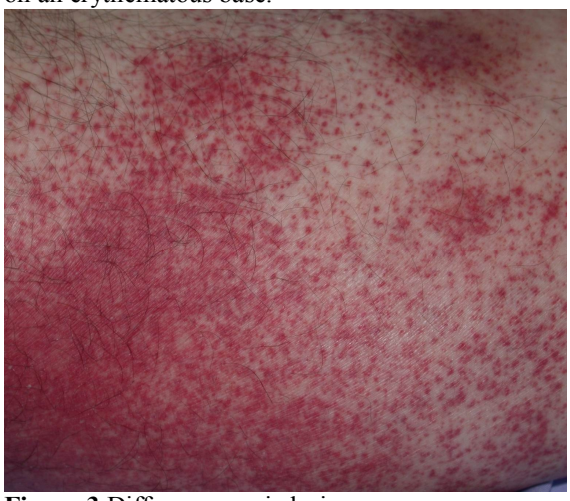

Figure 3 Diffuse purpuric lesions.

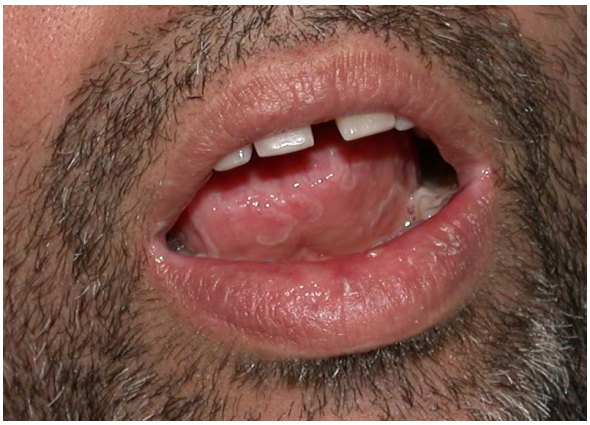

Figure 4 Small pustules on the lower lip.

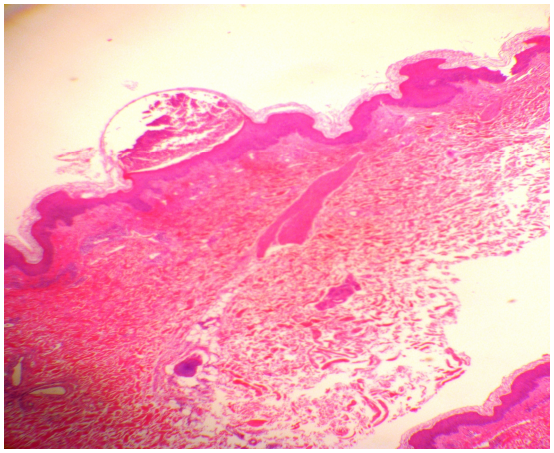

Figure 5 Subcorneal pustule filled with neutrophils. Focal areas of extravasated RBCs in the dermis are also seen.

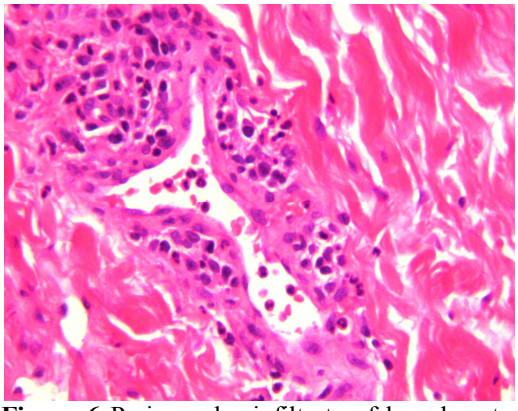

Figure 6 Perivascular infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils.

which is induced in more than 90% of cases by systemic drugs. It is a rare manifestation of an adverse drug reaction, mostly induced by anti-infective drugs.[20] The Drug Eruption

Reference Manual by some authors lists 63 drugs reported to cause AGEP.[21] Five criteria define AGEP: 1. small, mostly nonfollicular pustules on a widespread erythema; 2. typical histopathologic changes; 3. fever greater than 38ºC; 4. blood neutrophil counts above 7 x 10^9/l; 5. acute evolution with spontaneous resolution of pustules within 15 days.[2] Our case met all the criteria mentioned above. Pustular psoriasis is one of the challenges to differentiate from AGEP.

AGEP is defined by rapid onset following the introduction of the drug (less than 24 hours) and marked predominance of antibiotics as triggering agents (80% of the cases). Clinically, it is characterized by polymorphism of eruption, single episode, quick course of action, absence of arthritis and frequent administration of drugs.[22]

However, in pustular psoriasis, the eruption is monomorphic, lasts longer and recurs. Arthritis is associated in 32% of the cases, and drugs are rarely implicated in the etiology. The involution of the condition is slower, taking between 10 and 14 days (**Table 1**).[1]

There are also wide spectrums of cutaneous diseases or reaction patterns that can cause pustular eruptions. However, most of them can easily be distinguish from AGEP. These include the following: follicular eruptions such as bacterial folliculitis, furunculosis, pustular acne vulgaris, localized pustular contact dermatitis, dermatophyte infections, pyoderma vegetans, varicella, Kaposi's varicelliform eruption, sweet's syndrome, impetigo, impetiginized eczema, pemphigus foliaceus and other autoimmune bullous disorders, infantile chronic acropustulosis, migratory necrolytic eruption of glucagonoma, bowel bypass syndrome, Behçet's disease, staphylococcal scalded skin syndrome and others. Yet a couple of diseases remain where differentiation from AGEP may cause problems both clinically and conceptually.[1] These include the following:

Subcorneal pustular dermatosis (Sneddon-Wilkinson disease)

Sneddon-Wilkinson disease is characterized by larger, flaccid blisters with hypopyon formation often arranged in a circinate distribution pattern. In addition, evolution of the disease is far less acute than in AGEP.[1]

Pustular vasculitis

Bullous and/or pustular lesions may arise in purpuric lesions of leucocytoclastic vasculitis. In addition there seems to be a special variant of leucocytoclastic vasculitis which is characterized by the development of many small pustules which – as opposed to AGEP – are localized mainly on the dorsum of the hands and which might also be drug-induced. A marked leucocytoclastic vasculitis can be detected in histology.[23,24] Confusion may occur due to the report of some cases of the pustular vasculitis under the term pustulosis acuta generalisata,[22,25] or due to the occasional presence of vasculitis in AGEP.

Drug hypersensitivity syndrome

Drug hypersensitivity syndrome, also referred to as DRESS (an acronym for drug rash with eosinophilia and systemic symptoms) may also show papulo-vesicles and/or papulo-pustules. In addition, patients show fever, lymphadenopathy, eosinophilia,

Table 1 Pustular psoriasis versus AGEP

	AGEP	*Pustular psoriasis*
History of psoriasis	Possible	Mostly
Distribution pattern	Predominance in the folds	More generalized
Duration of pustules	Shorter	Longer
Duration of fever	Shorter	Longer
History of drug reaction	Usual	Uncommon
Recent drug administration	Very frequent	Less frequent
Arthritis	Rare	~30%
Histology	Spongiform subcorneal and/or intraepidermal pustules, edema of papillary dermis, vasculitis, exocytosis of eosinophils, single-cell necrosis of keratinocytes	Subcorneal and/or intraepidermal pustules, papillomatosis, acanthosis

mononucleosis and often severe visceral involvement like hepatitis, nephritis, pneumonitis, and/or myocarditis.[1]

Toxic epidermal necrolysis (TEN)

The presence of "atypical" target lesions and the confluence of pustules mimicking a positive Nikolsky sign may suggest the diagnosis of TEN in severe cases of AGEP. In general, the distinction can be easily made by experienced physicians as, among other criteria, epidermal detachment in AGEP is much more superficial, and mucous membrane involvement is much more pronounced in TEN. Whereas differentiation in some cases might be difficult on clinical grounds alone, histology is significantly different in TEN, typically showing full thickness epidermal necrosis and only a very sparse inflammatory infiltrate. Yet, even some overlap cases might exist that fulfill the criteria for both diseases both clinically and histologiclly.[1]

Clinically the lesions of AGEP start on the face and within a few hours, they spread to the trunk and limbs, or arise in intertriginous areas. Afterwards, there is some annular desquamation for a few days, possibly accompanied by polymorphic lesions, especially purpuric lesions on the legs and feet. The mucous membranes are affected in 25% of the cases. Sometimes the pustules converge, giving the false impression of positive Nikolsky sign, and staphylococcal scalded skin syndrome (SSSS).[6,18,19,26,27]

Comparable to other cases reported in the literature, in our case, the skin rash started with an erythematous patch on the face which in a period of 24 hours spread to the rest of the body and was covered by small discrete pustular lesions. Moreover, the purpuric lesions were more evident on the lower abdomen and thigh and less so on the legs, feet and the hands and the patient was febrile. However, there was also involvement of the lower lip and ventral surface of the tongue. The skin eruption resolved after cessation of meropenem and initiation of systemic corticosteroid.

Hypersensitivity reactions to meropenem are among the most common drug adverse effects. The first case of AGEP due to meropenem occurred in a septicemic patient who had recurrent episodes of AGEP, caused by three beta-lactam antibiotics (piperacillin, ceftazidime and meropenem). This could be related to the beta-lactam structure shared by the three groups.[28] In laboratory tests there may be leukocytosis with neutrophilia and eosinophilia. Hypocalcemia may also be found mainly in the cases accompanied by hypoalbuminemia. Transitory renal failure may occur. In some

cases there is a momentary increase in aminotransferases. The culture of pustules is negative.[2,27]

In our present case, leukocytosis with neutrophilia, hypocalcemia and sterile culture of pustules were observed. The histopathological picture of the skin biopsy in our patient was compatible with the diagnosis of AGEP, including the presence of spongiform superficial pustules, papillary dermal edema, perivascular infiltrate with eosinophils and extravasation of RBCs. Histologically, pustular psoriasis was ruled out by the lack of hyperplasia of the epidermis and papilloacanthosis.[2,22] in the present case, clinical and histological characteristics, chronological reaction with administration of meropenem and above all, the quick resolution of the rash with discontinuance of the medication, met the criteria for diagnosis of AGEP.

In a search of MEDLINE only one patient with meropenem-induced AGEP could be found in English-language literature. The objective for reporting this case and review of literature is to shed more light on AGEP caused by meropenem. Dermatologists and clinicians must be aware of this unusual side effect.

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