Acute Generalized Exanthematous Pustulosis (AGEP)

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Introduction

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare dermatological manifestation of the adverse drug reaction that manifests for a varied duration after the receipt of certain drugs, especially antibiotics.

AGEP has a characteristic clinical presentation and rapid resolution soon after the removal of the offending drug. Special findings on histology of include single-cell necrosis of keratinocytes with edema out papillary dermis accompanied by components of vasculitis and /or exocytosis of eosinophils.

Management consists of Moist antiseptic dressings, topical steroids, Infliximab, and the use of systemic steroids if needed, and avoiding antibiotics as much as possible. Here, we present a case of AGEP in a setting of usages of antibiotics like Vancomycin, Cefepime, and Ceftriaxone in a setting of cutaneous lymphoma.

Case details

A 75-year-old female with a past medical history significant for Diabetes Mellitus, hypertension, coronary artery disease, history of cutaneous lymphoma, lumbar spinal stenosis secondary to a motor vehicle accident in 2009, status post multiple spinal surgeries, bedridden presented to the emergency department due to worsening of sacral wounds and knee pain. The patient informed that she had been recently discharged from another hospital in which she was started on multiple medications and presented a rash a few days later.Upon arrival at the emergency department, the patient was tachycardic (110 bpm), the temperature was 98.5F, and blood pressure was 91/61 mmHg. Physical exam revealed 4 sacral decubitus ulcers, stages 1-4 with the presence of eschar. The patient also had perioral and periorbital hyperpigmented patches, multiple pink to violaceous keratotic nodules on forearms, generalized skin erythema, and dryness/scaliness. (*Image 1,2*)
The patient was then given Vancomycin, and Morphine and obtained laboratory and imaging analysis. Initial testing was remarkable for leukocytosis (19,700 uL) with mild left shift and anemia (hemoglobin 9.3 gm/dL). The patient was admitted to the general medical floor under the impression of decubitus ulcer infection, was started on Cefepime and Metronidazole, and continued on Vancomycin. Preliminary blood culture results revealed Gram-negative bacilli. MRI of the lumbar spine demonstrated a deep sacral decubitus ulcer, without evidence of osteomyelitis. Wound care was consulted and recommended Surgery evaluation for wound debridement.

Case details continue..

Two days after admission, the patient presented an episode of hypotension and tachycardia, generalized skin sloughing, namely, on bilateral arms, chest, abdomen, and back, and lower mucosal lip desquamation. Laboratory analysis revealed worsening leukocytosis (47,400 uL), and lactic acidemia (9.2 mmol/L). At this point, medical records from the previous admission at another hospital were assessed and disclosed that the patient had been previously diagnosed with AGEP in the context of being on Ceftriaxone given for Streptococcus mitis bacteremia. The antibiotics were switched to Meropenem and Daptomycin. Blood culture results showed Enterobacter cloacae complex, and Meropenem was switched to Ciprofloxacin. Dermatology was consulted, and due to concerns for Steven Johnson Syndrome, the patient was empirically started on intravenous immunoglobulin treatment, while a skin biopsy was arranged.
The results from fresh frozen pathology revealed skin with no evidence of apoptotic keratinocytes and/or necrosis; aggregates of neutrophils were seen in the hyperkeratotic layer(*Image 3,4*). The intravenous immunoglobulin was discontinued and the patient remained on skin emollients.
The patient had progressive improvement with no sloughing seen after a few days. However, due to frequent infection of the sacral ulcer, she succumbed to death in 3 months following this presentation.

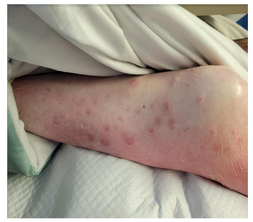


Image 1 : limb lesions

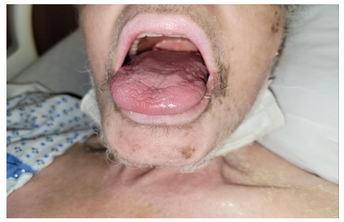
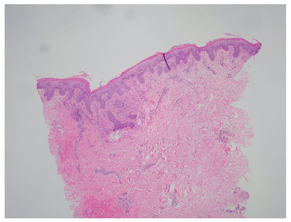


Image 2 : perioral lesions



IImage 3 : low power H&E,

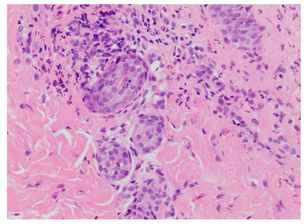


Image 4: High pwer H&E stain

Discussion

The term AGEP was first coined by Beylot et. al in 1980 when referencing drug-induced pustular eruptions with clinical and histological criteria [1]. With an approximate incidence of 1 to 5 cases per million patients every year [2], it is believed that many AGEP cases go unreported or incorrectly reported as "drug-induced pustular psoriasis". Antibiotics like aminopenicillins, pristinamycin, sulphonamides, quinolones, hydroxychloroquine, terbinafine, and diltiazem are the more frequent causative agents [3]. The timing of the appearance of the rash varies from 24-48 hours to 10-14 days after the medication use.

AGEP is diagnosed by history, clinical examination, and histology. AGEP presents with pustules on an erythematous edematous base and can be found initially within the folds and spreads rapidly to larger surface areas, i.e, trunk, and limbs. Pustules rapidly resolve in hours-days after removal of the offending drug. Histology may indicate “single-cell necrosis of keratinocytes, edema of the papillary dermis, vasculitis, or exocytosis of eosinophils”[4].

It is suspected in a patient who presents with fever and non-follicular pustules on an erythematous base, without mucosal involvement, within hours to days after starting a new drug. The pustules are intraepidermal and also sub/intracorneal. Histopathological analysis reveals spongiform features, necrotic keratinocytes, papillary edema, and dermal eosinophils. There are also dermal neutrophilic infiltrate, with an absence of dilated or tortuous blood vessels. A patch test, after the lesions have cleared, is used to confirm the diagnosis [4].
Differentials include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Steven Johnsons Syndrome (SJS), and/or toxic epidermal necrolysis (TEN). The criteria set by the EUROSCAR study [5] (Table 1) can help in identifying and isolating cases of AGEP. The patients are classified as having definite, probable, possible, or no AGEP using this score.
AGEP can be differentiated from pustular psoriasis and SJS/TEN and DRESS by its time of onset, characteristic morphology, and histopathology(Table 2). Pustular psoriasis has a slower onset, with personal or family history of psoriasis. Histologically, the presence of eosinophils and the absence of tortuous blood vessels favors AGEP, while the presence of parakeratosis. Onset for DRESS is 2-6 weeks and an erythematous morbilliform rash that spreads from the face to the trunk, upper extremities, and lower extremities, with mucosal involvement. TEN involves full-thickness necrosis of the epidermis along with lymphocytic infiltrates at the dermo-epidermal junction. Sweet syndrome has a dermal neutrophilic infiltrate.

Withdrawal of the suspected offending drug should be the first step in the management. It usually results in complete resolution. Moist antiseptic dressings can be used. Antibiotics are avoided unless there is evidence of infection. Topical steroids are sometimes recommended. For selected cases therapies like oral corticosteroids, and infliximab have proven useful.

Table 1 : EUROSCAR Criteria

Variable	Score
Morphology	
Pustules	
Typical	+2
Compatible	+1
Insufficient	0
Erythema	
Typical	+2
Compatible	+1
Insufficient	0
Distribution	
Typical	+2
Compatible	+1
Insufficient	0
Postpustular desquamation	
Yes	+1
No/Insufficient	0
Course	
Mucosal involvement	
Yes	-2
No	0
Acute onset within 10 days	
Yes	0
No	-2
Resolution within 15 days	
Yes	0
No	-4
Fever >38˚C	
Yes	+1
No	0
Polymorphonuclear Cells >7000/mm³	
Yes	+1
No	0
Histology	
Other disease	-10
Not representative/no histology	0
Exocytosis of Polymorphonuclear cells	+1
Subcorneal and/or intraepidermal non spongiform or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustules without papillary edema (NOS=Not Otherwise Specified)	+2
Spongiform subcorneal and/or intradermal pustules with papillary edema	+3

Interpretation: 0: No AGEP, 1-4: possible, 5-7: probable, 8-12: Definite, Typical: Typical morphology, Compatible: not typical, but not strongly suggestive of other disease

Table 2: Differential diagnosis

	AGEP	SJS/TEN	DRESS
Onset	48 hours	1-3 weeks	2-6 weeks
Duration	1-2 weeks	1-3 weeks	Many weeks
Clinical Findings	Fever, non-follicular pustules	Fever, mucositis	Fever, pustules, exfoliative dermatitis
Lymphadenopathy	+	-	+++
Lab findings	Neutrophilia	Lymphopenia, granulocytopenia	Eosinophilia
Mortality (%)	5	5-35	10

Conclusion

AGEP is a rare disorder, commonly confused with the diagnosis of TEN, SJS, & DRESS.
The typical onset time, pattern of distriabution, and resolution of discontinuation of the offending agents-antibiotics, is important for the clinical diagnosis as well as management.

Summary

The use of antibiotics for a patient with cutaneous lymphoma for treatment of other presenting infections, can lead to an under-determination and mixing with a diagnosis of other cutaneous reactions to the drugs. The clinical presentation, histology findings, need for discontinuation of offending agents, and keen observation along with timely multidisciplinary involvement lead to a better prognosis as well as patient care.

Contact Information

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Acknowledgements

Dermatology team