



Review Article

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A REVIEW ON ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS

Aryendu Kumar Saini ^{1*}, Sanjeev Yadav ¹, Rachana Yadav ¹, Anurag Singh ¹, Heena Parveen ¹, Suresh Chandra ²

¹M. Pharm Student, Pharmacology Department, Pranveer Singh Institute of Technology, Kanpur, Uttar Pradesh, India

²Assistant Professor, Pharmacology Department, Pranveer Singh Institute of Technology, Kanpur, Uttar Pradesh, India

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*Corresponding author

E-mail: aryendu77@gmail.com

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ABSTRACT

Acute Generalised exanthematous pustulosis (AGEP) is a drug-induced severe cutaneous adverse reaction. This is one of a kind of severe cutaneous adverse reactions that is rare and has the incidence of 1 to 5 cases per million per year. The major characteristic clinical feature of AGEP is the presence of many small, pin-head sized, nonfollicular, sterile pustules on an erythematous oedematous base, and accompanied by fever and leukocytosis. The exact pathophysiology behind is not known but the role of T Cell, IL (Interleukin)-8, the mutation in the IL-36 receptor antagonist has been proposed. The differential diagnosis is required in this case of skin lesions because the clinical features are similar to other SCAR (Severe Cutaneous Adverse Reaction) like generalized pustular psoriasis, TEN (Toxic Epidermal Necrolysis) and SJS (Steven Johnson Syndrome). Pustules resolve if the causative drug is abated and this is a very important feature to distinguish it from GPP (Generalised Pustular Psoriasis). Treatment options are only steroids, supportive care, infection treatment and antipyretics to stabilize the condition of the people with this skin reaction. All the current aspects of Acute Generalized Exanthematous Pustulosis are encompassed that is the sole intention of this review.

Keywords: Exanthematous, Neutropenia, Leukocytosis, Pustulosis

INTRODUCTION

Acute generalized exanthematous pustulosis is a rare and severe cutaneous reaction that is mainly caused due to drugs. The presence of pinhead-sized, pus-filled, and a sterile pustule on an erythematous oedematous base is the characteristic feature of acute generalized exanthematous pustulosis¹. The exact pathogenesis is not known but a role of T cell is important especially CD4 and CD8 T cell. The mutation in the gene encoding the IL-36 receptor antagonist has been found². This receptor antagonist is very important for reducing the inflammatory activity of other cytokines like IL-36 alpha, IL-36 beta, and IL-36 gamma. The EuroSCAR study and histopathology is of utmost importance while diagnosing the AGEP. Mostly, the regions where skins rub each other e.g. intertriginous area, are affected³.

The number of reports is high that are related to drug-induced AGEP but still in the developing countries, it does not reach the excellence. The pharmacovigilance of this rare adverse cutaneous reaction is extensively needed so that health care professionals can become aware of the drugs causing this kind of reaction.

Epidemiology and Background

Acute Generalised Exanthematous Pustulosis was firstly described by Baker and Ryan as a drug-induced pustular eruption without any history of psoriasis in 1968 but the term acute generalized exanthematous pustulosis was first introduced by the Beylot et al in 1980. As the number of adverse drug reaction reports coming from a particular country is not enough, so, an exact number of reports is not known⁴. Reporting culture should be encouraged as this can generate the signal and helps to find the responsible drug. However, the incidence of AGEP is

one to five cases per million per year. It is seen frequently in the women than men. It can occur at any age.

Etiology

Acute Generalised Exanthematous Pustulosis is a rare and severe skin eruption that is characterized by the multiple, small, and nonfollicular sterile pustules on erythematous oedematous base and is usually accompanied by fever and leukocytosis. This is represented in the Figure 1 and Figure 2. This kind of skin eruption is mostly caused due to adverse drug reaction by some drugs like aminopenicillin, sulphonamide, hydroxychloroquine, pristinamycin, and terbinafine. Some cases of adverse drug reaction due to acetylsalicylic acid were found⁵. These drugs had been identified in the (European Study of Scar) EuroScar Study which was an international multicenter case-control study which was conducted in the Europe between 1997 and 2001 to find the drugs inducing the SCAR. In almost 90 percent of cases, drugs ingestion is the underlying cause and resoluteness occurs within one or two weeks after abating the drug administration⁶. Although in most of the cases, the drug is the cause but there are some other causes that provoke this reaction like bacterial infections, viral infections, and parasitic infections. Besides, some other factors like venoms, xenobiotics, foods, lacquer, spider bites, and Psoralen which is a light-sensitive drug that absorbs the long wave- UV (UltraViolet) and acts as ultraviolet radiation, have also shown the potency to cause this skin eruption.

Pathogenesis

This skin reaction is mainly attributed to drugs. The involvement of the activation, migration, differentiation of drug-specific T cells (CD4⁺ and CD8⁺) and the production of CXCL8/IL-8 play a very important role in the pathogenesis. The values of in vivo (patch test) and in vitro test (the cytokine

release test and lymphocyte transformation test) have been shown to identify the causative agent. A lot of articles suggest that cytotoxic proteins like granzyme B, perforin, and cytotoxic T cells induce the apoptosis of keratinocytes and leads to the formation of the subcorneal vesicle.

It has been found very recently that apart from toxic epidermal necrolysis (TEN), granulysin is expressed also by CD4 and CD8 T cells and natural killer cells in different drug-mediated reactions including Acute Generalized Exanthematous Pustulosis (AGEP). In this way, granulysin might play an important role in the pathogenesis of AGEP. In vitro tests have shown that drug-specific T cells produce more interleukin-8 that is chemokine (C-X-C motif) ligand 8. Interleukin is a cytokine and it is known as a neutrophil chemotactic factor and it confers two essential functions, inducing chemotaxis of the neutrophils, and inducing phagocytosis. This cytokine plays an important role in the formation of a pustule by the recruitment of neutrophils. The pathogenesis is not confined up to the involvement of only IL8 (Interleukine), but also IL-17 and IL-22, another cytokines that have predominant effects on the epithelial cell.

Their increased level with granulocyte-macrophage colony stimulating factor (GM-CSF) in AGEP suffering people, participate in the prevention of apoptosis of the neutrophil. In this manner, there is more neutrophilic activity in the skin⁷. Besides, deficiency of the IL-36 receptor antagonist in few AGEP people increases the expression of a lot of proinflammatory cytokines and chemokines like IL-1, IL-12, IL-23, IL-6, and the tumor necrosis factor, that can further intensify the neutrophil recruitment⁸.

Genetics of AGEP

The genetic tendency for the development of AGEP is not known with clarity but a correlation between mutations in the IL-36 receptor antagonist gene and the AGEP progress has been found in some published articles. The IL-36 (interleukine) receptor antagonist works as the anti-inflammatory and simultaneously blocks the proinflammatory cytokines, for example, IL-36 alpha, IL-36 beta, and IL-36 γ .

Clinical Features

This rare and severe adverse drug reaction manifests itself as a development of a number of pinhead-sized pustules on an erythematous edematous base. These pustules are nonfollicular, nonsterile and very often start to develop in the intertriginous regions like groin, followed by fast wide spreading of a pustule on the trunk and limb². Adverse drug reaction onset is normally within 48 hours of drug ingestion. A pustule has white or yellow pus-filled center with a red base. The extent of inflammation usually determines the pustule size⁹. Oral mucosal involvement has been found and reported in about 20 to 25% of patients suffering from the AGEP.

In the acute phase of ailment, fever is more than 38°C, leukocytosis, increased level of neutrophils (7000/ml), and elevated level of C-reactive protein exist. Apart from these, in some people, mild eosinophilia has also been noted¹⁰. Hepatocellular dysfunction, lymphadenopathy, and low level of creatinine clearance are often accompanied with skin eruption. Skin lesions resolve within few days of drug abate. The pustules are then followed by post pustular desquamation¹¹. This is given

in the Figure 3. Post-inflammatory pigments are there, but usually, no residues are left after acute generalized exanthematous (pustules) resolve.

Apart from the normal presentation of AGEP, there are many overlap syndromes and atypical variants¹². As mentioned and clear from the definition, there should be generalized eruptions, but there are also many cases where lots of localized reactions have been reported.

Histopathological Findings

The knowledge of histopathology is very much important to differentiate this type of eruption from other pustular eruption. The period up to which this eruption lasts is usually of shorter duration. Biopsy of skin (a pustule) is advisable to favor the diagnosis¹³. Spongiform subcorneal or/and intraepithelial pustule are most seen histological finding, given in the Figure 4. Some cases also involve the single cell keratinocytes necrosis. Edematous papillary dermis, neutrophilic infiltrate in the dermis which is mostly perivascular, and presence of eosinophils are some other findings.

Diagnosis

Differential diagnosis is very important to diagnose the AGEP and differentiate it from other pustular eruptions. The disease which shows the similar clinical picture is pustular psoriasis. Histological findings and right diagnosis can easily help to differentiate AGEP from GPP. Euro SCAR study, a European case-control study of severe cutaneous adverse reaction (SCAR) by the drug was conducted in 6 countries that are Austria, France, Netherland, Italy, Germany, and Israel to check the responsible drugs causing cutaneous adverse drug reactions. Euro SCAR study has given us AGEP validation score, on the basis of a score; it can be found that if the disease is AGEP. If poly-medication has been done, then patch test is performed to detect the responsible drug after complete skin resolution. AGEP can be differentiated from subcorneal pustular dermatosis on the premise of blister that is flaccid with hypopyon formation.

Drug rash with eosinophilia and systemic symptoms (DRESS), manifests itself as more organ involvement than AGEP, after the withdrawal of the causative factor, rashes do not resolve quicker than the pustules in the AGEP. When the pustular confluence takes place, it may lead to large blisters and erosion that can resemble lesions of the Steven Johnson Syndrome/ Toxic Epidermal Necrolysis. The sensitivity of patch test is higher in the case with AGEP than other drug reactions².

Therapy

The drug should be abated as soon as possible as this is the best method to stop the disease course. In lots of patients with AGEP, complete resolution of lesions has taken place. After a resolution has taken place, the regions of a pustule may develop post pustular desquamation for few days. Redness and swelling can be treated with the help of topical steroid. Antipyretic can be used to stabilize the condition of the people with AGEP and turn down the fever. The important thing to understand is that the physician should be cautious about the drug that is being administered as any drug can cause a reaction. If the rashes are in the extensive phase, systemic steroids can be taken but for the only short duration¹⁴.



Figure 1: Pustular rash in AGE P¹⁶

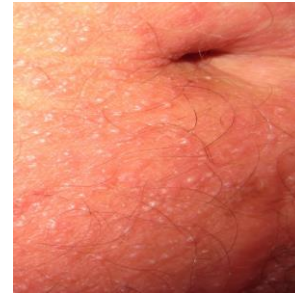


Figure 2: Superficial pustules in AGE P¹⁷



Figure 3: Post Pustular Desquamation¹

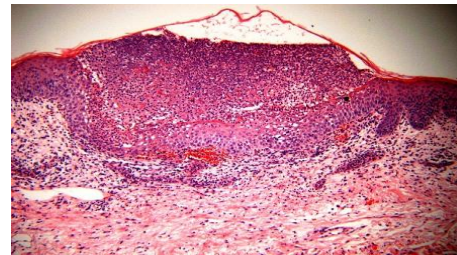


Figure 4: Spongiform Subcorneal Pustule¹⁵

CONCLUSION

Acute Generalised Exanthematous is a rare and severe drug-related skin reaction that has very low rate of incidences. This reaction is characterized by the presence of small pinhead-sized and sterile pustules on an erythematous oedematous base. The histopathological findings of AGE P are very important to diagnose and distinguish it from other severe cutaneous adverse reaction like generalized pustulosis psoriasis. Usually, the lesions or the pustules resolve spontaneously within one or two weeks after the drug administration has been abated. EuroSCAR study has given the scoring system to easily diagnose the reaction. There are many drugs that have been found to be causative, but proper monitoring of the disease and pharmacovigilance of this reaction by dermatologists is very important as the number of case reports involving AGE P is still less. More work should be done on the treatment of these kinds of allergic reactions as only potent topical and systemic steroids are used that may lead to adverse effect.

REFERENCES

1. Feldmeyer L, Heidemeyer K, Yawalkar N. Acute Generalized Exanthematous Pustulosis: Pathogenesis, Genetic Background, Clinical Variants and Therapy. *International Journal of Molecular Sciences* [Internet]. 2016 [cited 21 September 2017]; 17(8):1214. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5000612>
2. Acute Generalized Exanthematous Pustulosis [Internet]. TheDoctorsDoctor.com. 2017 [cited 21 September 2017]. Available from: <http://www.thedoctorsdoctor.com/diseases/agep.html>
3. Sidoroff A, Halevy S, Bavinck J, Vaillant L, Roujeau J. Acute generalized exanthematous pustulosis (AGE P) - A clinical reaction pattern. *Journal of Cutaneous Pathology* [Internet]. 2001 [cited 21 September 2017]; 28(3):113-119. Available from: <http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0560.2001.028003113.x/full>
4. Sidoroff A, Chu CY. Acute generalized exanthematous pustulosis (AGE P) [Internet]. Uptodate.com. 2017 [cited 21 September 2017]. Available from: <http://www.uptodate.com/contents/acute-generalized-exanthematous-pustulosis-agep>

5. Burgin S. Acute Generalized Exanthematous Pustulosis. *Clinical Advisor.com*. 2017. Available from: <http://www.clinicaladvisor.com/dermatology/acute-generalized-exanthematous-pustulosis/article/592785>
6. Bailey K, McKee D, Wismer J, Shear N. Acute generalized exanthematous pustulosis induced by hydroxychloroquine: first case report in Canada and review of the literature. *Journal of Cutaneous Medicine and Surgery* [Internet]. 2013[cited 21 September 2017]; 17(6): 414-8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24138979>
7. Sulewski RJ, Blyumin M, Kerdel AF. Acute generalized exanthematous pustulosis due to clindamycin. *Dermatology Online Journal* [Internet]. 2008[cited 21 September 2017]; 14(7):14. Available from: <http://escholarship.org/uc/item/9gk9f1sn>
8. Purvis D, Acute Generalized Exanthematous Pustulosis. *Dermnetnz.org*. 2017. Available from: <https://www.dermnetnz.org/topics/acute-generalised-exanthematous-pustulosis>
9. Kapoor R. Acute Generalized Exanthematous Pustulosis Induced by Clindamycin. *Archives of Dermatology* [Internet]. 2006 [cited 21 September 2017]; 142(8):1065. Available from: <http://jamanetwork.com/journals/jamadermatology/article-abstract/406986>
10. Eyerich S, Eyerich K, Cavani A, Schmidt-Weber C. IL-17 and IL-22: siblings, not twins. *Trends in Immunology* [Internet]. 2010 [cited 21 September 2017]; 31(9):354-361. Available from: [http://www.cell.com/trends/immunology/abstract/S1471-4906\(10\)00090-6](http://www.cell.com/trends/immunology/abstract/S1471-4906(10)00090-6)
11. Sarkar R, Gupta T, Garg V, Madan A. Acute generalized exanthematous pustulosis induced by fexofenadine. *Indian Journal of Dermatology* [Internet]. 2016 [cited 20 September 2017]; 61(2):235. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4817469>.
12. Bahuguna A. Acute generalized exanthematous pustulosis: A rare side effect of a common over-the-counter drug, Acetylsalicylic acid. *Indian Dermatology Online Journal* [Internet]. 2013 [cited 21 September 2017]; 4(3):231. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3752486>
13. Criton S, Sofia B. Acute generalised exanthematous pustulosis. *Indian J Dermatol Venereol Leprol* [serial online]

- 2001 [cited 2017 Sep 21]; 67:93-5. Available from: <http://www.ijdv.com/text.asp?2001/67/2/93/11117>
14. Condon CA, Downs AM, Archer CB. Terbinafine-induced acute generalized exanthematous pustulosis. *British Journal of Dermatology*. 1998; 138(4):709-710. Available from: <http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2133.1998.02195.x/full>
15. Sulwski RJ, Blyumin, Kerdel FA, Acute generalized exanthematous pustulosis due to clindamycin. *Dermatology Online Journal*. 2008; 14(7):14. Available from: <http://escholarship.org/uc/item/9gk9f1sn#>
16. Leclair M, Maynard B, St-Pierre C. Acute generalized exanthematous pustulosis with severe organ dysfunction. *Canadian Medical Association Journal [Internet]*. 2009 [cited 24 September 2017]; 181(6-7):393-396. Available from: <http://www.cmaj.ca/content/181/6-7/393.full.pdf+html>
17. Burgin S. Acute Generalized Exanthematous Pustulosis [Internet]. *Mdedge.com*. 2017 [cited 2 October 2017]. Available from: <http://www.mdedge.com/jfponline/dsm/10034/dermatology/acute-generalized-exanthematous-pustulosis>

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