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A Case Study on Paracetamol Induced Acute Generalized Exanthematous Pustulosis in Female Patient

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Abstract

Acute Generalized Exanthematous Pustulosis (AGEP) is a severe pustular reaction. Beta-lactam antibiotics and macrolides are the main causative agents of AGEP. There are also other drugs which induce AGEP as the calcium channel blocker diltiazem and antimalarial hydroxychloroquine, oral antifungal terbinafine, anticonvulsant carbamazepine and sulfonamides. AGEP is also induced by bacterial, viral or parasitic infections. This disease is characterized by fever which is associated with an acute onset of sterile numerous pinhead d-sized non-follicular pustules on edematous erythematous bases. It is also characterized by neutrophilia. The pustules are desquamated and spontaneous resolved within two weeks. Systemic involvement occurs in about 20% of cases. There are genetic variations in interleukin-36 receptor antagonist gene (IL-36RN) in the pathogenesis of AGEP. Treatment is based on the stoppage of the causative drug, supportive care, infection prevention, potent topical or systemic steroids and topical emollient cream.

Key words: Paracetamol, Acute generalized exanthematous pustulosis, Beta-lactam antibiotics, Macrolides, AGEP.

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1. Background and Epidemiology

The term Acute Generalized Exanthematous Pustulosis (AGEP) was introduced by Beylot and team in 1980 [1-2]. AGEP is a rare adverse drug reaction with an incidence of one to five cases per million per year [3]. It has low reports, can occur at any age and AGEP seems to be more frequent in women [4].

2. Case Report

Female patient, 18 years old, presented in the Emergency Room with acute fever and sudden eruptions of skin lesions all over the body since 2 days after treated for acute tonsillitis by oral Augmentin capsule 1 gm every 12 h and oral paracetamol (acetaminophen) tablets in dose of 500 mg three times per day. There was no history of medical problems. She has no history of drug allergy. The past history is irrelevant. She has positive family history of same disease.

3. On Examination

Female patient, 18 years old and single. She was ill, irritable and in acute distress. She was conscious, alert and oriented. She was feverish, her temperature was 39°C, her blood pressure was 115/74 mm Hg with a heart rate of 87 beats/minute, respiratory rate of 17 breaths/minute , and oxygen saturation of 97% in room temperature air. She had generalized mildly pruritic pustular lesions over erythematous bases on the face, neck, chest, back, upper and lower extremities as shown in Figure 1. She had no nail lesion.

4. Laboratory Investigations

4.1. Her Complete Blood Count

The clinically significant results are as follows:

- White blood cell count (WBC) of 23.45 k/µl (High) (n 4-10 k/µl), with a neutrophilic predominance of 92.5% (n 40-80%).
- Red blood cell count (RBC) of 4.05 M/µL (n 3.8-4.8 M/µl) with hemoglobin of 11.7 gm/dL.
- Platelet count of 532 K/µL (High) (n 150-410 K/µL).

4.2. Her Chemistry

Her random glucose of 110.7 mg/dL (n 70-140 mg/dL), Creatine Kinase (CK) of 21U/L (n 26-192 U/L), calcium of 9.52 mg/dL (n 8.6-10.20 mg/dL). Cholesterol of 84.4 mg/dL (n 50-200 mg/dL), triglycerides of 88.5 mg/dL (n 40-200 mq/dL), HDL of 59.3 mg/dL (n 45-65 mg/dL). Serum glutamic oxaloacetic transaminase (Aspartate Aminotransferase) of 12.6µ/L (n 0-35 µ/L), Serum glutamic pyruvic transaminase (Alanine Aminotransferase) of 18.7µ/L (n 0-41 µ/L), bilirubin (total) of 1.098 mg/dL (0-1.1 mg/dL), low total protein (6.38 g/dL) (n 6.6-8.7 g/dL) and low albumin of 3.68 g/dL (L) (n 3.97-4.94 g/dL).

4.3. Culture and Sensitivity of Pus in the Skin

It showed no growth.

4.4. Urine Analysis

Pus cells: 10-15 WBCs/hpf, RBC: 60-70 RBCs/hpf, acetone: +2.

Culture and sensitivity of urine showed: bacterial growth which is sensitive to Gentamicin, Imipenem, Nitrofurantoin and Amikacin.

4.5. Histological Findings

The epidermis showed mild to moderate acanthosis with elongation of the rate ridges. There were also spongiosis and parakeratosis with Spongiform subcorneal-intraepidermal pustule filled with pale eosinophilic edema fluid and neutrophilic inflammatory infiltrate andred blood cells. The upper dermis showed perivascular infiltrate formed of lymphohistocytic mainly with few neutrophils as shown in Figure 2.

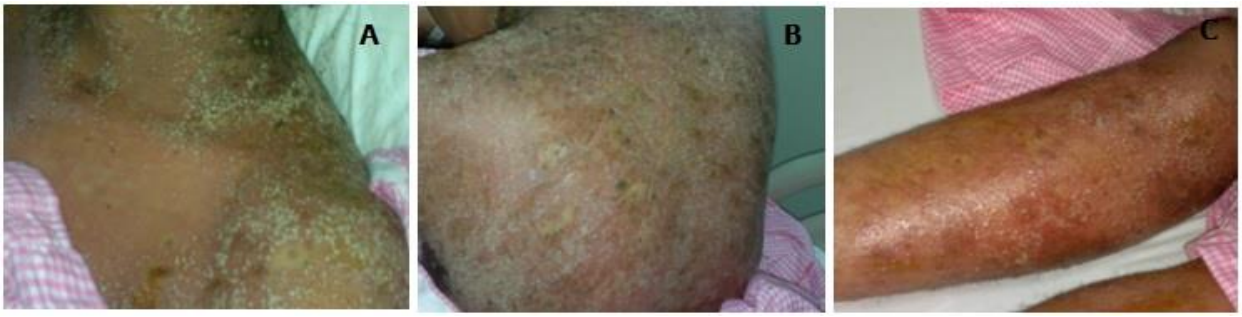

Figure 1. A. Showed neck and left shoulder had pinhead-sized non-follicular pustules on an edematous erythematous base. **B.** Showed back had pinhead-sized non-follicular pustules on an edematous erythematous base with exfoliation of some lesions. **C.** Showed right forearm had pinhead-sized non-follicular pustules on an edematous erythematous base, and some lesions were healed.

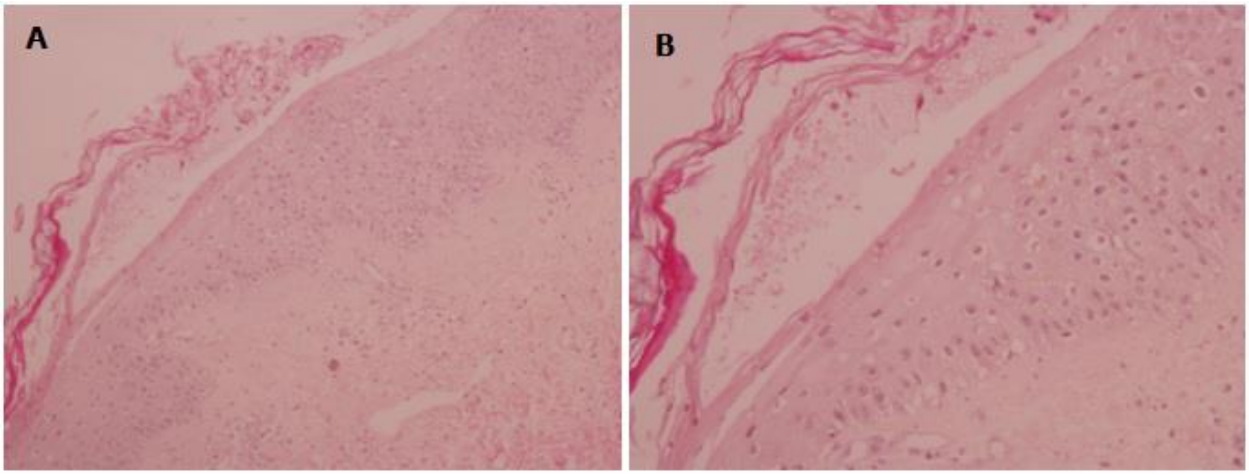

Figure 2. A. Low power microscopic picture showed spongiform subcorneal-intraepidermal pustular eruptions, with a superficial and mid-dermal, perivascular and interstitial mild mixed dermal infiltrate. Slightly minor acanthotic rate ridge changes, spongiosis, papillary edema dilated papillary and mid dermal vessels. **B.** High power microscopic picture showed Spongiform subcorneal-intraepidermalpustular eruptions filled with pale eosinophilic edema fluid and neutrophilic inflammatory infiltrate, spongiosis, papillary edema and dilated papillary vessels.

5. Discussion

The patient was admitted as case of AGEP due to Augmentin capsule. The leucocytosis (23.45 k/µl), with a neutrophilic predominance of 92.5% was associated with diagnosis of AGEP. The low total protein (6.38 g/dL) and low albumin (3.68 g/dL) were expected for this case due to loss of fluid in generalized pustular lesions. The no growth of culture of pus in the skin pustular lesions is also associated with AGEP. Due to loss of body fluid in this pustular reaction, there was urinary tract infection, as there were pus cells in urine examination (10-15 WBCs/hpf) and hematouria (RBC: 60-70 RBCs/hpf) with positive bacterial culture growth.

Two days after admission, erosions in the tongue were developed. The patient was hydrated and treated by oral 30 mg of prednisolone, oral acitretin 30 mg, ceftriaxone 1 gm iv bid, oral paracetamol 1 gm when necessary (PRN), antiseptic oral gargle, miconazole 2% oral gel, topical emollient and topical potent corticosteroid. The lesions were improving, but there were new lesions in the forehead and both palms and erosions in the tongue, so we stopped paracetamol tablet. After stoppage of oral paracetamol, the patient conditions showed good improvement and there were no forming of new lesions. So we considered the paracetamol tablet was the causative agent for this case. There was a similar AGEP case who was induced by paracetamol tablets [5]. The histopathology showed pustular psoriasis (as a most probable), but did not show Munro's microabscess. The family history of psoriasis is positive. AGEP is considered a variant of pustular psoriasis.

6. Differential Diagnosis

1. Acute Generalized Exanthematous Pustulosis (AGEP).
2. Pustular Psoriasis (but there was No nail lesion)
3. Drug Hypersensitivity Syndrome (but there was No eosinophilia).
4. Toxic Epidermal Necrolysis (TEN) (but there was No detachment of full skin layer)

6.1. Acute Generalized Exanthematous Pustulosis (AGEP)

It is characterized by widespread pustules. It is induced by drugs in about 90% of cases. Systemic involvement affects hepatic, renal, and pulmonary systems. AGEP is associated with *IL36RN* mutations similar to those found in pustular psoriasis, palmoplantarpustulosis, and acrodermatitis continua of Hallopeau. Some consider AGEP is a drug-induced form of pustular psoriasis [6].

T lymphocytes are central in the activation and recruitment of other effector cells in the skin, secreting diverse cytokines responsible for further activation, such as granulocyte-monocyte colony-stimulating factor (GM-CSF); regulated upon activation, normal T-cell expressed and secreted (RANTES); interleukin 8 (CXCL8); and the fairly novel cytokine, interleukin 17. In the efferent arm, effector cells, mainly neutrophiles but also eosinophiles, are recruited to the skin by the above chemokines, attach by upregulated adhesion molecules at the inflammation site, and accumulate intraepidermally to form pustules [7].

6.2. Pustular Psoriasis

Pustular psoriasis is an uncommon form of psoriasis. It is characterized by widespread pustules on erythematous bases. This disease may result in erythroderma. Psoriasis vulgaris can be present before, during, or after an acute pustular episode [8].

6.2.1. Types of Pustular Psoriasis

The acute generalized type is known as von Zumbusch variant. This form of pustular psoriasis is accompanied by fever and toxicity. It may be fatal.

The annular type is also known as subacute generalized pustular psoriasis. It has sub acute or chronic course. A disproportionately high number of cases are found in the pediatric population [8].

A juvenile or infantile type of pustular psoriasis has been described, but it is the least common form. Several diseases are considered to be variants of pustular psoriasis. These include the following,

- Pregnancy-associated impetigo herpetiformis

  It occurs predominately in the third trimester of pregnancy.Itcarries an increased risk of subsequent stillbirth or fetal abnormalities [1].

- Acrodermatitis continua of Hallopeau

  It is characterized by pustular eruptions of the tips of fingers and toes [10].

- Sneddon-Wilkinson syndromeor subcornealpustulardermatosis (SCPD)

  This disease has a relapsing and remitting course.It may develop into generalized pustular psoriasis. Itis associated with some malignancies as multiple myeloma and IgA monoclonal gammopathy. It is also associated withpyodermagangrenosum [11].

6.3. Drug Hypersensitivity Syndrome

Drug Hypersensitivity Syndrome (DHS) is called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). This syndrome is a severe, idiosyncratic multi-system reaction. It is characterized by fever, rash, and internal organ involvement as hepatitis, myocarditis, nephritis, and pneumonitis. DHS may occur after oneto eight weeks after medicine exposure. The skin lesions often progress to exfoliative dermatitis [12].

Eosinophilia and atypical lymphocytosis are common, occurring in up to 30% of cases [13]. Allopurinol, anticonvulsants (particularly carbamazepine, phenobarbitone and phenytoin) and sulphonamides are the most frequent causative agents [14-15].

6.4. Toxic Epidermal Necrolysis (TEN)

Toxic epidermal necrolysis (TEN) is a life-threatening disease. It is characterized by widespread erythema, necrosis, bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and sepsis which can lead to death. Mucous membrane involvement has also serious complications as ocular abnormalities, respiratory failure, gastrointestinal hemorrhage, and genitourinary complications [14].

TEN can be induced by drugs and infection. There are many drugs that induce TEN as antibiotics particularly ampicillin, antiepileptic drugs, allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs), and the antiretroviral drugs nevirapine and abacavir [15-17].

7. Diagnosis

Acute Generalized Exanthematous Pustulosis (AGEP) due to paracetamol tablet.

8. Treatment

The patient is hydrated and treated by 30 mg of prednisolone, acitretin 30 mg, ceftriaxone 1 gm iv bid, topical emollient paraffin cream and topical potent corticosteroid betamethasone valerate 0.1% cream.

9. Conclusion

Although Acute Generalized Exanthematous Pustulosis (AGEP) is a severe pustular reaction, it is usually not life-threatening disease and has a high rate of spontaneous resolution. Beta-lactam antibiotics and macrolides are the main causative agents of AGEP, but in this case report, paracetamol is the causative agent.

10. Ethical Consideration

Ethical approval was obtained from ethical committee of College of Applied Medical Sciences, Taif University and written consent was taken from the patient.

11. Conflicts of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

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NA

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