



Case Report

Acute generalized exanthematous pustulosis secondary to spider bites: Clinico-dermoscopic findings and review of literature

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) or toxic pustuloderma is a febrile adverse cutaneous reaction, characterized by small non-follicular sterile pustules. AGEP can occur in any age group and is found to be more common in women. A large proportion (>90%) of cases are triggered by medications, particularly macrolides and aminopenicillins. The occurrence of AGEP following spider bite has been rarely documented in the literature. We report two cases who presented to us with AGEP following spider bite along with dermoscopic findings and also present a brief review of literature on the same.

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1. Introduction

Acute generalized exanthematous pustulosis (AGEP) is an uncommon severe cutaneous adverse reaction pattern characterized by sudden onset of generalised erythematous, edematous, non-follicular aseptic papules and pustules that first appear on the face or in flexures and subsequently spread to other parts of the body, associated with itching and burning sensations.^{1,2} All age groups and both sexes are susceptible. It is primarily brought on by intake of drugs (in >90% of cases). Viral illnesses, food allergies, toxins and vaccines have sporadically been linked to it.^{1,2} AGEP following infections and insect bites, such as from the *Loxosceles* spider (e.g. brown recluse) has been reported.^{1,2} Generalized pustular psoriasis (Von Zumbusch's type), subcorneal pustular dermatoses, toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms are among the clinical differential diagnosis considered.^{1,2} Herein, we

present the case report of two patients presenting with clinical features suggestive of AGEP secondary to insect bite along with dermoscopic findings.

2. Case Report

Two patients presented to the outpatient department of dermatology with diffuse redness all over her body, and pin-point pus-filled lesions, and a continuous, moderate-grade fever that had been present for 2-3 days during the summer months. The clinic-demographic details have been tabulated. [Table 1] There was no history of drug intake, concurrent infections, or personal or family history of psoriasis prior to onset of symptoms. The patients belonged to a rural area, and had a history of insect bite prior to the emergence of rash. They had previously experienced itching, pain and swelling as well as the appearance of a tiny papulo-vesicle on face 2 days prior to the onset of rash, which they attributed to an insect bite. The insect bite were presumed to be spider bites since the patients reported frequent occurrence of spiders

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at their homes (circumstantial evidence) and both gave history of having found a dead and crushed spider in their bed. General physical and systemic examination was normal. Cutaneous examination revealed diffuse bright erythema present all over the body including face, as well as swollen face and non-follicular pin-point pustules present on the lower abdomen, flexural aspect of bilateral upper and lower limbs, anterior chest and axillary area. In case-1, right eye was closed with right periorbital swelling and erythematous plaque with central ulceration and blackish crust was present on the right medial canthus, measuring 0.5cm x0.5cm in size. In case-2, there was an erythematous and oedematous plaque on right cheek with a crusted papule in the centre. Figure 1a – f Examination of mucosae, nail and scalp did not reveal any abnormality. Patients presented within 2 days of the onset of symptoms. Cutaneous eruption was accompanied by erythematous edema of the hands and face. Dermoscopic evaluation on polarized mode revealed small, milky, roundish globules, histologically corresponding to non-follicular subcorneal pustules, and a pinkish-red background, consistent with dermal inflammation. Figure 2 a-d Laboratory investigations like complete blood count (CBC), including total and differential leukocyte count, absolute eosinophil count, C-reactive protein, serum calcium, kidney function test (KFT), liver function test (LFT), blood sugars routine urine examination, chest X-ray, and electrocardiogram (ECG) were ordered. Table 1

Histopathological examination from a fresh pustule was performed to support the diagnosis that revealed superficial (subcorneal) bulla formation with edema of papillary dermis and perivascular chronic dermal inflammatory cell infiltrate. Figure 2d The AGEPE validation score of the EuroSCAR study group was applied to establish the diagnosis.¹⁻³ Our patients fulfilled the EuroSCAR validation score of 11 and 9 respectively, indicating definite diagnosis of AGEPE. Patients did not exhibit symptoms suggestive of loxoscelism. Also, there was no overlap with drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis (TEN) and toxin identification was not possible due to a lack of resources.

For AGEPE, patients were started on supportive treatment in the form of antipyretics, cold sponging, antihistaminics, systemic antibiotics, and systemic steroids in tapering doses. For the insect bite, rest, ice therapy (RICE therapy) was prescribed along with ophthalmologist's / plastic surgery consultation, topical antibiotics. After 4 to 5 days, there was resolution of pustules with desquamation of skin that was treated with application of moisturizers and the patient showed significant improvement within 10 days. Patients were followed up thereafter to assess the recurrence of the disease but no recurrence was observed after 3 months.

3. Discussion

AGEPE (toxic pustuloderma) is one of the cutaneous adverse reaction usually caused by drug intake, however it can also be associated with food allergens, toxins or viral infections.¹⁻⁴ Specific drugs such as antibiotics, particularly macrolides and beta-lactams, quinolones, and tetracyclines and calcium channel blockers like diltiazem and anticonvulsants like carbamazepine are frequent contributors to AGEPE secondary to drug intake.¹⁻⁴ In the recent past, incidences of AGEPE owing to insect bites have been seen in the literature with few reports from India as well. Spider bites have in particular been reported to cause such reactions where spider venom containing spingomyelinase is known to stimulate the release of cytokines and chemokines particularly IL-8 and GM-CSF triggering AGEPE.¹⁻⁴

AGEPE has been reported to occur in all age groups and more commonly in females as compared with males.²⁻⁴ The development of AGEPE due to spider bites have been documented in adults aged 37 to 56 years, except a 9-year-old child by Lee et al.²⁻⁵ The latency period between the bite and appearance of an eruption has been reported to range between 1 to 3 days. Bhat et al reported a history of insect bite by spiders 2 to 4 days before the onset of symptoms in all their cases.^{2,4,5}

Davidovici et al described a series of 3 cases of AGEPE following spider bites from Israel. The eruption in their case had occurred 24-48 hours after a spider bite.⁶ Similarly, Makris et al found such an eruption characterized by erythematous and edematous non-follicular papules and pustules starting in flexures or on face and then generalizing to other parts of the body with associated history of itching and burning sensation along with leukocytosis and eosinophilia. These findings were similar to the current case report.⁷ In another study by Ben Said et al, three cases of AGEPE following spider bite were reported, where diagnosis was based on the chronology of event, typical skin lesions and exclusion of other common causes as did Milman et al who described a similar case of AGEPE caused by a spider bite.^{8,9} Ermertcan et al on the other hand described a case of AGEPE with lymphangitis caused by a spider bite.¹⁰ There have also been reports of AGEPE following loxosceles spider bites, as described by Lane et al and Pippers et al, however features of loxoscelism were characteristically absent in our patients.^{5,11} Recently, a localized form, ALEPE has been reported in a 52 year old female, where a localized edematous erythema with a necrotic lesion in the center, covered with numerous non-follicular sterile pustules with annular disposition was observed on abdomen at the site of bite.¹²

Cases of spider bites have been on the rise in Kashmir, northern most state of India having a temperate environment and this could be attributed to climate change due to global warming. Bhat et al reported a 3 cases of AGEPE caused

Table 1: Clinico-demographic details of patients with AGEP secondary to spider bites

Parameters	Case 1	Case 2
Age	54	11
Gender	Femal	Male
Site of bite	Right eyelid	Right cheek
Cutaneous findings at site of bite	Erythema, odema, necrosis, ulceration	Erythema, odema, papulo-vesicle
Onset of AGEP	2 days	2 days
H/O drug intake	Nil	Nil
H/O vaccination	Nil	Nil
H/o concurrent infections	Nil	Nil
Constitutional features	Mild to moderate	Mild
Haematological findings	Leucocytosis, neutrophilia, eosinophilia, positive C-reactive protein	Leucocytosis, with neutrophilia
EuroScar group Score*	11	9
Dermoscopic findings		
Gram staining of pustule, pus and blood culture	Sterile	Sterile
Histopathology	Consistent with AGEP	Consistent with AGEP

* Interpretation: 0-No AGEP,1-4- Possible AGEP, 5-7-Probable AGEP, and 8-12-Definite AGEP, AGEP: acute generalised exanthematous pustulosis

Table 2: Dermoscopic and histopathological features of AGEP and Generalised pustular psoriasis

Disorders	Dermoscopy	Histopathology
AGEP	Globules are exclusively sparing follicles, are more creamy white, roundish, tending to coalesce and larger in size. A central brown dot in some of the globules representing protruding follicle from them, indicating that pustules may be peri-follicular in case of AGEP due to insect bites. Background is pinkish to orangish red, has a variegated appearance, Yellow-brown to dirty-brown crust is prominent. Orange-brown globules/clods are appreciable in the background. No prominent vasculature is seen.	Presence of the intracorneal, subcorneal, or intraepidermal pustules, Spongiform changes are seen in both intracorneal and subcorneal pustules. Epidermis shows spongiosis along with exocytosis of neutrophils and presence of necrotic keratinocytes. Odema at the papillary dermis and perivascular infiltrates containing neutrophils and eosinophils is seen. Erythrocyte extravasation, discrete leukocytoclasia, mixed perivascular and interstitial infiltrate including eosinophils.
Generalised pustular psoriasis	Yellow-white globules and irregular areas representing discrete pustules and lakes of pus are seen that bear no relationship to hair follicles. Background is dull red to pink. Crust is scanty and white in color. Regularly arranged dots and glomeruli like vessels in a uniform distribution	Hyperkeratosis, parakeratosis, club-shaped psoriatic rete ridges with Munro abscesses, epidermal plate thinning and sub-/intracorneal pustule with dilated, tortuous papillary vessels and superficial perivascular mononuclear infiltrates.

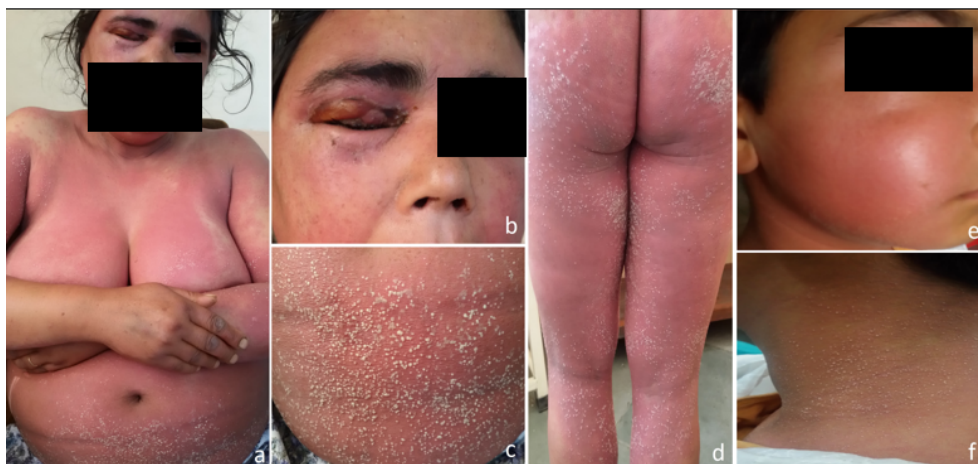


Figure 1: a:Diffuse erythema with overlying numerous monomorphic pin-point pustules present over neck.

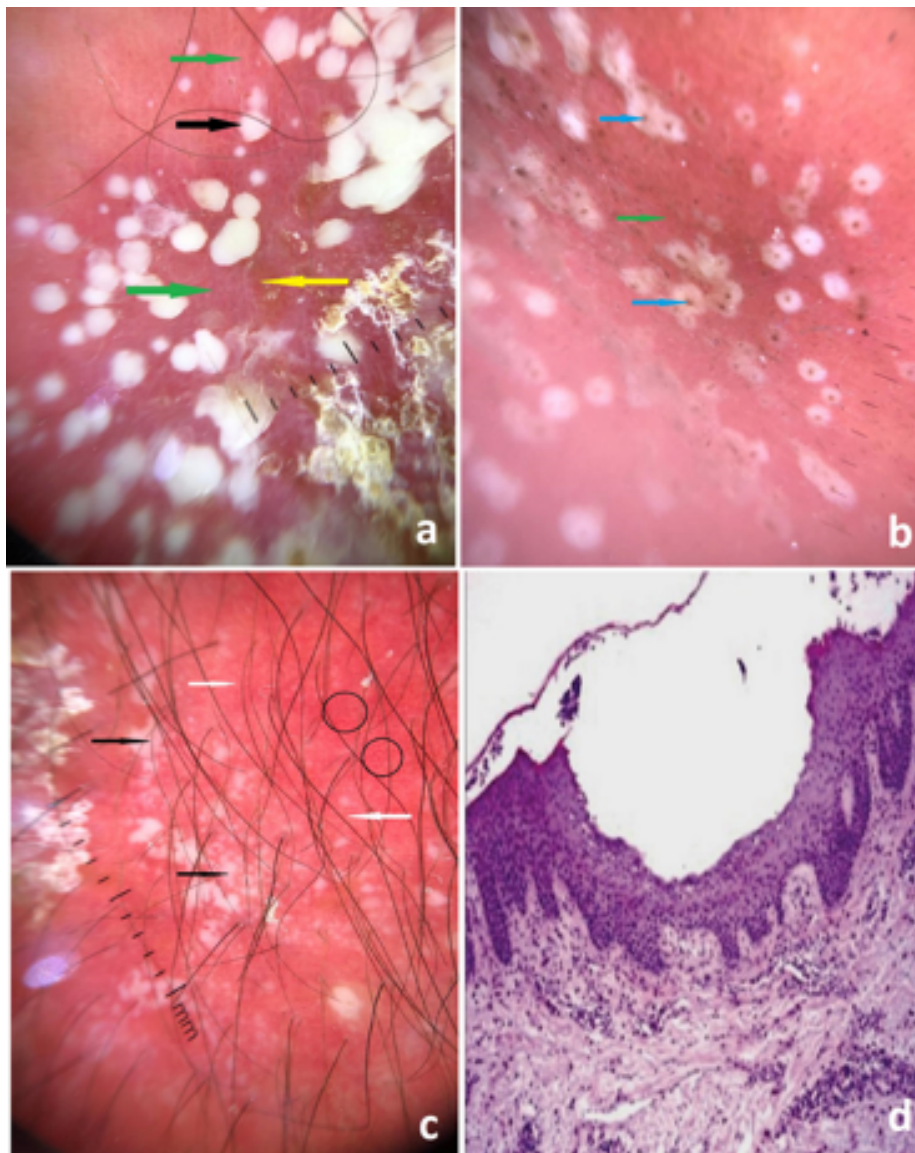


Figure 2: **a:** Dermoscopy of AGEP due to insect bite showing small, creamy white, roundish globules corresponding to non-follicular pustules. (Black arrows); **b:** A central brown to black dot in some of the globules representing protruding follicle from them indicating that pustules may be peri-follicular also in case of AGEP due to insect bites.(Blue arrows); **a,b:** Background is pinkish to orangish-red, and has a variegated appearance which is consistent with dermal inflammation and oedema.(Green arrows); **a,b:** Yellow-brown to dirty-brown crust is prominent. Orange-brown globules/ clods are appreciable in the background corresponding to spongiosis.(Yellow arrows) **(a,b):** Non-evident vasculature due to dermal odema; **c:** Dermoscopy of generalized pustular psoriasis shows yellow-white globules and irregular areas representing discrete pustules and lakes of pus that bear no relationship to hair follicles.(Black arrows) Background is dull red to pink.(White arrows) Crust is scanty and white in color. Regularly arranged dots and glomeruli like vessels in a uniform distribution represent dilated and tortuous vessels in dermis with suprapapillary thinning of epidermis.(Black circles) (Dermlite DL4, Polarized, 10×); **d:** Photomicrograph showing subcorneal bulla formation, with edema of superficial dermis and acute perivascular dermal inflammatory cell infiltrate. (H and E×100).

by insect bites. There was no history of drug usage and all three cases attributed the bite to spiders in their homes.¹³ In another study on etiopathology of AGEPE, the same authors found that 25% (4 out of 16 cases) of their AGEPE cases were secondary to insect bites which was fairly high when compared to other studies, although medications were the primary cause of AGEPE in their study.^{2,13}

So far, of the twenty cases of AGEPE triggered by spider bite have been documented in the literature, dermonecrotic form with mild systemic symptoms was seen in the majority of cases.^{6–11} Dirican et al in a brief review of literature found that there were only two cases of AGEPE following *Loxosceles* spider bites with systemic features of loxoscelism.⁴ Similar to other reports, our patient did not experience any severe systemic features such as hemolytic anaemia, DIC, or renal failure.

Existing literature on utility of dermoscopy in diagnosis of AGEPE is predominantly based on few case reports. The dermoscopic evaluation of the lesions in the present study in the form of small, milky, roundish globules and a pinkish-reddish background, consistent with dermal inflammation shared similarities to other such descriptions of dermoscopy of AGEPE in literature.^{14,15} However, certain points were observed that could help differentiating between various disorders presenting as pustular eruption. [Table 2] Dermoscopy may help in highlighting the clinically inappreciable micropustules when the rash is predominantly maculopapular or during early stages as was reported by Aditya K et al in a 33 year old female, who presented with cutaneous loxoscelism, and spider-bite triggered AGEPE with a predominantly maculopapular rash.^{14,15}

Histopathology in the current report revealed superficial bulla formation with edema of papillary dermis and perivascular chronic dermal inflammatory cell infiltrate. [Figure 1f] These findings were consistent with other reports of AGEPE in literature.^{1–3}

Vaccines have infrequently been linked to the AGEPE in a small number of published reports.^{2,4} AGEPE reactions following vaccination are hypothesized to be caused by hyper immunization and/or dysregulated cytokine production rather than an allergic response. However, the other probable causes of AGEPE such as medications, and vaccination as reported by Bhat et al were ruled out in the current study. In most of the reported cases similar to our report, a combination of systemic corticosteroids medication in tapering doses and symptomatic management have been successful in managing symptoms as well as progression as in the current study as well.^{2,4}

The pathogenesis of AGEPE has not been extensively studied. AGEPE is a T-cell dependent Type IV-d reaction and the development of disease is significantly influenced by the activation, proliferation and migration of drug specific CD4 and CD8 T cells. The apoptosis of keratinocytes and

subsequent formation of subcorneal vesicles are believed to be induced by drug specific cytotoxic T lymphocytes and cytotoxic proteins such as granzyme and perforin. The recruitment of neutrophils by the chemokine (C-X-C motif) ligand 8(CXCL8)/ IL-8 is considered to be a key factor in the development of pustules. Furthermore, elevated levels of IL-17, IL-22 and granulocyte-macrophage colony stimulating factor (GM-CSF) in AGEPE patients are also believed to be a major contributor to high neutrophil activity in these patients.^{1–4}

4. Conclusion

Although medications remain the primary aetiological concern, AGEPE associated with spider bites is quite prevalent. A comprehensive history and examination are required to rule out the cause of AGEPE. Dermoscopy as a non-invasive modality may help in differentiating between various disorders presenting as pustular eruption but needs to be studied in larger number of patients. Histopathology to differentiate it from other pustular eruptions and neutrophilic disorders should be considered in all cases.

5. Source of Funding

None.

6. Conflict of Interest

None.

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