Acute Localized Exanthematous Pustulosis (ALEP): Review of Literature with Report of Case Caused by Amoxicillin-Clavulanic Acid

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ABSTRACT

Acute localized exanthematous pustulosis (ALEP) is a localized form of acute generalized exanthematous pustulosis, characterized by acute onset of multiple nonfollicular, pinhead-sized, sterile pustules following drug administration. Antibiotics, especially β-lactams and macrolides, have been implicated in the majority of cases, although eruption after non-steroidal antiinflammatory drugs and many other medications has also been reported. Skin reaction arises quickly within a few hours, resolving rapidly within a few days without treatment, and it is usually accompanied by fever and neutrophilic leukocytosis. We report herein all cases of ALEP described in literature, adding the case of a 35-year-old woman admitted to our hospital with outbreak of erythematous pustules on her face, neck, and chest after amoxicillin–clavulanic acid treatment.

Keywords: AGEP; ALEP; Amoxicillin–clavulanic acid; Corticosteroids; Exanthematous pustulosis; Hypersensitivity reaction; Sterile pustules

INTRODUCTION

Acute localized exanthematous pustulosis (ALEP) is an acute skin reaction characterized by acute onset of multiple nonfollicular, pinhead-sized, sterile pustules, developed on an erythematous and edematous background, localized typically to face, neck, or chest [1, 2]. It is a rare variant of acute generalized exanthematous pustulosis (AGEP), also called toxic pustoloderma [3], both being described histologically as sterile subcorneal pustules rich in neutrophils and clinically characterized by either widespread or localized sterile monomorphic pustules [4]. ALEP can be considered an atypical form of AGEP [1]. The definition of ALEP was introduced in 2005 by Prange et al. [5] to describe a woman who, according to criteria for AGEP, was diagnosed as having localized pustular eruption on the face. Skin reaction arises quickly within a few hours and resolves rapidly within a few days without treatment [6]; moreover, it is usually accompanied by fever and neutrophilic leukocytosis [7]. Although, in 90% of cases, AGEP and ALEP represent an unusually severe cutaneous hypersensitivity reaction to a systemic drug,
some cases have also been linked with viral infections and insect bites. Antibiotics, especially β-lactams and macrolides, are the most frequent causative drugs, although eruption after nonsteroidal antiinflammatory drugs (NSAIDs) and many other medications has also been reported [4, 8]. This review reports all cases of ALEP described in literature, adding the case of a 35-year-old woman admitted to our hospital with outbreak of ALEP after amoxicillin–clavulanic acid treatment.

METHODS

We searched English-language literature in the PubMed, Embase, Google Scholar, and Scopus databases for publications regarding ALEP through 24 July 2017 using the keywords “acute localized exanthematous pustulosis,” “toxic pustoloderma,” “toxic pustulosis,” “pustulosis,” “exanthematous pustulosis,” “acute generalized exanthematous pustulosis,” “antibiotics,” “drug reaction.” This article reviews all data regarding this rare form of skin reaction, to provide an update on this disease and its management. Furthermore, we report a new case of ALEP, in a young woman after amoxicillin–clavulanic acid therapy. Informed consent was obtained from the patient for inclusion in the study. All evidence was evaluated by the authors, who then combined this with clinical experience from everyday practice in an effort to provide a complete review of this rare skin reaction.

CASE REPORT

A 35-year-old woman was admitted to our hospital for acute outbreak of multiple small nonfollicular pustules, single and occasionally with herpetiform disposition, and an underlying erythematous and edematous base, affecting face, neck, and trunk (Fig. 1). There was no mucous membrane, nail, or joint involvement. No itch or sting was referred. At presentation, the patient was febrile (temperature 37.2 °C) and presented cervical lymphadenopathy. She had no personal or family history of dermatological diseases. The patient had been taking amoxicillin–clavulanic acid (1 g/day for a week) up to 3 days before for pharyngotonsillitis. She took no other medications. Laboratory investigations showed increased white cell count (11,000/mm^3) with normal differential. Eosinophilia was not present. Erythrocyte sedimentation rate (ESR, 20 mm), C-reactive protein (CRP, 2.6 g/L), and antistreptolysin O (ASO, 376 UI) titer were elevated. Blood chemistry, liver function, and renal function tests were within normal limits. Bacterial and fungal cultures were negative. Results for immunoglobulins [herpes simple virus (HSV)1 and HSV2 immunoglobulin M (IgM) ≤ 0.5] and viral
polymerase chain reaction analysis proved absence of herpes simplex virus. Furthermore, skin biopsy from a pustular lesion of the neck was taken. It showed acanthosis of epidermis with mild spongiosis. Moreover, in dermis, there was dense perivascular infiltrate of lymphocytes and neutrophils, resulting in formation of subcorneal, intraepidermal pustules. Patch test for amoxicillin–clavulanic acid was positive. Indeed, use of antibiotics was discontinued and she was treated with systemic corticosteroid (prednisone 37.5 mg daily). The pustules rapidly started to resolve within 5 days after corticosteroid treatment, followed by transient residual hyperpigmentation (Fig. 2.). Furthermore, given the temporal relationship between antibiotic administration and skin disease development and its histologic findings, our case can be considered an unusual type of AGEP, defined as ALEP induced by amoxicillin–clavulanic acid.

RESULTS AND DISCUSSION

Acute localized exanthematous pustulosis occurs only rarely as a particular form of AGEP [1]. About 25 reports have been published in literature (Table 1), confirming that this is a severe cutaneous eruption, which develops abruptly, in the context of recent drug administration, as monomorphic papulopustules with few or no comedones. ALEP characteristically presents with onset of localized 1–2-mm sterile pustules 3–5 days after commencement of a culprit drug, resolving soon after drug withdrawal [9]. Fever and leukocytosis may be present, accompanied by itching or sometimes burning sensation. Mucous membrane involvement is rare, commonly mild, and generally restricted to one site, mostly the oral lips. More than 80% of cases are drug induced, with antibiotics, especially β-lactams and macrolides, being the most frequent triggers [10, 11], although in particular cases it is induced by bacterial, viral, or parasitic infection [12, 13]. Although the pathophysiology of both ALEP and AGEP remains unclear, several studies have suggested that AGEP is due to drug-specific T-cell-mediated immune processes (type IVd reaction) [13–15]; in fact, activation, proliferation, and migration of drug-specific cluster of differentiation (CD)4 and CD8 T cells play an important role in development of the disease, as confirmed by patch test and drug lymphocyte stimulation test (DLST) responses [13]. Clinical differential diagnosis includes follicular eruptions, such as bacterial folliculitis, furunculosis, acne and acneiform pustules, localized pustular contact dermatitis, dermatophyte infection, pyoderma vegetans, varicella, Kaposi varicelliform eruption, Sweet’s syndrome, bullous impetigo, impetiginized eczema, pustular erythema multiforme, pemphigus foliaceus and

![Fig. 2 Within 5 days after withdrawal of amoxicillin–clavulanic acid, the rash resolved slowly, with oral corticosteroid therapy (prednisone 37.5 mg daily)](image)
other autoimmune bullous disorders, infantile chronic acropustulosis, migratory necrolytic eruption of glucagonoma, bowel bypass syndrome, Behçet’s disease, staphylococcal scalded skin syndrome, and others. Most of these can easily be differentiated from AGEP based on clinical appearance, clinical course, and histology, but some diseases whose differentiation from AGEP can cause problems remain [12]. After exposure to the causative agent, antigen-presenting cells present the cognate antigen using major histocompatibility complex (MHC)

| Author(s)          | Date  | Sex, age | Drug(s)                        | Site                            |
|--------------------|-------|----------|--------------------------------|---------------------------------|
| Shuttleworth       | 1989  | –        | Amoxicillin                    | –                               |
| Jay et al.         | 1994  | M, 46    | Ampicillin                     | –                               |
| Fitzgerald et al.  | 1994  | F, 27    | Allopurinol                    | Trunk                           |
| Lim                | 1995  | M, 24    | Ampicillin                     | Face                            |
| De Argila et al.   | 1996  | M, 53    | Amoxicillin                    | Face                            |
| Prieto et al.      | 1997  | M, 46    | Amoxicillin                    | Face                            |
| Novalbos et al.    | 2000  | –        | Ceftibuten and amoxicillin     | Face                            |
| Corbalán-Vélez et al. | 2000 | F, 40    | Amoxicillin–clavulanic acid    | Face, neck, trunk               |
| Wohl et al.        | 2004  | F, –     | Paracetamol                    | Face                            |
| Prange et al.      | 2005  | F, –     | –                              | Face                            |
| Corral de la Calle et al. | 2005 | M, 70    | Levofloxacine                  | Face, neck                      |
| Betto et al.       | 2008  | F, 40    | Amoxicillin–clavulanic acid    | Face                            |
| Rastogi et al.     | 2009  | F, 64    | Ibuprofen                      | Face                            |
| Kim et al.         | 2010  | F, 44    | Docetaxel                      | Face                            |
| Liang et al.       | 2011  | F, 59    | Sorafenib                      | Limbs                           |
| Ozkaya-Parlakay et al. | 2011 | F, 17    | Amoxicillin–clavulanic acid    | –                               |
| Sim et al.         | 2011  | F, 26    | Cephalosporin, trimethoprim-sulfamethoxazole, and vancomycin | –                               |
| Tresch et al.      | 2012  | M, 21    | Finasteride                    | Trunk, abdomen                  |
| Huilaja et al.     | 2014  | M, 44    | Piperacillin–tazobactam        | Thighs                          |
| De Cruz et al.     | 2015  | F, 34    | Clindamycin                    | Chest                           |
| Di Meo et al.      | 2016  | F, 40    | Flurbiprofen                   | Face                            |
| Qu et al.          | 2016  | F, 72    | Cefoperazone and sulbactam sodium | Face                           |
| Bala et al.        | 2017  | F, 47    | Amoxicillin–clavulanic acid    | Face, neck, trunk               |
|                    |       | F, 30    |                                | Trunk                           |
| Our case           | 2017  | F, 35    | Amoxicillin–clavulanic acid    | Face, neck, trunk               |
| Jha et al.         | 2017  | M, 29    | Diclofenac                     | Trunk                           |
molecules, causing activation of specific CD4 and CD8 cells that proliferate then migrate into dermis and epidermis [13]. Drug-specific CD8 T cells use perforin/granzyme B and Fas ligand mechanisms to induce apoptosis of keratinocytes within epidermis, leading to tissue destruction and epidermal vesicle formation. These cells release increased amounts of C-X-C motif chemokine ligand 8 (CXCL8), a potent neutrophilic cytokine, leading to chemotaxis of neutrophils into vesicles, causing transformation of vesicles into sterile pustules [16, 17]. Furthermore, in vitro tests have shown that Th17 cells may also play a role in the strong neutrophilic activity, by releasing interleukin (IL)-17 and IL-22, which have a synergistic effect on production of CXCL8 and prevention of apoptosis of neutrophils [14]. Some authors have suggested that there is also a genetic component in the development of pustular eruption [18]. Patients with mutations in the IL-36 receptor antagonist (IL36RN) gene are more predisposed to develop AGEP after drug exposure [18]. The IL-36RN gene encodes the IL-36 receptor antagonist, a molecule that blocks inflammatory cytokines such as IL-36α, IL-36β, and IL-36γ. Therefore, mutations in the IL-36RN gene can result in uncontrolled IL-36 signaling and increased downstream production of IL-6, IL-8, IL-1α, and IL-1β and might predispose to pustular eruptions [12]. Initially, these cases were described as unusual drug eruption, clinically and histologically different from fixed drug eruption [18]. In 1989, Shuttleworth [19] reported the first case of an unusual localized pustular reaction to amoxicillin. The rash was recurrent and always appeared in the same region, but histological findings differed from those of fixed drug eruption. Indeed, the histology of AGEP and ALEP shows spongiform, subcorneal, and/or intraepithelial pustules, edematous papillary dermis, and perivascular infiltrates with neutrophils and some eosinophils. Necrotic keratinocytes and leukocytoclastic vasculitis can also be found [12]. Moreover, our case of ALEP is not the first induced in association with amoxicillin–clavulanic acid treatment; five other cases [7, 15, 20–22] of amoxicillin–clavulanic acid-induced ALEP have been reported in literature previously (Table 1). Interestingly, all patients were women and the major areas affected by pustular lesions were photoexposed such as face, neck, and chest, simulating acneiform eruption. Recently, Bala et al. reported the cases of two Caucasian women with a diagnosis of amoxicillin-induced localized folliculitis in the spectrum of ALEP [20], based on the clinical presentation of localized monomorphic pustulosis and pathological findings of suppurative folliculocentric acute inflammatory reaction. The time period from drug exposure to reaction onset is typically within 48 h, as reproduced in a double-blind placebo-controlled test in a 53-year-old man who developed recurrent localized exanthematous pustulosis at day 7 of 8 days of amoxicillin treatment (500 mg daily) [3]. Since the first description of the disease, the list of drugs involved has grown. There has been only one case showing a relationship between ALEP and levofloxacin [23], in a 70-year-old man treated for pneumonia. The patient presented multiple nonfollicular pinhead-sized pustules over head and neck with fever, which disappeared on interruption of the antimicrobial drug [20]. Other cases of ALEP, including treatment with cefoperazone and sulbactam sodium, piperacillin–tazobactam, and vancomycin, have also been described [1, 11, 24, 25]. Although ALEP is typically localized to photoexposed areas, a particular case reported development of annular erythematous lesions with dozens of tiny nonfollicular pustules on the inguinal area of a 44-year-old man after 1 day of piperacillin–tazobactam therapy for pancreatitis [24]. Although AGEP and psoriasis are the most common vesiculopustular eruptions occurring during pregnancy, two cases of ALEP in pregnant women have been reported. One case described a pustular eruption, localized on the right breast, in a 34-year-old woman who was 19 weeks pregnant after 3 days of treatment with oral clindamycin (300 mg twice daily) [26], while the other case reported acute exanthematous pustulosis localized in the neck region after paracetamol therapy [27]. Other nonantibiotic drugs causing ALEP include NSAIDs (flurbiprofen, ibuprofen, and diclofenac) [28–30], allopurinol [31], and finasteride [32]. Dermoscopy may help in diagnosis at an early stage, as described by Jha et al. in their article; on polarized dermoscopy,
ALEP appears as small, milky, roundish globules, histologically corresponding to nonfollicular subcorneal pustules, and a pinkish-reddish background, consistent with dermal inflammation [30]. Associations with docetaxel and sorafenib in two patients with carcinoma have also been reported [33, 34]. Finally, information extracted from published case reports in literature shows that, as ALEP is a self-limited disease, the mainstay of treatment is removal of the suspected drug, which leads to improvement in symptoms within several days [35]. Supportive therapy with topical or oral corticosteroids may be appropriate for treatment of pruritus and inflammation in prolonged cases [4].

CONCLUSIONS

ALEP is an uncommon cutaneous drug reaction characterized by eruption of localized sterile pustules following drug administration. Most published cases involved antibiotics, but many other drugs have been reported to be responsible for this skin reaction. There are no standardized guidelines, and data regarding pathogenesis and treatment of this disease are still unclear, so physicians usually have to rely on published experience from case reports and case series. Indubitably, more studies and international registry are needed to better recognize and treat this disease.

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Compliance with Ethics Guidelines. Informed consent was obtained from the patient for inclusion in the study.

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