Localized acute generalized exanthematous pustulosis with amoxicillin and clavulanic acid

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SUMMARY: Özkaya-Parlakay A, Azkur D, Kara A, Yıldız Y, Orhan D, Cengiz AB, Ersoy-Evans S. Localized acute generalized exanthematous pustulosis with amoxicillin and clavulanic acid. Turk J Pediatr 2011; 53: 229-232.

Acute generalized exanthematous pustulosis (AGEP) is a rare skin disorder, characterized by acute development of numerous, pin-head sized, non-follicular pustules on erythematous skin, with high fever and neutrophilia. The condition is frequently caused by hypersensitivity reaction to drugs or viral infections. Diagnosis is established according to clinical and histological criteria. Herein, we report a 17-year-old girl with localized AGEP related to the use of amoxicillin-clavulanate.

Key words: acute generalized exanthematous pustulosis, amoxicillin, clavulanate.

Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous reaction characterized by fever and a generalized pustular skin eruption that occurs mostly after exposure to drugs, and less commonly, viral infections[1] or heavy metals such as mercury[2]. It is a self-limited disorder that resolves with desquamation usually within 1-2 weeks. AGEP was largely investigated by Beylot et al.[3], who described AGEP as a pustular eruption with acute onset following an infection and/or drug intake. The most common triggering drugs for AGEP are antibiotics[4]. Several other drugs such as paracetamol, ibuprofen, diltiazem, hydroxychloroquine, omeprazole, and bleomycin[5-10], etc. have been reported in the etiology of AGEP as well. Amoxicillin–clavulanate (ACA) is a commonly used, wide-spectrum beta-lactamase inhibitor, which was reported to cause AGEP. Herein, we report a case of AGEP that developed in a very short time and in a localized fashion after the intake of ACA. It is prudent for pediatricians to be aware of this self-limited drug reaction, in order to avoid unnecessary and costly investigations.

Case Report

A 17-year-old girl was consulted for a rash and fever that had been present for two days. It was learned that a day before the rash she was given ACA for toothache by a dentist, and subsequent to taking the first dose, itching had started on her neck and hands. Fever started two days after the drug administration. It was noted that she had a similar reaction to ACA five years before. Her past medical and family histories were otherwise unremarkable. Dermatological examination revealed numerous erythematous, non-follicular pustules (<5 mm in diameter) only over her extremities (Figs. 1, 2). Her eyelids and legs were edematous. Her conjunctivas were hyperemic. Physical

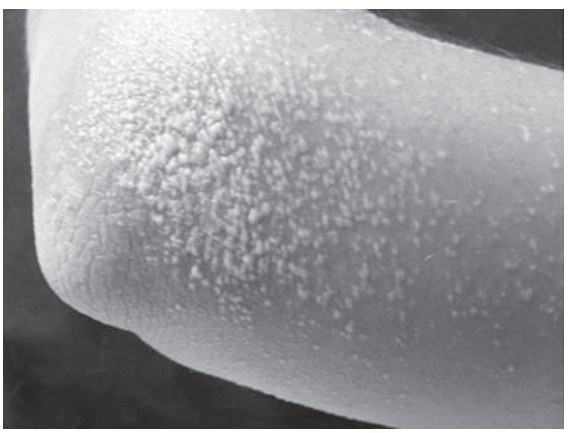

Fig. 1. Erythematous eruption with diffuse superficial nonfollicular pustules on the elbow.

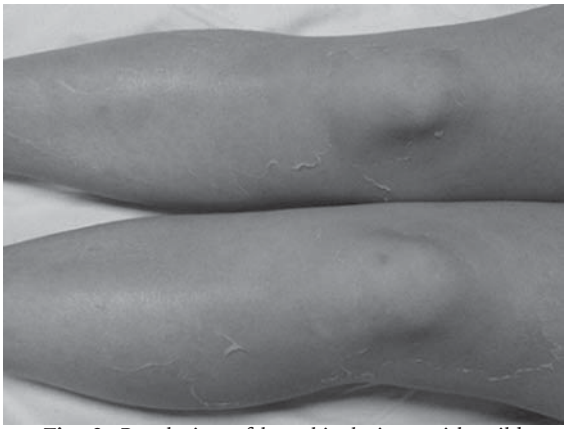

Fig. 2. Resolution of her skin lesions with mild desquamation as seen on the 10th day.

examination was otherwise normal. A skin biopsy was performed from her leg (Fig. 3), and was consistent with AGEP. Laboratory investigations showed mild leukocytosis (white blood cells [WBC]: 10,800/mm^3, range: 4,300-10,300/ mm^3) and elevated transaminases (alanine aminotransferase [ALT]: 90 IU/L (range: <41 IU/L), aspartate aminotransferase [AST]: 70 IU/L (range: <37 IU/L)). Serologic screening for Epstein-Barr virus, cytomegalovirus, hepatitis B virus, Parvovirus and mycoplasma was negative. Bacterial culture of the pustule and blood revealed no growth of microorganisms. Her mercury level was below the toxic level. She was admitted to the hospital due to widespread rash and fever, and oral methylprednisolone 0.5 mg/kg/day and hydroxyzine were started. On the second day of admission, she became afebrile and pustular lesions started to resolve. Oral methylprednisolone was discontinued with gradual tapering within a month. Epicutaneous testing with ACA was performed two months after the recovery, which yielded a positive result.

Discussion

Acute generalized exanthematous pustulosis (AGEP) is characterized by sudden and simultaneous onset of high fever and widespread edematous non-follicular, small, superficial pustules. The most striking feature of AGEP is the short interval between the drug administration and the onset of the disease (2-4 days). It usually begins in the intertriginous areas or on the face, and then becomes widespread. Confluence of pustules may sometimes mimic a positive Nikolsky's sign and may lead to misinterpretation as toxic epidermal necrolysis (TEN). Other skin findings, like marked edema of the face, purpura (especially on the legs), atypical targetoid lesions, blisters, and vesicles have been described but are not characteristic of AGEP. Mucous membrane involvement may occur in about 20% of the cases but it is usually mild and remains limited to one location (mostly oral)[11]. Fever above 38°C and leukocytosis are commonly observed. Mild eosinophilia may be present in about one-third of the patients[12]. Lymphadenopathy may be seen in some cases[13]. Apart from a slight reduction in creatinine clearance (60 ml/min in 30% of the cases) and a mild increase in aminotransferases, involvement of other internal organs is not expected.

Various drugs such as antibiotics, anticonvulsants, and anti-inflammatory drugs, etc. have been implicated in AGEP[12]. There are only a few case reports in the literature about ACA causing AGEP[14,15]. In one of the reports, the eruption caused by ACA was localized only to the face. Similarly, in our patient, the lesions were acral in distribution, only localized to the face and extremities. However, severe cases with hypotension and requiring intensive care can be seen[16].

The disease is self-limited, and fever and pustules resolve spontaneously within 7 to 10 days with desquamation. Therefore, no treatment is necessary, and the use of systemic corticosteroids is controversial. In this case, her fever lasted 5 days, pustules lasted 6

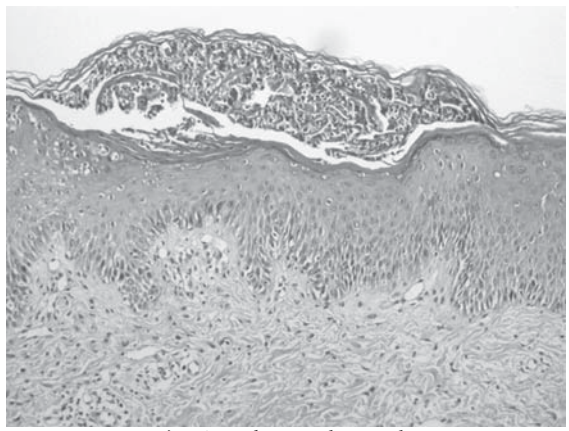

Fig. 3. Subcorneal pustule.

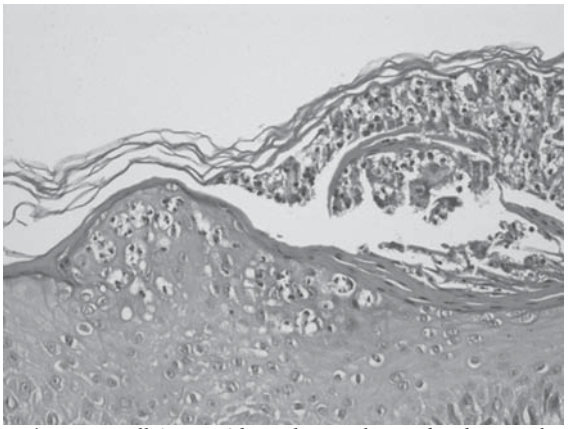

Fig. 4. Small intraepidermal pustules and subcorneal pustule.

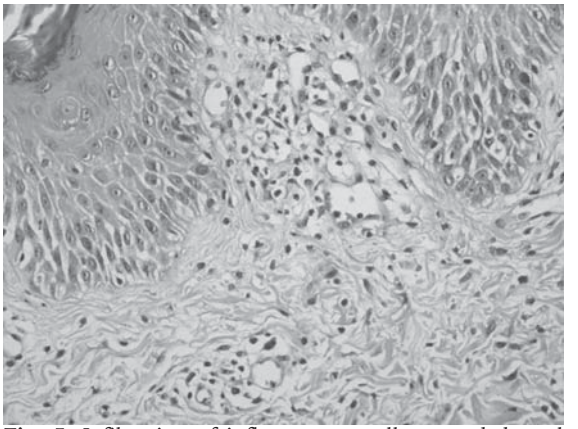

Fig. 5. Infiltration of inflammatory cells around dermal vessels and extravasation of eosinophils.

days, and resolution started the day after the administration of systemic corticosteroids.

Acute generalized exanthematous pustulosis (AGEP) is an immune-mediated reaction, in which specific T cells play an important role. They produce cytokines such as interleukin-8, which attract neutrophils to the epidermis causing pustules. Some investigators suggest that specific CD4 + T cells and probably some CD8 + cells are involved initially. Elevated interleukin-5 production by T cells and an increased production of eotaxin are the other findings in the AGEP pathogenesis. Additionally, keratinocytes produce cytokines to attract polymorphonuclear neutrophils (PMNS) and eosinophils, which play an important role in the pathogenesis of the disease[12].

For confirmation of the role of the implicated drug in AGEP, both in-vivo (especially patch tests) and in-vitro tests (the lymphocyte transformation test and cytokine release tests) are used. Patch tests are widely used and show positive reaction (pustule) with the causative drug in AGEP; however, there is little data about the efficacy of in-vivo tests.

Acute generalized exanthematous pustulosis (AGEP) can be misinterpreted as an acute infectious disease due to high fever, leukocytosis and generalized pustules. However, the pustules in AGEP are sterile. Pustular psoriasis is another disease that needs to be differentiated from AGEP. Some authors still discuss that AGEP and pustular psoriasis are related. AGEP is induced usually by drugs, has a more acute course and in most cases regresses spontaneously. Cardinal histopathological findings in AGEP are spongiform superficial pustule (intraepidermal pustules and subcorneal pustule are shown in Fig. 4), papillary edema, polymorphous perivascular infiltrate with eosinophils, and leukocytoclastic vasculitis with fibrinoid deposits[17]. Histopathology of pustular psoriasis shows spongiform pustules and a perivascular lymphocytic infiltrate with neutrophils (infiltration of inflammatory cells around dermal vessels and extravasation of eosinophils in our case can be seen in Fig. 5); papillary dermal edema, parakeratosis, acanthosis, and papillomatosis may also be present. In pustular psoriasis, eruption classically begins in the intertriginous areas and then spreads centrifugally; however, the lesions can also begin on the abdomen.

In our patient, the symptoms occurred quite early, as itching started 24 hours after the intake of the first dose. This may be explained by previous sensitization of the patient five years before when she had a similar pustular eruption with ACA. AGEP usually involves the body in a generalized fashion[15] but interestingly, in our patient, pustules were localized, limited only to the extremities and face.

In conclusion, recognition of AGEP, which can be caused by ACA, is important to avoid unnecessary investigations and/or the administration of expensive and sometimes hazardous drugs.

REFERENCES

1. Ersoy S, Paller AS, Mancini AJ. Acute generalized exanthematous pustulosis in children. Arch Dermatol 2004; 140: 1172-1173.

2. Goh TK, Pang SM, Thirumoorthy T, Goh SG. Acute generalized exanthematous pustulosis and toxic epidermal necrolysis induced by carbamazepine. Singapore Med J 2008; 49: 507-510.
3. Beylot C, Bioulac P, Doutre MS. Pustulosis exanthematiques aigus generalisees; a propos de 4 cas. Ann Dermatol Venereol 1980; 107: 37-48 as quoted in Roujeau JC, Bioulac-Sage P, Bourseau C, et al. Acute generalized exanthematous pustulosis - analysis of 63 cases. Arch Dermatol 1991; 127: 1333–1338.
4. Shelly ED, Shelly WB. The subcorneal pustular drug eruption: an example induced by norfloxacin. Cutis 1988; 42: 24–27.
5. De Coninck AL, Van Strubarq AS, Pipleers-Marichal MA, et al. Acute generalized exanthematous pustulosis induced by paracetamol. A case with severe hemodynamic disturbances. Dermatol 1996; 193: 338–341.
6. Blodgett TP, Camisa C, Gay D, et al. Acute generalized exanthematous pustulosis secondary to diltiazem therapy. Cutis 1997; 60: 45-47.
7. Paradisi A, Bugatti L, Sisto T, et al. Acute generalized exanthematous pustulosis induced by hydroxychloroquine: three cases and a review of the literature. Clin Ther 2008; 30: 930-940.
8. Nantes Castillejo O, Zozaya Urmeneta JM, Valcayo Peñalba A, et al. Acute generalized exanthematous pustulosis induced by omeprazole. Gastroenterol Hepatol 2008; 31: 295-298.
9. Altaykan A, Boztepe G, Erkin G, et al. Acute generalized exanthematous pustulosis induced by bleomycin and confirmed by patch testing. J Dermatolog Treat 2004; 15: 231-234.
10. Rastogi S, Modi M, Dhawan V. Acute localized exanthematous pustulosis (ALEP) caused by Ibuprofen. A case report. Br J Oral Maxillofac Surg 2009; 47: 132-134.
11. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP) – a clinical reaction pattern. J Cutan Pathol 2001; 28: 113–119.
12. Roujeau IC, Bioulac-Sage P, Boursean C, et al. Acute generalized exanthematous pustulosis - analysis of 63 cases. Arch Dermatol 1991; 127: 1333-1338.
13. Eeckhout I, Noens L, Ongenae K, al Sarraf Z, Schelfhout A, Naeyaert JM. Acute generalized exanthematic pustulosis: a case with a lymphoma-like presentation. Dermatology 1997; 194: 408.
14. DeThier F, Blondeel A, Song M. Acute generalized exanthematous pustulosis induced by amoxycillin with clavulanate. Contact Dermatitis 2001; 44: 114-115.
15. Betto P, Germi L, Bonoldi E, et al. Acute localized exanthematous pustulosis (ALEP) caused by amoxicillin–clavulanic acid. Int J Dermatol 2008; 47: 295–296.
16. Riten K, Shahina Q, Jeannette J, et al. A severe case of acute generalized exanthematous pustulosis (AGEP) in a child after the administration of amoxicillin-clavulanic acid: brief report. Pediatr Dermatol 2009; 26: 623-625.
17. Criton S, Sofia B. Acute generalized exanthematous pustulosis. Indian J Dermatol Venereol Leprol 2001; 67: 93-95.