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Case Report

An Atypical Case of Acute Generalized Exanthematous Pustulosis with Steven Johnson's Syndrome-Like Features Triggered by a Bacterial Infection

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Abstract

Acute generalized exanthematous pustulosis (AGEP) is a rare clinical entity characterized by sudden onset of non-follicular sterile pustules over erythematous skin and accompanied by fever and leukocytosis. Although the most frequent cause of AGEP is systemic drug administration, AGEP cases triggered by infections have occasionally been described. We report a case of a 74 year-old-female who developed an atypical presentation of AGEP, induced by a bacterial infection of her pubic region. To the best of our knowledge, this is the first case of AGEP associated with a *Pseudomonas aeruginosa* infection.

Keywords: Acute generalized exanthematous pustulosis (AGEP); Bacterial infection, mucous involvement; Therapy

Abbreviations: AGEP: Acute Generalized Exanthematous Pustulosis; SCARs: Cutaneous Adverse Reactions to Drugs; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis

Introduction

AGEP is one of the clinical entities in the spectrum of Severe Cutaneous Adverse Reactions to drugs (SCARs), along with drug reaction with eosinophilia and systemic symptoms (DRESS) and epidermal necrolysis (Stevens-Johnson syndrome–toxic epidermal necrolysis [SJS-TEN]). SCARs present with a variety of cutaneous manifestations, systemic symptoms, laboratory findings and histological features, some of which may overlap and therefore pose diagnostic challenges. More specifically, AGEP is a severe reaction characterized by an acute onset of small non-follicular sterile pustules on an erythematous background, fever and neutrophilia. It is considered drug-related in over 90% of cases [1-3], but other causative factors have been described, including bacterial, viral and parasitic infections [4]. Skin eruptions can be accompanied by lymphadenopathy, but multi-organ involvement is uncommon. In 20-25% of cases, mucosal erosions are present [1,5] and in severe cases, SJS/TEN can be mimicked. However, despite ambiguities among SCARs, an accurate diagnosis is imperative for the appropriate management of these severe reactions in order to limit morbidity and potentially chronic sequelae. In this paper, we report a clinical case of an atypical AGEP triggered by a bacterial infection of the groin which demonstrates the necessity for early recognition and distinction between SCARs. Furthermore, it highlights the importance of diagnosing atypical forms of SCARs which are attributed to an infection, rather than an offending drug.

Case

A 74-year-old obese female with a history of arterial hypertension treated for the last twelve years with hydrocholothiazide and amlodipine combination, presented to our clinic with a generalized pruritic erythematous eruption with widespread non-follicular pustules (Figure1) mainly around the skin folds, and collarette-shaped desquamation on her upper trunk, abdomen, palms and soles (Figure 2). The hypogastric, pubic and inguinal area appeared edematous, erythematous, with erosions and ulcers with purulent discharge (Figure 3).The initially rash was observed 10 days ago and limited to the hypogastric region and femoral folds. Despite the treatment with methylprednisolone 16mg and itraconazole 200mg p.o. daily for the last 7 days, the exanthema extended all over the skin and involved the oral and nasal cavity.

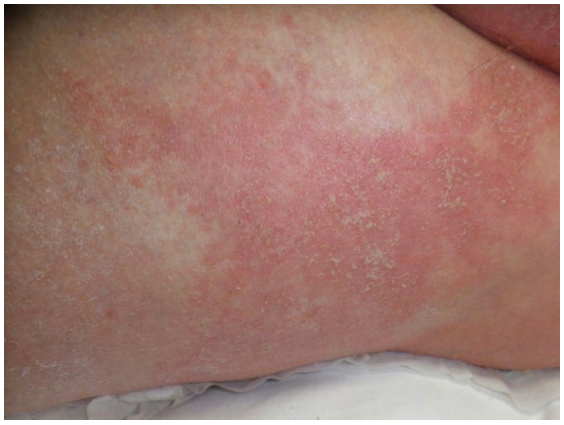

Figure 1: Pruritic erythematous eruption with widespread non-follicular pustules mainly around the skin folds.

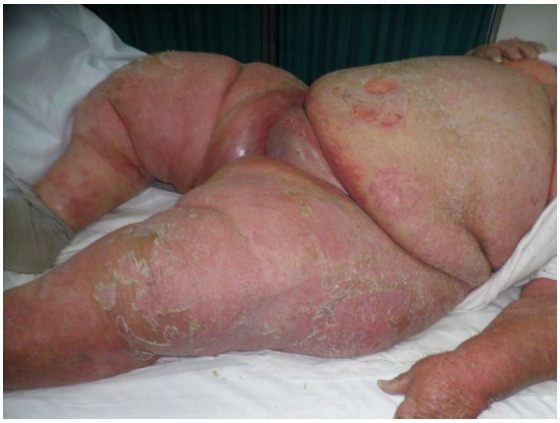

Figure 2: Collarette-shaped desquamation on her upper trunk, abdomen, palms and soles.

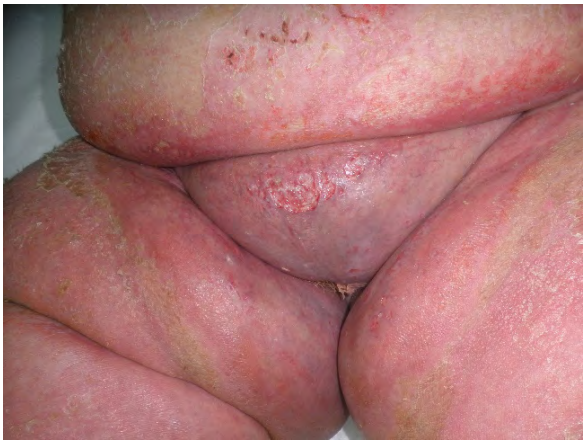

Figure 3: The hypogastric, pubic and inguinal area appeared edematous, erythematous, with erosions and ulcers with purulent discharge.

The patient was admitted hemodynamically stable and afebrile. Laboratory tests showed elevated CRP (98.5mg/L), leukocytosis (WBC: 21.7 10^3/μL) with neutrophilia (93.7%), anemia (hematocrit: 36.3%) hypoproteinemia and slightly increased creatinine levels (1.4 mg/dL). Histopathological exam revealed subcorneal pustules and edema of the papillary dermis (Figure 4). Perivascular imflammatory infiltrates of mainly neutrophils and lymphocytes were also noted.

Since her blood pressure measurements were within normal range, her hypertensive treatment was suspended. Cefuroxime 1.5gr I.V. t.i.d. was administered to empirically treat her hypogastric and inguinal region infection, which resulted in an immediately improvement of her eruption. However, urine cultures and cultures from the purulent erosions of the groin revealed *Pseudomonas aeruginosa* involvement, susceptible to ceftazidime, and her antibiotic was switched to ceftazidime 1g I.V. b.i.d for the following 10 days. Topical emollients, compresses with potassium permanganate and boric acid were applied. A topical mixture containing mupirocin, miconazole and betamethasone was also applied to the nasal and oral cavities. Intravenous fluids were also administered and her fluid and electrolyte balance were closely monitored. Acetaminophen i.v. was also given upon request to minimize the pain, particularly of her oral cavity and inguinal area.

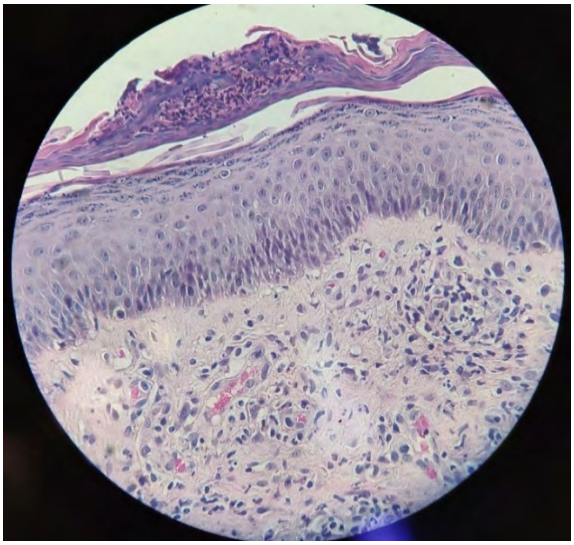

Figure 4: Histopathological exam revealed subcorneal pustules and edema of the papillary dermis.

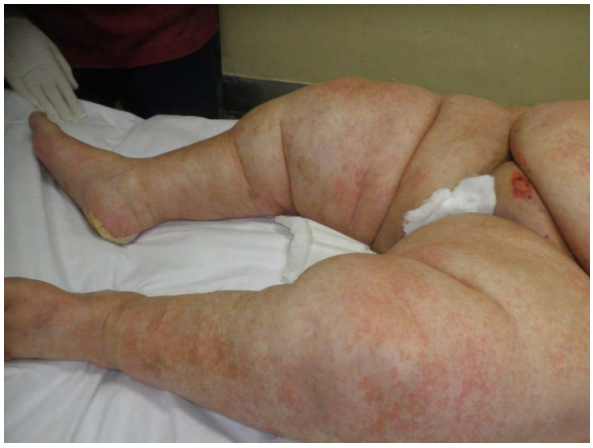

Figure 5: A typical collarette-shaped desquamation in most areas of her body.

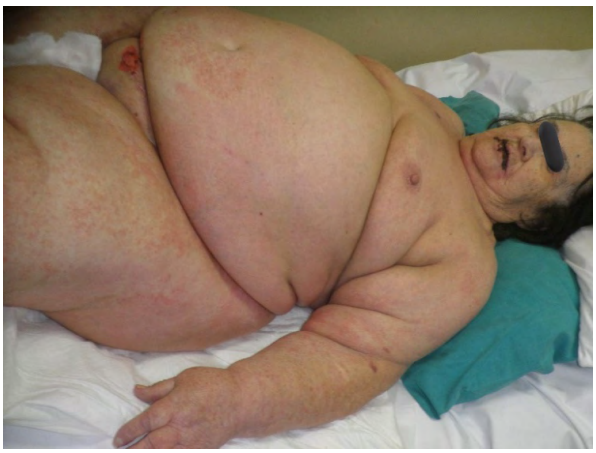

Figure 6: The oral and groin lesions healed and the pain subsided.

In the following days, the patient remained hemodynamically stable and spiked a low grade fever of 37.6 C on her second day of hospitalization. Ten days after the antibiotic initiation, the eruption showed significant improvement, with spontaneous resolution of pustulosis, which was succeeded by a typical collarette-shaped desquamation in most areas of her body (Figure 5). The oral and groin lesions healed (Figure 6) and the pain subsided. Furthermore, the leukocyte and neutrophil counts and creatinine returned to normal. However, CRP remained elevated. A second urine culture revealed an *E. coli* urinary tract infection, which was treated with nitrofurantoin 100mg t.i.d. in an outpatient setting.

Discussion

According to the Acute Generalized Exanthematous Pustulosis EuroSCAR validation score [5], the patient had a diagnosis of AGEP. AGEP is a rare condition which, although in the majority of cases, constitutes a severe drug reaction, in this particular case it seems that it was triggered by a bacterial infection. Apart from drugs, AGEP can be induced by viral [6,7], bacterial [8-11], or parasitic infections [12], hypersensitivity to mercury [13] and spider bites [14]. Therefore, it is critical to consider AGEP in differential diagnosis when confronted with patients with compatible clinical, laboratory and histology findings, even in the absence of a possible drug as an etiologic factor.

Our case is an atypical case of AGEP. High grade fever was not reported possibly because of corticosteroid therapy that proceeded and the promptly instituted antibiotic therapy along with acetaminophen administered for pain. Mucosal involvement, especially oral, is not unlikely in AGEP. It is usually mild, and frequently affects only one mucosal region [1], in contrast to SJS where mucous membrane lesion is the norm and has a dramatic clinical presentation [15]. SJS is generally more severe than AGEP, characterized clinically by secondary detachment of the epidermis, visceral organ involvement and histopathologically by epidermal necrosis, all of which were absent in our case. In our case, the histology findings correlated with the laboratory tests, were critical for the final diagnosis. Although overlap cases of AGEP and SJS/TEN have been reported in the literature [16-21], whether they qualify for both entities is up to debate. Retrospective studies have shown that confirmed overlap SCARs are rare [22]. Moreover, even in AGEP cases with SJS characteristics, it is unclear whether a true overlap exists, and it can be thought as a developmental process where AGEP progresses to a more severe condition, SJS or even TEN. In our case, it was considered the manifestation of a severe, aggressive form of AGEP with erosive oral and nasal mucosal involvement since the diagnosis of AGEP is supported by a convincng biopsy result.

All SCARs are considered to be delayed, type IV hypersensitivity reactions according to the classification by Coombs and Gell. However, AGEP, unlike SJS, is believed to be a T cell-mediated neutrophilic inflammatory response (type IVd) [23], where activation of cytotoxic T- cells induce the apoptosis of keratinocytes, leading to subcorneal vesicles [24]. In addition, T-cells in AGEP patients produce significantly more IL-8, a potent neutrophil chemotactic chemokine, which plays a central role to neutrophilic recruitment and pustule formation [24,25]. In contrast, in SJS, granulysin is the key cytokine responsible for the destruction of the epidermis [26]. These distinct inflammatory mediators in different forms of SCARs lead to the individual clinical, histopathological and laboratory findings that characterize each reaction and might even explain the difference in latent periods between SJS and AGEP. Unlike SJS, drug-induced AGEP eruptions can present 48-96 hours after the introduction of the offending drug. We speculate that the latent period in our case was longer and the rash expended slower than in usually drug-induced AGEP, due to the persistence of the bacterial infection

as a causative factor of her exanthematous pustulosis and the systemic administrated corticosteroid. A recent article proves that non-invasive MRSA adhesion to corneocytes induces a local inflammatory response in underlying skin layers [27]. This signalling recruits neutrophils to the skin, where they control bacterial numbers, mediating transiency in colonization. As IL-8 is a major mediator for inflammatory response and neutrophils, we assume that the persistence of the asymptomatic urinary infection proceeded or followed the Pseudomonas Aeruginosa skin infection and led to a dysregulation of IL-8 and neutrophil "conversation" in the process of AGEP clinical evolution. Neutrophils can play a dual role and apart from their antimicrobial function, deregulation of neutrophils and their hyperactivity can lead to tissue damage in severe inflammation [28]. Besides, it has already been mentioned in a case report that recurrent AGEP might be closely related to recurrent urinary tract infections [10].

Treatment of drug-induced AGEP is based on the discontinuation of the causative drug, topical steroid application, antipyretics and in severe cases systemic corticosteroid administration [4,5]. Furthermore, increasing evidence suggests that IL-17 plays a key role in the pathogenesis of AGEP and increased levels of IL-17 have been found in AGEP patients [29]. Indeed, recent therapeutic approaches, targeting the IL-17-signaling pathway have helped treat prolonged, recalcitrant AGEP [30,31]. It is therefore imperative that the causative factor is clarified when confronted with AGEP cases, especially since immunosuppressants and immunomodulatory drugs such as IL-17 inhibitors are being used therapeutically. In cases where infection is the triggering factor, use of such agents could be detrimental. Although mortality rate for AGEP is relatively low [5,32], it is imperative that it is correctly diagnosed in the elderly and in patients with co-morbidities or those with existing infections. In such cases, administration of systemic antibiotics, albeit the main culprit for drug-induced AGEP, can be life-saving.

Conclusion

In conclusion, we report a case of an atypical AGEP with SJS-like features, triggered by a bacterial infection of the groin. Our case suggests the necessity to remain vigilant in order to properly diagnose AGEP cases not related to drugs, but rather to an infectious process. It also underlines the fact that in these cases, antimicrobials should be promptly administered in spite of the fact that antibiotics are the leading cause of SCARs. Lastly, it demonstrates the importance of distinguishing AGEP from SJS/TEN since prognosis and management differ considerably.

Declarations

Ethics approval and consent to participate - yes
Consent for publication - yes
Availability of data and material - yes
Competing interests - none
Funding - none

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