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LT Mark C. Hubbard, LT John C. Walsh, LCDR Megan A. Brelsford

ABSTRACT

Introduction: Cutaneous symptoms are highly common in patients presenting to their primary care providers. However, severe cutaneous adverse reactions are most likely to present to the urgent care and emergency departments. Physicians practicing in routine primary care clinics should also be familiar with the presentation, early diagnosis, and treatment of severe drug reactions that may present to ambulatory clinics at the early clinical stages.

Case Report: Here we present a case of acute generalized exanthematous pustulosis which developed in the setting of exposure to unknown brands of sunscreen and aloe vera in an otherwise healthy 19-year-old male. Upon presenting to his primary care physician all possible inciting agents were discontinued and systemic involvement was ruled out. He recovered completely within two weeks of eliminating all potential exposures to inciting agents.

Conclusion: Proper triage, workup, treatment, and disposition are essential in cases of acute, rapidly progressive rashes, even when identification of the offending agent may not be apparent. Ambulatory care providers should be familiar with the diagnosis of acute generalized exanthematous pustulosis and its management, especially since many of the causative drugs are obtained on an outpatient basis.

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CASE REPORT

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should be familiar with the diagnosis of acute generalized exanthematous pustulosis and its management, especially since many of the causative drugs are obtained on an outpatient basis.

Keywords: Acute generalized exanthematous pustulosis (AGEP), Drug rash, Pustular rash, Severe adverse cutaneous reaction

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INTRODUCTION

Skin disease is prevalent in nearly one-third of patients seen in the primary care setting, requiring physicians in these practices to have a broad based knowledge of a variety of cutaneous disease presentations [1]. This includes the ability to recognize, initiate proper treatment, and swiftly refer rare presentations of emergent and rapidly evolving rashes. While many of the most severe cutaneous reactions are likely to present initially to the emergency department, it is important not to neglect the role of the ambulatory care provider in managing those cases which present to a clinic. In one such reaction, acute generalized exanthematous pustulosis (AGEP),

early and accurate intervention can prevent unnecessary treatments and diagnostic tests and will usually quickly lead to spontaneous resolution of symptoms [2].

AGEP is rare cutaneous reaction that falls in the category of severe cutaneous adverse reactions along with Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash eosinophilia and systemic symptoms, and serum-sickness-like reaction [3]. It can occur in any person with exposure to one of a variety of inciting agents, most commonly antibiotic or antimalarial drugs [2]. The presentation begins rapidly with an eruption of dozens to hundreds of small, sterile pustules on the face or intertriginous regions and is mediated by drug-specific T cells [4]. The mainstay of treatment is discontinuation of the eliciting agents and supportive care [2]. Most cases will resolve over 14 days without further intervention, however, there have been reports of lethal cases of AGEP [2, 5].

A case of acute generalized exanthematous pustulosis (AGEP) which presented to our ambulatory clinic will be presented below. Our case is unique in that the patient presented to his primary care provider the same day the rash began. We were able to obtain a rapid workup and quick referral to dermatology. Also unique is our suspicion that the inciting agent was a topical lotion, however, no etiology was objectively confirmed. By immediately discontinuing any possible inciting exposures, ruling out systemic involvement, making an accurate diagnosis, and avoiding additional unnecessary medications and procedures, the ambulatory care provider can initiate the most important steps in preventing progression and ultimately treating this condition.

CASE REPORT

An otherwise healthy 19-year-old male developed tender right submandibular lymphadenopathy and subjective fever the evening of disembarkation following a Caribbean cruise. The next evening, a diffuse pustular rash erupted on the left side of his neck. Over the following 48 hours, while traveling home, it progressed to cover his face, part of his neck, upper chest, and upper back despite self-treatment with diphenhydramine and 1% hydrocortisone cream (Figure 1). The rash was pruritic and accompanied by a mildly painful burning sensation made worse with pressure against the skin. The morning of his arrival home, three days after symptoms began, he presented to his primary care provider.

The patient reported he had used a new chemical sunscreen beginning one week prior to symptom onset and over the counter aloe vera lotion beginning 48 hours prior to symptom onset. He adamantly denied any other drug use in the previous 12 weeks. His only known allergy is shellfish, to which he denied exposure. He had an otherwise unremarkable review of systems. At presentation, his subjective fevers had resolved and all his vital signs remained within normal ranges throughout

the course of the eruption. His physical examination included tender right cervical lymphadenopathy and a diffuse pustular eruption on his face, neck, back, chest, and arms set on an erythematous base. No mucous membranes were involved. No ulcerations or bulla were noted.

The patient was referred to the emergency department for further evaluation. His C-reactive protein was elevated to 31.7 mg/L and the neutrophil count was 7952 cells/ μ L. A basic metabolic panel was unremarkable. He received a 60 mg dose of oral prednisone and was discharged.

The day following his treatment in the emergency department his symptoms were mildly improved (Figure 2A–B). A same day dermatology consult was placed. He was diagnosed with acute generalized exanthematous pustulosis (AGEP) based on the history and appearance of the cutaneous eruption. No biopsy was obtained. He was treated with topical 1% hydrocortisone ointment

Figure 1: Appearance of the rash on the day of presentation.

Figure 2: (A, B) Appearance one day following steroid treatment and discontinuation of all medications.

Figure 3: Resolution of rash two weeks following initial presentation.

daily and managed symptomatically with hydroxyzine and pramocaine lotion. His lesions resolved with desquamation over the next two weeks (Figure 3). The patient did not suffer any permanent or long-term sequela from his AGEP.

DISCUSSION

Acute generalized exanthematous pustulosis (AGEP), which was first described in 1968 and later identified as a unique diagnosis in 1980, is a relatively rare cutaneous eruption occurring in less than 1 in 5 million persons per year without a predilection for age or gender [2]. AGEP is characterized by the acute onset of dozens of non-follicular pustules (<5 mm) on a diffusely edematous and erythematous background. It most often begins on the face or in the intertriginous regions before rapidly becoming generalized in either a patchy or diffuse pattern [2]. The rash may be accompanied by symptoms of pruritus and burning which can worsen with pressure against the skin.

AGEP is considered a hypersensitivity reaction mediated by sensitized drug-specific T cells [4]. Presentation of symptoms can occur over a range of hours to weeks after exposure to a new drug [2]. In one study, symptoms presented a median of 1 day after exposure to antibiotics, while all other causative drug agents had a median presentation of symptoms 11 days following initiation of the inciting drug [6]. The rash is expected to resolve with desquamation within two weeks after the offending agent is discontinued [2, 7].

Acute generalized exanthematous pustulosis (AGEP) defining features are the abrupt onset of fever, non-follicular pustulosis, peripheral neutrophilia, and rapid resolution (<15 days) with removal of the inciting agent [7]. However, the differential diagnosis remains broad in the acute phase of AGEP, including: toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), subcorneal pustular dermatosis (Sneddon-Wilkinson disease), pustular vasculitis, sweet syndrome, and pustular psoriasis (von Zumbusch type) [8]. DeClerk [9] et al. developed a table to help differentiate AGEP from many other similar rashes based on the timing interval from drug exposure, associated symptoms, and appearance of the eruption. Additionally, the EuroSCAR validation score for AGEP can be used to determine the likelihood that the eruption is consistent with AGEP based on the eruption's morphology, course, and histology [2]. Using this 18 point scoring system, which breaks the likelihood of AGEP into possible, probable, and definite, our patient met the criteria for definite AGEP.

To assist in confirming the diagnosis, a sterile gram stain is likely to support drug rash over an infectious etiology in the acute setting. A biopsy may be required to differentiate AGEP from other pustular eruptions. A histologic sample of AGEP will show sterile intraepidermal, intracorneal or subcorneal spongiform

pustules which may include embedded eosinophils. The surrounding tissue is typically associated with dermal edema, acantholysis, dermal neutrophilic invasion, and focal keratinocyte necrosis. There will be an absence of tortuous dilated blood vessels [10].

Generally, AGEP presents with minimal systemic symptoms. It is commonly associated with mild mucous membrane involvement (20%), mild eosinophilia (33.3%), lymphadenopathy, reduced creatinine clearance, and mildly elevated aminotransferases [2, 7]. If the patient has significant eosinophilia, cytopenia, or organ impairment, SJS or DRESS may be more likely diagnoses than AGEP [9]. While organ involvement is uncommon, it may be more likely to occur if the patient is elderly or immunocompromised [11]. One review identified systemic involvement in the acute phase of the disease in approximately 17% of patients, including liver, kidney, bone-marrow, and lung involvement [11]. Mortality rates have been reported between 2–5% [9, 11].

Definitive treatment of AGEP depends on removal of the offending agent, supportive care, and prevention of infection. The offending agent is a drug in >90% of cases [2]. More than 54 reported drugs have been implicated. The most commonly associated are penicillins, cephalosporins, macrolides, calcium channel blockers, and antimalarials [2, 12]. AGEP has also been linked to contrast media, infective agents (Parvovirus b19, CMV, Coxsackie B4, *Mycoplasma pneumonia*), brown recluse spider bites, and herbal medications; however, the association with infective agents is debatable [2, 6]. Additionally, there have been links of AGEP to topical medications. Most notable is proposed a link between methylchloroisothiazolinone and a pustular drug eruption [13]. Isothiazolinones are highly prevalent in cosmetic products and well known to cause contact dermatitis in sensitized patients. Given our patient's inability to recall the brand of topical products he used, it is unclear if this was the case.

Additional testing may be required to determine the inciting factor in AGEP cases. To confirm the diagnosis and association with a specific agent, patch testing with the suspected drugs may be useful 4–6 weeks after disease resolution. This method has been successfully used to identify the offending drug in approximately 60 percent of cases [12, 14]. Patch testing is considered to be safe, though there have been reports of systemic AGEP-like reactions with skin patch testing [15]. Our patient declined skin patch testing for aloe vera or other common sunscreen ingredients.

The etiology of our patient's case AGEP is unclear. It would be difficult to determine whether the cause was a topical product (sunscreen/aloe vera), a virus, or unacknowledged drug use without further testing. Most importantly, he was instructed to discontinue all unnecessary topical products and oral medications, which led to a rapid resolution of his symptoms. Fortunately, he had no end organ involvement with his case of AGEP. At

8 months follow up, this patient had no reoccurrence of his symptoms with avoidance of aloe vera products.

Primary care physicians must be aware of potential serious adverse drug reactions when they present in order to appropriately triage the patient to a higher level of care, dermatologist or burn center as required. It is paramount that possible eliciting agents are discontinued and systemic involvement is ruled out. If the patient is not rapidly improving, a biopsy for further investigation is warranted early.

CONCLUSION

Acute generalized exanthematous pustulosis (AGEP) is an acute, rapidly progressive pustular rash caused predominately by medications (anti-infective agents most commonly) that can lead to serious complications if not properly diagnosed and intervened upon. This rare diagnosis requires quick recognition of complications and cessation of all possible contributing causes. Physicians should expect rapid resolution if the offending agent is appropriately discontinued.

Author Contributions

LT Mark C. Hubbard – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data; Drafting the article; Final approval of the version to be published

LT John C. Walsh – Substantial contributions to conception and design, Analysis and interpretation of data; Revising it critically for important intellectual content; Final approval of the version to be published

LCDR Megan A. Brelsford – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data; Revising it critically for important intellectual content; Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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SUGGESTED READING

- Bellew SD, Kummer T. Figures in emergency medicine. Acute generalized exanthematous pustulosis. *Ann Emerg Med*. 2015;65(2):146.

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