

ORIGINAL CONTRIBUTION

A Unique Pattern of Staphylococcal Scalded Skin Syndrome–Like Erosions in Patients with Atopic Dermatitis: Dermatitis flammeus

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ABSTRACT

We describe the clinical features of a novel complication in patients with atopic dermatitis (AD). Twenty patients, mean age 23 years, with AD who presented with staphylococcal scalded skin syndrome (SSSS)–like lesions were included between January 2008 and September 2010. Skin lesions followed a triphasic progression pattern from erythema to hyperpigmentation and then erosions. A symmetric and predominant flexural involvement was observed. *Pseudomonas aeruginosa* (PA) (38.9%) and *Staphylococcus epidermidis* (38.9%) were the most frequently cultured bacteria from skin swabs. Complete resolution was evident in all cases, and the recurrence rate was 35%. In conclusion, a unique complication characterized by triphasic progression to painful erosions was found in a cluster of AD patients. We propose the new term “dermatitis flammeus” to describe this phenomenon, with PA being one of the etiologies. (SKINmed. 2018;16:309–313)

AD is a common inflammatory disease characterized by a chronic relapsing course and significant pruritus. The lifetime prevalence of AD ranges from 10% to 20% in children and 1% to 3% in adults.¹ The worldwide prevalence of AD has increased two- to threefold over the past few decades.² Classic signs of AD are erythema, edema/papulation, crust/oozing, excoriations, and lichenification. Impetigo, erysipelas, furuncles, and eczema herpeticum are associated cutaneous infections caused by *Staphylococcus aureus*, *Streptococcus* species, and herpes simplex virus respectively. We encountered 20 patients with underlying AD who presented with a distinctive pattern of SSSS-like skin lesions from January 2008 to September 2010. To the best of our knowledge, such a pattern of skin condition has not been described in association with AD. In our study, we reviewed the demographic patterns, clinical features, microbiologic profile, treatment, and prognosis of this novel complication of AD.

METHODS

A retrospective medical record review was conducted in the dermatology unit of a tertiary university hospital (Queen Mary Hospital) and a private specialist clinic in the 32-month period between January 2008 and September 2010. Patients with AD who presented with a distinctive pattern of SSSS-like erosions were included. All patients had been assessed by at least one of the three dermatologists in the aforementioned centers. AD severity was classified into mild, moderate, or severe according to the Physician's Global Assessment.

Intercooled Stata (version 9.2) was used for statistical calculations. Dichotomous variables were analyzed with the χ^2 test or Fisher's exact test as appropriate, and continuous variables were analyzed with the Student t test. A P value of .05 was considered statistically significant.

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RESULTS

DEMOGRAPHIC DATA

A total of 20 patients were included in the case series. No sex predilection was observed. The mean age was 23 years (range 17 months to 52 years). Pediatric patients (age less than 18 years) accounted for more than one third of cases (8 of 20 [40%]). Four patients (20%) had severe AD, 10 (50%) had moderate AD, and 6 (30%) had mild AD. All patients were on topical corticosteroid, and two patients were on systemic immunosuppressants on presentation (mycophenolate mofetil in case 4, cyclosporine A in case 8).

CLINICAL FEATURES

Characteristic skin lesions were observed in all 20 patients in our series. A pattern of triphasic progression—1, erythematous phase; 2, hyperpigmented phase; 3, erosive phase—was observed in all patients, with variable severity and duration. Skin lesions started acutely as large (more than 5 cm in the longer diameter), ill-defined erythematous patches on the pre-existing eczematous lesions (erythematous phase) (Figure 1). All patients experienced significant pain during and persisting beyond this phase. The pain was consistently described to be sharp, burning in nature, and sometimes so severe as to render the patients unable to flex their necks or limbs. The phase of tender patches typically lasted for 1 to 2 weeks, when the erythema gradually evolved into a dark brown pigmentation (hyperpigmented phase) (Figure 1).

The development of hyperpigmentation occurred in parallel to spontaneous shedding of the superficial part of the skin in the affected areas (erosive phase) (Figure 2). Extension of the erosion was noted upon application of lateral pressure to the involved areas, analogous to the classic Nikolsky sign. While the burning sensation persisted, the erosive process typically smouldered over the next 2 weeks. Significant postinflammatory hyperpigmentation was a prominent feature upon resolution of the erosions. Pyrexia or other constitutional clinical manifestations were not observed. A predominant flexural involvement was observed in the majority of patients (17 of 20 [85%]), with symmetrical distribution of the lesions in all cases. The distribution of the affected areas is summarized in Figure 3.



Figure 2. Spontaneous shedding of large areas of superficial parts of skin (the “erosive phase”) was evident after the transient “hyperpigmented phase.” In case 2, extensive erosive lesions were observed over the lower abdomen, groin regions, and legs.



Figure 1. Case 18. Erythematous lesions appeared bilaterally on the groin and inner thighs over pre-existing eczematous lesions in a 27-year-old woman. Hyperpigmentation was noted to appear gradually after the “erythematous phase.”

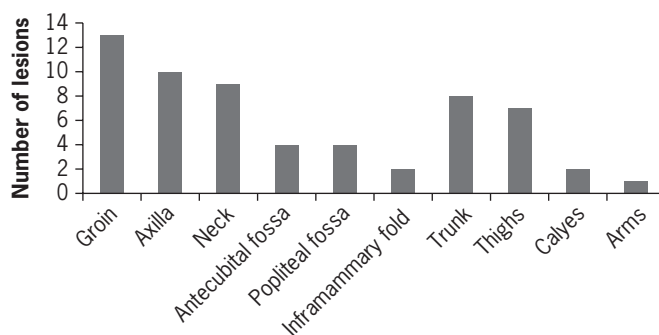


Figure 3. Distribution of the skin lesions.

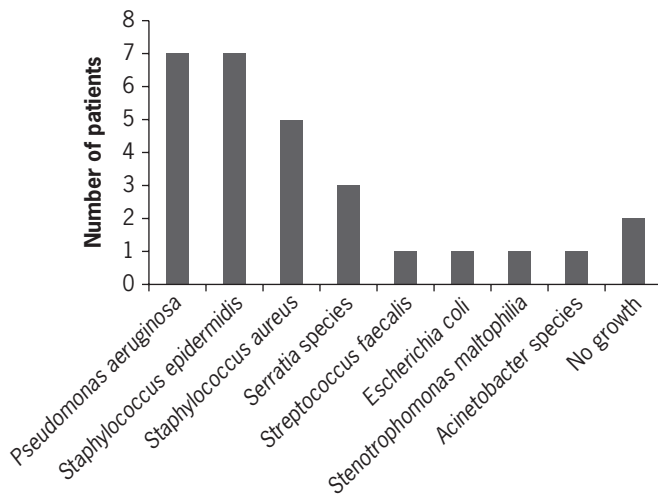


Figure 4. Results of bacterial cultures in superficial skin swabs.

MICROBIOLOGIC PROFILE

Superficial skin swabs for bacterial culture were performed in most cases (18 of 20 [90%]). Positive bacterial cultures were found in 16 patients (80%). PA (7 of 18 [38.9%]) and *S. epidermidis* (7 of 18 [38.9%]) were the most frequently cultured bacteria in the series, followed by *S. aureus* (5 of 18 [27.8%]) (Figure 4). Positive cultures for PA from the superficial skin swabs were observed in five out of the six (83.3%) hospitalized patients (cases 1, 2, 12, 16, and 18) on the first day of admission. The culture results are summarized in Figure 4.

HISTOPATHOLOGIC AND SEROLOGIC FINDINGS

Four hospitalized adult patients underwent skin biopsies of the active lesions during the erythematous phase (see the Table for details). Focal acantholysis in the stratum spinosum was observed in one case (case 1). Subcorneal pustules with neutrophilic

Table. Skin Biopsy Findings and Immune Markers Profile of Four Hospitalized Patients

CASE NO.	SEX	AGE (YEARS)	SKIN BIOPSY SITE	HISTOLOGIC FINDINGS	IMMUNE MARKERS
1	F	29	Back	Compact hyperkeratosis and parakeratosis	Anti-skin Ab 1:160 (ICS)
				Subcorneal micropustules containing abundant neutrophils	
				Focal acantholysis in superficial stratum spinosum	
				Direct immunofluorescence of nonlesional skin -ve	
2	F	36	Left thigh	Compact hyperkeratosis and parakeratosis	Anti-skin Ab 1:40 (ICS)
				Mild perivascular lymphocytic infiltrate	Antinuclear Ab -ve
				No acantholysis or subepidermal or intraepidermal blisters	
				Direct immunofluorescence -ve	
18	F	27	Left thigh	Parakeratosis with surface crust	Anti-skin Ab 1:40 (ICS)
				Subcorneal micropustules containing neutrophils, fibrin, and degenerating keratinocytes	Antinuclear Ab 1:320 (Ho)
					Anti-dsDNA Ab not elevated
				Direct immunofluorescence -ve	Anti-ENA Ab -ve
20	F	39	Right shoulder	Compact hyperkeratosis and parakeratosis	Anti-skin Ab -ve
				Perivascular lymphocytic infiltrate	Antinuclear Ab -ve
				No acantholysis or subepidermal or intraepidermal blisters	
				Direct immunofluorescence -ve	

Abbreviations: -ve, negative; Ab, antibody; dsDNA, double-stranded DNA; ENA, Extractable Nuclear Antigens; Ho, homogeneous; ICS, intercellular spaces.

content were noted in cases 1 and 18. Direct immunofluorescence studies were negative for immunoreactants in all biopsies. No interface change or increased dermal mucin deposition was identified in the four cases. Microbiologic staining was only positive in one case, where Gram-negative rods were identified on the epidermal surface in case 1. PA was cultured from a superficial skin swab from that patient. Serum anti-skin antibodies using monkey esophageal epithelium were positive in four patients (antibody titre 1/160 in case 1, 1/40 in case 2, 1/40 in case 18, and 1/20 in case 19), with an intercellular substance pattern.

MANAGEMENT

All patients were treated with antimicrobials. Mupirocin 2% ointment was used in all patients during the initial course of epidermal shedding. Fifteen patients (75%) were treated with systemic antipseudomonal antimicrobials, namely quinolones (ofloxacin and levofloxacin), ticarcillin-clavulanate, or piperacillin-tazobactam. Cefuroxime was ordered in 13 patients (65%). Eight patients (40%) received more than one class of antimicrobials during the course of treatment in response to their clinical condition or with reference to bacterial culture results. Ertapenem was started in case 13 due to a positive culture of extended-spectrum *bactam* lactamase producing *Escherichia coli*. Clindamycin was used in case 20 for a positive culture of methicillin-resistant *S. aureus*.

Immunomodulatory therapy with intravenous immunoglobulin (IVIG) infusion was commenced in five patients (cases 1, 2, 12, 16, and 20) with progressive skin erosion despite the use of systemic antimicrobials. IVIG was given at a dose of 1 g/kg daily for 3 consecutive days. An excellent response was achieved in all patients in which complete resolution of skin lesions was evident within 2 weeks after IVIG infusion. The average time from onset to complete resolution of skin lesions in these patients was 5 weeks (range 4 to 7 weeks).

PROGNOSIS

This skin condition has a tendency towards a smoldering clinical course. The average time from onset to complete resolution of skin lesions was 3.7 weeks (range 2 to 7 weeks). The skin erosions were confined and localized in 70% of patients, with an average time to resolution of 3.1 weeks (range 2 to 6 weeks) after outpatient management. Thirty percent of the patients had a more protracted course with progressive erosions of 10% to 30% of the total body surface area. They were hospitalized for wound care, pain control, and delivery of systemic antimicrobials. There was a statistically significant association between the presence of PA in skin swabs and hospitalization ($P=.01$).

Recurrence was common and occurred in seven patients (35%). The average time to relapse was 5.8 months (median 4 months, range 1 to 15 months). Localized recurrence of erosions, milder than the previous episodes and confined to the flexures, was encountered in cases 5, 8 and 11, and antimicrobial treatment was adequate for complete recovery. More than one recurrence was observed in cases 1 and 12.

DISCUSSION

We described here a novel distinctive pattern of SSSS-like erosions in a cluster of patients with AD. In our series, the patients shared common clinical features of triphasic progression. The first (erythematous) phase was characterized by an acute onset of tender erythema at pre-existing sites of eczematous lesions, which usually lasted for up to 2 weeks. The second (hyperpigmented) phase was characterized by transient dark brown pigmentation. This was shortly followed by the third (erosive) phase. The characteristic feature of this phase was spontaneous shedding of the superficial part of the skin. Significant pain was experienced throughout the whole course of progression. The differential diagnoses included SSSS, pemphigus foliaceus, impetigo, and Kawasaki disease. A prolonged clinical course, lack of fever and systemic upset, and good prognosis clearly excluded SSSS and Kawasaki disease.

Pemphigus foliaceus seldom goes into remission without systemic steroids and is unlikely given the negative direct immunofluorescence studies from the skin biopsies. *Staphylococcus aureus* was cultured from only 25% of our patients, and none presented with typical impetiginized lesions. No suspicious drug history was implicated in our series, and an alternative diagnosis of severe drug eruption was not favored. Based on the unique clinical features, we propose the term “dermatitis flammeus” for this novel complication of AD. “Flammeus” is Latin in origin and means “flaming” or “the color of fire.” “Dermatitis flammeus,” with the meaning of burning dermatitis, best suits the condition, as a severe burning sensation was often described throughout the disease course.

It was of particular interest that PA was found in 38.9% of the skin swabs in our series. The prevalence was even higher among patients with extensive disease (83.3%). While *S. aureus* is well known to be associated with AD,³⁻⁶ the prevalence of PA colonizing the skin of AD patients is rarely mentioned in the literature. PA is well known to colonize chronic wounds.⁷ In our series, bacterial cultures were all obtained from the superficial skin swabs at the onset of skin erosions, at time when a chronic wound status had yet to develop. We therefore suggest that PA is more likely to be pathogenic rather than existing as a quiescent colonizer in our cases.

Based on the close resemblance of the clinical features of SSSS and pemphigus to this newly described condition, we hypothesize

that the pathogenesis may involve (1) a toxin resembling *S. aureus* exfoliative toxin, or (2) autoantibodies directing the adhesive molecules of keratinocytes resembling anti-skin antibodies in pemphigus foliaceus. Studies show that exfoliative toxins produced by *S. aureus* can cleave desmoglein 1, which contributes to the classical clinical picture of epidermal detachment in SSSS.^{8,9} We propose that the pathogenesis of dermatitis flammeus may involve a similar toxin that can also cleave desmoglein 1. PA can produce several virulence factors, such as exotoxin A and type III secretion, and may be involved in hydrolysis of ceramides on atopic skin.^{10,11} A neonatal case presenting with an SSSS-like picture had also been reported to be associated with *Pseudomonas putida* infection.¹² Further investigation is needed to evaluate PA role in pathogenesis of dermatitis flammeus. It is also well known that autoantibodies against desmoglein 1 and 3 cause blisters with typical histological features of pemphigus foliaceus and pemphigus vulgaris, respectively.^{13,14}

We believe that PA or other environmental agents may act as triggering factors for the production of antibodies directing the adhesive molecules of keratinocytes. The detection of anti-skin antibodies in 80% (4 of 5) of the hospitalized patients and the satisfactory treatment response with IVIG may support the possibility of involvement of autoimmune antibodies in dermatitis flammeus; however, positive direct lesional immunofluorescent studies and detection of a unique autoantibody will be essential to substantiate such a hypothesis.

Despite the severe pain and rapid progression of erosive lesions, disease in most of the patients (two thirds) ran a modest course with localized lesions for which topical and oral antimicrobial treatment was often adequate to achieve complete recovery. No mortality was recorded in our series. The only statistically significant factor associated with hospitalization was the presence of PA in skin swabs. This is consistent with our hypothesis that PA may be involved in the pathogenesis of dermatitis flammeus.

Recurrence was unfortunately a fairly common phenomenon, occurring in 35% of patients. Due to the limitation of a retrospective study, important data such as bacterial culture results were not obtained for recurrences to further evaluate the role of PA. It will also be important that future studies aim to identify risk factors for recurrence.

In our series, mupirocin 2% ointment was employed as a local antimicrobial agent over the erosive lesions. A systemic antimicrobial was used in all patients, based on the assumption of infection complicating AD. Further studies are needed to justify the appropriate use of antimicrobials to avoid the emergence of resistant strains. Tentative use of IVIG, with the aim of systemic immunomodulation, brought about an excellent outcome in selected severe cases with extensive involvement; however, the use of IVIG

has to be further justified by more organized prospective studies and controlled trials.

CONCLUSIONS

We have described a novel complication of AD in a cluster of children and adults. We proposed the term “dermatitis flammeus” to describe this condition, which is characterized by triphasic progression to erosions with pain. We postulate that an infectious agent, PA, may be involved in the pathogenesis. Prognosis was good, but recurrence was common. Antimicrobials and IVIG may be helpful in such patients.

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