

# Recurrent Toxin-Mediated Perineal Erythema

## Eleven Pediatric Cases

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**Background:** Recurrent toxin-mediated perineal erythema is a cutaneous disease mediated by superantigens made by staphylococci and streptococci, which, to our knowledge, has only been reported in young adults. We describe recurrent toxin-mediated perineal erythema in 11 children and outline the differences between recurrent toxin-mediated perineal erythema and Kawasaki disease in this age range.

**Observations:** Eleven children (7 male and 4 female) presented with the sudden appearance of asymptomatic erythema, which was salmonlike in color and rapidly desquamating, involving the perineum in 10 patients and extending to the perianal area in 1 patient. At the onset of the rash, all patients were in good health, although 9 had mild fever for 1 to 2 days before its appearance. Physical examination also revealed an erythema of the hands

and feet in 4 patients and strawberry tongue in 7. Two patients had a facial impetigo, and another showed a perianal streptococcal dermatitis. A group A  $\beta$ -hemolytic streptococcus was isolated from the throat in 10 cases and from a perianal culture in 1 case. In 8 cases, resolution was spontaneous, but all patients were treated with systemic antimicrobial therapy for 10 days. Three patients had a personal history of cutaneous rashes on the perineal area during the last years before consultation. Rash recurrence was observed in 3 of the 11 patients at the follow-up examination.

**Conclusion:** Recurrent toxin-mediated perineal erythema can be observed not only in young adults but also in childhood

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**I**N THE PAST DECADES, SEVERAL FACTORS have contributed to the re-emergence of staphylococcal and streptococcal infections.<sup>1,2</sup> These include bacterial properties, such as their antimicrobial resistance and their surface proteins, which bring about a major invasiveness, and host factors, such as AIDS or other conditions or diseases causing congenital or acquired immunodeficiency (eg, premature birth, diabetes, malignancy).<sup>2,3</sup> The ability of these bacteria to produce circulating toxins functioning as superantigens further enhances their virulence.<sup>2-5</sup>

*For editorial comment  
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Superantigens differ from conventional antigens in a number of important ways, including polyclonal B-cell activation, extensive proinflammatory cytokine production, and changes in the number of circulating T lymphocytes that bear a specific surface receptor (specifically V $\beta$ -restricted T cells). Superantigens are able to

bypass antigen-presenting cells, binding directly to the major histocompatibility complex class II (MHC II) complex outside of the groove of lymphocytes. Therefore, they are able to stimulate nonspecific T-cell proliferation and may activate as many as 20% to 30% of circulating lymphocytes. This T-cell expansion leads to massive cytokine production, especially tumor necrosis factor  $\alpha$ , interleukin 1, and interleukin 6. These cytokines lead, in turn, to various different clinical signs, such as fever, hypotension, emesis, diarrhea, shock, and cutaneous eruptions. The spectrum of diseases mediated by superantigens caused by toxins made by staphylococci and streptococci encompasses some well-known older diseases (eg, scarlet fever and staphylococcal scalded skin syndrome) and some lesser-known diseases such as toxic shock syndrome, streptococcal toxic shocklike syndrome, recalcitrant erythematous desquamating disorder, and recurrent toxin-mediated perineal erythema (RTPE),<sup>1-3</sup> which was first described by Manders et al<sup>6</sup> in 2 healthy young adult men. We describe herein 11 cases of RTPE in children.

**Table 1. Patient Data for 11 Children With Recurrent Toxin-Mediated Perineal Erythema**

Patient No./ Sex/Age, y	Personal History	Prodromes	Skin Manifestations	Mucosal Signs	Laboratory Findings and Microbiological Signs	Therapy	Follow-up Examination
1/M/6	Unremarkable	Fever 7 d before and sore throat for 2 d	Perineal erythema; erythema on third, fourth, and fifth fingers and feet	Strawberry tongue	Neutrophilic leukocytosis; normal ECG and echocardiogram; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	No recurrence
2/F/6	Unremarkable	Fever for 2 d 6 d before	Perineal erythema	Strawberry tongue	Neutrophilic leukocytosis; normal ECG and echocardiogram; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	No recurrence
3/M/3	Unremarkable	No	Perineal erythema	Strawberry tongue	Neutrophilic leukocytosis; normal ECG and echocardiogram; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	No recurrence
4/M/5	Unremarkable	Fever 10 d before and sore throat for 1 d; perianal erythema, swelling and itching 2 d before	Perineal erythema	Strawberry tongue	Neutrophilic leukocytosis; throat culture negative; perianal swab positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	No recurrence
5/M/3	Recurrent sore throat	No	Perineal and axillary erythema, reddening of palms	None	Neutrophilic leukocytosis; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	3 Recurrences
6/M/3	Unremarkable	Fever for 2 d 5 d before	Perineal and inguinal erythema; reddening of palms and soles with desquamation	Strawberry tongue	Neutrophilic leukocytosis; normal ECG and echocardiogram; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	No recurrence
7/F/6	1 Year before perineal and genital erythema with desquamation	Fever 2 d before	Perineal erythema; facial impetigo	None	Neutrophilic leukocytosis; throat and cutaneous cultures positive for group A $\beta$ -hemolytic streptococcus	Topical and oral antibiotics	No recurrence
8/F/6	Unremarkable	Fever for 2 d 6 d before	Perineal erythema	None	Neutrophilic leukocytosis; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	1 Recurrence after 1 mo
9/M/4	2 Episodes of perineal and genital erythema with desquamation, 6 and 4 mo before associated with strawberry tongue	Fever 6 d before with sore throat for 1 d	Perineal erythema	Strawberry tongue	Neutrophilic leukocytosis; normal ECG and echocardiogram; throat culture positive for group A $\beta$ -hemolytic streptococcus	Oral antibiotics	3 Recurrences
10/M/3	2 Episodes of perineal and genital erythema with desquamation, 12 and 6 mo before, associated with strawberry tongue	Fever 2 d before	Perineal erythema; facial impetigo	None	Throat culture positive for group A $\beta$ -hemolytic streptococcus; cutaneous culture positive for <i>Staphylococcus aureus</i>	Oral antibiotics	No recurrence
11/F/5	Unremarkable	Fever 5 d before	Perineal erythema; edema with desquamation fingers and feet	Strawberry tongue	Throat culture positive for group A $\beta$ -hemolytic streptococcus	None	No recurrence

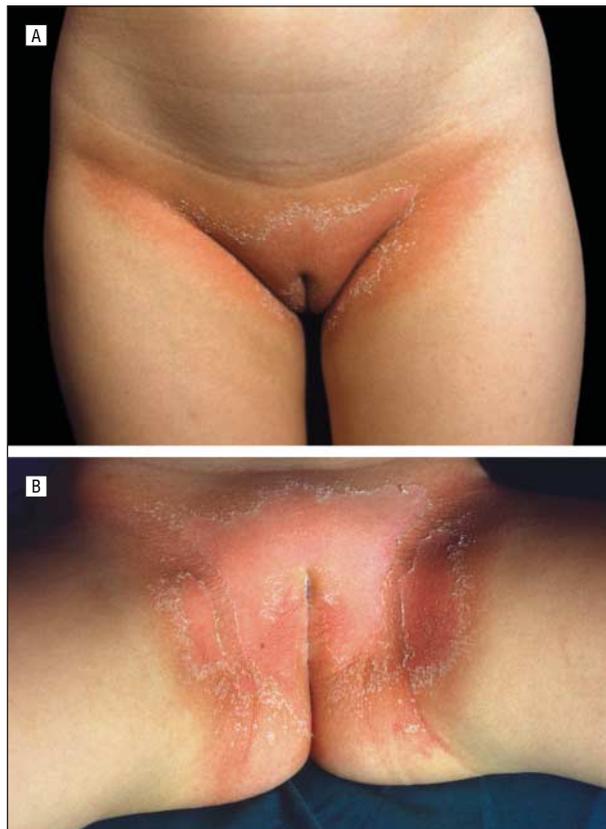
Abbreviation: ECG, electrocardiogram.

### REPORT OF CASES

Between 1997 and 2006, 11 patients (7 male and 4 female) aged from 3 to 6 years presented with the sudden appearance of asymptomatic erythema, which was salmonlike in color and rapidly desquamating, involving the

perineum in 10 patients and extending to the perianal area in 1 patient (**Table 1**).

In 9 patients, this erythema had started some days after the onset of a pharyngotonsillitis or a febrile illness lasting 1 to 2 days. Three patients (cases 7, 9, and 10) had a personal history of other episodes of pharyngo-



**Figure 1.** A margined slightly edematous symmetrical erythema, salmonlike in color, with desquamating peripheral borders located on the perineal area and lower abdomen (A) and upper thighs (B).

tonsillitis during the last year before consultation, which was followed once (case 7) and twice (cases 9 and 10) by an identical cutaneous eruption on the perineal area, with strawberry tongue only in cases 9 and 10. In 2 patients (cases 7 and 10), a facial impetigo had started that was associated with sore throat. In 1 patient (case 4), 2 days before the skin eruption, an intensive itching and swelling that was associated with redness and exudation of the perianal area had been observed by the parents. Finally, in 1 patient (case 3), the eruption started without any associated or previous symptoms or signs.

At examination none of patients complained of fever or arthralgias and all were in good health. Physical examination revealed well-margined, slightly edematous symmetrical erythema with desquamating peripheral borders located on the perineal area, lower abdomen, and upper thighs (**Figure 1**). In 1 patient, erythema and desquamation were also present on the axillary folds (case 5), whereas in 4 other cases (cases 1, 5, 6, and 11), erythema of the hands and feet without edema was present. In 7 cases, strawberry tongue was observed (cases 1-4, 6, 9, and 11) (**Figure 2**).

Throat and cutaneous perineal cultures for bacteria were assessed in all patients. A perineal culture for bacteria was obtained in 1 patient (case 4), and cutaneous (other than perineal) culture for bacteria were obtained in 2 patients (cases 7 and 10). In 10 patients, a throat culture revealed group A  $\beta$ -hemolytic streptococcus. In case 4, this culture was negative, but a perineal culture revealed the same



**Figure 2.** Strawberry tongue in a patient with recurrent toxin-mediated perineal erythema.



**Figure 3.** Palmar desquamation in a patient with recurrent toxin-mediated perineal erythema.

bacterium. Cultures of the skin revealed a group A  $\beta$ -hemolytic streptococcus in case 7 and a *Staphylococcus aureus* in case 10 from the lesions of impetigo, while in all cases the culture of the perineal skin was negative. Laboratory evaluation always revealed leukocytosis with neutrophilia. The remainder of the laboratory findings, including the platelet count, erythrocyte sedimentation rate, and serum chemistry profile, were within normal limits.

In 5 cases (cases 1-3, 6, and 9), the electrocardiogram and echocardiogram obtained 2 weeks after the onset of the patients' illness were normal.

In cases 4, 7, and 10, amoxicillin-clavulanic acid systemic therapy and therapy with mupirocin ointment, applied 3 times daily, were initiated soon after consultation, with resolution of the erythema as well as of impetigo in cases 7 and 10, and perineal streptococcal dermatitis in case 4 within 7 to 10 days. In the other 8 cases, we waited for throat swab results. Spontaneous resolution of the perineal rash was reported by the family of these patients 7 to 10 days after consultation. In 3 cases, a mild palmoplantar desquamation was observed (**Figure 3**). On the basis of the results of the throat swabs, the same

**Table 2. Main Differences Between Kawasaki Syndrome and Our Cases of Recurrent Toxin-Mediated Perineal Erythema (RTPE)**

Variable	Kawasaki Syndrome	RTPE (Our Patients)
Age	<2 y	3-6 y
Fever ( $\geq 5$ d duration)	Present	Absent
Polymorphous exanthem	Present	Absent
Perineal erythema	Frequent	Always present
Conjunctival injection	Present	Rare
Strawberry tongue and oral mucosal changes	Present	Present
Cervical acute macrolymphadenopathy	Present	Absent
Extremity changes (palmoplantar erythema with desquamation)	Present	Present
Recurrences	Rare	Frequently present
Alterations of instrumental and laboratory tests (electrocardiography, 2-dimensional echocardiography, coronary angiography, and platelet count)	Frequent	Rare
Streptococcal or staphylococcal pathogenesis	Undetermined	Yes

systemic antimicrobial therapy was prescribed for 10 to 14 days to all 8 patients.

A diagnosis of RTPE was hypothesized, but it was not possible to isolate the toxin produced by the bacterium because this test is not performed in our microbiologic laboratory. At the follow-up examination, 3 recurrences were observed in cases 5 and 9, and 1 recurrence was observed after 1 month in case 8.

#### COMMENT

Perineal erythema represents one of the physical signs frequently present in toxin-mediated illness such as staphylococcal toxic shock syndrome, scarlet fever, and RTPE.<sup>1</sup> However, in children this cutaneous picture has been mainly reported in conditions with different prognosis such as Kawasaki syndrome (KS) in children and RTPE in young adults.<sup>3,7,8</sup>

While RTPE is a benign self-limiting mucocutaneous disorder mediated by superantigens, KS is an acute multisystemic illness, being the most common cause of acquired heart disease (25% of untreated children).<sup>9,10</sup> In the past decades, the hypothesis that KS is also a toxin-mediated staphylococcal or streptococcal disease has been proposed because some of the major diagnostic criteria of KS (fever of at least 5 days' duration plus at least 4 of the 5 following conditions: peripheral extremity changes [eg, edema, erythema, and desquamation], polymorphous exanthem, changes of lips and oral cavity [eg, erythema and strawberry tongue], acute nonpurulent cervical lymphadenopathy, and/or conjunctival injection) are characteristic of other toxin-mediated diseases.<sup>11</sup> However, in a re-

cent study Leung et al<sup>12</sup> reported that the isolation rate of superantigen-producing streptococci and staphylococci in KS is not statistically different from that of control patients. The etiology of KS is therefore still unknown.

In 1988, Fritter and Lucky<sup>7</sup> noted the occurrence of a perineal eruption in 39 of 58 infants and children (67%) with KS. All of these patients met at least 5 of the 6 diagnostic criteria of KS.

Incomplete<sup>7</sup> or atypical cases<sup>13-15</sup> of KS, with fewer than 6 clinical criteria, have also been reported in the literature. In some of these cases, the diagnosis was made only when a coronary artery aneurysm had been diagnosed, but it should be noted that in all of them, high fever lasting at least 5 days was present, and recurrence of the cutaneous rash was not observed at the follow-up examination.<sup>7</sup>

On the contrary, all of our patients were in good health when the cutaneous eruption started, suggesting the presence of a very benign disease. Moreover, findings from laboratory and instrumental tests were also normal or negative except for the presence of a group A  $\beta$ -hemolytic streptococcus isolated from the throat or cutaneous culture. Finally, the personal history revealed a previous identical perineal erythema during the last years before consultation in 3 of the 11 cases, and recurrences of the perineal cutaneous rash was observed in 3 of the 11 cases. Overall, 6 of the 11 patients presented a recurrent clinical picture. In addition, the age range of our children was 3 to 6 years, while the majority of KS cases occur in children younger than 2 years. All these data suggest the diagnosis of RTPE. In **Table 2**, the main clinical and laboratory differences between our cases and KS are reported.

Recurrent toxin-mediated perineal erythema is caused by the action of toxins produced by both staphylococci and streptococci due to a homology at the molecular level between the toxins produced by these bacteria, determining a substantial clinical overlap. Furthermore, a single bacterial toxin acting as a superantigen can lead to a broad spectrum of clinical diseases. In the 2 cases reported by Manders et al<sup>6</sup> the testing for the toxins revealed streptococcal pyrogenic exotoxins A and B in one patient and toxic shock syndrome toxin 1 in the other patient. Our report represents only a clinical study about new cases of RTPE, unconfirmed by the testing revealing the production of streptococcal and staphylococcal toxins. Nonetheless, we think that the characteristic clinical picture that we have observed can be more than enough to place our cases in the new variant of the toxin-mediated disease, first described by Manders et al<sup>6</sup> in 2 young adults.

In one of our patients, the diffuse erythema involving the perineum had begun some days after the onset of a perianal itching and swelling. In this case, the throat culture was negative, but the perianal culture was positive for group A  $\beta$ -hemolytic streptococcus. The positivity of perianal culture and the different course of the 2 cutaneous manifestations led us to consider the hypothesis of the coexistence of RTPE with streptococcal perianal dermatitis. In this case, the focus of toxin-producing group A  $\beta$ -hemolytic streptococcus was the perianal region. This association has been previously reported in a febrile 2-year-old boy in a study by Vélez and Moreno.<sup>16</sup> Although the authors hypothesized that their

case might be considered a variant of RTPE, they nevertheless referred to it as an unusual febrile perianal streptococcal dermatitis. Moreover, their patient was febrile, and recurrences were not reported.<sup>16</sup>

We believe that cultures should be obtained not only from the pharynx or the throat but also from the perianal region and in the skin, as in 2 of our patients who were also affected by facial impetigo. In one of these cases *S aureus* was isolated from the lesions of impetigo, but it is well-known that in many cases of crusted impetigo both staphylococci and streptococci may be cultured.

In conclusion, RTPE can also occur in children, and in such patients, the recurrences are less frequent, while the possibility of cutaneous streptococcal infection should be investigated.

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