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Staphylococcal Scalded Skin Syndrome in Two Immunocompetent Adults Caused by Exfoliatin B-Producing *Staphylococcus aureus*

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An exfoliatin B-producing strain of *Staphylococcus aureus* was isolated from two adults with typical staphylococcal scalded skin syndrome (SSSS). One patient developed desquamation after a local staphylococcal infection of the hand, and the other developed exfoliation after nosocomially acquired staphylococcal endocarditis. Neither patient was immunocompromised, had evidence of renal insufficiency, or manifested other potential risk factors for SSSS. Purified toxin, isolated from the causative organisms, produced a Nikolsky sign in neonatal mice. The toxins were shown to be exfoliatin B by biochemical and immunologic methods and heretofore had been described only in children with SSSS. Analysis of plasmid DNAs from both strains revealed a 23-megadalton plasmid with identical restriction endonuclease digestion fragments. One isolate belonged to phage group II (3B/3C/6/7/47/54/55), whereas the other isolate belonged to phage groups I and III (7/29/52/52A/53/54/80). The observation that a non-phage group II exfoliatin-producing strain of *S. aureus* may produce SSSS in adults indicates the need to better define the diagnostic criteria for SSSS. Immunocompetent adults may remain susceptible to some strains of exfoliatin B-producing *S. aureus*.

The staphylococcal scalded skin syndrome (SSSS) is a bacterially induced condition that may occur as bullous impetigo, scarlatiniform rash, or a generalized desquamative process (12, 15). The disease is seen most commonly in infants and children and may result in large outbreaks in neonatal nurseries. The syndrome has rarely been described in adults who harbor *Staphylococcus aureus* and is usually related to phage group II. Exfoliatin is the extracellular toxin of *S. aureus* that fulfills Koch's postulates as the etiologic agent of SSSS. The toxin has both species and tissue specificities (15, 22).

Two serologic forms of exfoliative toxin have been independently isolated by several laboratories and are now referred to as exfoliatin A (ETA) or exfoliatin B (ETB) (7, 8, 12, 24). ETA is the most common toxin responsible for SSSS in the United States. This epidermolytic exotoxin is a heat-stable, chromosomally mediated product generally produced by *S. aureus* belonging to phage group II (17, 22). In contrast, ETB alone has been isolated mainly from non-phage group II *S. aureus*; these strains are most commonly reported to occur outside the United States, primarily in Japan (11). We now report the occurrence of SSSS in two previously healthy adults from whom an ETB-producing strain of *S. aureus* was isolated. The isolate from one patient belonged to phage group II, whereas the other patient had a non-phage group II strain of *S. aureus*. Moreover, we show that there may be host factors involved in the expression of this toxin-mediated disease. A physician caring for one of the patients harbored an identical toxin-producing strain but had no demonstrable clinical illness.

CASE REPORTS

Case 1. Patient 1, a 54-year-old man, enjoyed good health until 10 days before hospital admission when a fluid-filled blister appeared over a recently traumatized area of his left thumb. Three days before admission, an erythematous rash appeared on his left hand and progressed to involve both upper extremities, the perineum and lower half of his trunk anteriorly and posteriorly. The patient had not been taking medications before admission. On the day of admission, he was acutely ill, complained of pain and diffuse itching, and had a temperature of 39.2°C. The pulse was 148, and the blood pressure was 100/70 mm Hg. His skin had a generalized blanching erythema, while the distal portions of the upper extremities appeared violaceous and markedly edematous and had minute milia. A necrotic pustule measuring 3 by 3 cm and surrounded by cellulitis was present on the left thumb. Petechiae were present on the upper, but not the lower, extremities. He had widespread erythema, particularly over the buttocks and genitalia, as well as in the lower extremities, which were also slightly edematous. The remainder of the physical examination was unremarkable. Laboratory examination revealed a leukocyte count of 18,000 with a differential count of 80% neutrophils, 12% bands, 2% lymphocytes, 5% mononuclear cells, and 1% eosinophils. Serum electrolytes, blood urea nitrogen, and glucose were within normal limits. The platelet count was 200,000/mm^3. Urinalysis revealed 10 to 15 leukocytes per high-powered field and 4+ proteinuria. A gram stain of the milia revealed neither neutrophils nor bacteria. The throat culture had no group A beta-hemolytic streptococci, and the anti-streptolysin O titer was less than 166 Todd units. Culture of the purulent material from the left hand lesion grew phage group I and II *S. aureus*, but cultures of the milia on the right hand were sterile, as were blood and urine cultures. A skin biopsy showed minimal perivascular infiltrates in the papillary dermis and a line of cleavage at the stratum granulosum compatible with SSSS. The patient was treated with 12 g of nafcillin per day intravenously. Within a day, the violaceous appearance of the arms disappeared, and he developed diffuse desquamation of skin of the extremities and trunk. By day 3 of therapy, he became afebrile and his

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leukocyte and differential counts returned to normal. After 2 weeks of intravenous therapy, treatment was changed to orally administered oxacillin for an additional 2 weeks of outpatient therapy. Blood cultures remained sterile, and urinalysis returned to normal.

Case 2. Patient 2 was a 46-year-old female who was admitted for elective cardiac catheterization. The patient had a 20-year history of rheumatic heart disease manifested by mitral stenosis, mitral insufficiency, and aortic stenosis. She had undergone an open mitral comissurotomy 15 years before this admission. Cardiac catheterization confirmed severe mitral stenosis, moderate aortic stenosis, and mild mitral regurgitation. The patient was considered a candidate for mitral and aortic valve replacement and was scheduled for elective cardiac surgery. Three days after catheterization, she developed shaking chills, followed by a temperature elevation to 39.8°C. Physical examination revealed a toxic-appearing patient with multiple conjunctival petechiae, splinter hemorrhages, and a previously undetected murmur of aortic regurgitation. Numerous flaccid bullae were noted in the head, neck, and thorax. Multiple blood cultures, as well as a culture of the bullous fluid, were obtained. The patient was treated empirically with intravenously administered vancomycin and gentamicin. Four separate blood cultures subsequently were positive for *S. aureus* phage group II, susceptible to both antimicrobial agents. The culture of the skin lesion was negative. Within 6 h of the onset of fever, marked generalized exfoliation occurred. Large areas of the skin were affected, particularly on the face and thorax. Large plaques of skin were readily sloughed off when minimal traction was applied to the skin surface, such as during removal of cardiac monitoring leads. Nikolsky's sign was evident, even in seemingly uninvolved skin. A skin biopsy was obtained which demonstrated an exfoliative process with a high cleavage plane in the epidermis at the level of the stratum granulosum. No inflammatory cells or bacterial organisms were seen in the biopsy specimen. Surveillance cultures from house staff physicians revealed the same phage type of *S. aureus* from the anterior nares of the intern who treated this patient. The clinical course of the patient deteriorated, with persistent fever, exfoliation, and continuously positive blood cultures despite adequate bactericidal levels of vancomycin and gentamicin in the serum. The patient developed progressive heart failure and was taken to surgery 2 weeks after the initial onset of illness. The mitral and aortic valves were almost completely destroyed, and both were replaced by prosthetic valves. Histological examination revealed active bacterial vegetations involving both valves. Cultures of both valves grew *S. aureus* of the identical phage type. The postoperative course of the patient was complicated by progressive hepatic, renal, and respiratory failure. She developed disseminated candidiasis and died 6 weeks after valve replacement. At autopsy, the prosthetic mitral and aortic valves appeared normal, and no evidence of active bacterial or fungal endocarditis was found by culture or tissue examination.

MATERIALS AND METHODS

S. aureus (designated strain 501) was obtained from purulent discharge material of patient 1 and from blood cultures (designated strain 174) from patient 2. Antibiotic susceptibility testing indicated that both strains were resistant to penicillin (>10 μg/ml) but susceptible to methicillin, vancomycin, and gentamicin. Both cultures produced a small amount of alpha-hemolysin but no detectable beta- or delta-lysin. The phage type of strain 501 was 7/29/52/52A/53/54/80, groups I and III, and that of strain 174 was 3B/3C/6/7/47/54/55 group II (phage typing was kindly performed by Charles Zierdt, National Institutes of Health, Bethesda, Md.).

Toxin was elaborated by growth in liquid medium consisting of 17 g of Trypticase (BBL Microbiology Systems, Cockeysville, Md.), 10 g of yeast extract, 5 g of NaCl, and 2.5 g of K_2HPO_4 per liter. After 20 h at 37°C, a sample of the culture supernatant was tested for exfoliating activity by subcutaneous injection into neonatal mice as described by Melish and Glasgow (16). Purified toxin was isolated from the culture supernatant by sequential chromatography on carboxymethyl cellulose and hydroxylapatite by using methods previously described (9). The heat stability of the purified toxin was compared with those of purified ETA and ETB from known control strains and examined for immunologic reactions by previously described methods (9).

Plasmid DNA was isolated by the method of Ranhand (19). Restriction endonuclease digestion patterns determined with the enzymes *Eco*RI and *Hin*dIII (New England BioLabs, Inc., Beverly, Mass.) were generated as recommended by the manufacturer. Plasmid DNA and restriction fragments were separated by agarose gel electrophoresis on a horizontal apparatus in 0.75% agarose. Plasmid DNA was visualized by ethidium bromide and photographed with type 47 Polaroid film.

RESULTS

Culture supernatants from both clinical isolates produced a positive Nikolsky sign within 4 h, and mice were then sacrificed for histological examination. Lesions consisted of vesicle formation caused by cleavage of the epidermis in the stratum granulosum. This finding fulfills the classic definition of exfoliative toxin compared with other types of skin-damaging toxins which cause cleavage at a lower level of the dermis (1, 23).

Analysis of purified toxin by electrophoresis in 15% polyacrylamide gels containing 1% sodium dodecyl sulfate indicated that the molecular mass of the toxin was 26 kilodaltons. A comparable value has been reported earlier for both ETA and ETB (9).

The toxins produced by strains 501 and 174 were inactivated serologically and biologically by heat treatment at 56°C for 30 min. ETA retained full activity after identical treatment. Immunodiffusion reactions demonstrated that toxins from strains 501 and 174 were immunologically distinct from ETA and showed a line of partial identity with ETB (Fig. 1 and 2).

Each ETB-producing clinical isolate contained a 23-megadalton plasmid which had identical restriction fragments when subjected to endonuclease digestion (Fig. 3). Plasmid DNA of the *S. aureus* strain isolated from the house staff physician had the identical 23-megadalton plasmid.

DISCUSSION

SSSS in adults was first described in 1972 by Levine and Norden (14). A single strain of *S. aureus* may produce a single exfoliatin that results in all three clinical manifestations of SSSS: generalized exfoliative disease, generalized scarlatiniform eruption without exfoliatin, and bullous impetigo (15, 22).

SSSS is seen primarily in infants and is rare in adults. This has been attributed to the ability of adults to metabolize and excrete exfoliatin rapidly or to acquired immunity (14).

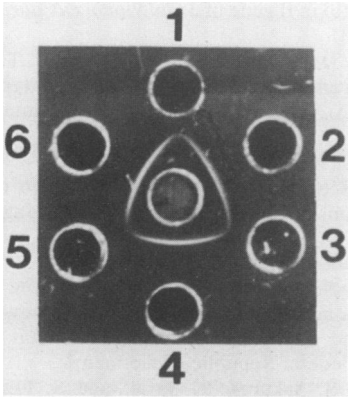

FIG. 1. Ouchterlony diffusion in agarose with antiserum to ETB, showing identity of *S. aureus* 501 toxin and ETB. Antiserum to ETB was in the center, culture supernatant from strain 501 was in well 6, purified toxin from strain 501 was in well 4, and purified ETB as a control was in well 2. Wells 1, 3, and 5 were empty.

Fewer than 20 instances of adult SSSS have been reported in the literature; none of the isolates produced ETB (18, 20). Both adult patients in this report had a staphylococcal strain isolated that produced a B-type exfoliatin. The adult form of SSSS is generally characterized by the ability to culture *S. aureus* from the bullae ("local form") (4). Most adults with SSSS have positive blood cultures and a substantial mortality rate (18, 20). In contrast, children usually have negative blood cultures and a low mortality rate (15, 22).

Previous cases in adults have emphasized three apparent risk factors for SSSS. These include renal insufficiency, steroid administration, or other immunocompromised states (14, 18, 20). Our patients had no evidence of any of these predisposing factors at the onset of illness.

In earlier reports, Melish and Glasgow (16, 17) reported that exfoliatin was associated only with *S. aureus* isolates of phage group II. On the basis of surveys of random isolates of *S. aureus* (i.e., not from patients with SSSS), Kapral (10) demonstrated epidermolytic activity in a mouse model in 19 of the 1,000 non-group II *S. aureus* strains (versus 40% among group II strains) and concluded that exfoliatin activity was not restricted to group II *S. aureus*. These observations were confirmed among isolates in the United Kingdom in a similar survey by de Azavedo and Arbuthnott (3). Kondo et al. (13) observed that production of ETB alone was usually associated with non-group II phages, while production of ETA alone tended to be associated with strains of phage group II. From 40 to 45% of exfoliatin-producing strains produce both A and B forms concurrently, and these isolates are represented among all phage groups. Thus, retrieval of *S. aureus* from phage groups other than II does not exclude the possibility of an exfoliatin-producing strain (5, 6, 21).

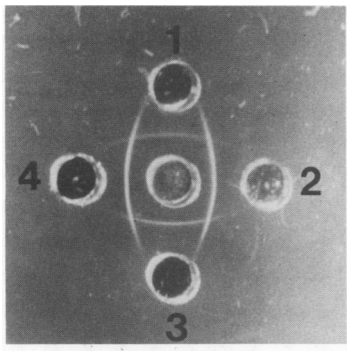

FIG. 2. Ouchterlony diffusion in agarose, showing nonidentity with ETA. Antiserum to ETA and ETB was in the center well. Purified toxin from strain 501 was in wells 2 and 4, and purified ETA was in wells 1 and 3.

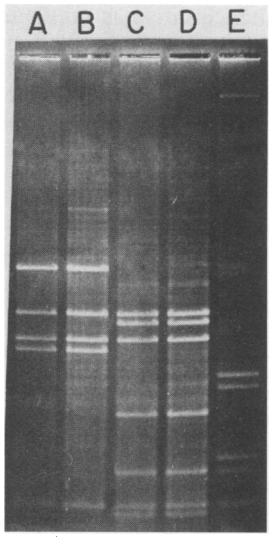

FIG. 3. Restriction endonuclease pattern of plasmid DNA from strains 174 and 501 obtained with *Eco*RI and double digestion with *Eco*RI and *Hin*dIII (lanes C and D). Lane E contained *Escherichia coli* V517 as a molecular weight standard.

In the United States, SSSS has rarely been observed in other than phage group II strains (22). In Japan, SSSS was originally found in phage group II isolates of *S. aureus*, but now non-group II isolates exceed those of group II (13). Antibodies to ETA are five to six times more prevalent among both Japanese adults and children than are antibodies to ETB (21).

Patient 1 had a well-defined primary lesion and, much as in the pediatric form of SSSS, sterile bullae and blood. The rash was most intense in the axillary and anogenital areas, an observation shared by others (4, 18), and may relate to the irritation between two opposing planes of skin or between skin and clothes.

This patient also had a markedly abnormal urinary sediment which cleared with resolution of the SSSS. He had no known underlying renal disease, and cultures of the urine were negative. Similar abnormalities were noted in otherwise healthy patients who acquired nonstaphylococcal toxic epidermal necrolysis. Examination of renal biopsy samples from these patients suggested an immunologic process (2). Renal abnormalities have been described in six adults with SSSS, but three had underlying chronic renal disease and three others had bacteremia. The course of patient 1 may also suggest some transient renal immunologic activity, since exfoliatin has no known renal site of activity and since we were unable to detect seeding of *S. aureus* beyond the local lesion. Alternatively, the transient proteinuria may be explained by the presence of fever.

Patient 2 apparently acquired endocarditis with an ETB-producing *S. aureus* after cardiac catheterization. The isolation of the same *S. aureus* phage type in a house staff member who treated this patient suggests that this organism was a nosocomially acquired pathogen. Adult SSSS as a

complication of endocarditis has previously been described in a drug addict (18). The clinical consequences of this infection were severe, with diffuse exfoliation and fluid and electrolyte disturbances which complicated the management of this patient with bivalvular staphylococcal endocarditis.

In the past decade, the diagnostic criteria for SSSS have required isolation of *S. aureus* of phage group II, verification of epidermolytic activity in the newborn mouse assay, and demonstration of characteristic dermal histopathological changes in patients with a compatible clinical presentation (15). Clearly, the requirement for a specific phage group of *S. aureus* must yield to demonstration of epidermolytic activity of any *S. aureus* isolate in the mouse assay. Unfortunately, this assay is not generally available. Furthermore, characterization of the form of exfoliatin would be very desirable in view of the changing pattern of SSSS already observed in Japan. Since the differential diagnosis of SSSS might include other entities of staphylococcal etiology (e.g., toxic shock syndrome) or unknown etiology (e.g., Kawasaki disease), it is essential to define accurately the disease process if we are to progress in our understanding of these puzzling diseases.

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