Staphylococcal Scalded Skin Syndrome in an Immunocompromised Adult

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Staphylococcal scalded skin syndrome, a generalized exfoliative dermatitis complicating infections by exfoliative toxin-producing strains of *Staphylococcus aureus*, is rarely observed in adults. In contrast to mortality in infants, mortality in adults is usually high. A case of generalized staphylococcal scalded skin syndrome in an immunocompromised woman is reported. Culture of skin biopsy and pleural fluid yielded identical strains of *Staphylococcus aureus* belonging to phage group II. Exfoliative toxins A and B were detected in both isolates. As far as can be determined, this is the first reported case of generalized staphylococcal scalded skin syndrome in an adult with detection of exfoliative toxins A and B in which the patient was treated successfully.

Staphylococcal scalded skin syndrome usually affects infants and children, occurring only rarely in adults (1). Clinical presentation is usually as a sudden development of unexplained generalized exfoliation with the appearance of a burn, which is known as toxic epidermal necrolysis. In addition, toxic epidermal necrolysis (Lyell's disease) can be seen secondary to drug hypersensitivity, usually to barbiturates and sulfonamides.

Staphylococcal scalded skin syndrome occurs in patients with occult or overt sites of colonization or infection with *Staphylococcus aureus*. The staphylococcal strains usually belong to phage group II and produce an epidermolysin (exfoliative toxin A and B), which causes cleavage of the epidermis within or immediately below the stratum germinativum, giving rise to the characteristic clinical presentation. As treatment for the two forms of toxic epidermal necrolysis differs widely, patient outcome depends on immediate and accurate diagnosis. We report the rare occurrence of staphylococcal scalded skin syndrome in an adult. Literature covering staphylococcal scalded skin syndrome in adults is reviewed.

Case Report. A 55-year-old woman was admitted to the intensive care unit of our university hospital because of bullous epidermolysis on the trunk and the lower legs involving approximately 90% of the skin (Figure 1). Initial laboratory studies revealed normal results, with the exception of an elevated leukocyte count of 13,400/mm^3. Nikolsky's sign was present around erosions and on unaffected skin. On the day of admission the patient had to be intubated and ventilated because of suspected acute respiratory distress syndrome. Significant past medical history included therapy with dexamethasone, indomethacin, and methotrexate for more than seven years because of severe rheumatoid arthritis. Seven weeks before admission the patient suffered a fracture of her right lower leg, and osteosynthesis with rush pins was performed. In addition, the patient had received trimethoprim-sulfamethoxazole two weeks prior to admission for treatment of a urinary tract infection. Therefore, our initial diagnosis was toxic epidermal necrolysis induced by sulfonamides, and the patient was treated with corticosteroids.

Multiple skin biopsies showed superficial intraepidermal cleavage. *Staphylococcus aureus* was cultured from skin biopsy and pleural fluid. The patient showed clinical and radiographic signs of osteomyelitis of the left lower leg, but culture of pus and repeatedly drawn blood cultures remained sterile. The suspected diagnosis was changed to staphylococcal scalded skin syndrome, and the patient was treated with flucloxacillin (8 g/day).

During the next four weeks the patient became more alert, and mechanical ventilation was discontinued on day 64. On day 78 the patient was discharged from the intensive care unit with complete healing of the skin. The patient was fully discharged on day 163.

Further microbiological investigations showed that both staphylococcal isolates belonged to phage group II (3A, 3C, 55). Phage typing was performed according to standard procedures (2) us-

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Table 1: Summary of reported cases of staphylococcal scalded skin syndrome in adults.

Authors (reference)	Underlying condition	Focus of infection	Phage group (reaction)/toxins
Birke et al. (6)	none	bone infection	n.d.
Levine & Norden (7)	chronic renal failure	abscess	II (71)/n.d.
Hawley & Aronson (8)	alcoholism	pneumonia	II (71)/n.d.
Rothenberg et al. (9)	alcoholism, neurosyphylis	abscess, osteomyelitis	II (3C, 55, 71)/n.d.
Reid et al. (10)	chronic renal failure, CVID	conjunctivitis, bursitis	II (3C)/n.d.
Norden & Mendelow (11)	AML	n.d.	II (3C, 55, 71)/n.d.
Lewis (12)	drug abuse	URTI	n.d.
Epstein et al. (13)	none	not found	untypable
Trentham et al. (14)	chronic renal failure, diabetes mellitus	septic arthritis	II (55, 71)/n.d.
Amon & Dimond (15)	Hodgkin's disease	parenteral injection	II (3C, 55, 71)/n.d.
Achten et al. (16)	none	pneumopathia	II (3A, 3B, 3C)/n.d.
Elias & Levy (17)	none	superinfected tinea pedis	II (3C, 71)/n.d.
Sturman & Malkinson (18)	none	n.d.	II (71)
Schlesinger (19)	nutritional debility	carbuncle, conjunctivitis	II (71)/ET
Peterson et al. (20)	chronic hepatitis	n.d.	II (71)/n.d.
Neefe et al. (21)	drug abuse	abscess	II (3B, 3C, 55, 71)/n.d.
Ridgway & Lowe (22)	HD	pneumonia, abscess	n.d.
Fine et al. (23)	sepsis, alcoholism	n.d.	n.d.
Diem et al. (24)	sepsis, cachexia	catheter infection	II (3A, 3C, 55)/n.d.
Janier et al. (25)	sepsis, RA	n.d.	II-V (3A, 3C, 55, 71–96)/positive
Richard & Matthieu-Serra (26)	CRF	n.d.	II (3A, 3C, 55, 187, 71)/n.d.
Takiushi et al. (27)	none	varicella-zoster lesion	I–III/n.d.
O' Keefe et al. (28)	polymyalgia rheumatica	n.d.	II (3A, 3C)/n.d.
	non-Hodgkin's lymphoma	n.d.	II (3A, 3C)/n.d.
Opal et al. (29)	none	tissue infection	II (3B, 3C, 6, 7, 47, 54, 55)/ET B
	rheumatic carditis	bacterial endocarditis	I/III (7, 29, 52, 52A, 53, 54, 80)/ET B
Saiag et al. (30)	psoriasis	n.d.	n.d.
	leukopenia	n.d.	n.d.
Petzelbauer et al. (31)	acute renal failure	abscess	n.d.
	acute renal failure	n.d.	n.d.
Goldberg et al. (32)	CML, BMT	BMT	II (71)/n.d.
Beers & Wilson (33)	acute renal failure, alcoholism	muscle abscess	II (3C)/positive
Herzog & Sexton (34)	carcinoma, chronic renal failure	n.d.	II/n.d.
Strumia et al. (35)	HIV infection	n.d.	n.d.
Donohue et al. (36)	chronic renal failure, HIV infection	shunt infection	II (71)/n.d.
Khuong et al. (37)	none	abscess	II (3A, 3C, 55, 71)/ET A, ET B
Cribier et al. (1)	none	parenteral injection	II/ET A, ET B
Present report	rheumatoid arthritis	osteomyelitis	II (3A, 3C, 55)/ET A, ET B

AML, acute myelogenous leukemia; BMT, bone marrow transplantation; CML, chronic myelogenous leukemia; CVID, combined variable immunodeficiency; ET, exfoliative toxin; HIV, human immunodeficiency virus; n.d., no data; URTI, upper respiratory tract infection.

ing the international phage set (I 29, 52, 52A, 79, 80; II 3A, 3C, 55, 71; III 6, 42E, 47, 53, 54, 75, 77, 83A, 84, 85; V94, 96; H 81, 95) and additional phages (D11, 16, 92, 187, 192).

Diagnosis of staphylococcal scalded skin syndrome was confirmed by the detection of exfoliative toxins A and B in both staphylococcal isolates. In brief, undiluted culture supernatants were screened for exfoliative toxin production by double immunodiffusion using the standard method of the National Reference Laboratory for *Staphylococcus aureus* Phage Typing, Bonn, Germany.

Discussion. Toxic epidermal necrolysis was first described by Lyell (3) in 1956 and has since been divided into two unrelated diseases: drug-induced toxic epidermal necrolysis and toxic epidermal necrolysis accompanying infections with certain strains of *Staphylococcus aureus*, first described by Ritter von Rittershain in 1878 (4). After isolation and partial characterization of the exfoliative toxins, the term "staphylococcal scalded skin syndrome" was introduced by Melish and Glasgow (5). Staphylococcal scalded skin syndrome typically occurs in newborns (Ritter's disease) and in children under the age of 10, but it is rare in adults (1). The first case of staphylococcal scalded skin syndrome in an adult was documented by Birke et al. (6) in 1971. Characteristics of 38 cases reported to date, including our case, are shown in Table 1.

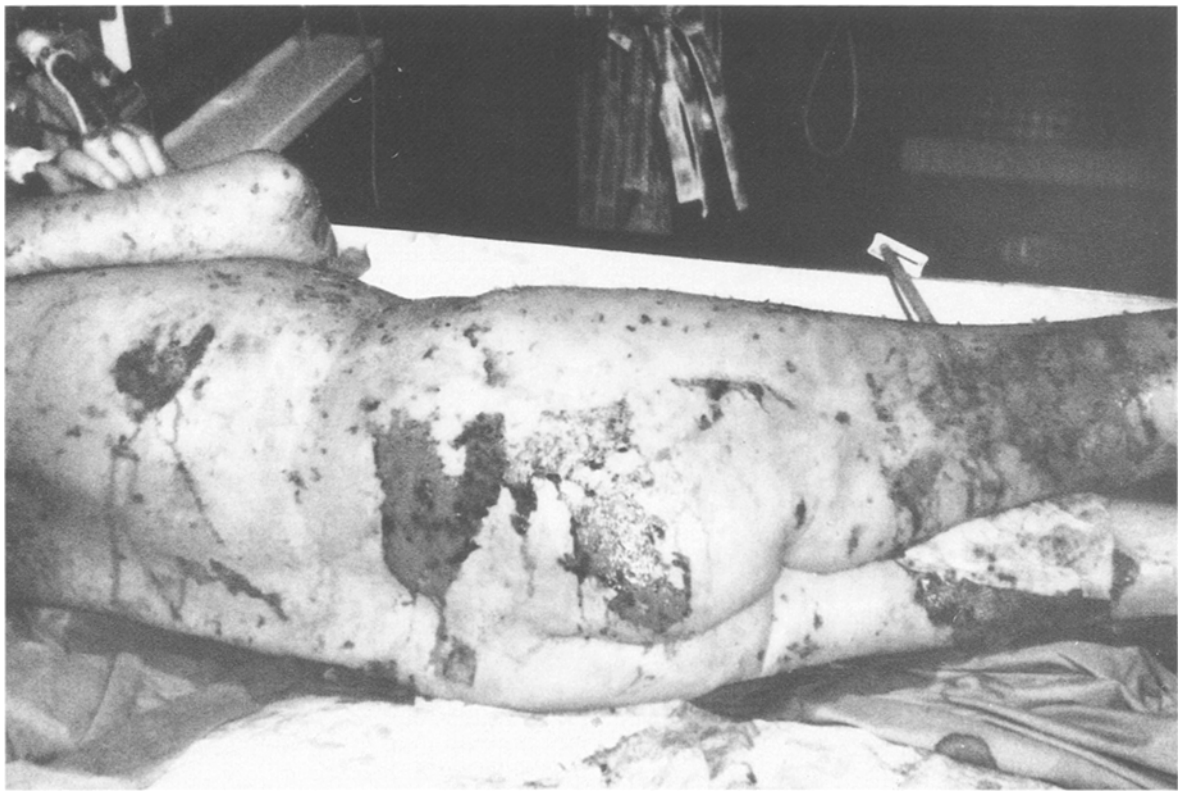

Figure 1: Skin lesions on day 2 after admission showing desquamation involving approximately 90% of the skin.

In contrast to mortality in infant cases, the mortality in adults is high, with approximately 50% (20 of 38 cases) having a fatal outcome. Men (21 of 38 cases) are more often affected than women, and most patients are older than 50 years.

Major risk factors for staphylococcal scalded skin syndrome include kidney failure (7, 10, 14, 26, 31, 33, 36), alcoholism (8, 9, 23, 33), HIV infection (35, 36), and leukemia, lymphoma, and other malignant diseases (11, 15, 22, 28, 32, 34). Nevertheless, nine of 38 patients were in good health before the onset of staphylococcal scalded skin syndrome. Treatment with immunosuppressive drugs is widely accepted as a risk factor for the development of staphylococcal scalded skin syndrome (18 of 38 cases). In the case reported here, reduction of immunity can be explained by long-term immunosuppressive therapy.

Deficient renal function may lead to reduced elimination of the exfoliative toxin (36) and has been shown to worsen clinical outcome of staphylococcal scalded skin syndrome. Petzelbauer et al. (31) reported two immunocompetent patients with acute renal failure who suffered from staphylococcal scalded skin syndrome preceded by a relatively minor staphylococcal infection. In the case reported here, no decrease in glomerular filtration or any other renal failure was observed despite long-term therapy with high doses of nonsteroidal anti-inflammatory drugs.

Data on the phage group of *Staphylococcus aureus* isolates were available in only 28 of the 38 cases. All but one infection was caused by phage group II isolates, as in the case reported here, which could be isolated from blood cultures (23 of the 38 cases) or other body fluids. The isolation of these strains from blood is regarded as characteristic of staphylococcal scalded skin syndrome in adults (1), whereas it is observed in only 3% of cases in children (32). In the case reported here the blood remained sterile, but *Staphylococcus aureus* was grown in cultures from skin biopsies and pleural fluid. Abscesses or bone infections have often been regarded as the focus of the staphylococcal infection. The latter may be suspected as the focus of infection in our case.

Most adult cases of staphylococcal scalded skin syndrome are not well documented with regard to the type of toxin. Opal et al. (29) described two cases in which exfoliative toxin B was detected.

There is one other documented case of generalized staphylococcal scalded skin syndrome caused by an exfoliative toxin A- and exfoliative toxin B-producing strain. In that case the patient died despite intravenous administration of vancomycin (1).

Skin biopsy specimens in our case showed the typical superficial intraepidermal cleavage in the granular layer. Subepidermal connective tissue was free of infection. In contrast to the other forms of toxic epidermal necrolysis, Nikolsky's sign was present in seemingly uninvolved skin.

Clinical data on the specific antibiotic therapy in adult staphylococcal skin syndrome are scant. Since most of the toxigenic strains belong to phage group II, in which methicillin-resistant *Staphylococcus aureus* are rare, penicillinase-resistant penicillins are usually recommended for the empirical treatment of staphylococcal scalded skin syndrome (1). Corticosteroids offer no additional therapeutic advantage and may, in fact, have some deleterious effects. Since it is widely accepted that they play a beneficial role in the management of drug-induced toxic epidermal necrolysis and the two entities of toxic epidermal necrolysis may be morphologically indistinguishable at onset, initial therapy with corticosteroids plus high doses of penicillinase-resistant penicillin might be reasonable. Further investigations should include microbiological and histological investigation of multiple skin biopsies, multiple blood cultures, and a search for the focus of staphylococcal infection. If *Staphylococcus aureus* is grown, steroid therapy should be discontinued. Phage typing and detection of exfoliative toxins should be performed by a reference laboratory to confirm the diagnosis of staphylococcal scalded skin syndrome.

Acknowledgement

This work is dedicated to Prof. Dr. med. Dr. h.c. W. Geroc on the occasion of his 70th birthday.

References

1. Cribier B, Piemont Y, Grosshans E: Staphylococcal scalded skin syndrome in adults. A clinical review illustrated with a new case. Journal of the American Academy of Dermatology 1994, 39: 319–324.
2. Lenz, W: Die Staphylokokken-Lysotopie als epidemiologisches Werkzeug. Hygiene und Medizin 1991: 18, 197–214.
3. Lyell A: Toxic epidermal necrolysis: an eruption resembling scalding of the skin. British Journal of Dermatology 1956, 68: 355–361.
4. Ritter von Rittershain G: Die exfoliative Dermatitis jüngerer Säuglinge. Centralzeitung Kinderheilkunde 1878, 2: 3–23.
5. Melish ME, Glasgow LA: The staphylococcal scalded skin syndrome: development of an experimental model. New England Journal of Medicine 1970, 282: 1114–1119.
6. Birke G, Liljedahl SO, Rajka G: Lyell's syndrome: metabolic and clinical results of a new form of treatment. Acta Dermatology and Venereology 1971, 51: 199–209.
7. Levine G, Norden CW: Staphylococcal scalded skin syndrome in an adult. New England Journal of Medicine 1972, 287: 1339–1340.
8. Hawley HB, Aronson MD: Scalded skin syndromes in adults. New England Journal of Medicine 1972, 288: 130.
9. Rothenberg R, Renna F, Drew T: Staphylococcal scalded skin syndrome in an adult. Archives of Dermatology 1973, 108: 408–410.
10. Reid L, Weston WL, Humbert JR: Staphylococcal scalded skin syndrome: adult onset in a patient with deficient cell mediated immunity. Archives of Dermatology 1974, 109: 239–241.
11. Norden CW, Mendelow H: Staphylococcal scalded skin syndrome in adults. New England Journal of Medicine 1974, 290: 577.
12. Lewis RJ: Scalded skin syndrome in a drug abuser. Journal of the American Medical Association 1974, 230: 375.
13. Epstein EH, Flynn P, Davis RS: Adult toxic epidermal necrolysis with fatal septicemia. Journal of the American Medical Association 1974, 229: 425–427.
14. Trentham DE, Silverman HA, Townes AS: Cause of adult toxic epidermal necrolysis. New England Journal of Medicine 1975, 292: 870.
15. Amon RB, Dimond RL: Toxic epidermal necrolysis: rapid differentiation between staphylococcal and drug induced disease. Archives of Dermatology 1975, 111: 1433–1437.
16. Achten G, De Dobbeleer G, Moriame M: Staphylococcal scalded skin syndrome in an adult. Dermatologica 1975, 151: 342–348.
17. Elias PM, Levy SW: Bullous impetigo: occurrence of localized scalded skin syndrome in an adult. Archives of Dermatology 1976, 112: 856–858.
18. Sturman SW, Malkinson FD: Staphylococcal scalded skin syndrome in an adult and a child. Archives of Dermatology 1976, 112: 1275–1279.
19. Schlesinger JJ: Staphylococcal induced toxic epidermal necrolysis in an adult: case report. Military Medicine 1977, 142: 791–793.
20. Peterson PK, Laverdiere M, Quie PG: Abnormal neutrophil chemotaxis and T-lymphocyte function in scalded skin syndrome in an adult patient. Infection 1977, 5: 128–131.
21. Neefe LI, Tuazon CV, Cardella TA, Sheagren JN: Staphylococcal scalded skin syndrome in adults: case report

and review of the literature. American Journal of the Medical Sciences 1979, 277: 99–110.
22. Ridgway HB, Lowe NJ: Staphylococcal scalded skin syndrome in an adult with Hodgkin's disease. Archives of Dermatology 1979, 115: 589–590.
23. Fine JD, Harrist TJ, Radford MJ: Adult scalded skin syndrome fatally complicated by mixed gram-negative sepsis and cellulitis. Cutis 1981, 27: 162–167.
24. Diem E, Konrad K, Graninger W: Staphylococcal scalded skin syndrome in an adult with fatal disseminated sepsis. Acta Dermatology and Venereology 1982, 62: 295–299.
25. Janier M, Bigel ML, Wallach D: Staphylococcie exfoliante et pustuleuse généralisée chez une immunodéprimée. Annals of Dermatology and Venereology 1984, 111: 705–706.
26. Richard M, Matthieu-Serra A: Staphylococcal scalded skin syndrome in a homosexual adult. Journal of the American Academy of Dermatology 1986, 15: 385–389.
27. Takiushi I, Sakasi H, Tagaki H: Staphylococcal scalded skin syndrome in an adult. Journal of Dermatology 1986, 13: 372–376.
28. O'Keefe R, Dag JH, MacKie RM: The staphylococcal scalded skin syndrome in two elderly immunocompromised patients. British Medical Journal 1987, 295: 179–180.
29. Opal SM, Johnson-Winegar AD, Cross AS: Staphylococcal scalded skin syndrome in two immunocompetent adults caused by exfoliative B-producing *Staphylococcus aureus*. Journal of Clinical Microbiology 1988, 26: 1283–1286.
30. Saiag P, Caumes E, Roujeau JC: Epidermolyse staphylococcique (syndrome de Lyell staphylococcique) de l'adult: 2 cas. Annals of Dermatology and Venereology 1988, 115: 1164–1166.
31. Petzelbauer P, Konrad K, Wolff K: Staphylococcal scalded skin syndrome in 2 adults with acute kidney failure. Hautarzt 1989, 40: 90–93.
32. Goldberg NS, Ahmed T, Robinson B, Ascensao J, Horowitz H: Staphylococcal scalded skin syndrome mimicking acute graft-vs.-host disease in a bone marrow transplant recipient. Archives of Dermatology 1989, 125: 85–87.
33. Beers B, Wilson B: Adult staphylococcal scalded skin syndrome. International Journal of Dermatology 1990, 29: 428–429.
34. Herzog JL, Sexton M: Desquamative rash in an immunocompromised adult. Archives of Dermatology 1990, 26: 815–819.
35. Strumia R, Bedetti A, Cavazzini L: Staphylococcal scalded skin syndrome in AIDS. Journal of Italian Dermatology and Venereology 1990, 125: 461–464.
36. Donohue D, Robinson B, Goldberg NS: Staphylococcal scalded skin syndrome in a woman with chronic renal failure exposed to human immunodeficiency virus. Cutis 1991, 47: 317–318.
37. Khuong MA, Chosidow O, El Solh N, Wechsler J, Piemont Y, Roujeau JC, Revuz J: Staphylococcal scalded skin syndrome in an adult: possible influence of nonsteroidal anti-inflammatory drugs. Dermatology 1993, 186: 153–154.

Candida Endophthalmitis in Non-Neutropenic Critically Ill Patients

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Six non-neutropenic critically ill patients who developed hematogenous endophthalmitis due to *Candida* spp. were studied prospectively. In all cases the yeast was isolated in blood cultures. The incidence of endophthalmitis in patients with candidemia was 13%, the predominant species being *Candida albicans*. Four patients were treated with fluconazole, but its efficacy could not be evaluated because three of the patients died. In patients at risk of candidemia, regular ophthalmoscopic examinations are recommended in order to enable early initiation of systemic antifungal therapy in those who develop endophthalmitis.

Hematogenous candidal endophthalmitis is an important marker for disseminated candidiasis (1). Its incidence has increased in recent years. Total parenteral nutrition, indwelling central venous catheters, gastrointestinal surgery, and prolonged use of broad-spectrum antibiotics are among the most common predisposing factors (1, 2).

To our knowledge there are no prospective studies regarding hematogenous endophthalmitis caused by *Candida* spp. in non-neutropenic critically ill patients. We report our experience with six cases of endophthalmitis in candidemic critically ill patients and describe the prevalence, outcome and antifungal therapy of this disease.

Materials and Methods. A prospective study was performed in consecutive medical and surgical patients with candidemia in 29 medical-surgical in-

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