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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Updated: Feb 20, 2009

Introduction

Background

Toxic epidermal necrolysis (TEN) is an acute dermatologic disease, the presentation of which may constitute a true emergency. The disorder is characterized by widespread erythematous macules and targetoid lesions; full-thickness epidermal necrosis, at least focally; and involvement of more than 30% of the cutaneous surface. Commonly, the mucous membranes are also involved. Nearly all cases of toxic epidermal necrolysis are induced by medications, and the mortality rate can approach 40%.

Stevens-Johnson syndrome (SJS) may also present as a dermatologic emergency characterized by purpuric macules and targetoid lesions; full-thickness epidermal necrosis, although with lesser detachment of the cutaneous surface; and mucous membrane involvement. As with toxic epidermal necrolysis, medications are important inciting agents, although *Mycoplasma* infections may induce some cases. The mortality rate is much lower and approaches 5% of cases.

Erythema multiforme (EM) is generally a far more benign process characterized by target or targetoid lesions, with or without blisters, in a symmetric acral distribution. Oral lesions are common. Severe presentations may have widespread involvement of the mucous membranes and epidermal detachment with a loss of less than 10% of the cutaneous surface. Most cases are secondary to prior infection with a herpes virus. The condition generally has low morbidity and no mortality and is often recurrent. Stevens-Johnson syndrome may have features of both EM and toxic epidermal necrolysis, which has led to confusion in nosology.

Stevens-Johnson syndrome and toxic epidermal necrolysis may represent a spectrum of a single disease process. Some evidence suggests that EM may be an entirely distinct disorder.[1,2] This article discusses Stevens-Johnson syndrome and toxic epidermal necrolysis.

Pathophysiology

Stevens-Johnson syndrome and toxic epidermal necrolysis are often drug induced, but the pathophysiologic mechanism is unknown. A number of theories have been proposed that may have implications for treatment. Patients and their first degree-relatives may have genetic defects in their metabolic pathways that lead to the accumulation of toxic metabolites. For example, patients with sulfonamide-induced toxic epidermal necrolysis have been shown to

have a slow acetylator genotype, resulting in increased production of sulfonamide hydroxylamine via the P-450 pathway. These drug metabolites may have direct toxic effects or act via a hapten-mediated mechanism to break self-tolerance to endogenous proteins.

Apoptosis of keratinocytes has been proposed secondary to a cell-mediated cytotoxic reaction. Keratinocyte apoptosis is rare in the healthy epidermis, but it has been shown to be increased in toxic epidermal necrolysis. In 1997, Inachi et al demonstrated perforin-mediated apoptosis in patients with Stevens-Johnson syndrome.[3] Perforin, a pore-making monomeric granule released from natural killer cells and cytotoxic T lymphocytes, kills target cells by forming polymers and tubular structures not unlike the membrane attack complex of the complement system.

A second proposed mechanism of apoptosis involves interaction between a cell-surface death receptor, such as Fas, and its receptive ligand, to form a Fas ligand (FasL). In 1998, Viard et al demonstrated high concentrations of soluble Fas ligand (sFasL) in toxic epidermal necrolysis sera.[4] In vitro, target cell death was blocked by a FasL-blocking antibody and by antibodies present in pooled human intravenous immunoglobulin (IVIG). An open trial of IVIG in 10 patients with toxic epidermal necrolysis resulted in a halt of progression within 24-48 hours, with no mortality.

Frequency

United States

Chan et al evaluated the hospital discharge diagnoses of 61 patients with EM, Stevens-Johnson syndrome, or toxic epidermal alvato da Windows Internet Explorer 8> Subject: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:32:05 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_0030_01CA2CF7.210D8980" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_0030_01CA2CF7.210D8980 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1124127-print

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Frequency

United States

Chan et al evaluated the hospital discharge diagnoses of 61 patients with EM, Stevens-Johnson syndrome, or toxic epidermal necrolysis from 1972-1986 and reported the incidence of toxic epidermal necrolysis to be 0.5 per million population per year.[5] Strom et al reviewed Medicaid billing data from 1980-1984 in Michigan, Minnesota, and Florida to determine the incidence of Stevens-Johnson syndrome; the incidence rates were 7.1, 2.6, and 6.8 cases per million population per year, respectively.[6]

International

The incidence of toxic epidermal necrolysis in Sweden has been reported to be 0.4 per million population per year, and a French group reported 1.2 cases per million population per year. A study in West Germany reported the incidences of toxic epidermal necrolysis and Stevens-Johnson syndrome to be 0.93 and 1.1 cases per million population per year, respectively.

Mortality/Morbidity

Stevens-Johnson syndrome may prove fatal in roughly 5% of patients; toxic epidermal necrolysis may prove fatal in as many as 40% of patients. Sepsis and respiratory distress are the most common complications and ultimately the direct causes of death. Important prognostic factors include the percentage loss of body surface area (BSA), age, persistent neutropenia (defined as neutropenia lasting >5 d), hypoalbuminemia (usually <2 g/dL), and persistent azotemia. Among 247 French patients, only 1 out of 70 died when BSA involvement was less than 10%. In contrast, the mortality rate was 11% for patients with 10-30% BSA involvement and 35% for patients with BSA involvement exceeding 30%.

While some patients rapidly progress to lose very large areas of the epidermis in a matter of days, the process suddenly ceases in others and reepithelialization begins a few days later. Predicting the course of disease in a given patient at the initial presentation is not possible. Reepithelialization is usually complete within 3 weeks, but pressure and mucosal areas may remain eroded and crusted for 2 weeks or longer.

Survivors of Stevens-Johnson syndrome/toxic epidermal necrolysis may experience numerous long-term sequelae; the most disabling are those of the eye. Cicatrization of conjunctival erosions may lead to inverted eyelashes, photophobia, a burning sensation in the eyes, watery eyes, a siccalike syndrome, and corneal and conjunctival neovascularization. As many as 40% of survivors of toxic epidermal necrolysis have residual potentially disabling lesions that may cause blindness.

Cutaneous lesions may resolve with a patchwork of hyperpigmentation and hypopigmentation. Fingernails and toenails may regrow abnormally. Lesions of the genitourinary system may lead to phimosis or vaginal synechiae.

Race

Stevens-Johnson syndrome and toxic epidermal necrolysis have been described worldwide in all races. Interestingly, disease is not limited to humans, and cases have been reported in dogs, cats, and monkeys.

Sex

Numerous epidemiologic studies have shown that females have higher incidences of toxic epidermal necrolysis than males. Reported adult male-to-female ratios have ranged from 0.5-0.7. However, the epidemic of human immunodeficiency virus (HIV) is normalizing sex ratios in some studies. One study found a ratio of 1:1 in 90 patients with toxic epidermal necrolysis, 20 of whom were HIV infected and 16 of those were men. Among patients not infected with HIV, the sex ratio was 0.62. Male and female children have similar rates of toxic epidermal necrolysis.

Age

Toxic epidermal necrolysis occurs in all age groups, including newborns. Because drug exposure increases with age, Stevens-Johnson syndrome and toxic epidermal necrolysis occur more frequently in the older population. Also, adults might be metabolically more susceptible to such drug reactions than children.

A French study of toxic epidermal necrolysis reported a mean patient age of 46.8 years, with a range of 1-93 years. Fourteen percent of the patients were younger than 16 years. A retrospective West German study of 259 patients with toxic epidermal necrolysis and 315 patients with Stevens-Johnson syndrome found average ages of 63 and 25 years, respectively. However, only 54% of cases of Stevens-Johnson syndrome could be attributed to drugs, and some cases of EM, which typically affects younger patients, were likely included in the analysis. Lastly, HIV infection is associated with toxic epidermal necrolysis, and those patients tend to be younger, with one study reporting 14 patients being affected, with an average age of 35.4 years.

Clinical

History

- Constitutional symptoms, such as fever, cough, or sore throat, may appear 1-3 days prior to any cutaneous lesions.
- Patients may complain of a burning sensation in their eyes, photophobia, and a burning rash that begins symmetrically on the face and the upper part of the torso.
- Delineation of a drug exposure timeline is essential, especially in the 1-3 weeks preceding the cutaneous eruption.

Physical

- Primary lesions
    - The initial skin lesions of Stevens-Johnson syndrome/toxic epidermal necrolysis are poorly defined erythematous macules with darker purpuric centers. The lesions differ from classic target lesions of EM by having only 2 zones of color: central dusky purpura or a central bulla, with surrounding macular erythema. A classic target lesion has 3 zones of color: central dusky purpura or a central bulla, a surrounding edematous pale zone, and a surrounding macular erythema.
    - Lesions, with the exception of central bullae, are typically flat. Lesions of EM are more likely to be palpable.
    - Less frequently, the initial eruption may be scarlatiniform.
    - Flaccid blisters are typically present with full-thickness epidermal necrosis (see Media Files 1-2).
    - Nondenuded areas have a wrinkled paper appearance.
    - A Nikolsky sign is easily demonstrated by applying lateral pressure to bullae.
- Arrangement: Individual macules are found surrounding large areas of confluence.
- Distribution: Lesions begin symmetrically on the face and the upper part of the torso and extend rapidly, with maximal extension in 2-3 days. In some cases, maximal extension can occur rapidly over hours.
    - Lesions may predominate in sun-exposed areas.
    - Full detachment is more likely to occur in areas subjected to pressure, such as the shoulders, the sacrum, or the buttocks.
    - Painful edematous erythema may appear on the palms and the soles.
    - The hairy scalp typically remains intact, but the entire epidermis, including the nail beds, may be affected.
    - A recent classification proposes that epidermal detachment in Stevens-Johnson syndrome is limited to less than 10% of the BSA. Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis has more extensive confluence of erythematous and purpuric macules, leading to epidermal detachment of 10-30% of the BSA. Classic toxic epidermal necrolysis has epidermal detachment of more than 30%.
    - An uncommon form of toxic epidermal necrolysis (toxic epidermal necrolysis without spots) lacks targetoid lesions, and blisters form on confluent erythema. Greater than 10% epidermal detachment is required for diagnosis of these cases.
    - In contrast, bullous EM, which has been previously grouped with Stevens-Johnson syndrome, may have epidermal detachment of less than 10% of the BSA, but typical target lesions or raised atypical targets are localized primarily in an acral distribution.
- Secondary lesions: Areas of denuded epidermis are dark red with an oozing surface.
- Mucous membranes: Mucous membrane involvement is present in nearly all patients and may precede skin lesions, appearing during the prodrome (see Media File 3).
    - Painful oral erosions cause severe crusting of the lips, increased salivation, and impaired alimentation.
    - Involvement of the genitalia may lead to painful micturition.
    - Lesions have been reported in the oropharynx, the tracheobronchial tree, the esophagus, the GI tract, the genitalia, and the anus.
    - Intact expectorated cylindrical casts of bronchial epithelium have been reported.
    - Patients may develop a profuse protein-rich diarrhea.
    - Internal involvement is not necessarily limited to patients with extensive cutaneous involvement.
- Ocular lesions: Ocular lesions are especially problematic because they have a high risk of sequelae.
    - Initially, the conjunctivae are erythematous and painful.
    - The lids are often stuck together, with efforts to loosen them resulting in tearing of the epidermis.
    - Pseudomembranous conjunctival erosions may form synechiae between the eyelids and the conjunctivae.

- Keratitis, corneal erosions, and a siccalike syndrome may develop.

Causes

Most cases of Stevens-Johnson syndrome/toxic epidermal necrolysis are drug induced. In establishing a drug exposure timeline, agents administered within 1-3 weeks are most suspect, although longer or shorter times do not necessarily rule out a particular medication. A case-control study of 245 patients and 1,147 control subjects in Europe identified potential drug triggers.

For medications used on a short-term basis, the relative risk was greatest for trimethoprim-sulfamethoxazole and other sulfonamide antibiotics, chlormezanone, aminopenicillins, quinolones, cephalosporins, and allopurinol. A case-control multinational study found that allopurinol was the drug most associated with Stevens-Johnson syndrome/toxic epidermal necrolysis.[7] Daily doses of 200 mg or greater were associated with a higher risk. The increased risk was limited to short-term use less than 8 weeks.

Among drugs used long term, the greatest risk of Stevens-Johnson syndrome/toxic epidermal necrolysis was seen in the first 2 months of use. The agents posing an increased risk were carbamazepine, phenobarbital, phenytoin, valproic acid, oxicam nonsteroidal anti-inflammatory drugs, and corticosteroids. The greatest excess risk was 4.5 cases per million users in 1 week for sulfonamides.

Epidemiologic studies in France have shown a greater risk of toxic epidermal necrolysis in patients infected with HIV, especially those with acquired immune deficiency syndrome (AIDS). In the greater Paris area, 15 cases of AIDS-associated toxic epidermal necrolysis occurred over a 6-year period, whereas 0.04 cases would be expected in the general population. This finding may be due to the increased use of sulfonamides in patients infected with HIV and abnormal patterns of production or detoxification of drug metabolites.

Toxic epidermal necrolysis may be related to bone marrow transplantation and acute graft versus host disease (GVHD). In a French series of 152 allogeneic bone marrow recipients, Villada et al reported toxic epidermal necrolysis occurring in 6% of patients.[8] This incidence is far higher than that expected in the general population. Moreover, toxic epidermal necrolysis has been described in an animal model of cutaneous acute GVHD.

Toxic epidermal necrolysis has been reported in patients with systemic lupus erythematosus, but these limited cases may be a mere coincidence. Infections with herpesvirus, *Mycoplasma pneumoniae,* or *Yersinia* have also been reported in patients with Stevens-Johnson syndrome, but these patients may have had EM. Other reported associations include leukemia, lymphoma, ulcerative colitis, and Crohn disease.

Differential Diagnoses

Bullous Pemphigoid
Burns, Chemical
Graft Versus Host Disease
Impetigo
Linear IgA Dermatosis
Lupus Erythematosus, Bullous
Pemphigus Vulgaris
Pemphigus, Paraneoplastic
Psoriasis, Pustular
Staphylococcal Scalded Skin Syndrome
Thermal Burns

Other Problems to Be Considered

Acute generalized exanthematic pustulosis

Linear immunoglobulin A (IgA) bullous dermatosis

Workup

Laboratory Studies

- The initial laboratory workup includes a CBC count, a chemistry profile, liver enzyme studies, renal function studies, prothrombin time, activated partial thromboplastin time, and cultures of blood and areas of denuded skin.

Imaging Studies

- A baseline chest radiograph should be obtained because tracheobronchial involvement and respiratory distress are frequent complications.

Procedures

- Bronchoscopy may be considered to verify involvement of the respiratory tract, but further epithelial trauma may be induced.
- Similarly, an upper GI series, esophagogastroduodenoscopy, and colonoscopy may be needed to confirm involvement of the GI tract.

Histologic Findings

The biopsy shows a normal stratum corneum with underlying necrosis of epidermal cells (either solitary or en masse). Interface dermatitis with sites of damage out of proportion to the number of lymphocytes is typical.

Diagnosing Stevens-Johnson syndrome/toxic epidermal necrolysis and ruling out staphylococcal scalded skin syndrome or a blistering disorder are important because the prognosis and the course differ markedly. To this end, routine or fresh-frozen section specimens of sloughed epidermis should be obtained for histologic examination. Full-thickness epidermal necrosis is consistent with Stevens-Johnson syndrome/toxic epidermal necrolysis, whereas a subcorneal split is consistent with staphylococcal scalded skin syndrome.

A biopsy sample of fully developed lesions reveals full-thickness epidermal necrosis with involvement of the sweat ducts, relative sparing of the hair follicles, and little alteration of the dermis. Immunofluorescence study results are negative.

Treatment

Medical Care

Recurrent EM minor is typically related to episodes of recurrent herpes simplexvirus infection and can be prevented by continuing use of antiviral agents.

Patients with Stevens-Johnson syndrome/toxic epidermal necrolysis should be treated in an ICU or burn unit under the coordinated care of an ICU team and consultants. Hospitalization should be considered for patients with an initially benign presentation of Stevens-Johnson syndrome because predicting which patients will progress to more severe manifestations or toxic epidermal necrolysis is not possible. The broad principles of management are fluid replacement, nutritional supplementation, sterile technique, and wound care. Studies have shown that early care by or transport to a burn center significantly reduces the mortality rate.

- Fluid replacement: Fluid rehydration is essential because epidermal loss results in massive fluid shifts and dehydration.
- Nutritional supplementation: Aggressive nutritional support should be initiated because protein losses through denuded skin are massive, predisposing the patient to complications and retardation of reepithelialization.
- Sterile technique
    - Epidermal loss predisposes patients to infection and sepsis.
    - Sterile technique is essential to prevent complications from endogenous and exogenous sources.
    - Silver sulfadiazine must be avoided because sulfonamides are a frequent inciting drug in toxic epidermal necrolysis.
    - Broad-spectrum prophylactic antibiotics are not recommended.
- Wound care
    - Debridement of all necrotic epidermis with replacement by using biologic dressings, such as collagen-based substitutes or porcine xenografts, is recommended.
    - Some physicians use biologic dressings only on denuded skin, leaving necrotic intact epidermis in place.
    - Adhesive tapes should be avoided because further skin loss may occur at the site of application.

    - Oral care and application of antiseptics may be necessary.
- Consultation with an ophthalmologist is essential.
    - Frequently applied eye drops may be necessary with daily blunt disruption of synechiae.
    - Eye drops must not contain sulfonamides because they are frequently implicated in toxic epidermal necrolysis.
- Other supportive treatment
    - Because epidermal slough leads to massive heat loss, the environmental temperature should be increased to 30-32°C.
    - Heated antiseptic baths, heat shields, infrared lamps, and air-fluidized beds may decrease heat losses.
    - As a caveat, air-fluidized beds can pose an evaporative effect, and fluid status should be corrected prior to use.

Consultations

- Obtain an early consultation with a dermatologist because the prognosis and the course differ markedly for toxic epidermal necrolysis/Stevens-Johnson syndrome and other diseases in the differential diagnosis.
- Consultation with an ophthalmologist is essential because early lesions may be subclinical.
- Consultation with a pulmonologist is prudent because interstitial edema may be evident on chest radiographs prior to the appearance of clinical symptoms.
- Consultation with a GI specialist is appropriate in cases of suspected involvement of the GI tract.

Medication

The first step in medical treatment is withdrawal of causative drugs. Retrospective studies have indicated that early withdrawal decreases the mortality rate.[9] Implicated medications are listed above (see Causes).

The use of corticosteroids in the management of the Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum is one of the most controversial areas in dermatology. Administration early in the course of disease has been advocated, but multiple retrospective studies demonstrate no benefit or higher rates of morbidity and mortality related to sepsis. This risk is probably proportional to the area of sloughed skin.

Halebian et al advised against the use of steroids based on 2 open nonrandomized prospective studies of corticosteroids in 30 patients admitted to a burn unit with Stevens-Johnson syndrome or toxic epidermal necrolysis.[10] Fifteen patients received corticosteroids and 15 did not. The groups were statistically similar in terms of age, morbid days before burn center admission, and the amount of skin sloughed. Thirty-three percent of the steroid group survived versus 66% of the nonsteroid group (P = .057). Sepsis occurred with similar frequency in both groups, but 91% of those in the steroid group died versus 56% of those in the infected nonsteroid group.

Steroids are suggested to predispose patients to gram-negative sepsis by impairing host resistance and ultimately leading to late clinical recognition of sepsis by suppression of symptoms. Because multiple studies, albeit uncontrolled, have demonstrated a higher morbidity and mortality in patients receiving corticosteroids, most authorities do not recommend their use.

A number of studies support the use of IVIG in the treatment of toxic epidermal necrolysis. Viard et al suggested that apoptotic cell death occurs via activation of a cell-surface death receptor.[4] In vitro, target cell death was blocked by a receptor-ligand blocking antibody and by antibodies present in pooled human IVIG. An open trial of IVIG in 10 patients with toxic epidermal necrolysis resulted in a halt of progression within 24-48 hours, with no mortality.

Since 2000, a number of case reports and 8 noncontrolled clinical studies containing 9 or more patients have analyzed the efficacy of IVIG in toxic epidermal necrolysis. Some studies have not demonstrated a therapeutic benefit, while others have shown decreased mortality.[11,12,13] Six of the 8 studies suggested a benefit of IVIG at doses greater than 2 g/kg. Schneck J et al published a retrospective study of patients from France and Germany enrolled in EuroSCAR, a case-control study of risk factors. Neither IVIG or corticosteroids decreased mortality when compared with supportive care alone.[14]

Given the potentially fatal nature of toxic epidermal necrolysis and the ethical issues involved, a randomized controlled trial will likely never be performed. Given the suggestion of a therapeutic benefit, many centers are incorporating IVIG into their treatment protocols. At University

Hospital at Stony Brook, New York, Stevens-Johnson syndrome/toxic epidermal necrolysis patients are treated with a dosage of 1g/kg/d for 4 consecutive days.

An open study from the trauma literature demonstrated the efficacy of cyclosporine. Arevalo et al presented 11 patients admitted consecutively to a burn unit, with toxic epidermal necrolysis involving a large BSA (83% ± 17%).[15] Each received cyclosporine 3 mg/kg/d enterally every 12 hours. This group was compared to a series of 6 historical control subjects treated with cyclophosphamide and corticosteroids. The time from the onset of skin signs to arrest of disease progression and to complete reepithelialization was significantly shorter in the cyclosporine group. All patients in the cyclosporine group survived versus 50% surviving in the cyclophosphamide group. Given a mortality rate of approximately 30% in patients not infected with HIV with toxic epidermal necrolysis, cyclosporine may prove to be a life-saving therapy, but randomized controlled trials are needed to make definitive recommendations.

Cyclophosphamide, *N*- acetylcysteine, and monoclonal antibodies directed against cytokines have been used in isolated case reports and small uncontrolled studies. Thalidomide has been shown to have a deleterious effect on patients' outcomes.[16]

Only early transfer to and care in a burn unit has been demonstrated to decrease mortality. Coupled with early withdrawal of offending agents, this intervention is the best treatment that can be offered at this time.

Immune globulins

These agents are used to improve clinical and immunologic aspects of the disease. They may decrease autoantibody production, and they may increase solubilization and removal of immune complexes.

Immune globulin intravenous (Gamimune, Gammar-P, Sandoglobulin, Gammagard S/D)

IVIG may block target cell death by a receptor-ligand blocking antibody and by antibodies present in pooled human immunoglobin.

Dosing

Adult

1 g/kg/d IV for 3 d

Pediatric

Not established

Interactions

Globulin preparation may interfere with immune response to live virus vaccine (MMR) and reduce efficacy (do not administer within 3 mo of vaccine)

Contraindications

Documented hypersensitivity; IgA deficiency

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Check serum IgA before IVIG (use an IgA-depleted product, eg, Gammagard S/D); infusions may increase serum viscosity and thromboembolic events; infusions may increase risk of migraine attacks, aseptic meningitis (10%), urticaria, pruritus, or petechiae (2-30 d postinfusion); increases risk of renal tubular necrosis in elderly patients and in patients with diabetes, volume depletion, and preexisting kidney disease; laboratory result changes associated with infusions include elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increase in ESR for 2-3 wk, and apparent hyponatremia

Immunosuppressants

These agents inhibit key factors in the immune system responsible for immune reactions.

Cyclosporine (Sandimmune, Neoral)

May block production of pathogenic antibodies.

Dosing

Adult

2.5-5 mg/kg/d PO in divided doses

Pediatric

Administer as in adults

Interactions

Carbamazepine, phenytoin, isoniazid, rifampin, and phenobarbital may decrease concentrations; azithromycin, itraconazole, nicardipine, ketoconazole, fluconazole, erythromycin, verapamil, grapefruit juice, diltiazem, aminoglycosides, acyclovir, amphotericin B, and clarithromycin may increase toxicity; acute renal failure, rhabdomyolysis, myositis, and myalgias increase when taken concurrently with lovastatin; methylprednisolone and cyclosporine mutually inhibit one another, resulting in increased plasma levels of each drug

Contraindications

Documented hypersensitivity; uncontrolled hypertension or malignancies

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Evaluate renal and liver functions often by measuring BUN, serum creatinine, serum bilirubin and liver enzyme levels; may increase risk of infection and lymphoma; reserve IV use only for those who cannot take PO

Follow-up

Further Inpatient Care

- Patients with Stevens-Johnson syndrome/toxic epidermal necrolysis should be treated in an ICU or burn unit under the coordinated care of an ICU team and consultants.
- Hospitalization should be considered for patients with an initially benign presentation of Stevens-Johnson syndrome because predicting which patients will progress to more severe manifestations or toxic epidermal necrolysis is not possible.

Further Outpatient Care

- Ophthalmologic follow-up care is essential for patients with ocular lesions.
- Patients with lesions of the genitourinary tract may require outpatient follow-up care with a urologist or a gynecologist for surgical correction of the lesions (eg, phimosis).
- GI follow-up care may be needed for patients with esophageal involvement and strictures.

Transfer

- Studies have shown that early care by or transport to a burn center significantly reduces mortality.

Complications

- Ocular complications must be taken seriously. Failure to lyse adhesions and treat keratitis and corneal erosions can result in blindness. Even meticulous ophthalmologic care can still eventuate long-term sequelae. Cicatrization of conjunctival erosions may lead to inverted eyelashes, photophobia, a burning sensation in the eyes, watery eyes, a siccalike syndrome, and corneal and conjunctival neovascularization. As many as 40% of survivors of toxic epidermal necrolysis have residual potentially disabling lesions that may cause blindness.
- Toxic epidermal necrolysis and Stevens-Johnson syndrome may result in cutaneous scarring, especially in the setting of impetiginization and inadequate wound care. Such scarring may eventuate in cosmetically problematic healing and, if severe, may lead to contractures and functional impairment. Lesions of the genitourinary system may lead to phimosis or vaginal synechiae. Ideally, patients are cared for in a burn unit, where meticulous wound care can be provided.

Prognosis

- The prognosis is largely a function of the degree of skin sloughing. As the percentage of skin sloughing increases, the mortality rate dramatically worsens. In some patients for unknown reasons, the disease process simply stops progressing and rapid epithelialization ensues. For patients experiencing sloughing over a large area of their skin surface, the mortality rate is much higher.
- The SCORTEN is a severity-of-illness score validated for toxic epidermal necrolysis and Stevens-Johnson syndrome.[17,18] It is calculated within 24 hours of admission to predict mortality. The presence of each of the features below is recorded as 1 point, and the summation of points generates a SCORTEN number, with the maximum score being 7.
    - Features
        - Age older than 40 years
        - Presence of malignancy

        - Pulse greater than 120 beats per minute
        - Glucose value greater than 252 mEq/L
        - Blood urea nitrogen level greater than 27 mg/dL
        - Bicarbonate value less than 20 mEq/L
        - BSA greater than 10%
    - SCORTEN mortality rates
        - Score of 0-1 - 3.2%
        - Score of 2 - 12.1%
        - Score of 3 - 35.3%
        - Score of 4 - 58.3%
        - Score of 5 or higher - 90%
- If a causative drug can be identified, early discontinuation is essential. Early discontinuation is associated with improved survival, especially for short-acting medications. Patients exposed to causative drugs with long half-lives have an increased risk of dying.

Patient Education

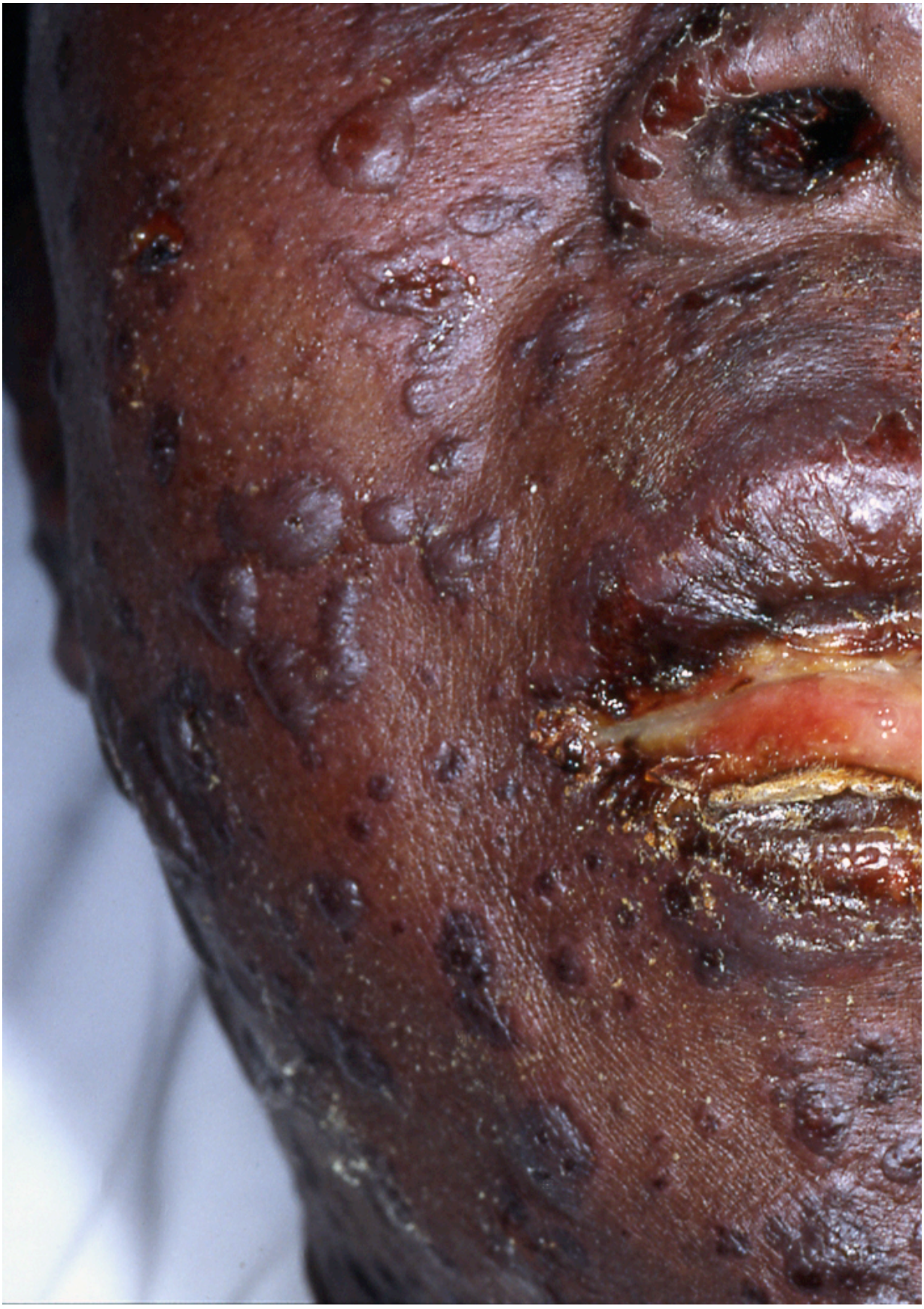
- For excellent patient education resources, visit eMedicine's Skin, Hair, and Nails Center. Also, see eMedicine's patient education article Life-Threatening Skin Rashes.

Miscellaneous

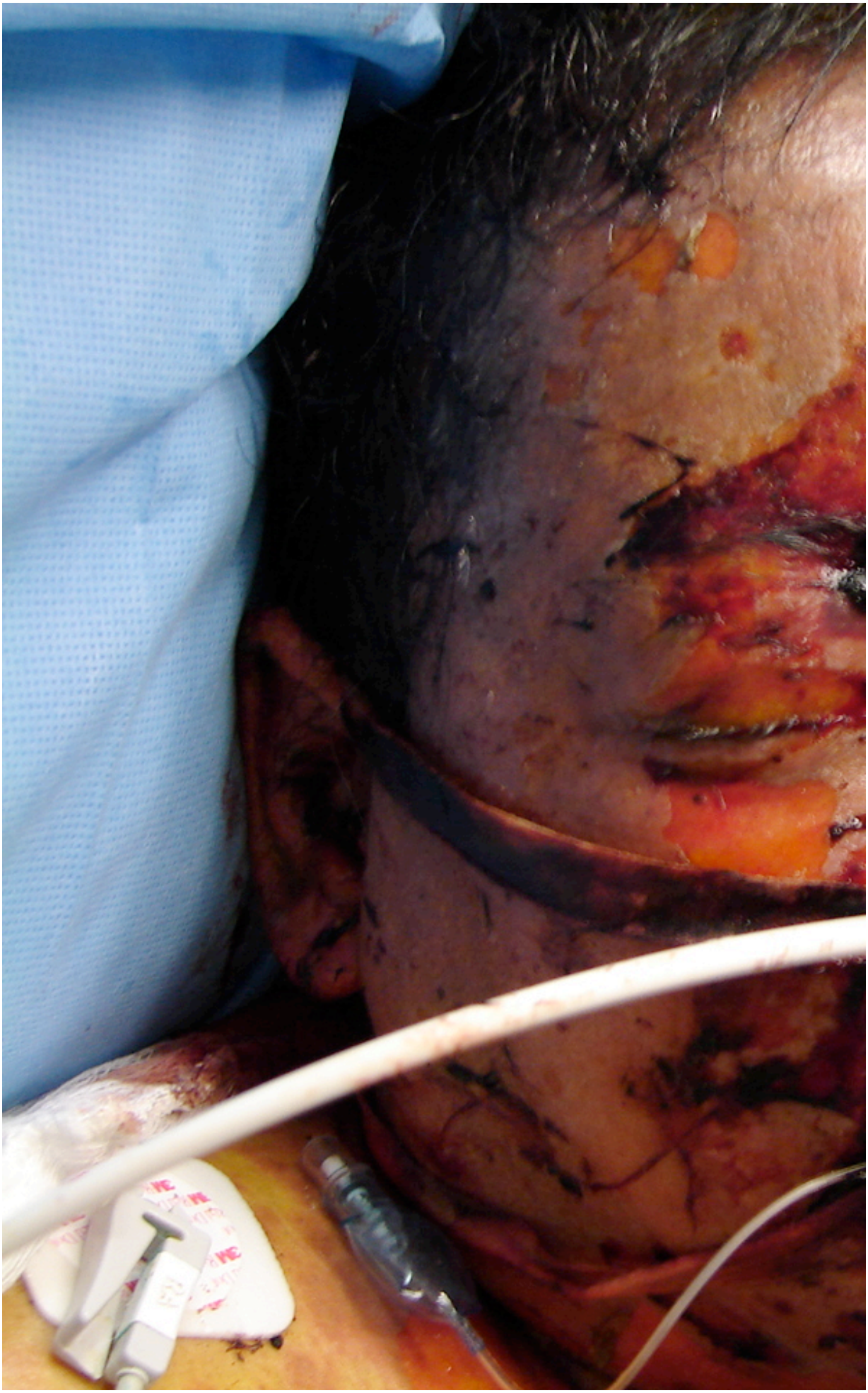
Medicolegal Pitfalls

- The following instances may lead to accusations of malpractice and litigation:
    - Failure to properly diagnose Stevens-Johnson syndrome/toxic epidermal necrolysis, especially when an offending drug continues to be administered as skin necrosis progresses
    - Failure to adequately care for patients in an ICU or burn center
    - Failure to consider emerging treatment options that have been reported in the literature
    - Failure to seek consultation of appropriate specialists
    - Mistakenly re-administering a drug thought to be the offending agent

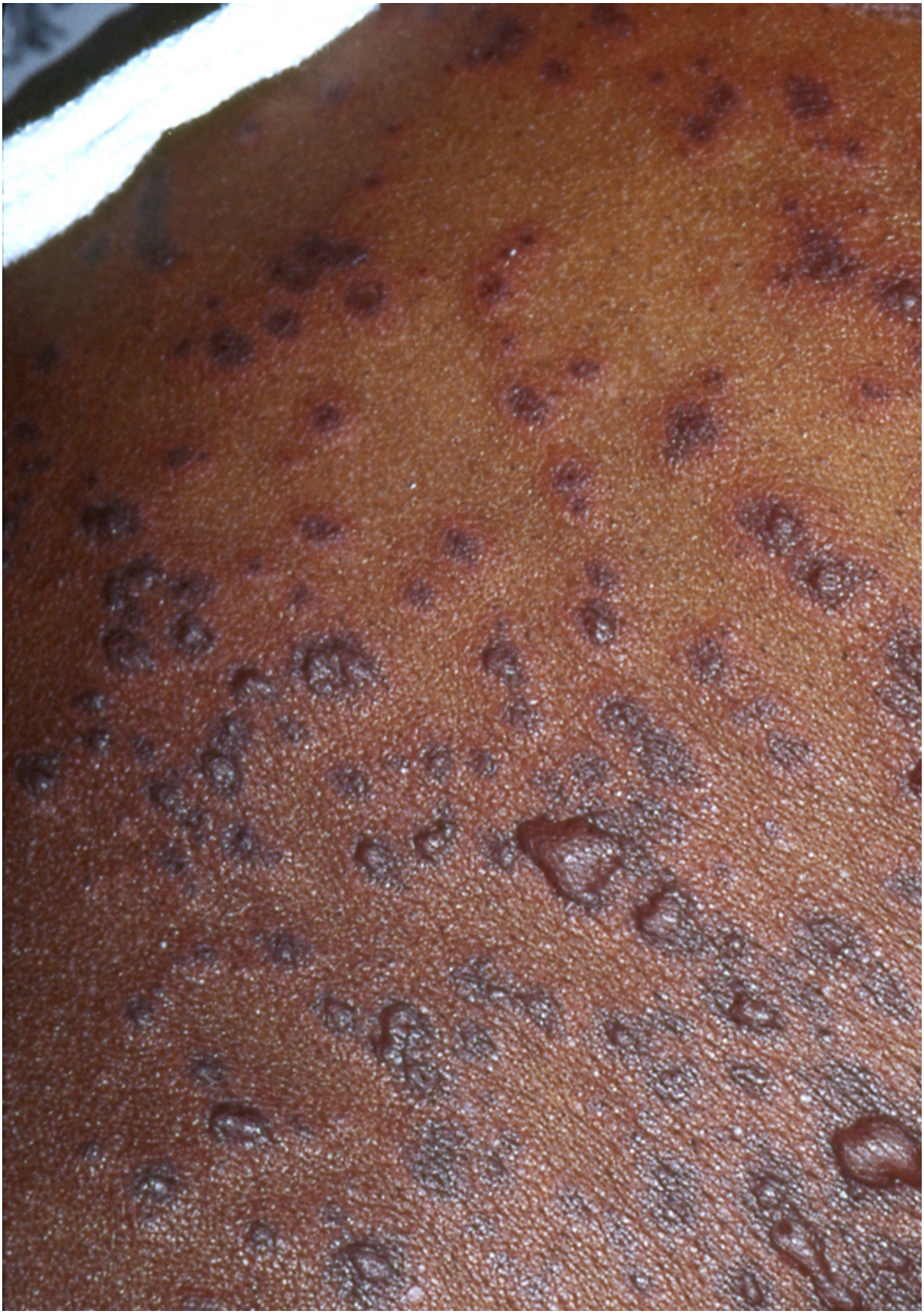
Multimedia



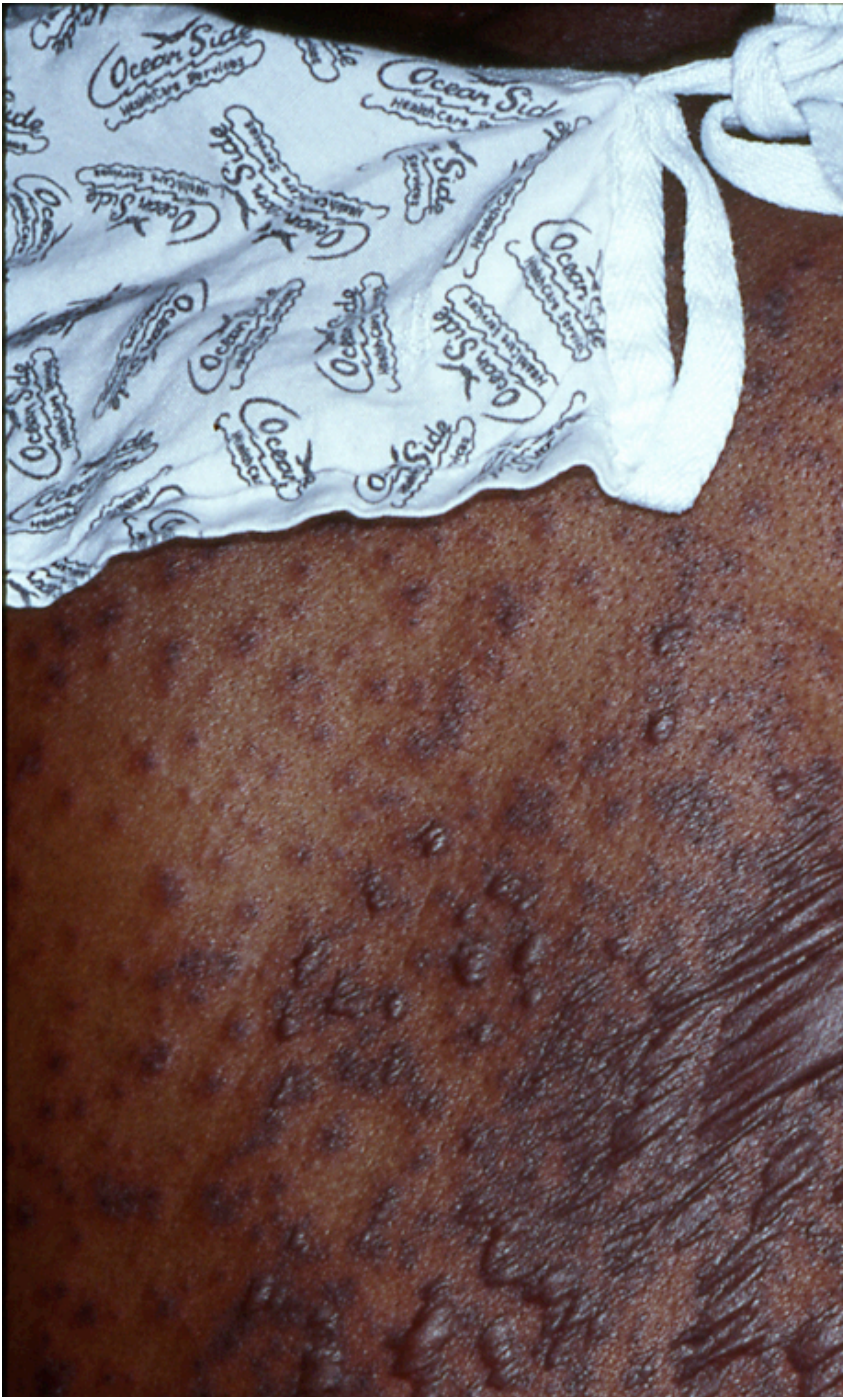
Media file 1: Note early cutaneous slough with areas of violaceous erythema.



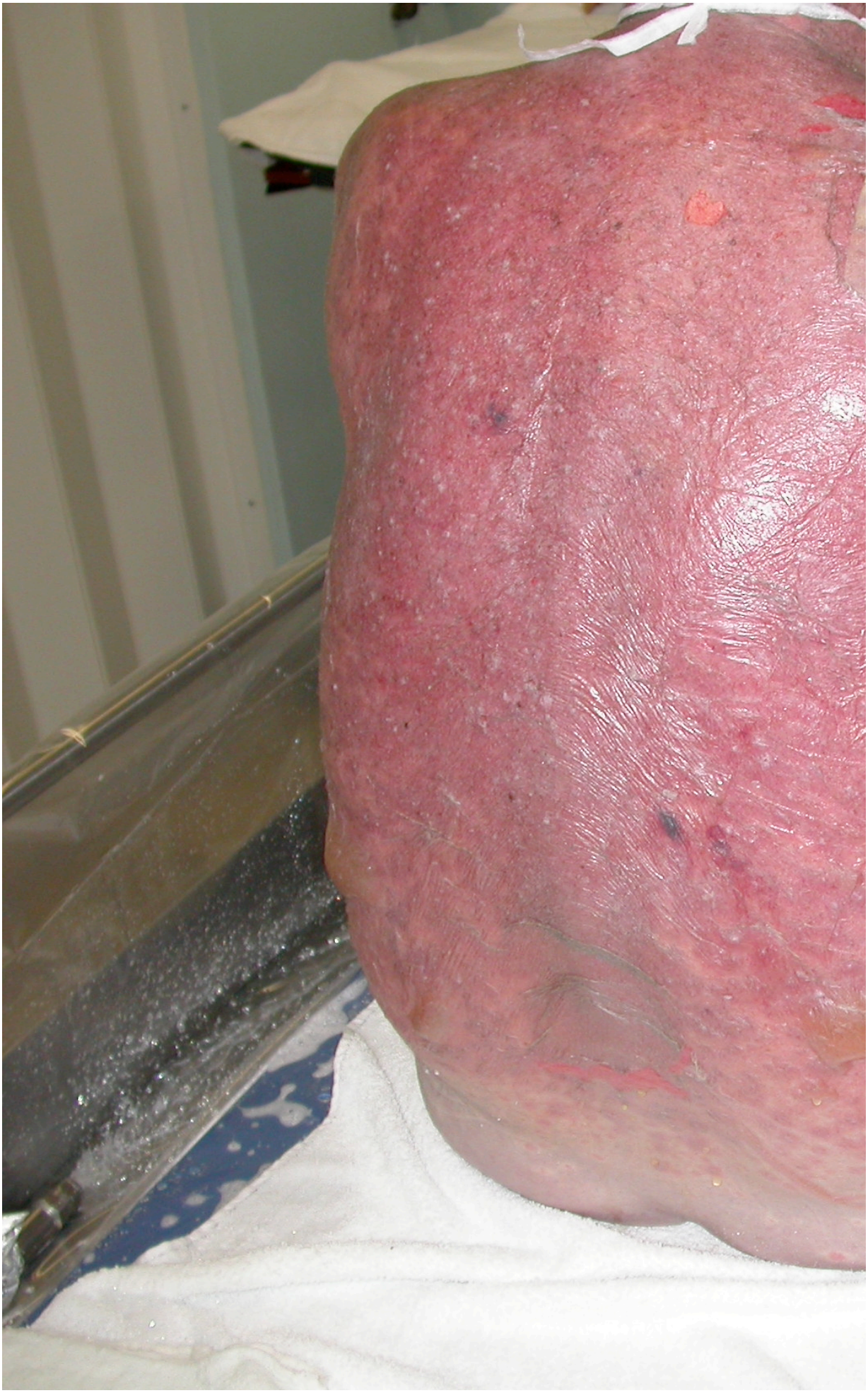
Media file 2: Extensive sloughing on the face.



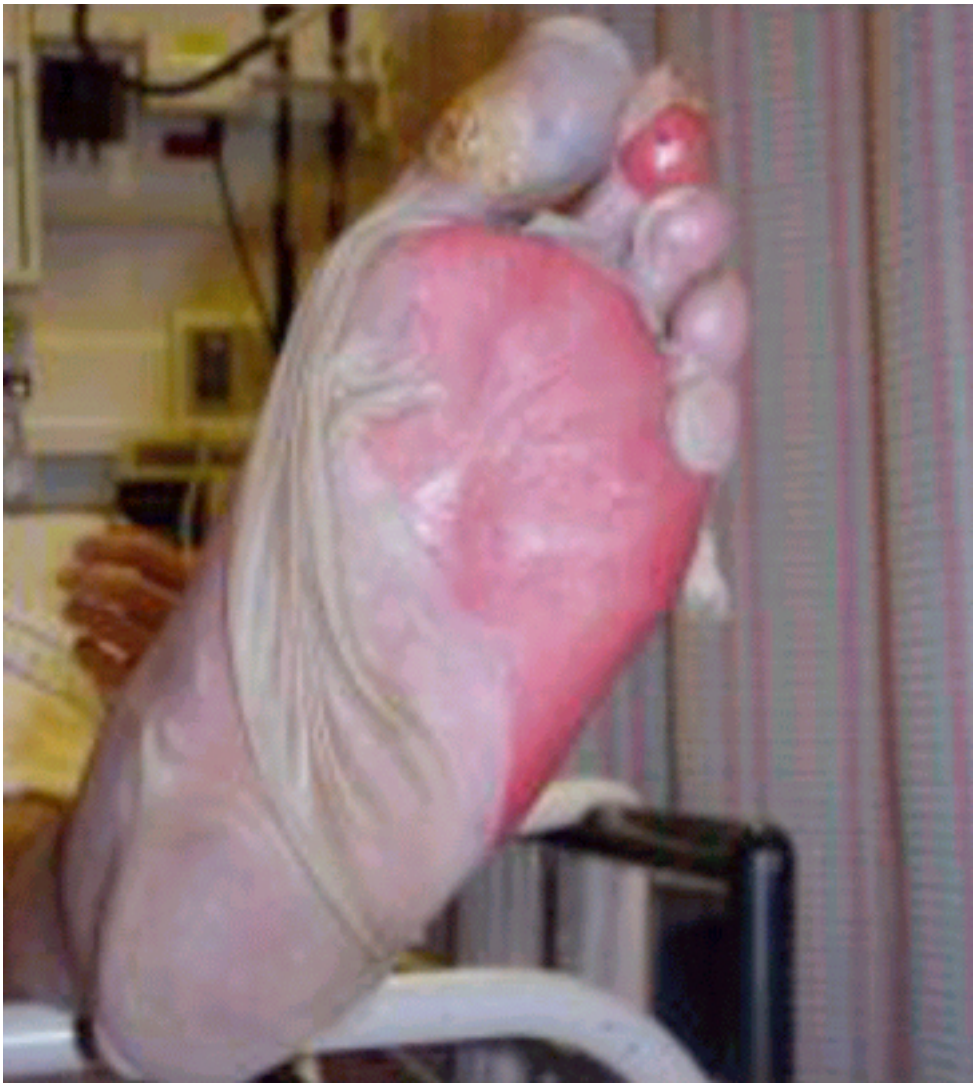
Media file 3: Note the presence of both 2-zoned atypical targetoid lesions and bullae.


Ocean Side
HealthCare Services

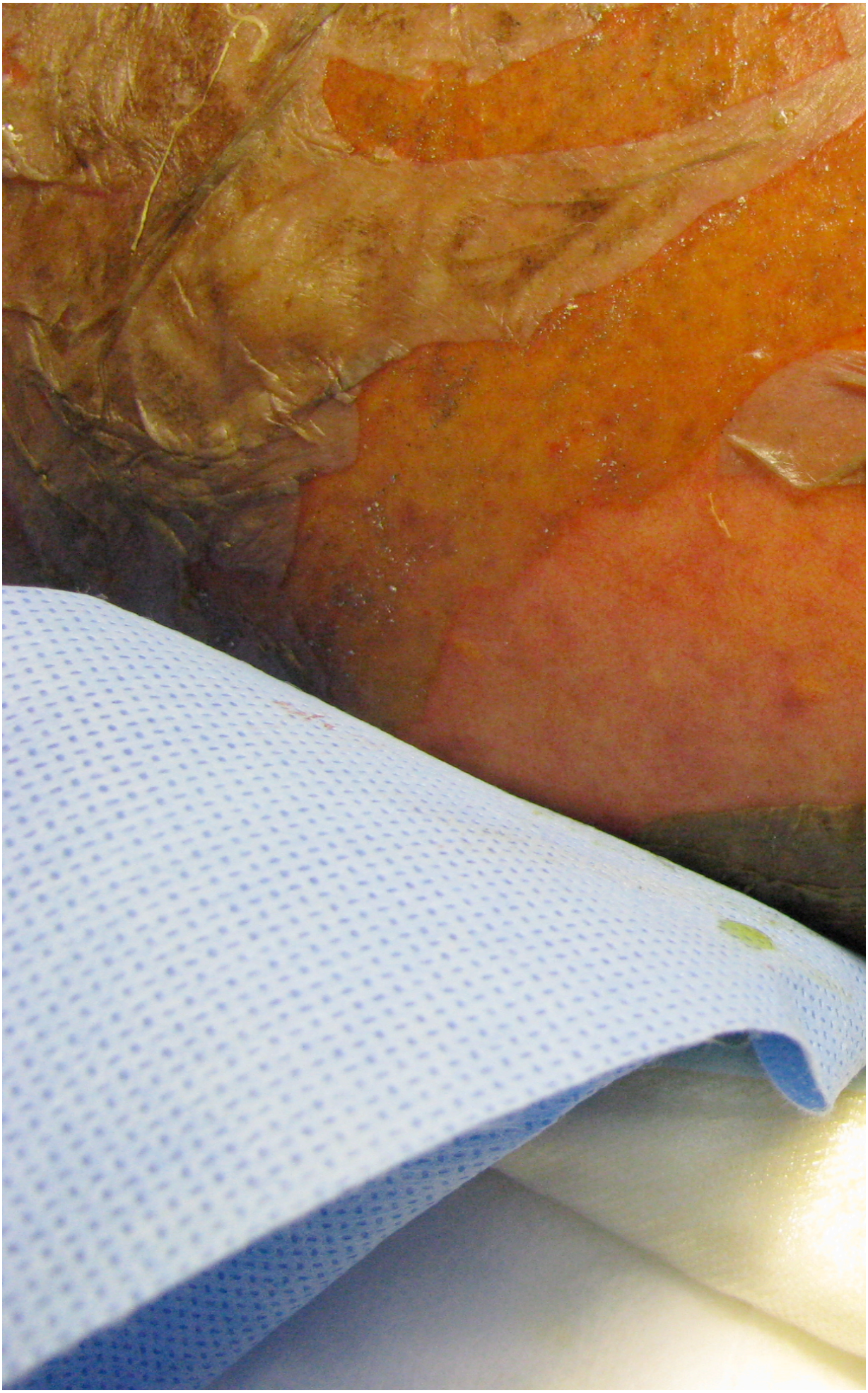
Media file 4: Extensive blistering and sloughing on the back.



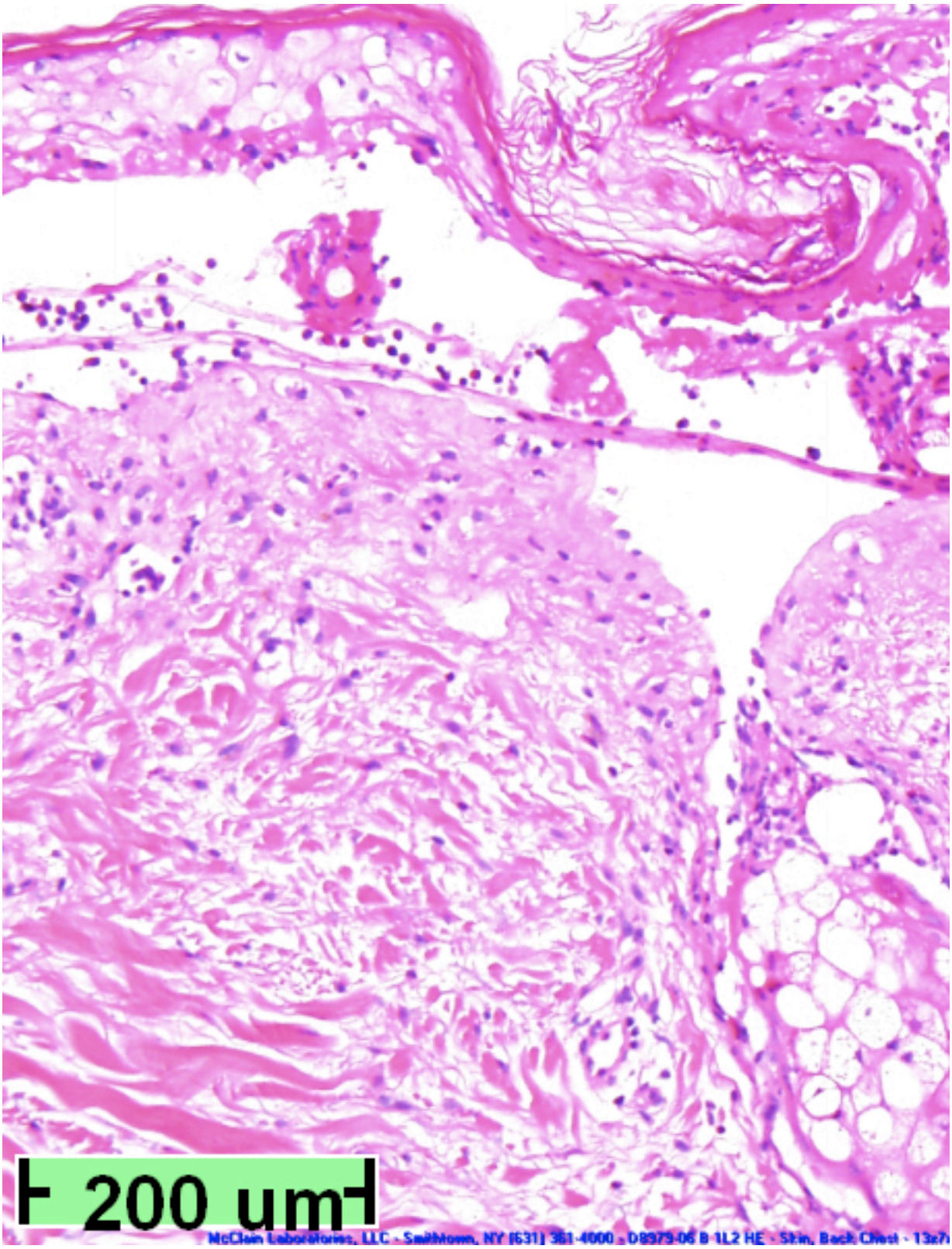
Media file 5: Extensive sloughing on the back.



Media file 6: Sheetlike desquamation on the foot in a patient with toxic epidermal necrolysis. Courtesy of Robert Schwartz, MD.



Media file 7: Note extensive sloughing.



Media file 8: Low-power view showing full-thickness epidermal necrosis.

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