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Drug-Induced Bullous Disorders

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Updated: Jan 6, 2009

Introduction

Background

Bullous or blistering drug eruptions and drug-induced anaphylaxis and hypersensitivity syndromes are among the most serious types of adverse drug reactions. Based on the various mechanisms, bullous drug eruptions may be classified into the following categories:

- Spongiotic or eczematous
- Acute generalized exanthematous pustulosis
- Fixed drug eruption
- Erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis
- Drug-induced pemphigus
- Drug-induced pemphigoid
- Drug-induced linear immunoglobulin A (IgA) dermatosis
- Pseudoporphyria cutanea tarda

Pathophysiology

As with other bullous disorders, drug-induced blistering reactions occur via a variety of pathophysiological mechanisms and at various levels within the epidermis/dermoepidermal junction. Examples of these mechanisms include the following: exocytosis/spongiosis, formation of subcorneal spongiform pustules, cytolysis and keratinocytic necrosis, antiepidermal antibody formation, deposition of immunoglobulin at the basement membrane zone, and photo-induced collagen alterations that lead to a mechanobullous disorder. Most bullous drug reactions are the result of an immunologically mediated inflammatory response, although pseudoporphyria cutanea tarda (pseudo-PCT) is not associated with significant inflammation. Studies have reported the preferential activation of drug-specific $CD8^+$ T cells in the pathophysiology of some bullous drug eruptions.

Frequency

United States

Overall incidence of adverse cutaneous reactions to drugs has been estimated at 0.1-2.2% of treatment courses; however, semisynthetic penicillins and sulfamethoxazole/trimethoprim may have a considerably higher incidence at 3-5% of treatment courses. Patients infected with HIV may be at greater risk for adverse cutaneous drug reactions.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have an incidence ranging from 1.8-9 cases per million and are more frequent in those younger than 20 years and older than 65 years.

International

The United Kingdom, France, Germany, and Italy have reported similar incidences of drug reactions and TEN as the United States. However, one survey in the United Kingdom found that only 2-10% of serious reactions are reported.

Mortality/Morbidity

Most bullous drug eruptions resolve without significant sequelae once the offending drug is removed. However, the morbidity of these reactions is proportional to the extent of skin surface area and mucous membrane involvement. Of patients who develop TEN, 25-30% die. Elderly patients have a higher mortality rate with TEN. Sepsis is the most common cause of death in TEN. SJS and TEN may result in a residual cutaneous pigmentary disorder and possible scarring of the ocular mucosa in those who survive.

Race

Bullous drug reactions have no racial predilections.

Sex

In general, adverse drug reactions occur more commonly in women, although erythema multiforme (EM) has been reported to occur more frequently in men.

Age

Elderly patients who take multiple medications are at higher risk for the development of adverse drug reactions. Young men seem to be aalvato da Windows Internet Explorer 8> Subject: Drug-Induced Bullous Disorders: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:30:44 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_0000_01CA2CF6.F0C834F0" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_0000_01CA2CF6.F0C834F0 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1062790-print

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Race

Bullous drug reactions have no racial predilections.

Sex

In general, adverse drug reactions occur more commonly in women, although erythema multiforme (EM) has been reported to occur more frequently in men.

Age

Elderly patients who take multiple medications are at higher risk for the development of adverse drug reactions. Young men seem to be at higher risk for EM.

Clinical

History

Symptomatology of cutaneous reactions varies depending upon type and extent of skin involvement.

- Eczematous or spongiotic drug reactions may be the result of previous contact sensitization to the drug or may occur de novo.
    - Incidence of contact eczematous reactions to topical medications may be as high as 12.1%. Systemic contact eczematous reactions, which result from systemic exposure (eg, oral, parenteral, rectal, intravenous, inhalation) to a previous contact sensitized drug, are less common.
    - Eczematous drug reactions begin with diffuse pruritus but may also cause headache, malaise, fever, nausea, vomiting, and diarrhea.
- Acute generalized exanthematous pustulosis (AGEP) (toxic pustuloderma) is a result of a systemic medication in 90% of cases.
    - Onset is abrupt, usually 1-5 days after starting the medication.
    - Patients report a diffuse pruritic or burning painful eruption associated with fever, malaise, and sometimes prostration. Seventeen percent of patients have a history of psoriasis.
- Fixed drug eruptions (FDEs) are a common cause of all drug eruptions, and their frequency is second only to urticaria/angioedema.
    - Careful patient assessment usually reveals that an FDE develops 6-48 hours after administration of the causative drug.
    - Symptoms of pruritus and burning accompanied by fever are not uncommon. In those patients with multiple episodes of FDE, reports of increasing hyperpigmentation at the site of a previous lesion are common.
- Nosology of EM is controversial and somewhat confusing. Historically, EM has been divided into 3 groups: EM minor, EM major or SJS, and TEN. Considerable overlap may exist between these 3 subgroups, and some authorities believe that TEN should be considered a distinct entity. An infectious agent, such as herpes simplex or mycoplasma, usually causes less extensive involvement of EM; drugs are implicated less often in EM minor. However, drugs cause most of the more severe and diffuse forms of EM.
    - EM minor may begin with prodromal symptoms suggestive of an upper respiratory infection (eg, coryza, cough, pharyngitis), but within 7-10 days skin lesions begin to develop acrally and symmetrically on the hands, feet, and distal extremities. EM minor may have involvement of the oral mucosa, but involvement of 2 or more mucosal surfaces usually indicates SJS or TEN.
    - EM major (SJS) affects young adult males more frequently. Prodromal symptoms of high fever, asthenia, muscular pains, diarrhea, vomiting, arthralgias, and pharyngitis precede mucosal involvement of 2 or more mucosal sites by several days. Skin involvement rapidly ensues. TEN has similar symptomatology but also demonstrates diffuse skin tenderness that resembles severe sunburn.
- Drug-induced pemphigus can develop days, weeks, or months after taking the offending agent.
    - Ruptured bullae leave painful erosions. Itching is not a common symptom. The oral mucosa is frequently involved; hoarseness, dysphagia, and unpleasant mouth odor follow.
    - Drugs may serve as either a cause or a trigger for pemphigus. In those patients in whom drugs serve as a trigger, other autoimmune disorders such as lupus, bullous pemphigoid, and myasthenia gravis may already be present. Therefore, the development of drug-induced pemphigus seems to be determined in part by genetic predisposition.

- Drug-induced pemphigoid may follow oral or topical administration of drugs.
    - Itching is a common symptom. Involvement of the epiglottis may lead to acute airway obstruction.
    - Patients with drug-induced pemphigoid are commonly younger than patients with idiopathic pemphigoid. Cicatricial pemphigoid is more common in patients of late middle age.
- Drug-induced linear IgA dermatosis (LAD) comprises a small portion of all cases of LAD.
    - The clinical presentation of drug-induced LAD is indiscernible from other causes of LAD, except that mucosal involvement may be less likely in drug-induced LAD.
    - Drug-induced LAD usually develops 1-2 weeks after taking the offending agent, although reactions may develop much sooner.
    - Patients who develop LAD usually are seriously ill. Symptoms of severe burning and pruritus are common.
- Porphyria cutanea tarda (PCT) may be precipitated or exacerbated by estrogens, iron overload, environmental hepatotoxins, and several drugs, but patients who have drug-induced pseudoporphyria have no underlying abnormality of heme biosynthesis. The symptoms of photosensitivity, skin fragility, and blistering of the hands and forearms are the same in both conditions.

Physical

The physical findings of bullous drug eruptions vary greatly depending on the type of reaction.

- On physical examination, the features of an eczematous drug eruption are similar to that of a diffuse contact dermatitis.
    - These features include diffuse patches of erythema, microvesiculation, vesicles, crusts, and oozing.
    - Other more specific features may include dyshidrotic hand dermatitis, EM-like lesions, purpura, urticarial lesions, and vasculitislike lesions.
    - Recrudescence of a positive patch test reaction may occur after systemic exposure to the offending medication. A diffuse eczematous eruption may mimic severe atopic dermatitis.
- Acute generalized exanthematous pustulosis
    - AGEP manifests as a diffuse scarlatiniform rash that rapidly develops numerous (>100) small pustules.
    - Pustules measure 1-5 mm (see Media File 1).
    - Nikolsky sign may be positive.
    - Some pustules may coalesce into bullae.
    - Facial swelling, purpura, and targetoid lesions may occur.
    - Oral mucosa may be involved in about 20% of cases. Once the offending drug is discontinued, the eruption rapidly dries up and desquamates within 2 weeks.
- Fixed drug eruption
    - FDEs start as a few sharply demarcated erythematous macules that rapidly become erythematous plaques occurring more commonly on the lips, genitalia, and trunk.
    - Lesions heal with hyperpigmentation and occur in the same site with readministration of the responsible drug (see Media File 2).
    - In 30% of cases, macules may become vesicles and bullae, which may lead to a more severe reaction known as generalized bullous FDE resembling SJS-TEN. In patients with generalized bullous FDE, physical examination reveals clearly demarcated erythematous and edematous patches surrounded by bullae that contain clear fluid.
- The characteristic physical finding of EM is the target or iris lesion (see Media File 3).
    - These lesions begin as sharply marginated erythematous annular macules or patches that become slightly raised.
    - A concentric color change takes place; the center of the lesion becomes darker, dusky, or more violaceous, and the periphery develops a ring of erythema. The classic iris lesion has 3 zones, a central dusky area with purpura and an edematous pale ring surrounded by an erythematous ring. The central dusky macule may actually form a tense vesicle or bulla.
    - These typical iris or target lesions are more commonly observed in EM minor caused by infections and occur acrally and progress in a centripetal fashion.
    - Larger, confluent, irregularly shaped, coalescing lesions with involvement of the trunk and 2 or more mucosal sites are common with SJS (see Media Files 4-5). The mouth and lips are the most commonly affected mucosal site in SJS, but other sites such as the pharynx, larynx, esophagus, bronchi, and genital mucosa may be involved.

    - TEN demonstrates diffuse sunburnlike erythema that often begins on the face and spreads downward. The hairy scalp is spared. Maximal extension occurs within 2-3 days. A characteristic feature of TEN is the sheetlike separation of the epidermis in the involved areas. Flaccid bullae may form. Nikolsky sign is positive. Two or more mucosal sites are involved in 85-95% of patients with TEN.
- Drug-induced pemphigus may be clinically indistinguishable from idiopathic pemphigus vulgaris or pemphigus foliaceus (see Media File 6).
    - Lesions are superficial flaccid bullae ranging in size from 1-10 cm.
    - They may initially occur in the mouth.
    - Nikolsky sign is positive when pressure is applied lateral to the bulla.
    - Lesions rupture easily, leaving denuded and weeping areas, which secondarily become crusted.
- Tense bullae on normal skin or on an erythematous base is the typical finding in drug-induced pemphigoid (see Media File 7).
    - Denuded areas, which are left after bullae rupture, heal spontaneously.
    - Erythematous patches, urticarial plaques, and targetoid lesions may also be observed. Lesions may be found on the face, trunk, limbs, palms, soles, and mucous membranes.
    - Nikolsky sign may be positive, unlike in idiopathic pemphigoid.
    - Cicatricial pemphigoid is distinguished from other forms of pemphigoid by the presence of scarring. Cicatricial pemphigoid occurs on the mucous membranes of the eyes, pharynx, genitalia, or anus. Adhesions, strictures, and the loss of function may result from the scarring process.
- Physical examination of a drug-induced LAD lesion may reveal one of several pictures.
    - The most common presentations include urticated plaques, papulovesicles resembling dermatitis herpetiformis, targetoid lesions as in EM, and bullae resembling those found in bullous pemphigoid (see Media File 8).
    - Bullous eruptions can become hemorrhagic.
    - Lesions are most commonly located on the trunk and limbs.
    - Cases of palmar lesions, although uncommon, have been reported.
- Pseudoporphyria demonstrates tense blisters, erosions, and milia especially on the dorsum of the hands and forearms (see Media File 9). Features of hypertrichosis, dyspigmentation, and skin sclerosis are not observed in pseudoporphyria as they are in true porphyria.

Causes

- Contact sensitization to certain topical medications may result in a predisposition to a systemic eczematous reaction to the same or a chemically related medication.
    - Contact sensitivity to penicillin may cause a diffuse eczematous reaction to systemically administered penicillin or even the small amounts of penicillin in cow's milk taken orally.
    - Contact sensitivity to topical sulfonamides may cause a reaction to systemically administered sulfamethoxazole or sulfonylureas (ie, tolbutamide, carbutamide) but not to dapsone or sulfapyridine.
    - Contact sensitivity to ethylenediamine found as a preservative in some topical medications may predispose an individual to a reaction to systemically administered aminophylline, theophylline, tripelennamine, antazoline, methapyrilene, hydroxyzine, and pyrilamine.
    - Contact sensitivity to tetramethylthiuram disulfide predisposes a person to a reaction to the antialcohol treatment Antabuse (tetraethylthiuram disulfide).
    - Patients sensitized to paraphenylenediamine may react to azo dyes taken orally or the group of para drugs.
    - Other drugs that may cause an eczematous eruption but are not preceded by contact sensitivity are the following: carbamazepine, gold, griseofulvin, phenytoin, piroxicam, thiazide diuretics, and vitamin K.
- The drugs most commonly implicated in causing AGEP are antibiotics, especially beta-lactams, macrolides, and cotrimoxazole. Ciprofloxacin has been reported in induce a bullous form of AGEP.[1] Furosemide and nonsteroidal anti-inflammatory agents have also been reported to be associated with the development of AGEP.[2]
    - Diltiazem has been reported to cause AGEP several times.
    - Other causes include the following: carbamazepine, hydroxychloroquine, clindamycin, ticlopidine, terbinafine, high-dose chemotherapy, chromium picolinate, chloramphenicol, sulfapyridine, metronidazole, lacquer chicken, protease

inhibitors, progesterones, mercury, nystatin, amoxapine, paracetamol, chloroquine and proguanil, nifuroxazide, lansoprazole, minocycline, dexamethasone injection, propicillin, aspirin, doxycycline, furosemide, and buphenine.

- Many drugs are capable of causing FDEs. Some of the more common etiologic agents of FDEs include aspirin, barbiturates, cotrimoxazole, phenolphthalein, feprazone, sulfonamides, and tetracycline.
    - Causative agents in generalized bullous FDEs include aminophenazone, antipyrine, barbiturates, co-trimoxazole, diazepam, mefenamic acid, paracetamol, phenazones, phenylbutazone, piroxicam, sulfadiazine, and sulfathiazole.
    - Knowledge of the potential drugs involved in a FDE is especially important because certain drugs have a predilection to cause FDEs at certain sites. Aspirin has a predilection for the trunk and limbs, tetracyclines for the genitalia, and phenylbutazone for the lips.
- No reproducible tests for the etiology of EM exist. Association with infectious agents, such as herpes simplex and mycoplasma, has been well described. Precipitation of SJS or TEN has most commonly been associated with certain medications. The most commonly associated medications are the following: antibiotics (eg, sulfonamides, trimethoprim-sulfamethoxazole, penicillins, cephalosporins, chloramphenicol, clindamycin, griseofulvin, rifampin, streptomycin, tetracycline, clarithromycin,[3] ciprofloxacin[4]), nonsteroidal anti-inflammatory agents (eg, ibuprofen, acetylsalicylic acid, ketotifen, naproxen,[5,6] piroxicam, sulindac), antihypertensives, anticonvulsants (eg, phenobarbital, carbamazepine, phenytoin), and allopurinol. More recently, COX-2 inhibitors have been reported to be associated with SJS.[7]
- Topical mechlorethamine reportedly caused a subepidermal bullous reaction in a patient with mycosis fungoides.
- Methotrexate has been reported to be associated with bullous acral erythema in a child.[8]
- The thiol group of drugs is the most common agent implicated in drug-induced pemphigus. Drugs known to cause pemphigus include amoxicillin, ampicillin, captopril,[9,10] cephalosporins, penicillamine, penicillin, pyritinol, and rifampin. Thiol drugs are more likely to cause pemphigus whereas nonthiol drugs are more likely to trigger pemphigus. For this reason, spontaneous recovery is lower in non–thiol-induced pemphigus where other factors may be predisposing a patient to develop pemphigus. Captopril has been reported to cause lichen planus pemphigoides.[11]
- Sulfur-containing drugs commonly cause drug-induced pemphigoid, with furosemide being the most common cause. Other agents commonly known to cause drug-induced pemphigoid include amoxicillin, ampicillin, phenacetin, penicillin, penicillamine, psoralen-ultraviolet-A light, and beta-blockers.[12] Cicatricial pemphigoid has occurred after the use of drugs including practolol, topical echothiophate, D-penicillamine, clonidine, topical pilocarpine, topical demecarium, indomethacin, topical glaucoma, and sulfadoxine. Oral terbinafine has been associated with the development of bullous pemphigoid.[13]
- Vancomycin is the most common cause of drug-induced LAD.[14,15,16] Other drugs known to cause LAD include diclofenac, somatostatin, lithium, phenytoin, captopril, amiodarone, cefamandole, amoxicillin,[17] and ampicillin-sulbactam.[18]
- True PCT may be precipitated by barbiturates, estrogens, griseofulvin, rifampicin, and sulfonamides. The drugs that are known to induce pseudoporphyria include furosemide, nabumetone, nalidixic acid, naproxen, oxaprozin, tetracycline, and voriconazole.[19]

Differential Diagnoses

Atopic Dermatitis
Bullous Disease of Diabetes
Bullous Disease of Dialysis
Bullous Pemphigoid
Candidiasis, Cutaneous
Cicatricial Pemphigoid
Contact Dermatitis, Allergic
Contact Dermatitis, Irritant
Dermatitis Herpetiformis
Epidermolysis Bullosa
Epidermolysis Bullosa Acquisita
Erythema Multiforme
Id Reaction (Autoeczematization)
Impetigo
Lichen Planus
Linear IgA Dermatosis
Lupus Erythematosus, Bullous
Nummular Dermatitis
Pemphigus Foliaceus
Pemphigus Vulgaris
Pemphigus, Paraneoplastic
Porphyria Cutanea Tarda
Psoriasis, Pustular
Reactive Arthritis
Staphylococcal Scalded Skin Syndrome
Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
Subcorneal Pustular Dermatosis

Other Problems to Be Considered

Eczematous drug eruption - Allergic or irritant contact dermatitis, intradermal reactions, photoallergic reactions, nummular dermatitis, atopic dermatitis

AGEP - Impetigo, staphylococcal scalded skin syndrome, pustular psoriasis, Reiter disease, subcorneal pustular dermatosis, pemphigus foliaceus, candidiasis, pustular dermatophyte infection

FDE - Erythema chronicum migrans, SJS-TEN, bullous disease of diabetes mellitus, bullous disease of dialysis, bullous reactions with drug overdose/coma and bullous phototoxic contact reactions to plants, postinflammatory hyperpigmentation, factitial dermatitis

EM - Paraneoplastic pemphigus, other autoimmune blistering diseases, lupus erythematosus, bullous lichen planus, urticaria, FDE

Drug-induced pemphigus - Pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, bullous pemphigoid, dermatitis herpetiformis, PCT, TEN, EM, bullous contact dermatitis

Drug-induced pemphigoid - Reflex sympathetic dystrophy, linear IgA bullous dermatosis, bullous disease of diabetes mellitus, EM, bullous systemic lupus erythematosus, dermatitis herpetiformis, burn, epidermolysis bullosa, leukocytoclastic vasculitis, chronic actinic dermatitis, and cicatricial pemphigoid

Drug-induced LAD - Non–drug-induced LAD, dermatitis herpetiformis, bullous pemphigoid, cicatricial pemphigoid, EM

Pseudoporphyria - True PCT, bullous pemphigoid, epidermolysis bullosa acquisita, photoallergic dermatitis, allergic contact dermatitis

Workup

Laboratory Studies

- Laboratory studies during an eczematous drug eruption may disclose eosinophilia, leukocytosis, and elevated sedimentation rate.
- In AGEP, laboratory studies demonstrate neutrophilia in 90% of cases and eosinophilia in 30% of cases. Liver function is usually normal.
- Laboratory studies in FDE may show leukocytosis, hypereosinophilia, and hypergammaglobulinemia. However, clinical and histologic features are the mainstay of diagnosis.
- Apart from leukocytosis, laboratory studies may not be helpful in the evaluation of patients with EM. Patients with widespread lesions may develop electrolyte abnormalities and hypoalbuminemia. Immunofluorescence study results are negative.
- Antinuclear antibodies may be found in patients with thiol drug-induced pemphigus.
- Blood eosinophilia and increased amounts of soluble interleukin-2 receptors may be present in patients with drug-induced pemphigoid.[20] The sera and blister fluids in drug-induced pemphigoid may show increased amounts of eosinophilic cationic protein and neutrophil-derived myeloperoxidase.
- Laboratory studies are not particularly helpful in diagnosing drug-induced LAD.
- In pseudoporphyria, laboratory studies do not demonstrate any abnormality in heme biosynthesis or hepatic abnormalities.

Other Tests

- Results of patch testing suspected drugs that cause eczematous drug reactions may be positive.
- Patch testing of the offending drug in AGEP may result in a pustular patch test reaction.
- Patch testing and oral provocation testing may be used to implicate a specific drug in a FDE.
- Apart from skin biopsy, other tests are not helpful in evaluating EM. First-degree relatives of patients with TEN have lymphocytes that are more susceptible to the toxic effect of the culprit drug than controls.
- Results of direct and indirect immunofluorescence studies in drug-induced pemphigus are identical to studies in idiopathic pemphigus. Deposition of immunoglobulin G (IgG) and C3 is observed intercellularly on direct immunofluorescence. On indirect immunofluorescence, pemphigus antibodies are found in the patient's serum.
- Linear deposits of IgG and C3 may be visualized along the basement membrane zone with direct immunofluorescence in patients with drug-induced pemphigoid. Indirect immunofluorescence studies are positive for circulating antibodies against the basement membrane zone. However, circulating antibodies are less commonly found in cicatricial pemphigoid.

- Direct immunofluorescence studies reveal the presence of IgA at the basement membrane zone in LAD. Results of indirect immunofluorescence studies using monkey esophagus or saline split human skin are usually negative for IgA at the basement membrane zone.
- Pseudoporphyria demonstrates normal urine and serum porphyrins.

Histologic Findings

Eczematous drug eruptions

Frequently seen histologic findings include the following: hyperkeratosis, parakeratosis, exocytosis of lymphocytes, spongiosis, and a superficial perivascular lymphocytic infiltrate. Occasional histologic findings include the following: eosinophilic spongiosis, vesicle or bulla formation, papillary dermal edema, and extravasation of erythrocytes. Rarely, features suggestive of mycosis fungoides may be observed.

Acute generalized exanthematous pustulosis

Subcorneal or spongiform pustules and a mild superficial perivascular and interstitial infiltrate composed of lymphocytes, neutrophils, and eosinophils may be observed. Papillary dermal edema, extravasation of erythrocytes, and acantholytic keratinocytes may also be observed.

Fixed drug eruption

Histologic examination of FDE reveals an interface or spongiotic dermatitis pattern. In the acute phase, the epidermis is characterized by dyskeratotic cells, exocytosis, edema, nuclear pyknosis, and hydropic degeneration of basal cells. An acute infiltrate consisting of lymphocytes, histiocytes, neutrophils, and eosinophils may be found around superficial and deep blood vessels. The quiescent lesion contains macrophages replete with melanin in the upper dermis. Papillary dermal fibrosis may develop consequent to prior episodes of FDE at the same site.

Erythema multiforme

An interface dermatitis with individual cell necrosis (necrotic keratinocytes) beneath a normal basket weave stratum corneum is characteristic of EM. Other findings may include spongiosis, intrabasilar blister formation, a superficial perivascular lymphohistiocytic infiltrate with variable numbers of eosinophils and neutrophils, and papillary dermal edema. TEN shows massive and confluent necrosis of the basal cells (and possibly the entire epidermis), and the dermal infiltrate is scanty.

Drug-induced pemphigus

The hallmark of pemphigus is acantholysis, or the loss of cohesion between epidermal cells. This gives rise to an intraepidermal bulla, which may be located above the basal cell layer (low acantholysis) or subcorneally (high acantholysis). Bullae may lack inflammatory cells or may contain abundant neutrophils. A lymphocytic infiltrate may be found in the dermis in addition to numerous plasma cells and eosinophils.

Drug-induced pemphigoid

The histologic hallmark of drug-induced pemphigoid is a subepidermal blister. Neutrophils, eosinophils, and fibrin may be present in the blister cavity. The dermis is characterized by a superficial infiltrate containing neutrophils, lymphocytes, eosinophils, and occasionally plasma cells. In cicatricial pemphigoid lesions, eosinophils are sparse, whereas a dense lymphocytic inflammatory infiltrate exists in the dermis. Variable dermal fibrosis may be observed based upon chronicity of the lesions and prior involvement at the same site.

Linear IgA dermatosis

A subepidermal blister containing neutrophils and eosinophils with a dermal perivascular infiltrate may be present. IgA antibodies, sometimes accompanied by C3, localize to the dermal side of the basement membrane.

Pseudoporphyria

Pseudo-PCT demonstrates the same histologic features of PCT. These features include the following: subepidermal blister, cell-poor infiltrate, festooning of dermal papillae, and thickened vessel walls, which are periodic acid-Schiff positive.

Treatment

Medical Care

Withdrawal of the offending medication is the most important aspect of treatment of bullous drug reactions. Most reactions are self-limited. Conservative treatment of these disorders involves using wet compresses of Burrow solution and the application of moderate- to high-potency topical corticosteroids. More severe reactions may require the use of systemic corticosteroids.

The use of corticosteroids in the treatment of SJS and TEN is controversial. Patients with SJS and TEN are usually managed as inpatients in the intensive care or burn units. Fluid hydration, electrolyte balance, and nutritional support are the cornerstones of therapy. Rigorously guard against infection. Intravenous gamma globulin (IVIG) shows promise in the treatment of TEN. The IVIG reduces apoptosis by blocking CD95 on T cells.[21] In TEN, early withdrawal of precipitating drugs may reduce mortality if the drug has a short half-life.[22]

Consultations

Limited forms of EM can be managed on an outpatient basis; however, careful consideration should be given to patients with SJS and TEN regarding an early referral to an intensive care unit or preferably a burn unit. Eye involvement that can occur in EM, SJS, and TEN requires an ophthalmologic evaluation.

Follow-up

Deterrence/Prevention

- Avoid use of the offending drug.

Prognosis

- Eczematous or spongiotic drug reactions usually have a good prognosis and resolve without significant sequelae.
- AGEP has a good prognosis and resolves without sequelae once the causative agent is removed.
- Bullous generalized FDEs have a favorable prognosis.
- EM most often has a good prognosis, but SJS and TEN can be lethal depending on the extent of skin involvement and the age of the patient.
- Pemphigus has a mortality rate approaching 10%. However, drug-induced pemphigus usually resolves with removal of the offending agent. In some patients, lesions may progress or persist. In these cases, the drug likely is serving as a trigger rather than a cause in patients who are already prone to develop pemphigus.
- Drug-induced pemphigoid has an excellent prognosis with discontinuation of the drug. However, some cases may involve persistent lesions. Cicatricial pemphigoid, in comparison to idiopathic bullous pemphigoid, shows a small tendency for remission. In severe cases of ocular cicatricial pemphigoid, scarring and blindness in both eyes has been reported.
- Drug-induced LAD has a good prognosis.
- Drug-induced PCT has a good prognosis.

Patient Education

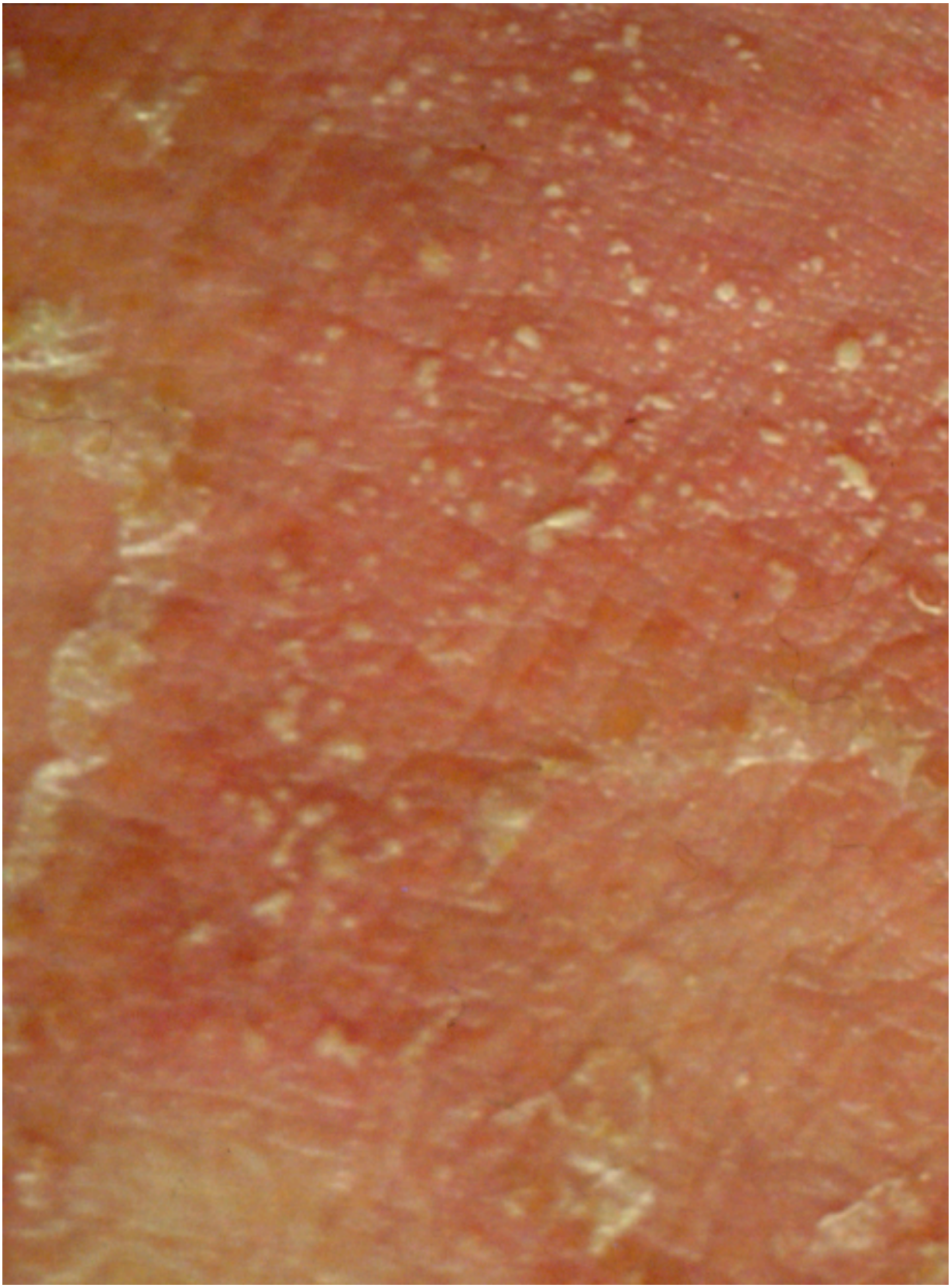
- For excellent patient education resources, visit Allergy Center and Skin, Hair, and Nails Center. Also, see eMedicine's patient education articles, Drug Allergy, Life-Threatening Skin Rashes, and Skin Rashes in Children.

Miscellaneous

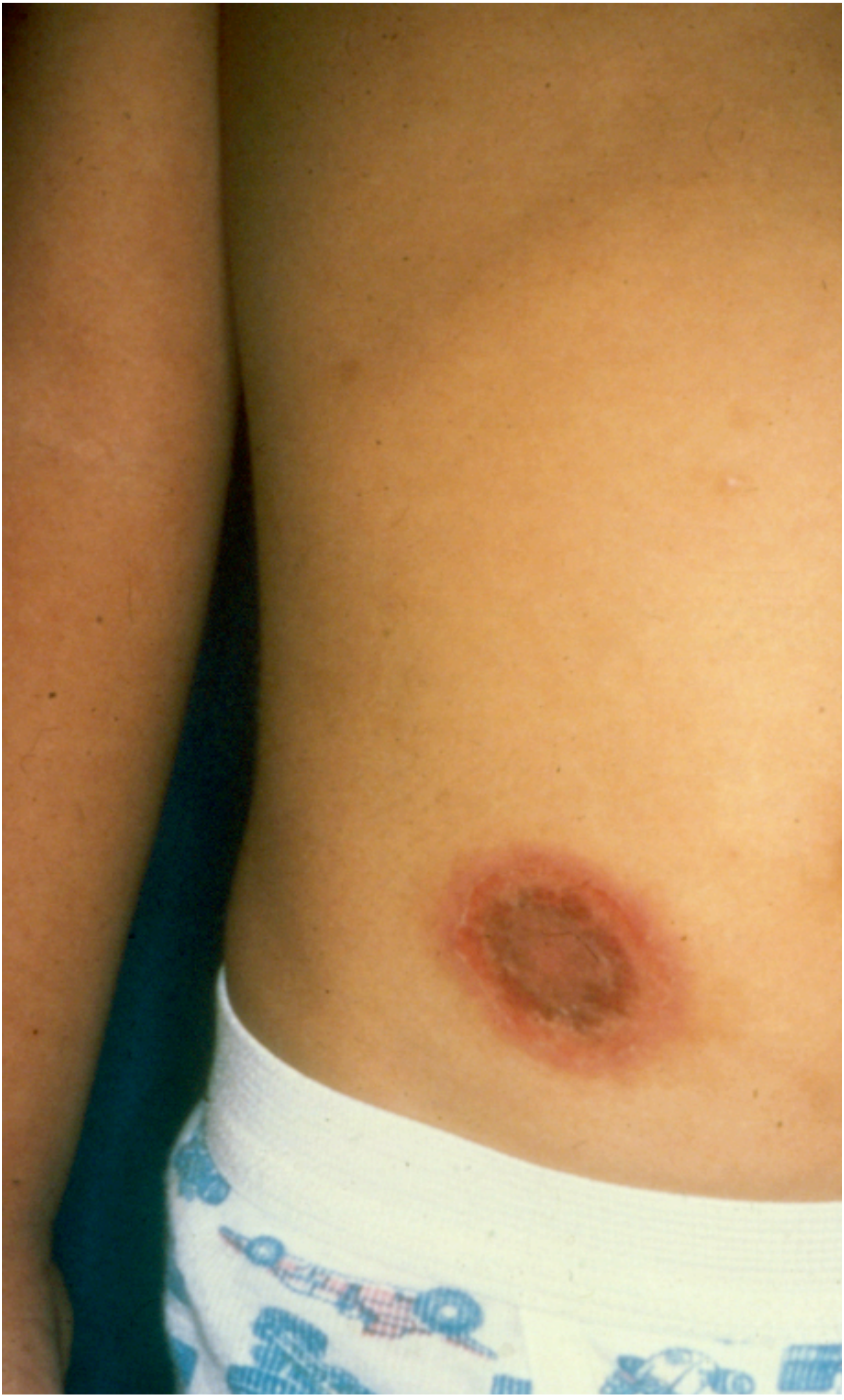
Medicolegal Pitfalls

- Drug reactions account for a large number of malpractice claims against dermatologists. The drugs most responsible for these claims are corticosteroids, isotretinoin, methotrexate, antibiotics, and chemotherapeutic agents.
- Failure to accurately disclose the risks and potentially serious adverse effects of the prescribed drug is often the basis of the malpractice claim.
- Failure to recognize the nature or cause of the reaction and failure to discontinue the medication in a timely fashion may also be the source of such claims.

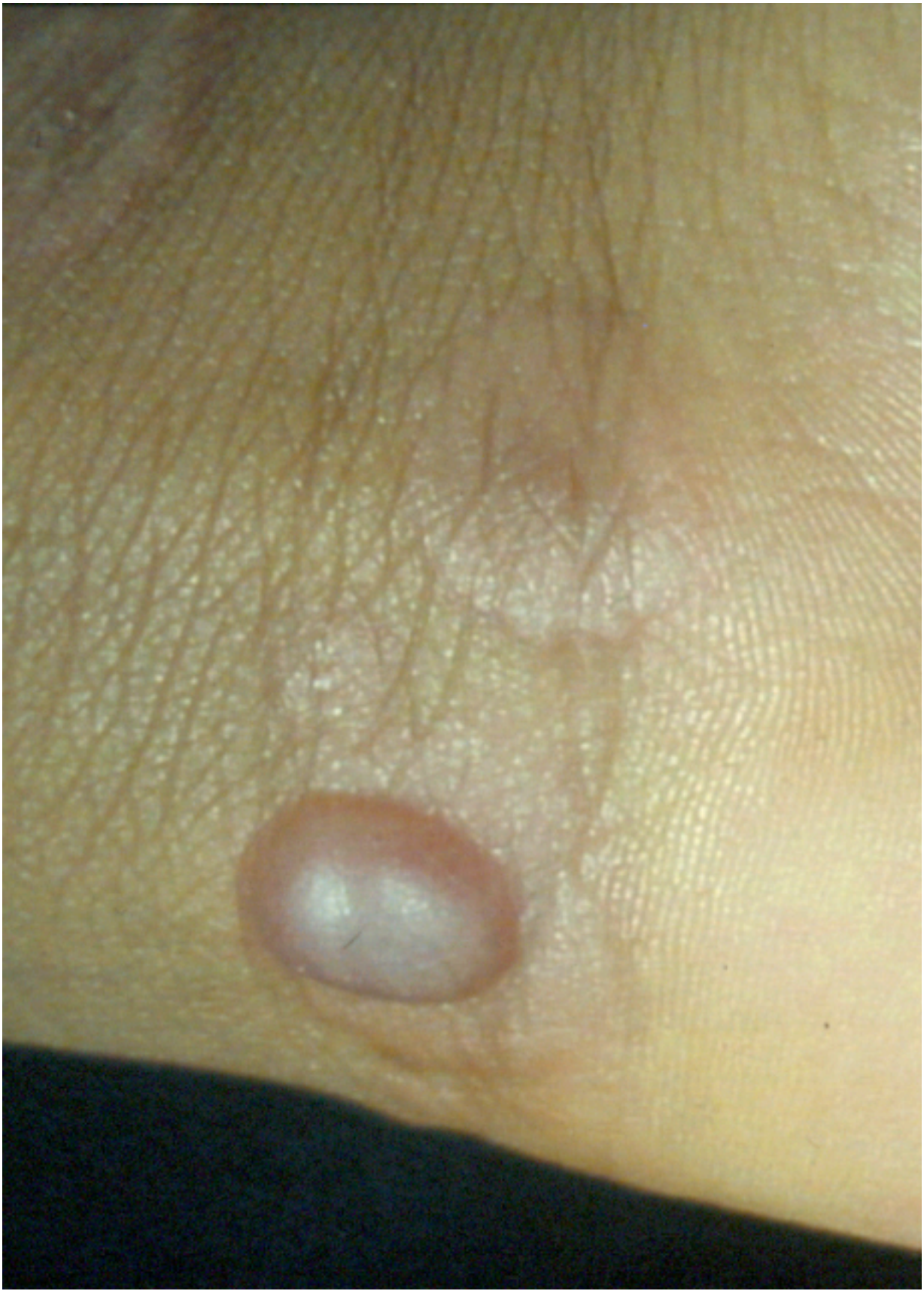
Multimedia



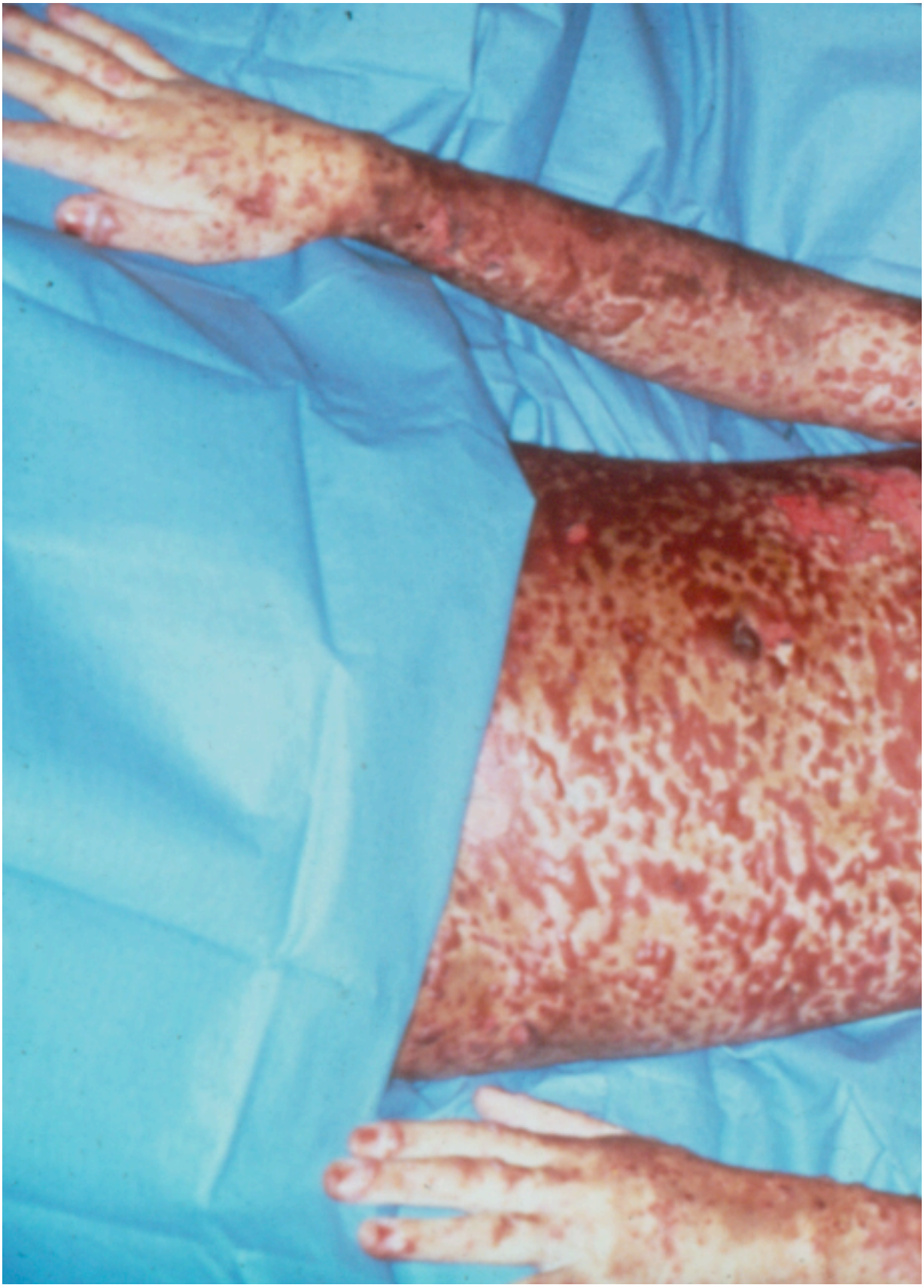
Media file 1: Small pustules on erythematous patch (acute generalized exanthematous pustulosis).



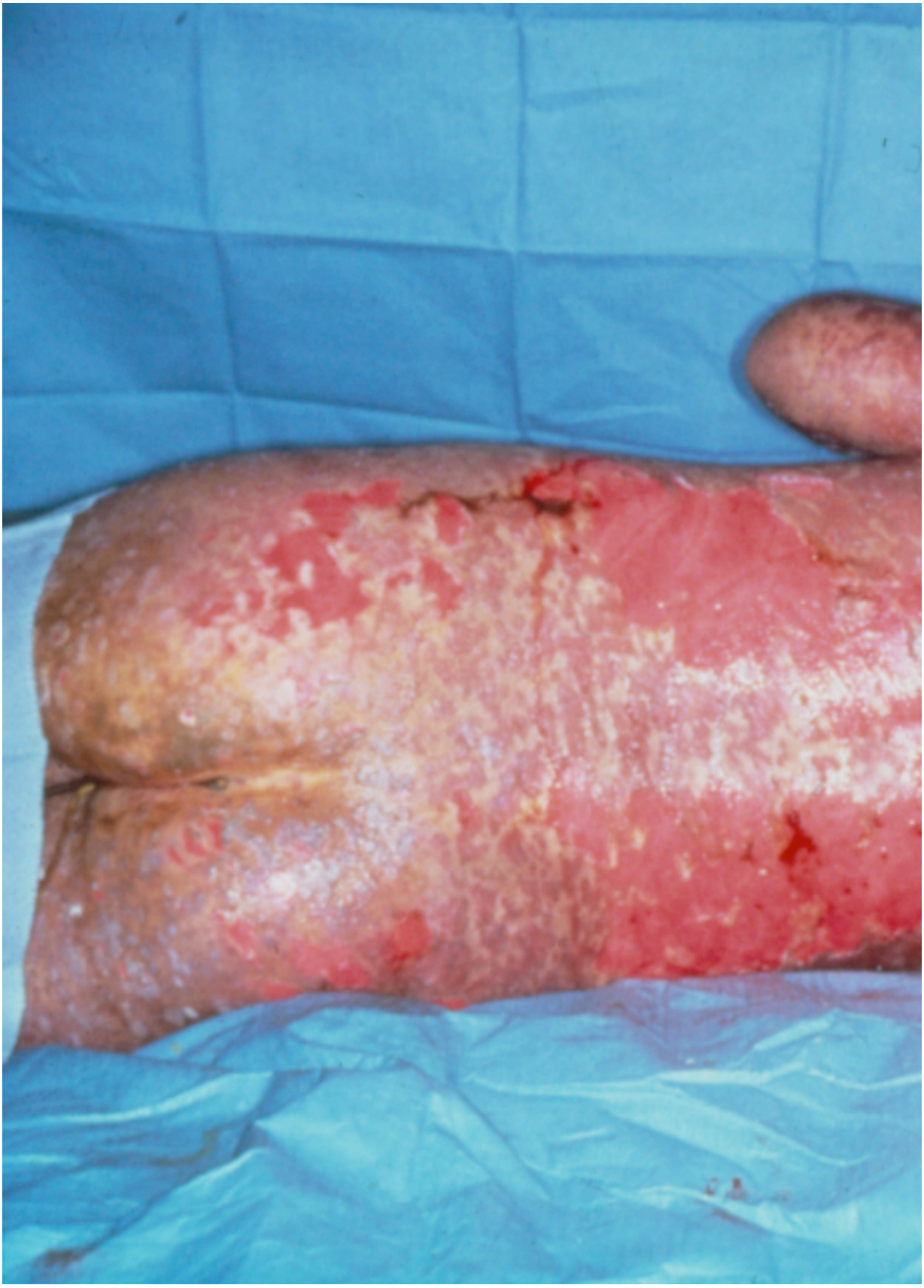
Media file 2: Annular hyperpigmented patch (fixed drug eruption).



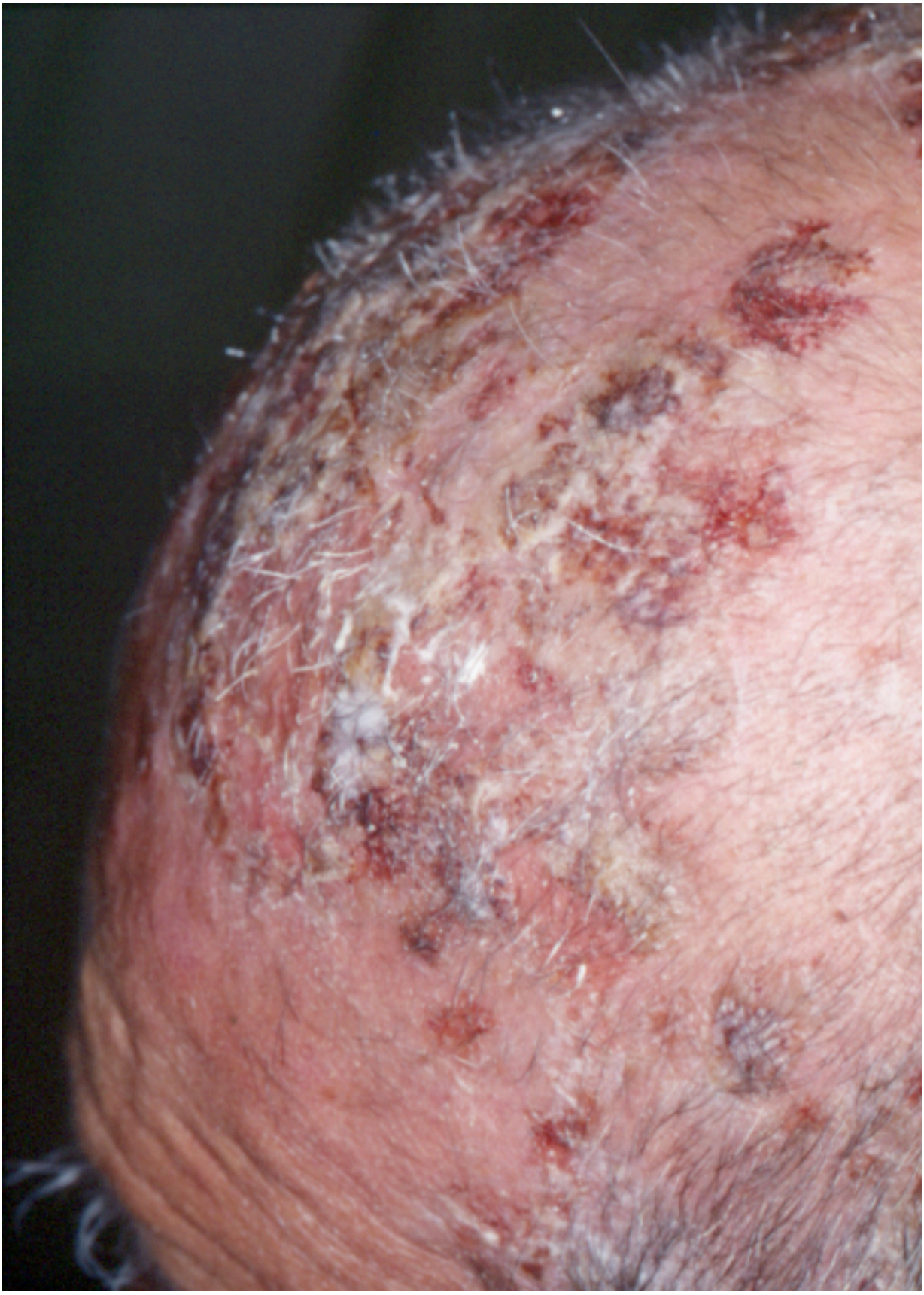
Media file 3: Target or iris lesions on palm (erythema multiforme).



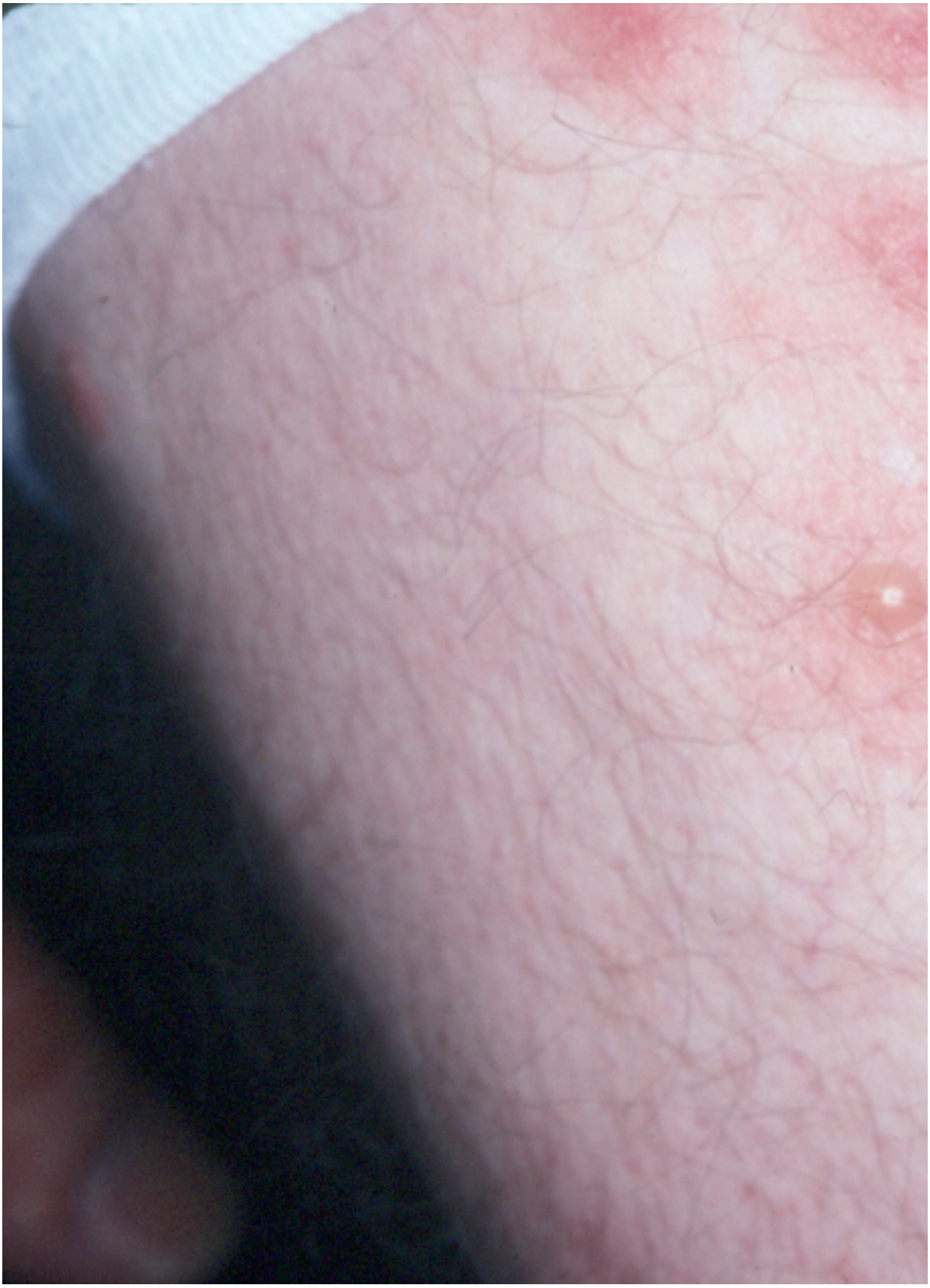
Media file 4: Coalescing eroded patches (Stevens-Johnson syndrome).



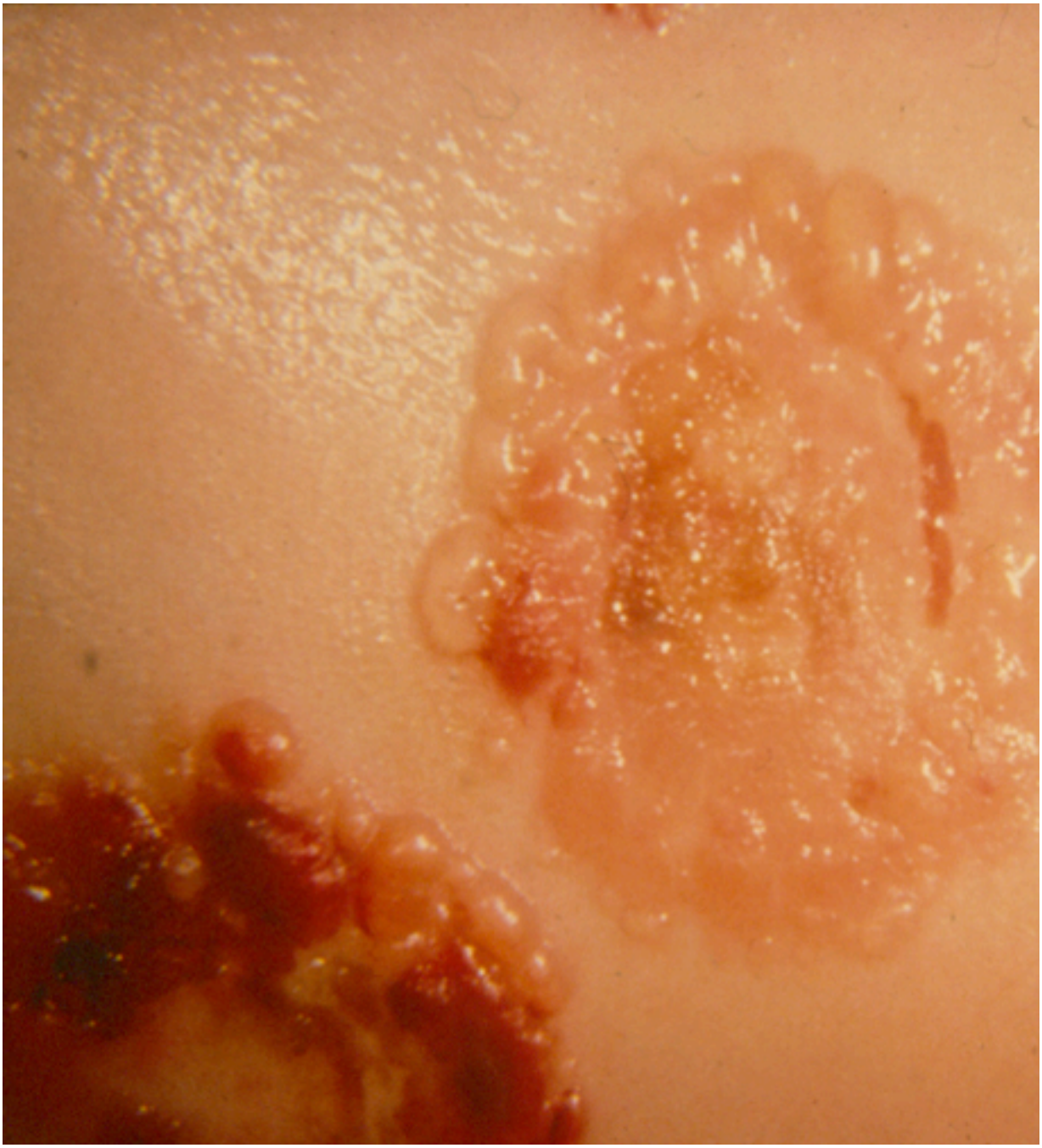
Media file 5: Stevens-Johnson syndrome.



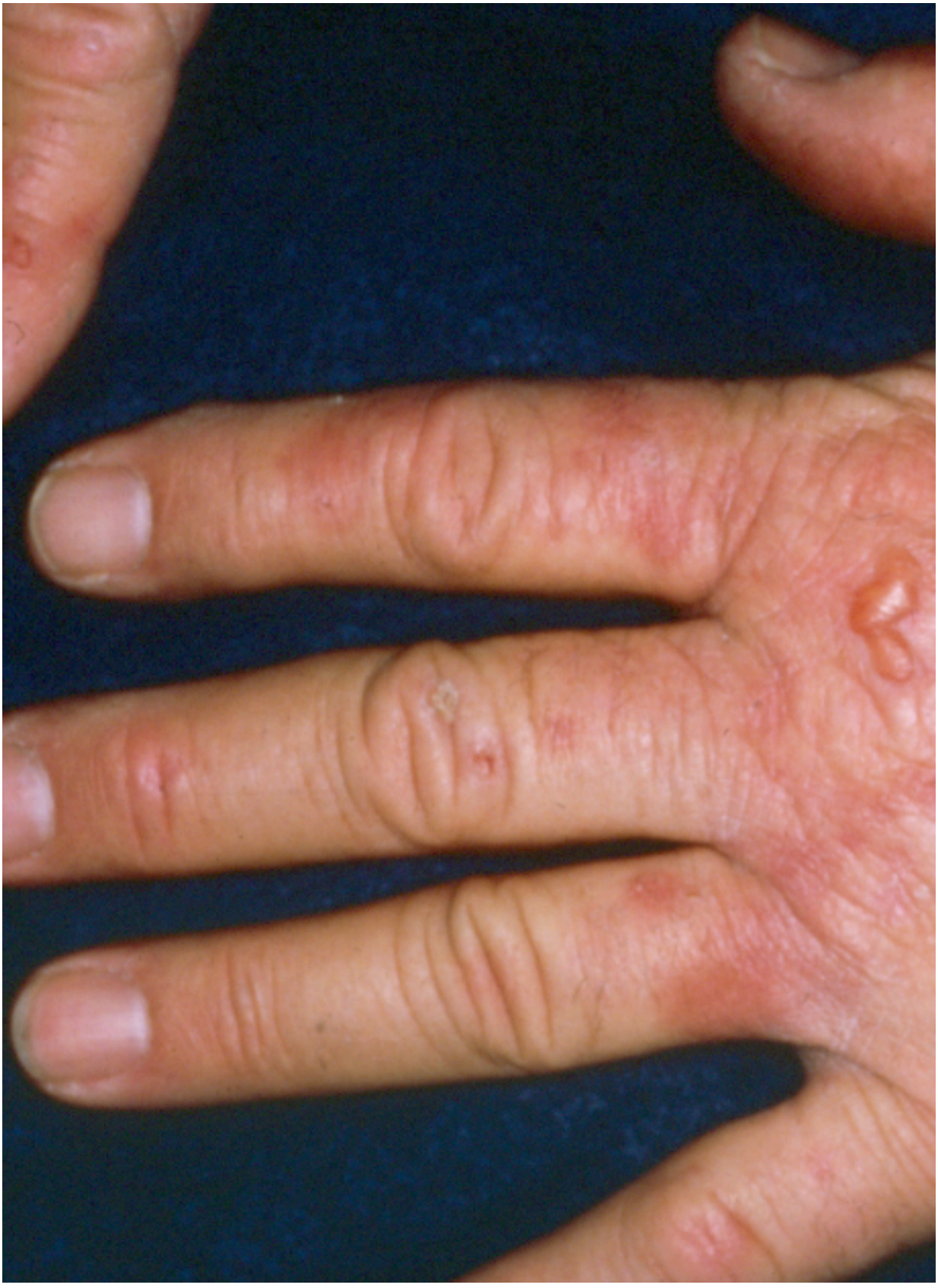
Media file 6: Crusted erosions on scalp (drug-induced pemphigus).



Media file 7: Small vesicle at edge of urticarial plaque (drug-induced pemphigoid).



Media file 8: Tense vesicles in annular array (linear immunoglobulin A dermatosis).



Media file 9: Erosions, scars, milia, and vesicle (pseudoporphyria).

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