Diagnosis and Management of Bullous Disease

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KEYWORDS

• Bullous diseases • Dermatoses • General population • Anatomic level

KEY POINTS

- Bullous diseases are a group of dermatoses primarily characterized by the presence of vesicles (0.1–0.9 cm) or bullae (>1 cm).
- The complex process of aging, which involves cumulative environmental, genetic, and cellular interplay, is evident in the skin.
- The clinical approach to reaching a diagnosis includes a thorough history and physical examination.

INTRODUCTION

Bullous diseases are a group of dermatoses primarily characterized by the presence of vesicles (0.1–0.9 cm) or bullae (>1 cm). There are various categories of bullous disease: allergic, autoimmune, infectious, mechanical, and metabolic. These diseases affect individuals in all decades of life, but older adults, age 65 and older, are particularly susceptible to bullous diseases of all etiologies. The incidence of these disorders is expected to increase given the advancing age of the general population.

The complex process of aging, which involves cumulative environmental, genetic, and cellular interplay, is evident in the skin. Vasculature atrophies, the dermis deteriorates, and the extracellular matrix and its components become more disorganized. The dermal papillae flatten causing attenuation in the surface area of dermal and epidermal adhesion that contributes to an increased risk of blister formation.[1] Simultaneously, the process of immune system dysregulation that accompanies normal aging contributes greatly to autoimmune bullous diseases.[2]

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Clin Geriatr Med 40 (2024) 37–74
https://doi.org/10.1016/j.cger.2023.09.002
geriatric.theclinics.com

In this comprehensive review, the bullous dermatoses will focus on those applicable to adults and will be categorized primarily by the anatomic level of the split. Additionally, this article includes clinical and epidemiologic data concerning the disease, pathophysiology, diagnostic methods, and therapies. Recognition and diagnosis of a bullous disease are crucial for timely intervention and limitation of complications.

RELEVANT CLINICAL QUESTIONS

The clinical approach to reaching a diagnosis includes a thorough history and physical examination. The following are focused points to consider while narrowing the differential diagnosis.

- Did the eruption coincide with a change in medication or general health status?
- Are the blisters flaccid or tense?
- Are the blisters pruritic, painful, or asymptomatic?
- Is there surrounding erythema/induration or noninflamed/normal skin?
- Are the blisters cutaneous, mucosal, or mucocutaneous?
- Are the blisters localized (acral, sun-exposed, extensor surfaces) or generalized?
- Does the morphology of the eruption have a particular pattern (annular, linear, clusters)?

INITIAL WORKUP CONSIDERATIONS

When a blistering disorder is suspected, but a diagnosis cannot be established, a skin biopsy is indicated. An early, intact lesion with adjacent skin should be biopsied to ensure that an accurate histopathological diagnosis is made. This sample is submitted in formalin for routine hematoxylin and eosin staining. If autoimmune blistering dermatoses are being considered, an additional biopsy for direct immunofluorescence (DIF) should be performed. To properly submit a specimen for immunobullous DIF testing, the ideal sample is taken from immediately adjacent unaffected, healthy-appearing skin surrounding the bulla and submitted in Michel media. Other special studies such as salt-split skin immunofluorescence, serum indirect immunofluorescence (IIF), and electron microscopy may be useful adjuncts. Serologic tests, specifically enzyme-linked immunosorbent assays (ELISAs), are available for bullous pemphigoid and pemphigus and can be used when the diagnosis is in doubt (**Box 1**).

Box 1
Diseases with an intracorneal/subcorneal split

Pemphigus foliaceus
Pemphigus erythematosus
Fogo selvagem
Subcorneal pustular dermatosis
IgA pemphigus
Acute generalized exanthematous pustulosis
Impetigo
Staphylococcal/Streptococcal scalded-skin syndrome
Dermatophytosis
Miliaria crystallina

Pemphigus Foliaceus

Pemphigus foliaceus (PF) represents 10% to 20% of all pemphigus cases. PF is the second most common form of pemphigus and considered milder compared to pemphigus vulgaris. Like pemphigus vulgaris, it can be associated with myasthenia gravis, thymoma, and autoimmune thyroiditis. The antibodies are directed toward desmoglein 1 which is why oral lesions are rare. Adult mucosal surfaces contain enough desmoglein-3 to compensate for the disruption of the desmoglein-1 attachments and are therefore not usually involved. A similar compensation is believed to protect the growing fetus from maternal autoantibodies against desmoglein-1. **Table 1** lists characteristics of variants of pemphigus foliaceus: Fogo selvagem and pemphigus erythematosus. Drug-induced PF is most caused by thiol-containing drugs, such as D-penicillamine and captopril. Other implicated drugs are listed in **Box 2**

Pathogenesis

- The pathogenesis is secondary to antibodies (immunoglobulin [Ig]G4 subclass) against desmoglein 1, which is a transmembrane glycoprotein of desmosomes in the epidermis.

Clinical features

- Superficial vesicles of the scalp, face, and trunk break open and lead to crusted erosions that heal without scarring. **Fig. 1**.
- "Cornflake" scale is common **Fig. 2**.
- Mucosal involvement is rarely seen.
- Nikolsky sign is positive (light rubbing of unaffected skin adjacent to a blister or erosion will cause separation of the skin).
- Adults are most affected, usually during midlife.

Differential diagnosis

- Seborrheic dermatitis
- Impetigo (especially the bullous form)
- Dermatitis herpetiformis

Table 1
Variants of pemphigus foliaceus

Disease		Clinical presentation
Fogo selvagem	• Endemic form of pemphigus foliaceus mainly found in rural areas of Brazil, Columbia, El Salvador, Paraguay, and Peru • Transmitted by *Simulium* species (black fly) • Increasing frequencies in families with HLA-DRB1 mutations	Identical clinical and histologic features to pemphigus foliaceus
Pemphigus erythematosus (Senear – Usher syndrome)	• Represents 10% of all cases of pemphigus foliaceus, with features of lupus erythematosus • Sunlight may worsen the disease • Clinical course is generally chronic	Localized to malar region of face and other seborrheic areas

Box 2
Medications associated with pemphigus

Captopril
Cephalosporins
Enalapril
Gold
Interferon-alpha
Interleukin-2
Levodopa
Oxyphenylbutazone
Penicillamine
Peniclillin's
Phenobarbital
Phenylbutazone
Piroxicam
Propranolol
Pyritinol
Rifampin

- Subacute cutaneous lupus erythematosus
- Drug reaction
- Allergic contact dermatitis
- Darier disease

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF.
- IIF on guinea pig esophagus.
- ELISA for desmogleins 1 and 3.

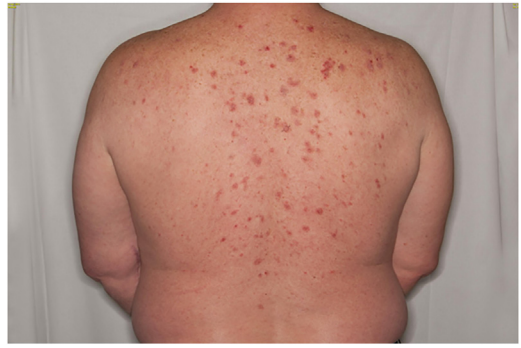

Fig. 1. Widespread erythematous plaques on the back of a patient with pemphigus erythematosus. (*Courtesy of* O Sokumbi, MD)

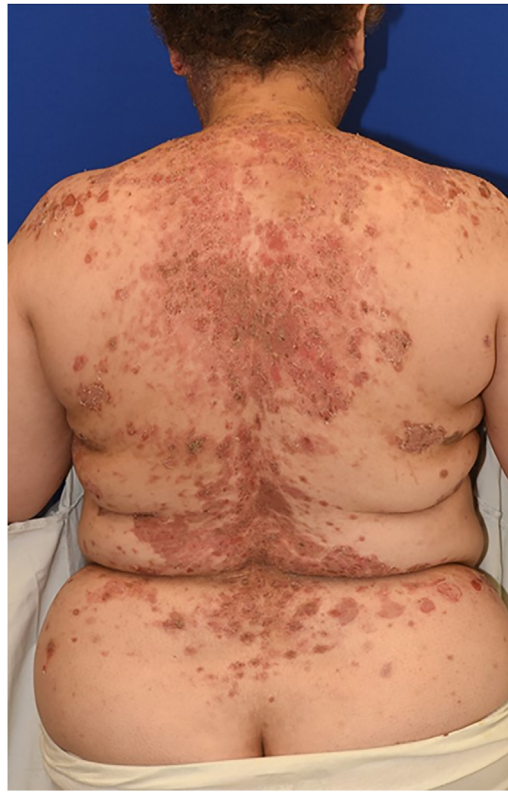

Fig. 2. Widespread erosions, crusts, and thin, erythematous, scaly plaques on the back of a patient with pemphigus foliaceous. (*Courtesy* of O Sokumbi, MD)

Treatment

- Localized disease can typically be managed by potent topical steroids.
- For more widespread disease, the mainstay is prednisone followed by steroid-sparing immunosuppressants such as azathioprine, mycophenolate mofetil, rituximab, or dapsone.

Subcorneal Pustular Dermatosis

Subcorneal pustular dermatosis (SPD), also known as Sneddon–Wilkinson disease, is a chronic, waxing-waning neutrophilic dermatosis characterized by sterile pustules that erupt into polycyclic patterns. Like the subcorneal pustular subtype of IgA pemphigus, the pustular lesions found in Sneddon–Wilkinson disease coalesce in an annular pattern and eventually evolve into crusted plaques. Diagnosis is made based on physical examination findings, histologic findings of a subcorneal neutrophilic vesicle, and by ruling out other potential and related diagnoses with laboratory evaluation. Associated conditions includehematologic disorders (polycythemia rubra vera, Ig A monoclonal gammopathy, and multiple myeloma), pyoderma gangrenosum, Raynaud's phenomenon, Sjogren's syndrome, systemic lupus erythematosus, and inflammatory bowel disease.

Pathogenesis

- The pathogenesis of SPD is poorly understood.

- SPD with associated autoantibodies to desmocollin 1 is best classified as SPD-like IgA pemphigus.
- Desmocollins function in cell adhesion with other structural proteins within the cadherin family; when these proteins are affected, the underlying scaffolding of a skin cell is compromised, leading to the formation of subcorneal bullae and vesicles.

Clinical features

- Flaccid, sterile pustules with yellowish fluid in the dependent half with clearer fluid in the top half of the lesion
- A predilection for the groin, trunk, axillae; avoids the mucosal surfaces
- It is mostly seen in women over 40 years old
- Chronic, relapsing clinical course

Differential diagnosis

- IgA pemphigus
- Acute generalized exanthematous pustulosis
- Amicrobial pustulosis associated with autoimmune disease
- Bacterial folliculitis
- Impetigo
- Pustular psoriasis
- Pustular vasculitis

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF is negative.
- IIF is negative.
- Serum protein electrophoresis and DIF may be repeated every few years.

Treatment

- The typical first-line treatment for patients with SPD is oral dapsone 50 to 200 mg once daily.
- Second-line and salvage therapies include sulfapyridine, sulfasalazine (prodrug to sulfapyridine), immunosuppressants, colchicine, systemic retinoids, phototherapy (broad and narrowband *ultraviolet* [UV]A or psoralen plus UVA); they are reserved for those unable to take dapsone or who failed to respond to therapy.
- Evaluation for associated cutaneous and systemic diseases should be undertaken when clinically indicated.

IgA Pemphigus

IgA pemphigus is a poorly understood bullous disease defined by the presence of IgA anti-keratinocyte cell surface autoantibodies. It may have some clinical overlap with SPD, and the SPD type of IgA pemphigus presents with similar annular, crusted vesicles and pustules in the axilla and groin. The intraepidermal neutrophilic dermatosis (IEN) type of IgA pemphigus may preferentially involve the trunk, rather than the intertriginous areas.

Pathogenesis

- Target antigen in SPD type is desmocollin 1.
- Target antigens in IEN type are desmoglein-1 or 3.

Clinical features

- Presents in the axillae and groin in the middle-aged to elderly with pruritic and flaccid vesicles and pustules in annular configurations and central crusting.
- Oral involvement is rarely seen.
- Can be associated with IgA paraproteinemia and multiple myeloma.[3]
- Two subtypes are known:
  - Subcorneal pustular dermatosis type (SPD) is clinically indistinguishable from Sneddon–Wilkinson disease; DIF/IIF is needed to distinguish.
  - Intraepidermal neutrophilic type (IEN) presents with a "sunflower" arrangement of vesicles and pustules and may preferentially involve the trunk rather than the intertriginous areas.

Differential diagnosis

- Dermatitis herpetiformis
- Eosinophilic pustular folliculitis
- Pemphigus foliaceus
- Subcorneal pustular dermatosis

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF shows intercellular staining with IgA in 100% of cases:
  - SPD type: intercellular IgA deposition in the upper epidermis
  - IEN type: intercellular IgA in the lower epidermis or throughout
- IIF is unreliable as only 50% have detectable circulating IgA.

Treatment

- Treatment is directed against neutrophils with dapsone 25 to 100 mg daily, being a medication in which dramatic responses are seen within 48 hours.
- Alternatively, if dapsone-intolerant: start sulfapyridine 500 mg twice a day and increase slowly.
- Some case reports include colchicine or retinoids as effective.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is a pustular, generalized drug eruption. Beta-lactam antibiotics, anticonvulsants, and calcium channel blockers are the most frequent culprits. Intravenous contrast and infections can also trigger the condition. Unlike other drug eruptions, such as drug rash with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN), AGEP can occur within 4 days of initial exposure. Hypocalcemia is a key laboratory finding in AGEP and is thought to occur due to hypoalbuminemia. Fever, neutrophilia, and eosinophilia are often found. The cutaneous eruption usually resolves in a few days, but hepatic and kidney involvement is possible.

Pathogenesis

- AGEP is thought to be T-cell mediated: drug-specific CD4+ T cells, cytotoxic CD8+ T cells, and inflammatory cytokines and chemokines are thought to be involved in tissue accumulation of neutrophils.
- 90% of reported cases of AGEP are drug induced with an onset of hours (antibiotics) to 3 weeks (other drugs).
- A minority of cases are linked to viral infections.

Clinical features

- The eruption begins as acute, erythematous edema on the face or intertriginous areas and is quickly followed by numerous pinpoint nonfollicular pustules.
- Most patients have a fever and a history of a recently added medication.
- Mucous membrane involvement is atypical but when present is limited to erosions of the lips.

Differential diagnosis

- Acute pustular psoriasis
- Bacterial folliculitis
- DRESS
- Cutaneous candidiasis

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF will be negative.

Treatment

- Remove offending drug
- Antipyretics as needed
- Supportive care

Bullous Impetigo

Bullous impetigo is a superficial staphylococcal skin infection. The condition is primarily seen in children but can occur in adults. Infection is spread by direct contact with colonized or infected individuals. Undiagnosed human immunodeficienc virus (HIV) infection should be considered in an adult with bullous impetigo and appropriate risk factors.

Pathogenesis

- Superficial skin infection caused primarily by phage group II staphylococci.
- Staphylococcus . *aureus* produces exotoxin-mediated cleavage of desmoglein-1 causing bullae formation.[4]

Clinical features

- Vesicles which enlarge and lead to flaccid, serous superficial bullae.
- Eroded and crusted plaques may appear at the site of denuded bullae.

Differential diagnosis

- Bullous arthropod assault
- Bullous drug eruption
- Bullous tinea
- Herpes simplex virus
- Contact dermatitis
- Autoimmune blistering disorders

Diagnostic testing

- Gram stain of blister fluid may show gram-positive cocci.
- Bacterial culture with sensitivities.
- Biopsy is usually not necessary.

- Lesional biopsy for histopathology.
- DIF is negative.

Treatment

- Topical antibiotic ointments such as mupirocin or retapamulin ointment can be used twice daily for 5 days in limited disease.
- For widespread infections, systemic antibiotics can be used; dicloxacillin or cephalexin for methicillin-sensitive *Staphylococcus aureus* (MSSA) or doxycycline, clindamycin, or sulfamethoxazole-trimethoprim if methicillin-resistant *Staphylococcus* aureus (MRSA) is suspected (**Box 3**).

Trauma Bullae

Trauma bullae are blisters that are typically found on acral surfaces due to repeated physical forces. Occupations or recreational activities that require prolonged running or walking are at the highest risk. Moist skin can produce higher frictional forces than wet or dry skin and increase the risk of bullae formation.[5]

Pathogenesis

- Development is linked to the magnitude of frictional force and the number of cycles across the skin.
- Shearing forces cause the disassociation of keratinocytes which leads to epidermal splitting and fluid filling.

Clinical features

- Noninflamed blister on the palms and soles.
- The most affected sites include the tips of the toes, the balls of the feet, and the posterior heel.
- Occurs in vigorously active populations.

Differential diagnosis

- Epidermolysis bullosa simplex
- Epidermolysis bullosa acquisita
- Bullous arthropod assault
- Bullosis diabeticorum
- Bullous fixed drug eruption
- Bullous tinea

Diagnostic Testing

- History and location
- Biopsy is usually not necessary

Box 3
Diseases with an intraepidermal split

Amicrobial pustulosis associated with autoimmune diseases

Trauma bullae

Spongiotic diseases

Palmoplantar pustulosis

Viral blistering

- Lesional biopsy for histopathology
- DIF is negative

Treatment

- Maintain blister roof intact to speed healing time; larger lesions may need to be drained.
- Prevention can be achieved by avoiding friction using acrylic socks, closed-cell neoprene insoles, and thin polyester socks combined with thick wool or propylene socks.

Herpes Zoster

Herpes zoster, also known as shingles, is caused by the reactivation of the varicella-zoster virus (VZV). This occurs in about 20% of immunocompetent individuals and is more commonly seen in immunocompromised individuals or the elderly. Clinically, they have grouped vesicles, and/or erosions on an erythematous base. Herpes zoster can be triggered by a condition such as immunosuppression, radiation, UV exposure, trauma, stress, or be idiopathic.

Clinical features

- Painful grouped vesicles with scalloped borders on an erythematous base in a dermatomal pattern. **Fig. 3**.
- Disseminated disease will have a dermatomal pattern and 20 or more lesions outside of the primary dermatome.
- The thorax is the most common location, followed by the face, lumbar, and sacrum.

Pathogenesis

- VZV is dormant in the dorsal root ganglia for life after primary infection (varicella).
- Reactivation of the latent varicella-zoster virus.

Differential diagnosis

- Herpes simplex virus infection
- Allergic contact dermatitis
- Bullous arthropod assault
- Other poxviruses

Diagnostic testing

- Polymerase chain reaction (PCR)-based testing from base of a blister is the test of choice as it is sensitive and can have a relatively fast turnaround time.
- Tzanck smear from base of blister
- Viral culture from base of blister
- Histology will show an intraepidermal vesicle with epithelial necrosis, ground-glass-appearing ballooned nuclei within keratinocytes and multinucleated cells.

Treatment

- Antiviral therapy with acyclovir and pro-drug forms; skin lesions remain contagious until all lesions are crusted over (**Box 4**).

Pemphigus Vulgaris

Pemphigus vulgaris is the most common type of pemphigus, representing 70% or more of all subtypes. Characteristic flaccid bullae rupture and leave denuded areas.

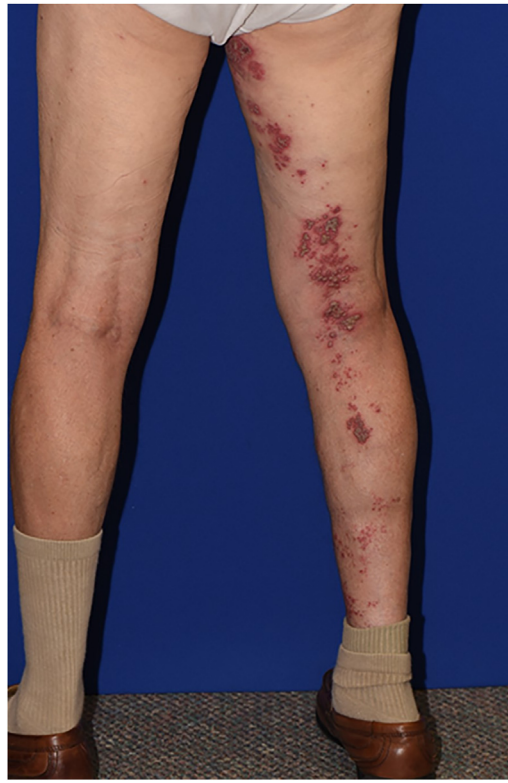

Fig. 3. Multiple grouped and confluent vesicles and bullae on a background of erythema in the S2 dermatome. (*Courtesy* of O Sokumbi, MD)

Pemphigus vulgaris is the classic disease associated with the Nikolsky sign, in which light friction on perilesional skin induces a blister. The Asboe-Hansen sign, in which pressure on the surface of a bulla causes the blister to spread laterally, is also positive. Mucosal, in particular oral involvement is often the initial manifestation in PV.

This disease process can be associated with myasthenia gravis, thymoma, and autoimmune thyroiditis. The hair follicles are extensively involved. Many different drugs have precipitated this disease, especially those with thiol groups, although pemphigus foliaceus rather than pemphigus vulgaris is more commonly induced.

Box 4
Diseases with a suprabasilar split

- Pemphigus vulgaris
- Pemphigus vegetans
- Paraneoplastic pemphigus
- Grover disease
- Hailey–Hailey disease
- Darier disease

Pathogenesis

- Both humoral and cell-mediated mechanisms contribute.
- Autoantibodies of the predominantly IgG4 subclass target desmoglein-3 early and later cross-react with desmoglein-1.
- In the adult, desmoglein-3 is concentrated in the basal and suprabasilar layers of the epidermis and mucosal surfaces.
- Desmoglein 1 is expressed in all levels of the epidermis and can compensate for desmoglein 3 loss in the upper layers of the skin; desmoglein 3 cannot compensate for the loss of desmoglein 1 in mucosa which leads to the oral manifestation seen in PV.

Clinical features

- Flaccid bullae break to form painful erosions **Fig. 4**.
- Oral involvement occurs first in 60% of cases, followed by the skin **Fig. 5**.
- Other mucosal surfaces may be involved
- Commonly involves the trunk, groin, axillae, scalp, and face
- Positive Nikolsky sign
- The average age at presentation is in the fifth or sixth decade
- More common in Jewish/Mediterranean populations
- Associations: other autoimmune disorders (myasthenia gravis and thymoma)

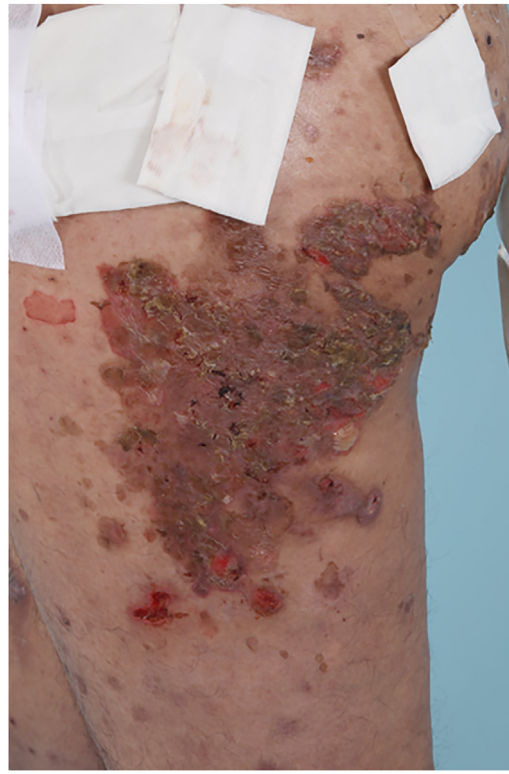

Fig. 4. Flaccid bullae with secondary erosion, crusting, and scale on the lower extremity of a patient with pemphigus vulgaris. (*Courtesy* of O Sokumbi, MD)

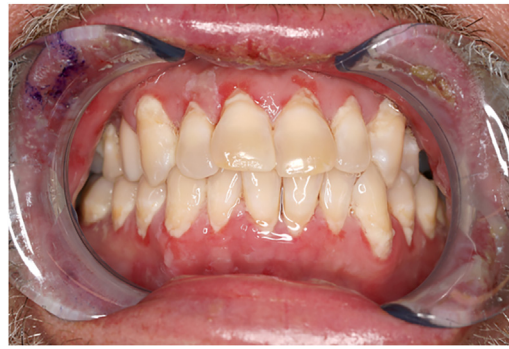

Fig. 5. Erosions along the gum line giving rise to marginal gingivitis in a patient with pemphigus vulgaris. (*Courtesy* of O Sokumbi, MD)

Differential diagnosis

- Pemphigus foliaceus
- Drug-induced pemphigus
- Erythema multiforme
- Stevens–Johnson syndrome
- Bullous pemphigoid

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF.
- IIF on monkey esophagus can be used to assess patient's sera for circulating IgG antibodies and as a proxy for disease state and treatment status.
- ELISA for desmogleins 1 and 3.

Treatment

- Rituximab has been Food and Drug Administration (FDA) approved for moderate to severe PV since June 2018.
- Short-term systemic corticosteroids (1 mg/kg/day) combined with adjuvant immunosuppressants (ie, azathioprine, mycophenolate mofetil, or rituximab) can also be used.[6]
- Other steroid-sparing immunosuppressive agents to consider include cyclophosphamide, intravenous immunoglobulin (IVIG), methotrexate, and plasmapheresis.
- Treatment response can be monitored clinically or with IIF and ELISA levels.

Pemphigus Vegetans

Pemphigus vegetans is the rarest clinical variant in the pemphigus group of vesiculobullous autoimmune diseases and represents less than 2% of all pemphigus.[7] Vegetative plaques in intertriginous areas and the oral mucosa help to distinguish it from pemphigus vulgaris. Pemphigus vegetans has traditionally been classified into Neumann and Hallopeau types.

- Neumann type: Lesions typically begin as typical flaccid blisters of pemphigus vulgaris, become eroded, and form vegetating plaques. Plaques are often studded with pustules. Tends to have a chronic course.
- Hallopeau type: Pustular lesions evolve into vegetating plaques. The Hallopeau type may be more benign and remit spontaneously.

Pathogenesis

- Autoantibodies against desmoglein-3 are pathogenic; often desmoglein-1 is also involved as in PF.
- IgG and IgA antibodies against desmocollins have also been reported[8].

Clinical features

- Vesicles or pustules that become vegetating plaques often on the axillae/groin (flexural), trunk, and extremities. **Fig. 6**.
- Most patients present with stomatitis.
- Mean age of onset is in the fifth decade.

Differential diagnosis

- Hailey–Hailey disease
- Iododerma/bromoderma
- Syphilitic condyloma
- Granuloma inguinale
- Leishmaniasis
- Condyloma acuminata
- Deep fungal infection

Diagnostic testing

- Lesional biopsy for histopathology.

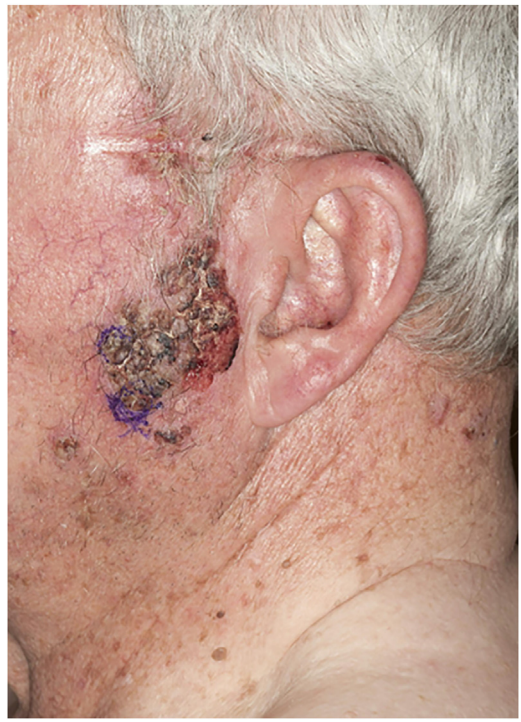

Fig. 6. Verrucous and vegetative plaque on the left cheek in pemphigus vegetans. (*Courtesy* of O Sokumbi, MD)

- DIF of perilesional skin.
- ELISA can identify desmoglein 3 autoantibodies in sera with a specificity and sensitivity of 98% to 100%, respectively.[9]

Treatment

- As with pemphigus vulgaris, the goal is to decrease or eliminate circulating anti-desmoglein antibodies and then the bound antibodies in the skin.
- The gold standard of therapy is systemic corticosteroids which are thought to up-regulate desmoglein expression.
- Transition to steroid-sparing immunosuppressive agents such as azathioprine, dapsone, methotrexate, rituximab, or mycophenolate mofetil.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is alternatively referred to as paraneoplastic autoimmune multiorgan syndrome. PNP is often fatal and pulmonary involvement in the form of bronchiolitis obliterans is significantly associated with decreased survival. Some cases have been described following treatment with interferon or radiation.[10] A variety of internal malignancies are associated with paraneoplastic pemphigus, with non-Hodgkin lymphoma being the most common. Other associations include chronic lymphocytic leukemia, Castleman disease (especially in children), thymoma, poorly differentiated sarcoma, Waldenström macroglobulinemia, inflammatory fibrosarcoma, Hodgkin disease, T-cell lymphoma, and treatment with fludarabine.

Pathogenesis

- Autoantibodies to envoplakin and periplakin, desmoplakin-1 and desmoplakin-3, desmoglein-1 and desmoglein-3, bullous pemphigoid antigen (BPAg1), and plectin.[11]
- Epitope spreading may be responsible for the diverse clinicopathologic findings and many antibodies.

Clinical features

- The presentation usually starts with severe, intractable stomatitis with characteristic lip involvement. **Fig. 7**.
- Mucositis can involve the conjunctiva, esophagus, anogenital, and nasopharynx.

Fig. 7. Diffuse hemorrhagic crusting of the lips in a patient with paraneoplastic pemphigus. (*Courtesy* of O Sokumbi, MD)

- Polymorphic skin lesions with features of bullous pemphigoid (tense and friable bullae and erosions), toxic epidermal necrolysis, erythema multiforme (targetoid plaques), pemphigus, lichen planus, or linear IgA disease.

Differential diagnosis

- Erythema multiforme
- Bullous pemphigoid
- Pemphigus vulgaris
- SJS/TEN
- Linear IgA bullous dermatosis
- Lichen planus
- Mucous membrane pemphigoid
- Bullous lupus erythematosus

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF.
- IIF shows intercellular IgG staining on rat bladder epithelium.

Treatment

- Includes treatment of the underlying neoplasms and initiation of immunosuppression.
- Systemic corticosteroids are the mainstay of therapy at 1 to 2 mg/kg per day.
- Adjunctive immunosuppressive drugs as needed (rituximab, IVIG, cyclophosphamide, azathioprine, mycophenolate mofetil).
- Plasmapheresis may be initiated.

Transient Acantholytic Dermatosis

Transient acantholytic dermatosis, also known as Grover disease, is a relatively common disorder that presents with excoriated papules and papulovesicles on the trunk. It tends to affect Caucasian middle-aged men with a significant history of sun damage. The disease is benign and, in some cases, self-limited.

Pathogenesis

- The exact pathogenesis is unknown but is linked to heat, sweating, and dysfunction of the sweat glands.

Clinical features

- Excoriated papules and vesicles on the central chest, abdomen, and back
- Middle-aged to older adults

Differential diagnosis

- Pityrosporum folliculitis
- Bacterial folliculitis
- Acne
- Miliaria rubra
- Pemphigus
- Darier disease
- Hailey–Hailey disease
- Galli–Galli disease

- Allergic contact dermatitis
- Drug eruption

Diagnostic testing

- Biopsy is usually not necessary.
- Lesional biopsy for histopathology.
- DIF is negative.
- Five histologic patterns can be seen: Darier-like, Hailey-Hailey–like, pemphigus vulgaris–like, pemphigus foliaceus–like, and spongiotic.

Treatment

- The goal of therapy is supportive care: avoidance of ultraviolet (UV) exposure, sweating, heat, and friction followed by emollient application.
- If conservative measures fail, mid to high-potency topical steroids twice daily and/or topical vitamin D-analogs can be utilized.

- Refractory cases can be treated with isotretinoin 0.5 to 1 mg/kg/day for 2 to 12 weeks, psoralen with ultraviolet A (PUVA), methotrexate, and dapsone (**Box 5**).

Bullous Allergic Contact Dermatitis

Allergic contact dermatitis is a type IV (cell-mediated) hypersensitivity reaction to allergen contact in a sensitized individual. An erythematous eruption develops within

Box 5
Diseases with a subepidermal split

Bullous pemphigoid
Cicatricial pemphigoid
Lichen planus pemphigoides
Pemphigoid gestationis
Epidermolysis bullosa acquisita
Dermatitis herpetiformis
Linear IgA bullous dermatosis
Bullous systemic lupus erythematosus
Arthropod bite
Cryotherapy blister
Burn blister
Suction blister
Drug overdose bullae
Bullous lesions in diabetes mellitus
Epidermolysis bullosa
Porphyria cutanea tarda
Toxic epidermal necrolysis
Bullous drug reaction
Erythema multiforme
Bullous fixed drug reaction

days, with the formation of plaques, papules, and rarely vesicles and bullae. A robust response can lead to bullae and systemic symptoms such as fatigue, fever, and diffuse myalgia.

Pathogenesis

- Sensitization occurs when Langerhans or dendritic cells present allergens to naïve T-helper lymphocytes causing clonal expansion of sensitized lymphocytes.
- Cell-mediated, delayed-type hypersensitivity occurs on subsequent exposure.

Clinical features

- The acute presentation is an erythematous eruption with vesicles or bullae.
- Chronic presentation commonly manifests as hyperkeratosis, fissuring, and lichenification.
- Symptoms occur 24 to 48 hours following exposure to an allergen for the acute presentation.
- On physical examination, rash distribution corresponds to contact exposure.

Differential diagnosis

- Phytophotodermatitis
- Bullous pemphigoid
- Bullous tinea

Diagnostic testing

- Historical correlation is essential to determine the clinical relevance of potential allergens.
- Lesional biopsy for histopathology.
- DIF is appropriately negative.
- Patch testing is the gold standard for identifying specific allergens.

Treatment

- Known allergens should be avoided.
- High or moderately potent topical steroids are usually effective in resolving symptoms.
- Systemic steroids are indicated for severe symptoms or if widespread areas are involved.
- Can consider oral antihistamines for pruritus.

Bullous Lymphedema

Bullous lymphedema blisters are non-infectious lesions that develop in the setting of poorly controlled edema. Concurrent medical conditions contributing to volume overload may include heart failure, renal failure, cirrhosis lymph node dissection, hypoalbuminemia, and venous thrombo-embolus.

Pathogenesis

- The rapid accumulation of interstitial fluid in patients with localized acute edema or anasarca causes these blisters to appear.

Clinical features

- Thin roofed bullae on dependent areas, typically the lower extremities, with associated acute edema.

- Bullae can drain sterile liquid although hemorrhagic or serous fluid can appear.
- Lesions are fragile and rupture easily.
- Bullae may increase in size and number over time.

Differential diagnosis

- Bullous arthropod assault
- Coma blister
- Bullosis diabeticorum
- Contact dermatitis
- Trauma blister
- Bullous pemphigoid

Diagnostic testing

- History of tense bullae that develop in temporal association with acute edema.
- Lesional biopsy for histopathology.
- DIF will be negative.

Treatment

- Supportive management with leg elevation, compression, a low-salt diet, diuretics.
- Optimize underlying medical conditions contributing to edema.

Bullous Pemphigoid

Bullous pemphigoid (BP) is the most common subepidermal bullous disease and it most commonly affects older adults (mean age 68–82 years). There is often a prodrome that lasts weeks to months, in which patients present with urticarial or eczematous lesions. Blisters are tense and heal without scarring. Milia are rarely present in areas of resolving erosions. Patients tend to have a chronic course with remission after about 6 years. Morbidity and mortality are low with treatment. Medications implicated in the cause of BP include furosemide, sulfasalazine, penicillins, penicillamine, and captopril. **Box 6** lists other medications that induce bullous pemphigoid. BP has also been described after treatment with ultraviolet light, PUVA, and radiation.

Pathogenesis

- BP180 (BPAG2) and BP230 (BPAG1) are vital components of the hemidesmosomes which adhere to the epidermis and dermis.
- Both antigens are targets of autoantibodies in pemphigoid; however, it is the NC16 A domain of BPAG2 that is thought to be pathogenic in bullous pemphigoid.
- This is the primary location for antibody binding in bullous pemphigoid and can be detected with the use of an ELISA assay in 85% of affected patients.[12]

Clinical features

- Tense bullae on normal or erythematous skin, urticarial/eczematous lesions **Fig. 8**.
- Early disease may be nonbullous as urticarial patches, plaques, and erythema.
- Bilateral, symmetric, often involving the lower abdomen and shins.
- Mucosal involvement in up to 20%.
- Onset usually in adults older than 65, but young adult and pediatric cases occur.

Box 6
Medications implicated in inducing bullous pemphigoid

Anti-influenza vaccine
Arsenic
Captopril
Clonidine
Dactinomycin
Enalapril
Furosemide
Gold
Ibuprofen
Interleukin-2
Methyldopa
Nadolol
Omeprazole
Penicillamine
Penicillins
Phenacetin
Poatassium iodide
Practolol
Psoralens (PUVA)
Risperidone
Sulfapyridine
Sulfasalazine
Sulfonamide
Terbinafine
Tolbutamide

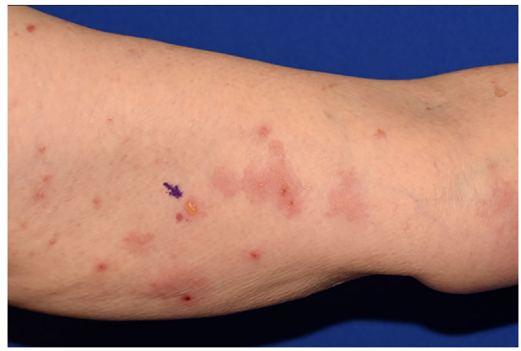

Fig. 8. Tense blisters and erythematous plaques on the upper extremity of a patient with bullous pemphigoid. (*Courtesy* of O Sokumbi, MD)

Differential diagnosis

- Cicatricial pemphigoid
- Lichen planus pemphigoides
- Epidermolysis bullosa acquisita
- Dermatitis herpetiformis
- Linear IgA bullous dermatosis
- Drug eruption
- Arthropod bite
- Urticaria

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF will show linear complement component 3 (C3) (in an n-serrated pattern) and/or IgG at the basement membrane zone; sometimes IgA and IgM are also present.
- IIF on salt-split skin shows immunoreactants bound to the blister roof.
- Tissue-bound and circulating autoantibodies detected by ELISA; ELISAs are more sensitive than IIF for bullous pemphigoid.

Treatment

- Many patients can be successfully managed with the topical use of class I steroids, such as clobetasol.
- Tetracycline and nicotinamide are thought to help via their anti-inflammatory effects.
- Systemic corticosteroids with a transition to steroid-sparing immunosuppressants can be utilized; these include methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, leflunomide, and rarely cyclophosphamide or chlorambucil.
- In recent years, off-label use of dupilumab and rituximab has been beneficial in moderate-to-severe cases.

Cicatricial/Mucous Membrane Pemphigoid

Mucous membrane pemphigoid encompasses a heterogeneous group of disorders characterized by autoantibodies against various proteins in the anchoring filament zone. There are many different target antigens found in patients with mucous membrane pemphigoid; it may be that this disorder represents a disease phenotype rather than a single entity. Limited cutaneous involvement may also be seen in about 25% of patients. Skin lesions resemble those seen in bullous pemphigoid and may be on the head, neck, or extremities. Patients may develop generalized bullae. There is a 2-to-1 female predominance, and the disease seems to affect older patients (sixth or seventh decade of life).

Significant morbidity may occur due to tissue destruction as the result of chronic mucosal inflammation, pain, and scarring. Oral lesions are the most common manifestation of this condition. Patients present with desquamative gingivitis, erythema, ulcers, and vesicles. The gingival and buccal mucosa, tongue, palate, and tonsillar pillars may be involved. Ocular involvement can also occur and begins with bilateral erythema and rare vesicles that develop into xerosis, fibrosis, and scarring. A localized variant of cicatricial pemphigoid referred to as Brunsting–Perry disease, consists of recurrent blisters on the head and neck that heal with scarring. These patients generally have no mucosal involvement.

Pathogenesis

- Suspected that molecular mimicry results in the development of autoantibodies that target different autoantigens (BPAg1 and 2, laminin 5 and 6, integrin subunit beta 4).

Clinical features

- Lesions tend to recur in the same area.
- Oral and ocular mucosal membrane erosions and painful ulcers that scar **Fig. 9**.
- Anogenital blisters and erosions that result in phimosis or vaginal scarring.
- Scarring may result in adhesions and strictures.
- Rare, tense bullae on erythematous plaques on the scalp, head, neck, and upper trunk.
- Scarring alopecia may develop.

Differential diagnosis

- Bullous pemphigoid
- Bechet disease
- Linear IgA bullous dermatosis
- Lichen planus
- Lichen sclerosus
- Epidermolysis bullosa acquisita

Diagnostic testing

- Lesional biopsy for histopathology:
  - Mucosal: subepidermal bullae with mixed infiltrate
  - Skin: subepidermal bullae with mostly neutrophils and eosinophils; dermal scarring
- Perilesional biopsy for DIF.
- 20% of IIF studies will show linear basement membrane zone with IgG and IgA.
- Anti-laminin 332 (Anti-epiligrin) positive cicatricial pemphigoid has an increased risk for solid organ cancers; therefore, malignancy screening is indicated.

Treatment

- Refer to an ophthalmologist and/or otolaryngologist.
- Minimize loss of gingival tissue and teeth through good oral hygiene.

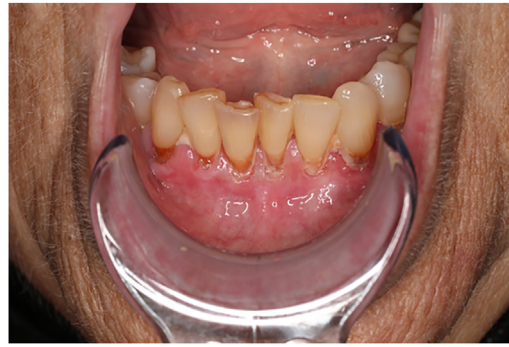

Fig. 9. Gingiva with several erosions. (*Courtesy* of O Sokumbi, MD)

- Mild disease limited to the mouth may respond to high-potency topical corticosteroids (clobetasol or dexamethasone) or topical tacrolimus.
- Treatment of chronic lesions may include intralesional triamcinolone acetonide.
- If ocular, laryngeal, or urogenital epithelia are scarred, then aggressive treatment with a short course of glucocorticoids 1 mg/kg per day with a transition to steroid-sparing immunosuppressants is warranted.
- Alternatives include IVIG, rituximab, azathioprine, cyclophosphamide, methotrexate, and plasmapheresis.

Ocular Cicatricial Pemphigoid

Ocular cicatricial pemphigoid is also known as ocular mucous membrane pemphigoid. It is a subcategory of mucous membrane pemphigoid. The disease is characterized by chronic conjunctivitis, conjunctival injection, and conjunctival and corneal scar formation. Squamous metaplasia with keratinization of the ocular surface epithelium results in blindness.

Pathogenesis

- IgA antibodies to the intraepidermal portion of the b4 subunit of the α6-β4 integrin.

Clinical features

- Erosions, ulcers with subsequent conjunctival and corneal scarring; blisters are rare. Fig. 10.
- Scarring is predominant with fornix obliteration and symblepharon (adhesion of the palpebral and bulbar conjunctiva) formation that leads to ankyloblepharon (fusion of eyelids).
- Entropion, trichiasis, and corneal neovascularization can occur.
- Uncontrolled disease may cause blindness.

Differential diagnosis

- Paraneoplastic pemphigus
- Mucous membrane pemphigoid
- Postinfectious conjunctivitis

Diagnostic testing

- Perilesional biopsy for DIF from conjunctiva will show linear basement membrane zone IgG and/or IgA in conjunctival biopsies.

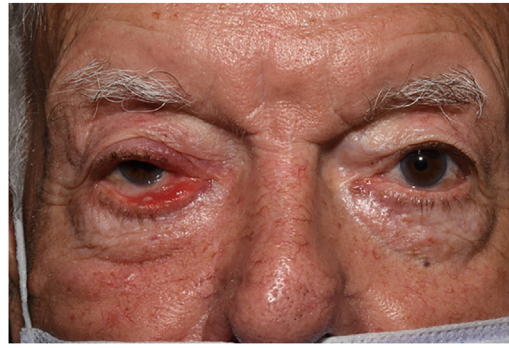

Fig. 10. Conjunctival injection and fibrosis in a patient with ocular cicatricial pemphigoid. (*Courtesy* of O Sokumbi, MD)

Treatment

- Referral to an ophthalmologist
- Dapsone 100 to 150 mg/day
- Oral low-dose weekly methotrexate or mycophenolate mofetil
- Systemic cyclophosphamide with short-term adjunctive high-dose prednisolone is the preferred treatment for severe and/or rapidly progressing ocular cicatricial pemphigoid.

Lichen Planus Pemphigoides

Lichen planus pemphigoides (LPP) is a rare autoimmune skin disorder that involves the simultaneous presence of 2 distinct skin conditions: lichen planus and bullous pemphigoid. In LPP, patients typically experience a combination of the skin lesions associated with lichen planus and the blisters associated with bullous pemphigoid. The skin lesions of lichen planus can occur before, after, or at the same time as the blisters of bullous pemphigoid.

Pathogenesis

- The exact pathogenesis of LPP is not fully understood. It is thought that autoantibodies against specific basement membrane proteins, such as BP180 and BP230, are produced and contribute to the development of bullous pemphigoid.
- Additionally, the T cells that are involved in the development of lichen planus may play a role in the activation of the immune response in LPP.

Clinical features

- Small, flat-topped, purplish, pruritic papules on the flexor arms, legs, and trunk.
- Bullae on skin uninvolved by lesions of lichen planus. **Fig. 11**.
- Erosions, blisters, and lichenoid striae can occur on mucosal surfaces.

Differential diagnosis

- Bullous pemphigoid (without lichen planus lesions)
- Bullous lichen planus
- Pemphigus vulgaris
- Epidermolysis bullosa acquisita
- Linear IgA bullous dermatosis
- Dermatitis herpetiformis
- Erythema multiforme
- Stevens–Johnson syndrome
- Drug-induced bullous eruptions

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF.

Treatment

- Topical and systemic corticosteroids
- Immunosuppressive medications such as azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide.
- In some cases, dupilumab, phototherapy, or plasmapheresis may also be used.

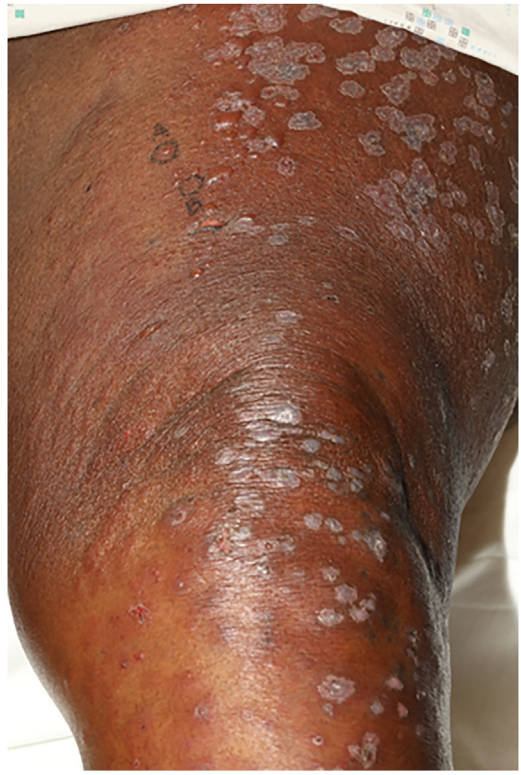

Fig. 11. Lower extremity with small, flat-topped, purple papules and bullae. (*Courtesy* of O Sokumbi, MD)

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is a chronic, immunobullous disease seen in association with inflammatory bowel disease, hematologic malignancy, and other autoimmune diseases. It is characterized by autoantibodies against collagen VII. EBA usually develops in adulthood but can present at any age.

Pathogenesis

- Type VII collagen is the targeted autoantigen in EBA and the primary constituent of the hemidesmosomal dermal anchoring fibers.[13]

Clinical features

- EBA has 1 non-inflammatory presentation and 4 inflammatory presentations:
  - Classical (non-inflammatory) type: Formation of non-inflammatory tense vesicles and bullae that rupture; locations most susceptible to minor trauma like the hands and feet are most affected with subsequent scarring and milia formation. Patients may also develop scarring alopecia, loss of nails, and esophageal stenosis.
  - Inflammatory:
- Bullous pemphigoid-like type: characterized by a general eruption of blisters that have features of bullous pemphigoid surrounded by inflamed skin or urticaria.

- Mucous membrane type: erosions and scars on mucosal surfaces including buccal, conjunctival, gingival, nasopharyngeal, esophageal, rectal, and genital.
- Brunsting–Perry-type: bullous eruption localized to the head and neck with scarring, minimal mucosal involvement. Fig. 12.
- IgA type: presents with linear IgA deposits in the basement membrane (BMZ) that can be observed by DIF.
- Onset usually in adulthood but can occur at any age, no predilection for older adults.
- Trauma often precedes the formation of lesions.

Differential diagnosis

- Bullous pemphigoid
- Cicatricial pemphigoid
- Linear IgA dermatosis
- Porphyria cutanea tarda
- Bullous systemic lupus erythematosus

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF.

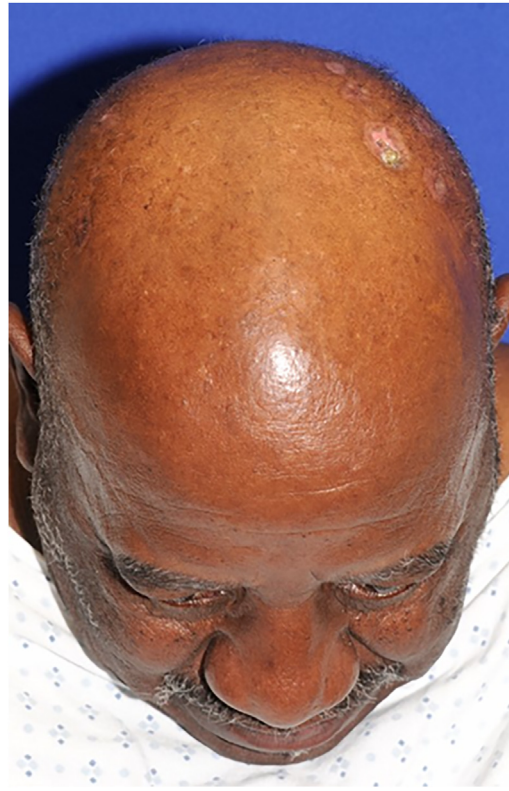

Fig. 12. Patient with Brunsting–Perry pemphigoid with erosions, and surrounding scarring on the parietal aspect of the left side of the scalp. (*Courtesy* of O Sokumbi, MD)

- IIF: linear basement membrane IgG in 50% of cases.
- Salt-split skin DIF demonstrates dermal pattern linear IgG, on the "floor" of the blister.
- ELISA will have autoantibody against non-collagenous (NC)1 domain of type VII collagen.

Treatment

- Minimize trauma to the skin and, if mucous membranes are involved, encourage good oral hygiene and a soft diet with little acid content.
- Oral corticosteroids and antineutrophilic agents or immunosuppressive agents are standard.
- Dapsone started at 50 mg daily and increase by 50 mg weekly, up to 300 mg once a day, until remission occurs. Maintain at remission dose for several months, then decrease slowly until the drug can be discontinued.
- Cyclosporine at 3 to 5 mg/kg per day divided into 2 doses, usually produces a rapid response.
- The noninflammatory variant is more resistant to treatment and may require intravenous immunoglobulin or extracorporeal photopheresis.

Dermatitis Herpetiformis

Dermatitis herpetiformis is a gluten-sensitive blistering dermatitis characterized by anti-transglutaminase 3 IgA antibodies. It is an extremely pruritic disorder that presents with clustered vesicles that are quickly excoriated. Vesicles arise in crops and are distributed symmetrically on the scalp, sacrum, and extensor extremities. Some patients, especially children, may have palmar involvement. The disease course is usually lifelong; spontaneous remissions occur in up to 10% of patients. Patients with dermatitis herpetiformis commonly have gluten-sensitive enteropathy or “celiac sprue.” Thyroid disease, small bowel lymphoma, non-Hodgkin lymphoma are also associated. Of note, there is a strong association with *human leukocyte antigen (*HLA)-DQ2 and HLA-DQ8. Other alloantigens that have been reported are HLA-B8, HLA-DR3, and HLA-A1.

Pathogenesis

- The pathogenesis is uncertain but involves extrinsic and intrinsic factors.
- Granular deposition of IgA in the dermal papillae, activation of the complement system, chemotaxis of neutrophils followed by the release of enzymes that alter or destroy laminin and type IV collagen all contribute to the formation of blisters.

Clinical features

- The onset is usually young adulthood to middle age.
- Small, pruritic, and often excoriated, papules and vesicles with a predilection for extensor surfaces.
- Symmetric distribution, especially on elbows, knees, buttocks. **Fig. 13** and **14**
- Mucous membranes are rarely involved.

Differential diagnosis

- Linear IgA bullous dermatitis
- Bullous pemphigoid
- Scabies
- Contact dermatitis
- Bullous arthropod assault

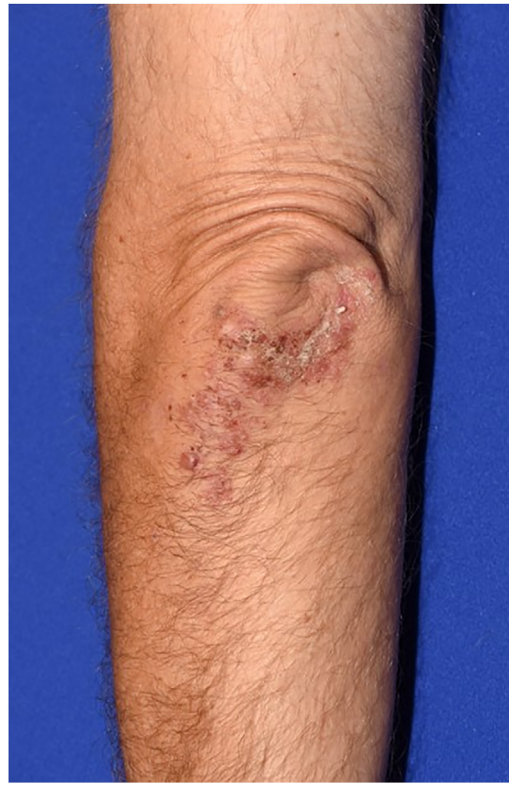

Fig. 13. Elbow with several excoriated papules and vesicles. (*Courtesy* of O Sokumbi, MD)

Diagnostic testing

- Lesional biopsy on an intact vesicle or pink papule (not an excoriated lesion) for histopathology.
- Perilesional biopsy for DIF.
- Serum antibodies include antiendomysial IgA, antireticulin, thyroid microsomal, antinuclear, and tissue transglutaminase.

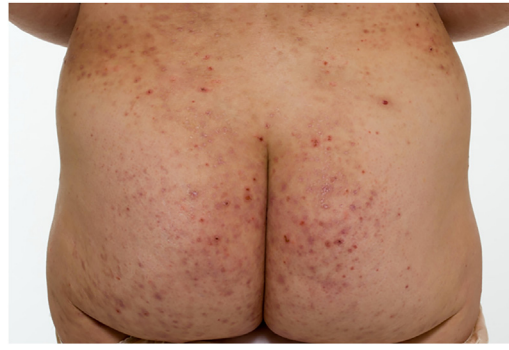

Fig. 14. Buttocks with several excoriated papules and vesicles. (*Courtesy* of O sokumbi, MD).

- Total IgA level is useful as IgA deficiency appears to be less common in dermatitis herpetiformis.[14]

Treatment

- A gluten-free diet is the preferred treatment for both cutaneous and gastrointestinal disease; long-term adherence decreases the risk of lymphoma.
- The skin often responds rapidly to dapsone:
  - Adult initial dose 25 to 50 mg daily
  - Average adult maintenance dose of 100 mg daily
  - Lesions return abruptly on discontinuation
  - Gastrointestinal disease is typically not adequately controlled with dapsone
- Alternative if dapsone-unresponsive or allergic: sulfapyridine 500 mg 3 times daily up to 2 g 3 times daily.
- Occasional application of topical steroids to control lesions.
- Lifelong treatment is needed.

Linear IgA Bullous Dermatosis

Linear IgA bullous dermatosis (LABD) is a rare, autoimmune subepidermal bullous disease that can affect the skin and/or mucous membranes. It has a bimodal age distribution with 2 forms of the disease: LABD occurs in older adults and chronic bullous disease of childhood occurs in children. LABD is marked by linear deposition of IgA along the basement membrane. It can present like other blistering cutaneous disorders, such as dermatitis herpetiformis or bullous pemphigoid. While it is often idiopathic, LABD can be drug induced, and vancomycin has historically been the most commonly associated drug. However, a strong causal relationship between vancomycin and LABD has not yet been established.

Pathogenesis

- Linear IgA bullous dermatosis-1 (LAD-1: 120 kDa) antigen and linear IgA bullous dermatosis (LABD: 97 kDa) antigen are breakdown products of the transmembrane protein BPAg2 (BP180).
- Rare cases in which the antigen is collagen VII of the anchoring fibril.
- The most common drug reported to be associated with LABD is vancomycin, but the pathophysiology remains unknown.[15]
- Other implicated medications include amiodarone, diclofenac, captopril, penicillins, ceftriaxone, metronidazole, interleukin-2, naproxen, and phenytoin.

Clinical features

- Discrete bullae that often are annular and occur in clusters: “cluster of jewels” or “string of pearls.” **Fig. 15**.
- The lesions can be extremely pruritic.
- Adults generally present with rapid onset of tense vesicles and confluent erythematous plaques and papules that affect the trunk, face, buttocks, and extensor extremities.
- Typically, children present with bullae or vesicles on the trunk, face, genitalia, and extremities.

Differential diagnosis

- Bullous pemphigoid
- Cicatricial pemphigoid

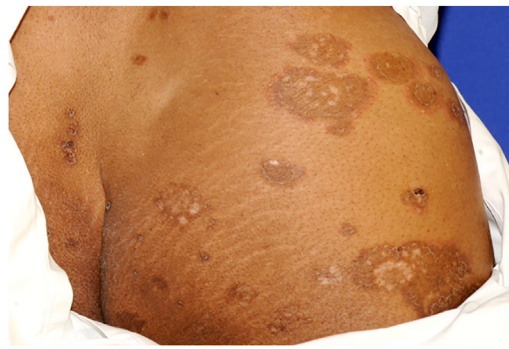

Fig. 15. Hyperpigmented plaques with peripheral "cluster of jewels" or "string of pearls" vesicles. (*Courtesy* of O Sokumbi, MD)

- Herpes simplex and zoster
- Dermatitis herpetiformis
- Pemphigus vulgaris
- Bullous impetigo

Diagnostic testing

- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF.
- IIF on salt-split human skin may show linear IgA antibodies in 33% to 50% of adult patients.

Treatment

- First-line treatment is dapsone; screening for glucose-6-phosphate dehydrogenase deficiency should be performed and if positive, dapsone should be avoided for increased risk of hemolytic anemia. It is important to note that patients who are sulfa allergic can still be treated with dapsone, a sulfone.
- In patients who cannot tolerate dapsone, consider sulfapyridine or sulfamethoxypyridazine, sulfonamide agents that share structural similarities with dapsone.
- If these methods fail to control the disease, corticosteroids and/or other immunosuppressive agents can be used.
- Penicillin and macrolides have also been found to be highly effective.[15]

Bullous Systemic Lupus Erythematosus

Bullous systemic lupus erythematosus (BSLE) is seen in patients who meet the criteria for SLE and is characterized by autoantibodies to collagen VII. BSLE is a rare presentation of systemic lupus erythematosus. Bullae arise on sun-exposed skin on a noninflammatory or inflammatory base. The prognosis is usually excellent with treatment.

Pathogenesis

- Autoantibodies to type VII collagen (290-kDa protein) in the anchoring fibrils, similar to epidermolysis bullosa acquisita.

Clinical features

- Herpetiform vesicles or more often large, tense, fluid-filled to hemorrhagic bullae **Fig. 16**.
- Acute onset, usually on sun-exposed skin

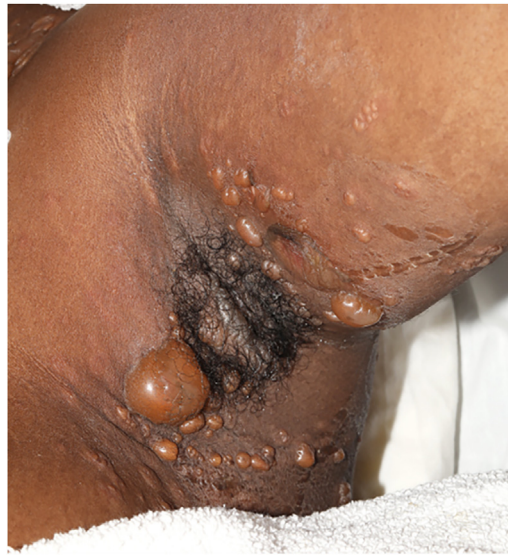

Fig. 16. The left axilla of a patient with bullous systemic lupus erythematosus with large, tense bulla. (*Courtesy* of O Sokumbi, MD)

Differential diagnosis

- Epidermolysis bullosa acquisita
- Dermatitis herpetiformis
- Linear IgA bullous dermatosis
- Bullous pemphigoid
- Bullous impetigo
- Bullous drug eruption
- Erythema multiforme

Diagnostic testing

- Lesional biopsy for histopathology.
- DIF demonstrates granular to linear basement membrane zone staining with IgG, IgA and/or IgM, and C3 ('lupus band').
- IIF is negative.

Treatment

- Dapsone (25–100 mg per day in an adult) is considered the treatment of choice for BSLE; new bullae formation usually ceases within days of starting therapy.
- Other treatments include hydroxychloroquine (200–400 mg per day), colchicine, corticosteroids, rituximab, anakinra, methotrexate, and mycophenolate mofetil.

Cryotherapy Blister

A cryotherapy blister is a blister that forms because of cryotherapy, which involves the use of extreme cold to treat various skin conditions, such as warts, skin tags, and precancerous lesions. Cryotherapy works by applying liquid nitrogen, which has a temperature of around −196°C, to the affected area, causing the cells to freeze and die.

Pathogenesis

- The disruption of the normal structure and function of the skin occurs due to the application of extreme cold, leading to damage to the skin cells and the accumulation of fluid and inflammatory cells, which can cause a blister to form.
- The blister is a natural part of the healing process and is important for tissue repair and regeneration.

Clinical features

- Tense blister at the site of prior cryotherapy.
- Usually, blisters form within 24 to 48 hours after the procedure and can range in size from small to large, depending on the extent of the treatment.

Differential diagnosis

- Herpes simplex virus
- Varicella-zoster virus
- Bullous pemphigoid
- Pemphigus vulgaris
- Epidermolysis bullosa
- Contact dermatitis
- Burn blister
- Arthropod assault

Diagnostic testing

- The clinical history of a recent cryotherapy procedure is the key.

Treatment

- Cryotherapy blisters are a normal part of the healing process after cryotherapy and usually resolve on their own within a few days to a week. However, if the blister is particularly large or causing discomfort, it may be drained using a sterile needle or scalpel.

Burn Blister

A burn blister forms on the skin because of exposure to heat or chemicals. Burn blisters occur when the skin is damaged by a burn, which causes the skin cells and tissues to separate and fluid to accumulate between the layers of the skin. The formation of a burn blister serves as a protective mechanism, as it helps to protect the underlying tissue from further damage and provides a moist environment for the healing process to occur. However, it is important to be cautious when dealing with burn blisters, as they can be fragile and easily ruptured, which can increase the risk of infection or slow down the healing process.

Pathogenesis

- The pathogenesis of a burn blister involves the disruption of the normal structure and function of the skin due to exposure to heat or chemicals.
- When the skin is exposed to extreme heat, it causes damage to the skin cells and the surrounding tissue, leading to the formation of a blister.

Clinical features

- The severity of the clinical features depends on the extent of the burn injury.

- Superficial or first-degree burns typically only affect the outermost layer of skin, causing redness and pain.
- Second-degree burns, on the other hand, affect the deeper layers of the skin and can cause blistering.
- Third-degree burns can damage the skin, underlying tissue, and even bone, and may cause extensive blistering or the absence of blisters due to the complete destruction of the skin.

Differential diagnosis

- Herpes simplex virus
- Varicella-zoster virus
- Bullous pemphigoid
- Pemphigus vulgaris
- Epidermolysis bullosa
- Contact dermatitis
- Cryotherapy blister
- Arthropod assault

Diagnostic testing

- The clinical history of a burn at the site of the blister is the key.
- Biopsy is usually not necessary.
- Lesional biopsy for histopathology.

Treatment

- Supportive care is the main therapy for a burn blister and involves keeping the affected area clean and dry, avoiding puncturing the blister, and protecting it with a sterile dressing.

Suction Blister

A suction blister is a blister that is artificially created by applying negative pressure to the skin, which separates the layers of the skin and produces a fluid-filled blister. The process of creating a suction blister involves using a device, such as a suction pump, to generate negative pressure on the skin, usually on the arm or leg. Suction blisters are commonly used in dermatology research for studying the properties of the skin and for grafting purposes.

Pathogenesis

- The pathogenesis of suction blisters involves the disruption of the normal structure and function of the skin due to the application of negative pressure.
- When negative pressure is applied to the skin, it causes the separation of the layers of the skin, including the epidermis and dermis.

Clinical features

- Blisters can be intentionally created by medical procedures such as grafting, particularly for the treatment of stable vitiligo. Alternatively, they can also develop due to unintentional or self-inflicted injuries, particularly in children.

Differential diagnosis

- Bullous pemphigoid
- Pemphigus vulgaris

- Epidermolysis bullosa
- Contact dermatitis
- Impetigo
- Herpes simplex virus
- Varicella-zoster virus
- Bullous erythema multiforme

Diagnostic testing

- Suction blisters are typically diagnosed based on their clinical appearance and history of their formation.

Treatment

- Suction blisters are usually a self-limited condition that will heal on their own within a few days to a week.
- In general, the treatment for suction blisters involves providing supportive care to relieve symptoms and promote healing.

Coma Bullae

Coma blisters may be a result of medications, metabolic disturbances, and stroke, among many other causes. They were originally described in the setting of carbon monoxide intoxication and are most reported in association with barbiturates.[16] They have also been reported following surgical procedures that require general anesthesia.

Pathogenesis

- Pathogenesis is not fully understood; local hypoxia from prolonged pressure has been suggested as the most likely cause.[17]

Clinical features

- Tense blisters that appear on otherwise normal skin.
- Erythematous plaques or patches first appear after about 24 hours of immobilization and progress to dusky plaques with erosions or bullae around 48 hours.

Differential diagnosis

- Trauma bullae
- Neutrophilic eccrine hidradenitis

Diagnostic testing

- Clinical history of coma.
- Lesional biopsy for histopathology.

Treatment

- With appropriate removal of pressure, lesions typically heal within 1 to 2 weeks, with scarring developing in some.

Bullosis Diabeticorum

Bullosis diabeticorum is also known as diabetic bullae or bullous eruption of diabetes mellitus. Lesions in diabetes mellitus are a rare complication of long-standing diabetes mellitus but have been reported as a presenting sign of diabetes. Lesions heal within several weeks without scarring but may recur.

Pathogenesis

- The pathogenesis is unknown.

Clinical features

- Noninflammatory bullae that are tense and vary in diameter from small to very large on the lower extremities of a diabetic patient.

Differential diagnosis

- Pseudoporphyria or porphyria cutanea tarda
- Bullous tinea
- Bullous fixed drug eruption
- Bullous impetigo
- Trauma bullae
- Poison ivy dermatitis

Diagnostic testing

- Clinical history of diabetes.
- Lesional biopsy for histopathology.
- Perilesional biopsy for DIF will be negative.

Treatment

- Glucose control should be optimized. Lesions are usually self-resolving and supportive care should be initiated.

Bullous Fixed Drug Eruption

Fixed drug eruption presents days to 2 weeks after initial drug exposure as sharply demarcated red edematous to dusky plaques on the skin. They are most commonly on the hands, feet, lips, or genitalia. These lesions can blister and become widespread (generalized bullous fixed drug eruption), which can be difficult to differentiate from SJS/TEN. These lesions often heal with post-inflammatory hyperpigmentation, and within 48 hours of drug re-exposure, they present in the same location as before. Other variants include non-pigmented (classically associated with pseudoephedrine) and linear fixed-drug eruption.

Pathogenesis

- It is thought that an antigen from the medication causes the activation of CD8+ cytotoxic T-cells in the epidermis of a fixed area of skin.
- These cytotoxic T-cells are thought to reside in certain locations on the skin or mucous membranes and are stimulated with antigen re-exposure.

Clinical features

- Erythematous macules or patches that develop into a vesicle or bullae minutes to days after drug exposure.
- Recurrence at the same site(s) on re-exposure to the drug.
- The most common sites are the lips, genital area, hands, and feet.

Differential diagnosis

- SJS/TEN
- Erythema multiforme
- Allergic contact dermatitis

- Erosive lichen planus
- Bullous impetigo

Diagnostic testing

- Inducible lesions will appear at previously involved sites with provocation with the possible agent (after allowing for a possible refractory period of weeks to months).
- Lesional biopsy for histopathology.
- DIF is negative.

Treatment

- Mid and high-potency topical corticosteroids can be used for supportive care.
- Drug cessation, if possible, although fixed drug eruption is not a severe cutaneous adverse drug reaction so continuation of medication is not contraindicated if the drug is necessary; although, generalized bullous fixed drug eruption is considered severe and potential culprit drugs should be discontinued.
- Patch testing can be done but must be performed at the site of previous areas of involvement after a refractory period.

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is the most common porphyria, a group of disorders characterized by dysfunction of the heme biosynthesis pathway. There are 3 types of PCT that can be classified as "familial" or "sporadic" based on the presence or absence of gene mutations of the hepatic enzyme, uroporphyrinogen decarboxylase (UROD). Type 1 (sporadic) accounts for 80% of cases and lacks a UROD mutation.[18] Type 2 (familial) has inherited UROD mutations affecting 1 allele in 20% of cases. Type 3 (familial) does not have an inherited UROD mutation but may have other inherited factors such as hemochromatosis.

Pathogenesis

- Due to decreased activity of UROD.

Clinical features

- Sun-exposed areas of skin with tense vesicles, bullae, erosions, and morpheaform plaques. **Fig. 17**.
- Dorsal hands may have scarring, milia, and hypo/hyperpigmentation in and around active bullae and erosions.
- Delayed photosensitivity with skin fragility.

Differential diagnosis

- Pseudoporphyria
- Epidermolysis bullosa acquisita
- Bullous systemic lupus erythematosus

Diagnostic testing

- First line test is plasma or urinary total porphyrins, PCT will have elevated porphyrins.
- Lesional biopsy for histopathology.

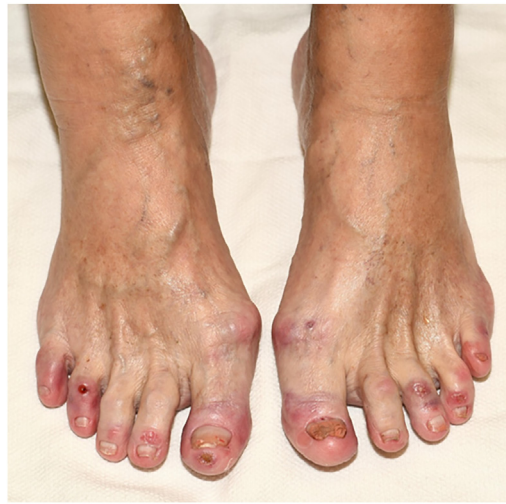

Fig. 17. Vesicles, bullae, erosions, and crusting on dorsal toes. (*Courtesy* of O Sokumbi, MD)

- DIF can show thick and homogenous staining of dermal vessels with IgG, IgA, C3, or fibrinogen. It can show weak granular and linear staining at the basement membrane zone.

Treatment

- First-line therapy is phlebotomy every 2 weeks and/or low-dose antimalarials (ie, hydroxychloroquine 200 mg twice weekly or chloroquine 125 mg twice weekly).
- Encourage the use of sun protection with broad spectrum sunscreens and sun-protective clothing.
- Limit precipitating factors by minimizing or eliminating alcohol consumption and estrogen use.
- Optimize management of comorbidities such as hepatitis or HIV.

CLINICS CARE POINTS

- Bullous dermatoses are primarily categorized by the anatomic level of the split.
- A biopsy for hematoxylin and eosin and direct immunofluorescence may be indicated to render an accurate diagnosis when evaluating bullous dermatoses.
- In older adults, the prevalence of polypharmacy and comorbid conditions complicates diagnosis by adding drug-induced and physical bullous dermatoses to the differential consideration.
- Owing to the relative rarity of these diseases, treatment is based on published evidence, expert opinion, and consensus requiring that physicians fully review all the available data to assist in therapeutic decisions.

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