***no patient handout*

Bullous pemphigoid

Synopsis

This summary discusses adult patients. **Bullous pemphigoid of childhood** is addressed separately.

Bullous pemphigoid (BP) is a chronic autoimmune subepidermal blistering disease most frequently seen in the elderly. IgG autoantibodies bind to antigens that comprise the hemidesmosome adhesion complex in the basement membrane of the skin (BP180 or BP230). This triggers complement activation and release of inflammatory mediators, resulting in the formation of local or generalized tense bullae. The disease can occur on any body surface, but mucous membrane involvement is rare.

Relapse of BP has been shown to be more likely in individuals with extensive involvement and **dementia**. BP has been associated with other neurologic disorders. BP has also been associated with other autoimmune diseases such as diabetes mellitus, **thyroiditis**, **dermatomyositis**, **lupus erythematosus**, **rheumatoid arthritis**, **ulcerative colitis**, **myasthenia gravis**, and **multiple sclerosis** in case reports and case series. Therapeutic radiation or drugs (furosemide, NSAIDs, captopril, penicillamine, and some antibiotics) have also been associated with BP. It may also follow certain nonbullous inflammatory skin diseases, such as **psoriasis** and **lichen planus**, or vaccination (most often in children).

In patients of Northern European descent, there has been a significant association with the DQB1*0301 allele, whereas patients of Japanese descent have a higher frequency of alleles DRB1*04, DRB1*1101, and DQB1*0302.

The condition is often self-limiting, but it can become chronic over months to years. There is a wide spectrum of clinical severity. The disease can be generalized and severe, or patients may have only a few asymptomatic, localized bullae. There is no ethnic or sex predilection.

In some instances, early BP lesions will appear as pruritic urticarial papules and plaques (known as urticarial BP). The urticarial prebullous phase may vary in length from weeks to many months.

Codes

ICD10CM:
L12.0 – Bullous pemphigoid

SNOMEDCT:
77090002 – Bullous pemphigoid

Look For

Bullae are tense compared to the flaccid bullae of pemphigus vulgaris. Bullae are most often seen on the lower abdomen, thighs, and forearms. They can be extensive or localized, and there is a flexural predilection. They may appear on normal-appearing skin or have an erythematous, urticarial base. Bullae typically heal without scarring. However, as they heal, milia can appear (as is seen in other subepidermal blistering diseases such as porphyria cutanea tarda and epidermolysis bullosa acquisita).

In the prebullous urticarial phase, fixed urticarial plaques only may be present.

Unusual variants include prurigo pemphigoides, which resembles prurigo nodularis, and an acral form that resembles dyshidrotic eczema.

Nikolsky sign (characterized by lateral friction inducing an erosion) is absent.

Diagnostic Pearls

Pruritus is prominent and may precede the appearance of skin lesions.

BP should always be highly considered when tense bullae are present in patients older than 60 years.

BP rarely has mucosal lesions, as compared with pemphigus vulgaris, which frequently begins with oral erosions.

Urticarial plaques may precede bullae for up to many months, so BP should be considered as the diagnosis in an older patient who presents with itchy urticarial plaques without bullae.

Differential Diagnosis & Pitfalls

- **Diabetic bullae**, which often erode and are large in size, may be confused with BP, but they are commonly solitary.
- **Stasis dermatitis** with bullae
- **Insect bite reaction**
- Bullae secondary to **lymphedema**
- **Bedbug bite**
- **Flea bite**
- **Contact dermatitis** with bullae
- **Poison ivy dermatitis**
- **Bullous impetigo** will have associated honey-colored crust.

- Bullous **cellulitis**
- **Epidermolysis bullosa acquisita** can be difficult to distinguish but may have the additional findings of **milia**; biopsy with direct immunofluorescence is helpful.
- **Cicatricial pemphigoid** is a scarring, blistering disease that involves the mucosal surfaces.
- **Pemphigoid gestationis** is a variant of BP that presents in pregnant or postpartum females.
- **Linear IgA dermatosis** often presents with a cluster of vesicles on an erythematous base.
- **Dermatitis herpetiformis** rarely has intact bullae secondary to excoriation.
- **Porphyria cutanea tarda** or **pseudoporphyria** presents with bullae, milia, and hypertrichosis in sun-exposed areas.
- **Pemphigus vulgaris** or foliaceus have flaccid (fragile) bullae.

Urticarial phase of bullous pemphigoid:

- **Urticaria**
- **Urticarial vasculitis**

Best Tests

Take a complete medication history.

Skin biopsy of the edge of a bulla for H&E staining will reveal a subepidermal bulla with associated eosinophilic infiltrate. Diagnosis is confirmed by positive direct immunofluorescence (DIF) findings on a perilesional biopsy. Eosinophilia is common.

Serologic tests for BP such as an ELISA for BP180 and BP230 can be used to clinch the diagnosis in clinically suspicious cases in which the DIF is falsely negative.

Histopathology Findings:

- Eosinophilic spongiosis, especially in early lesions
- Subepidermal cleft / blister
- Perivascular lymphocytes and eosinophils
- Variable degree of eosinophilic inflammation, can be "cell-rich" or "cell-poor"

- Direct immunofluorescence exhibits linear IgG and C3 along basement membrane zone
- Salt-split skin shows IgG deposition in an epidermal pattern (roof)

Management Pearls

If there is suspicion of a triggering drug, it should be discontinued.

Secondary infection should be treated aggressively with appropriate systemic antibiotics.

There is usually no relationship to an underlying neoplasm in BP. A thorough history and general physical exam are usually sufficient, and malignancy screening is not routinely needed. However, systemic symptoms or an atypical presentation should warrant further workup of underlying malignancy.

An extensive study in France found that relapse was more frequent in patients with extensive disease and with dementia.

Involve a dermatologist in the patient's care to assist with making the diagnosis and directing the choice of therapies. Depending on the extent and severity of disease, consultations with dentistry, ophthalmology, and/or otolaryngology may be indicated.

Therapy

Avoid mechanical skin trauma. Patients with oral disease may require a modified diet (eg, soft foods).

Localized disease:

- High-potency topical corticosteroids (clobetasol propionate) or intralesional steroids (triamcinolone acetonide).

Extensive disease:

- Prednisone at 1 mg/kg/day is often used for severe and extensive disease, tapering slowly with clearing. Prednisone at 0.5-0.75 mg/kg/day is used for less extensive and severe disease.
- A large multicenter trial demonstrated that 200 mg/day doxycycline was non-inferior to treatment with prednisone and had a better long-term safety profile.
- Data suggests that strong topical corticosteroids (eg, clobetasol) are superior to systemic corticosteroids with regards to relapse rate, complications, and time to response. Consider the use of 30-40 grams a day of a superpotent topical steroid, such as clobetasol, in place of oral therapy if daily application of a cream is a feasible alternative for the patient.

- Patients taking long-term systemic corticosteroids should receive calcium (at least 1 gram every 24 hours) and vitamin D supplementation with or without other method(s) of osteoporosis prevention.

Other therapies used in bullous pemphigoid include:

- Tetracycline (500 mg every 6 hours) in combination with nicotinamide (500 mg every 8 hours) has been used for anti-inflammatory effects and as steroid-sparing agents, though controlled studies have not yet been done to prove efficacy. Minocycline (100 mg every 12 hours) has also been used, or
- Dapsone (50-100 mg every 24 hours), or
- Antimetabolites including azathioprine (75-150 mg every 24 hours), mycophenolate mofetil (1.0-1.5 g every 12 hours), cyclophosphamide (1-3 mg/kg every 24 hours), cyclosporine (1-5 mg/kg every 24 hours), and methotrexate (5-10 mg weekly) also serve as important steroid-sparing agents. Their use should be considered if the patient requires several months of systemic corticosteroids in the range of 40-60 mg, or
- For resistant cases IVIg, or
- Rituximab (anti-CD20)

The presence of significant levels of IgE anti-BP180 may indicate the usefulness omalizumab for treatment.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
5-aminosalicylic acid derivative	3
ACE inhibitor	5
Acetylcholinesterase inhibitor	1

Medication	Citations
adalimumab	3
aldesleukin	2
Alpha-adrenergic agonist	2
Alpha-adrenergic antagonists	1
amlodipine	2
amoxicillin	4
amoxicillin + clavulanic acid	1
ampicillin	4
ampicillin + sulbactam	1
Angiotensin II receptor blocker	2
Anticonvulsant	4
Antidiabetic	6
Antifungal	2

Medication	Citations
Antimalarials	3
Antimetabolite	3
Antimycobacterial	2
Antineoplastic antibiotic	3
arsenic	2
aspirin	3
Atypical antipsychotic	3
Beta blockers	6
Beta-lactam antibiotic	1
bumetanide	1
Calcium channel blocker	4
captopril	3
carbamazepine	1

Medication	Citations
Carbonic anhydrase inhibitor	1
cephalexin	3
cephalosporin	3
Chelating agents	11
chloroquine	3
ciprofloxacin	2
clonidine	2
coal tar	2
dactinomycin	3
diclofenac	2
Diuretic	17
dorzolamide	1
doxazosin	1

Medication	Citations
efalizumab	3
enalapril	2
erlotinib	2
etanercept	3
fluoroquinolone	2
fluorouracil	2
fluoxetine	2
furosemide	11
gabapentin	2
galantamine	1
hydrochlorothiazide	2
ibuprofen	4
levetiracetam	2

Medication	Citations
levobunolol	1
levofloxacin	1
linagliptin	2
lisinopril	2
losartan	2
mefenamic acid	3
mesalamine	1
metformin	2
methotrexate	1
methoxsalen	1
methyldopa	2
metoprolol	1
nadolol	2

Medication	Citations
nifedipine	3
nivolumab	2
NSAID	8
omeprazole	3
pembrolizumab	1
penicillamine	11
penicillin antibiotic class	9
pilocarpine	1
potassium iodide	3
Proton pump inhibitor	3
psoralen + ultraviolet A	5
psoralens	7
rifampin	1

Medication	Citations
risperidone	3
Salicylates	3
Selective serotonin reuptake inhibitor	2
sitagliptin	3
spironolactone	3
streptomycin	1
sulfasalazine	2
sulfonamide	1
sulfonylurea	2
terbinafine	2
timolol	3
tolbutamide	2
Tyrosine kinase inhibitor	2