Presentations of bullous pemphigoid and management

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Outline of today’s presentation

Clinical spectrum and management of bullous pemphigoid (BP)

1. Key points about bullous pemphigoid
   - Epidemiology
   - Spectrum of clinical presentations

2. Diagnostic algorithm

3. Management
   - General clinical context
   - Place of topical steroids in management
Bullous pemphigoid - Key points

1. Most frequent autoimmune subepidermal bullous dermatosis
   - Onset after the age of 70 years
   - Polymorphous clinical features

2. Subepidermal blistering with a dermal inflammatory infiltrate (neutrophils and eosinophils)

3. Autoantibodies and autoreactive T cells to BP180 (BPAG2) and BP230 (BPAG1e), components of hemidesmosomes

Epidemiology of bullous pemphigoid
A disease of elderly patients

- Overall incidence: 10-40 new cases/10^6 inhabitants/year

Clinical presentations and diagnostic delay in BP

• Swiss prospective study with 117 cases of BP  
  Della Torre R et al., 2012
  • Features at time of diagnosis
    • 80% of cases, “typical” BP: blisters and postbullous erosions
    • 20% of cases, “atypical” BP: excoriations, eczematous or urticarial lesions
  • Time required for diagnosis
    • Mean time: 6.1 months; median time: 2.3 months

• French epidemiological study  
  • Analysis of 502 cases
    • 21% with atypical features: prurigo, eczema-like, urticaria-like….

➢ Take home message: consider the diagnosis of BP in all patients with chronic pruritic lesions!
Proper diagnosis of typical BP

Clinical suspicion of BP
  ↓
Positive direct IF
  ↓
Linear IgG/C3 deposits at BMZ
  ↓
Typical clinical features
  ↓

3 out of 4 criteria
1. Absence of atrophic scars
2. Absence of head and neck involvement
3. Absence of mucosal involvement
4. Age > 70 years

Positive predictive value of 95%
Diagnosis of non-bullous or atypical forms of BP

Clinical suspicion of BP

Positive direct IF: linear IgG/C3 deposits along BMZ

Compatible clinical features, non bullous lesions

Immunopathological confirmation
- IIF on salt-split skin (E or E/D labelling)
  or
- ELISA-BP180 (and ELISA- BP230)
- Other: n-serrated pattern, biochip, immunoblot, FOAM, IEM
Management of bullous pemphigoid - challenges

Prior to starting therapy, consider the characteristics of BP patients

1. Bullous pemphigoid occurs in elderly patients (Joly et al. 2002)
   - French prospective RCT: n=341, mean age 82 years

2. Significantly association with neurological diseases (Langan et al, 2010)
   - Stroke, dementia, Parkinson’s disease, multiple sclerosis...

3. Poor general condition (Joly et al. 2002 and 2005)
   - Often cardiovascular diseases, diabetes, bedridden...

4. Age- and sex-adjusted mortality rate high in BP
   - 1st year mortality: 6% to 44%, higher standardized mortality (Roujeau et al. 1998; Garcia Doval et al. 2005; Langan et al. 2008, Cortes et al.2011)

➤ Now, which treatment should we give to our patient?
Management of bullous pemphigoid (BP)
Place of systemic corticosteroids

*Background*
- For decades considered the *golden standard*
- Prednisone/prednisolone doses between 0.5 to 2 mg/kg per day

*Evidence from literature, analysis of interventions*

1. **High doses** of oral corticosteroids (prednisone >0.75 mg/kg)
   - Responsible for high mortality: 35% to 40%: *to be avoided*

2. **Low doses** of oral corticosteroids (prednisone 0.3 mg /kg)
   - Ineffective in controlling extensive BP: *to be avoided*
     - Roujeau JC et al. Lancet 1984
Topical corticosteroids in BP

The only treatment with demonstrated superiority compared to oral corticosteroids (efficacy, side effects, mortality)
  • Clobetasol propionate 0.05% 20-40g/d to progressively reduce over 4 to 12 months

Limitations

1. Practical problems
  • Need to apply the cream on the whole body: compliance!
  • Practical feasibility: assistance of a relative or a nurse often required

2. Side effects
  • Local side effects Bourgara et al. Ann Dermatol Venereol 2010
    • Skin atrophy, skin infections (up to 30%, including erysipelas, necrotizing fascitis),…
    • Systemic effects: diabetes, adrenal suppression,…. (but: overall less mortality!!)

3. Economical aspects
  • Higher costs than oral corticosteroids
    • BUT: fewer severe side effects compared to oral CS (mortality)
    • Shorter hospital stays (in France)
  • Lower costs than immunosuppressive drugs, biologics, immunoabsorption…
Management of bullous pemphigoid
Place of immunosuppressants

1. Often used as first-line therapy as corticosteroid (CS)-sparing adjuvants
2. Wide choice: azathioprine, mycophenolate mofetil, chlorambucil, MTX
3. Evidence available
   - Several uncontrolled series
   - One RCT comparing prednisolone with azathioprine versus prednisolone
   - One RCT comparing MP-solone + AZA versus MP-solone + MMF
     ✓ So far, no clear benefit demonstrated (disease control, cumulative doses of CS)
     ✓ More severe complications…

➢ Indications
   - Cortico-resistant bullous pemphigoid
   - If contraindications to corticosteroids
   - As relay after topical steroids?
Bullous pemphigoid and methotrexate

• Retrospective study: 70 patients treated by topical steroids and MTX followed by maintenance with MTX alone (10mg/w for 8 months)
  • Protracted control of the disease in 76% of patients
  • 16% with side effects leading to MTX discontinuation


• French group of bullous diseases
  • Ongoing prospective « BP3 » study assessing the value of topical steroids compared to MTX in maintenance of remission…
    • Useful…
    • But: significant side effects in MTX–treated group (infections)…
    • Attention: reduced renal function in elderly patients…
Bullous pemphigoid - Therapeutic ladder

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<th>Localized/limited disease with mild activity</th>
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<td><strong>1st choice</strong></td>
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<td>• Superpotent topical corticosteroids</td>
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<td>on lesions only (1, validated)</td>
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<td><strong>1st choice</strong></td>
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<td>• Superpotent topical corticosteroids on whole body sparing the face (1, validated)</td>
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<td>• Oral corticosteroids (1, validated for prednisone)</td>
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Bullous pemphigoid - Treatment-resistant cases

- A number of BP patients show no response, have either severe side effects or contraindications to “standard” therapies
- Alternatives (anecdotes, cases reports, non-validated)
  - Intravenous immunoglobulins (useful in immunocompromised patients)
    - Gürkan et al. 2010
  - Anti-CD20 mAb (Rituximab, Mabthera)
  - Anti-IgE mAb (Omalizumab, Xolair)
    - Fairley J et al. 2009
  - Immunoadsorption/immunoapheresis
    - Schmidt et al. 2010; Marker et al. 2011
  - Cyclophosphamide
    - Dawe RS et al. 1997; ItoT et al. 1996
When should we stop treatment in BP patients?

1. Optimal duration of treatment unclear
2. High relapses rate
   - in up to 40% of cases after stopping therapy
   - usually *within 6 months* *Bernard et al. Arch Dermatol 2009,*
3. Factors associated with increased risk of relapse during the first year of treatment in a prospective study (n=120)
   - Extensive disease at inclusions (more than 10 new blisters/day)
   - Presence of associated dementia
   - Low decrease of ELISA-BP180 value during first 60 days
   - ELISA-BP180 value >23 U/ml at day 150 (Month 5) *Bernard et al. JAMA Dermatology 2014*
When should we stop treatment in BP patients?

*Experts’ recommendation* (EADV-EDF consensus 2015)

1. Treat for between 4 to 12 months
   • Except in cases of steroid-resistance
2. Discontinue treatment in patients, who *are free of symptoms for 3 to 6 months under minimal therapy*
   • Prednisone <0.1 mg/kg/day (5 mg-10 mg/d)
   • Potent topical CS < 20 g/week
   • Minimal adjuvant therapy
3. Pay attention, predictors of relapse:
   • if ELISA-BP180 value >23 U/ml at time of therapy cessation
   • Extensive disease and dementia…
Management of pemphigoid - Take home message

1. Elderly patients: be cautious
   • Poor general condition, neurological comorbidities
   • Increased mortality rate

2. Whenever possible, use topical corticosteroids as first-line therapy
   • More effective and less side effects and mortality than oral CS
   • Self application should be feasible
   • External help should be available to ensure compliance

3. Alternatives (USA)
   • For localized disease, topical corticosteroids
   • For mild disease, try doxycycline and nicotinamide (Lancet 2018, in press) plus topical steroids
   • For mild/severe disease, oral prednisolone 0.5 - 0.75 mg/kg/day
Bullous pemphigoid
Take home messages - Key points

Autoimmune blistering disease of the skin and mucosae

1. Most frequent autoimmune subepidermal bullous disease

2. Wide spectrum of clinical presentations
   • Consider in all elderly patients with prurigo and chronic eczematous eruption, with relapsing localized blisters and erosions

3. Avoid aggressive non-validated treatments
   • Elderly patients with multiple co-morbidities
   • High potency topical steroids: first line therapy in BP in Europe
   • Oral prednisolone : doses not more than 0.75 mg/kg
Author’s conflict of interest disclosure statement

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I will speak about off-label use of medications