Highlighting the role of IgE autoantibodies in bullous pemphigoid

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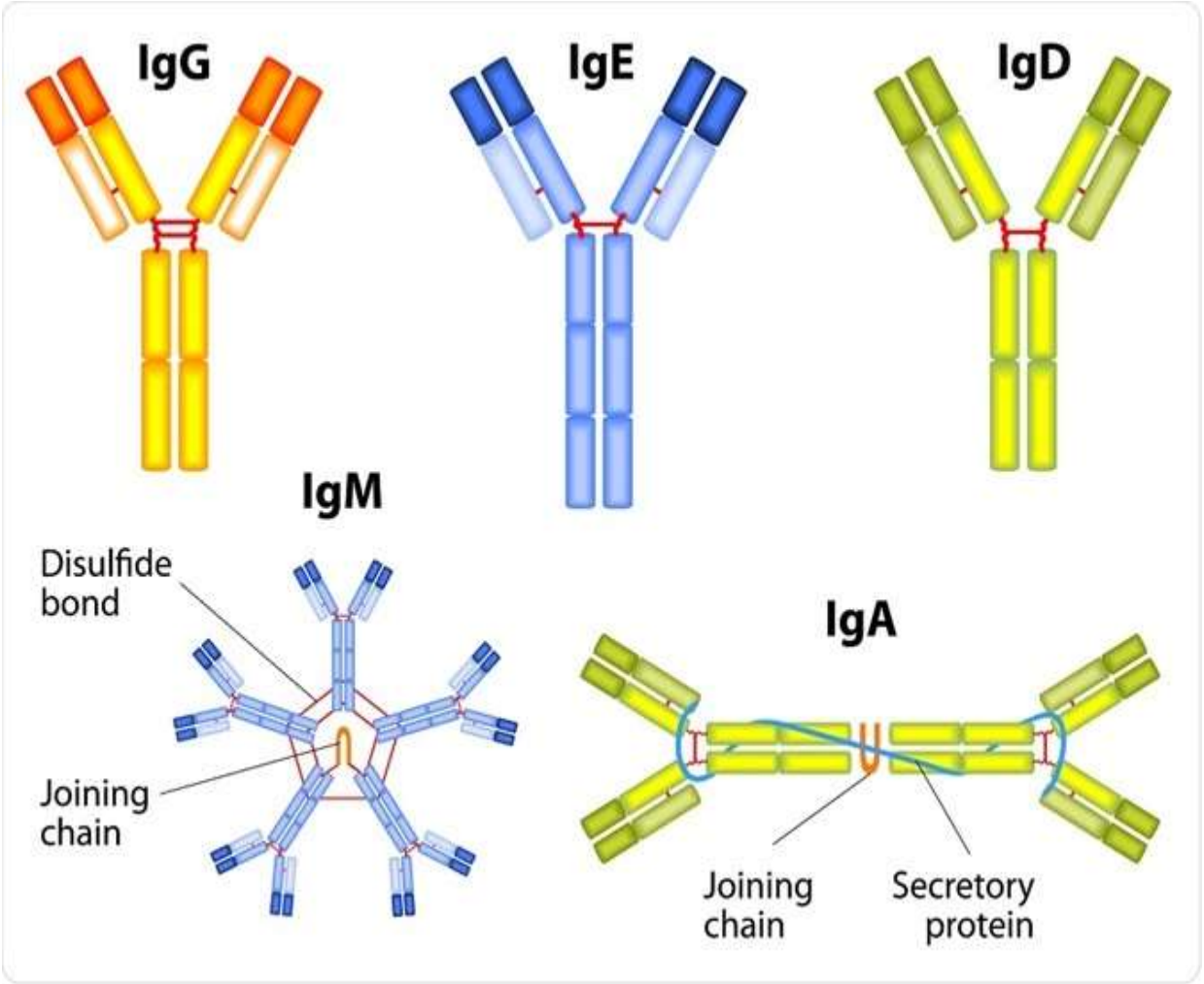
Overview

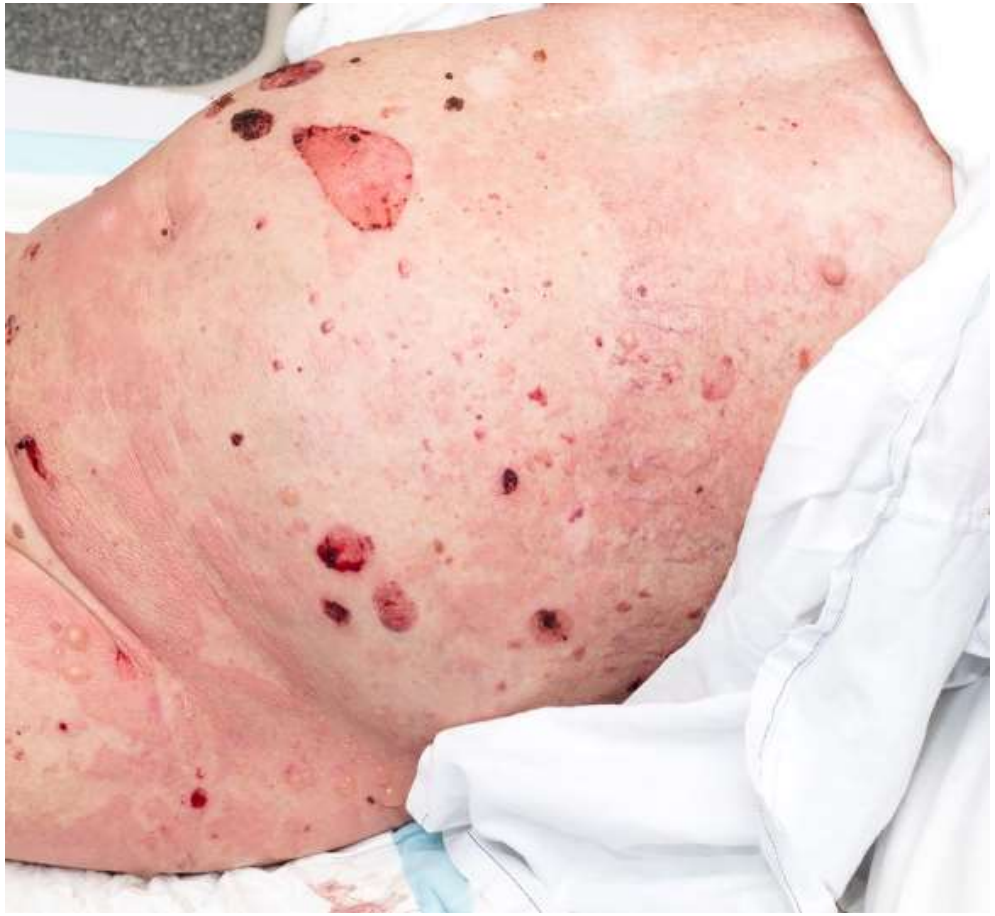
- Case presentation
- Role of IgE
  - Experimental
  - Laboratory
  - Clinical
- Case outcome
- IgE autoantibodies in other settings



Background

- 72 year old man
- Past medical history
  - T2DM well controlled with diet (HbA1c = 5.6)
  - Stage IV CKD
  - HIV with long term viraemic control
  - Legally blind from glaucoma many years earlier
  - Ischaemic heart disease
- Lives alone with supports for shopping

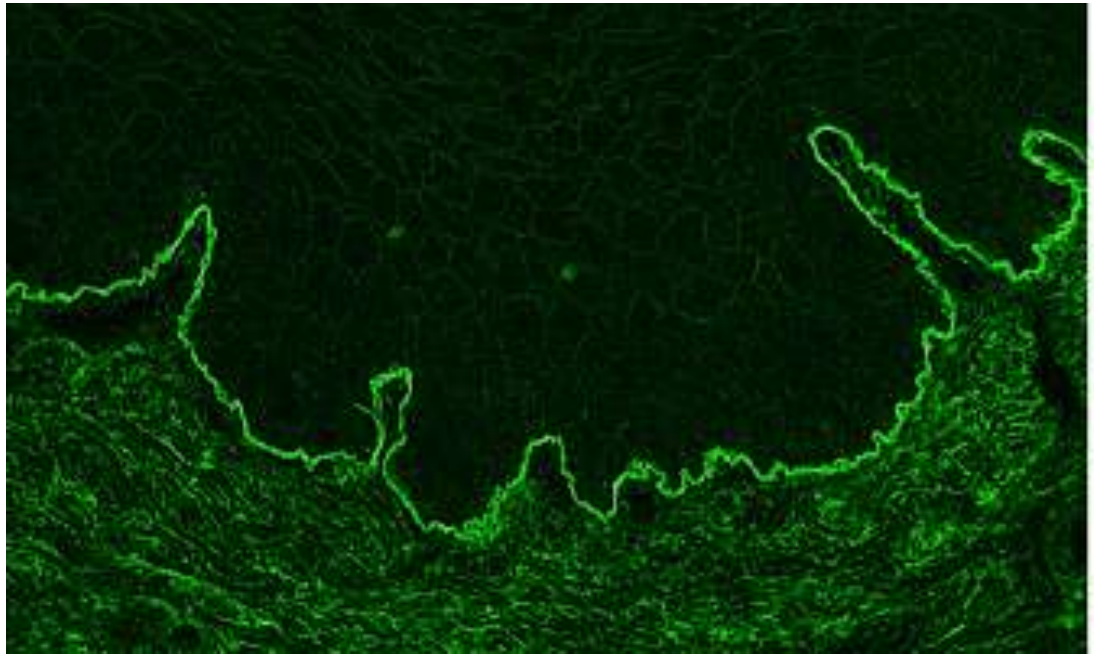
Presentation



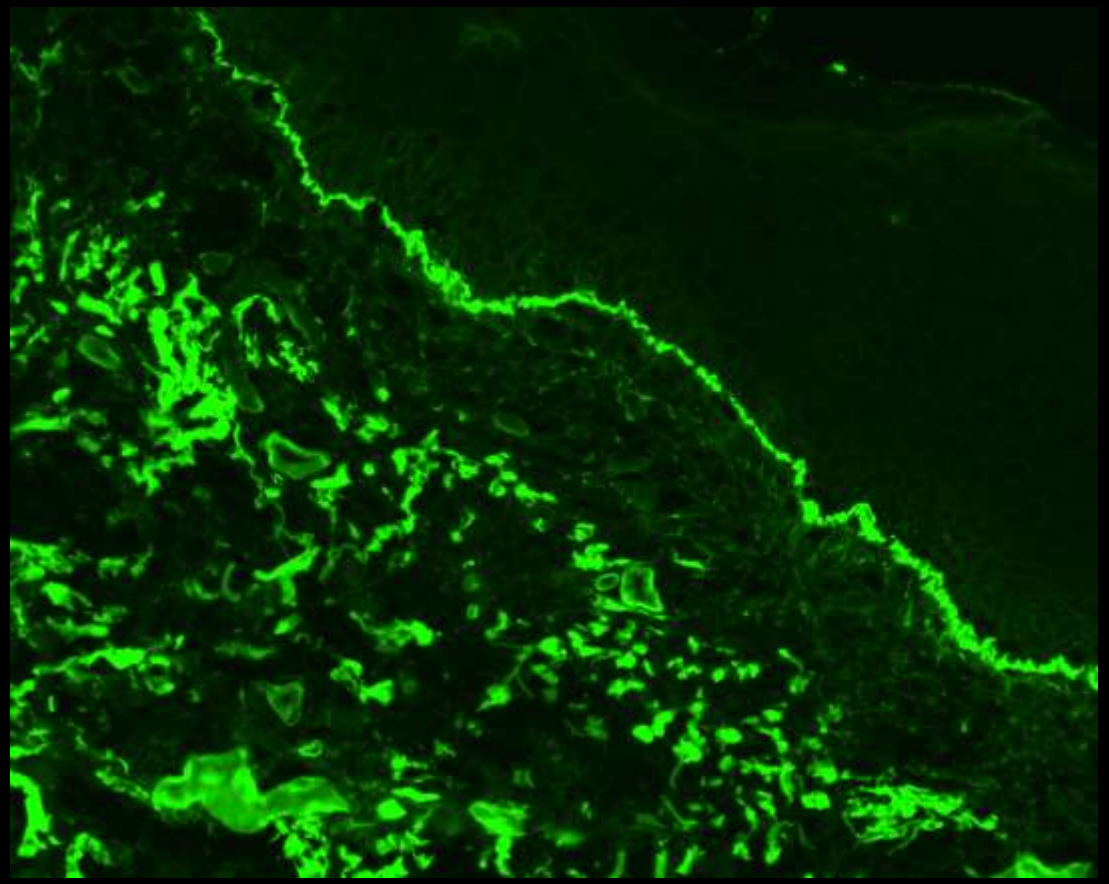
- Itch, particularly at night and affecting the back
- Persistent and worsening despite topical therapy initiated from GP, therefore referred to ED
- Multiple vesicles -> large bullae
- Eosinophilia at 0.78 $x10^9/L$
  - Later peaked at 2.19 $x10^9/L$
- Total serum IgE of 6,241kU/L

Disease specific laboratory findings

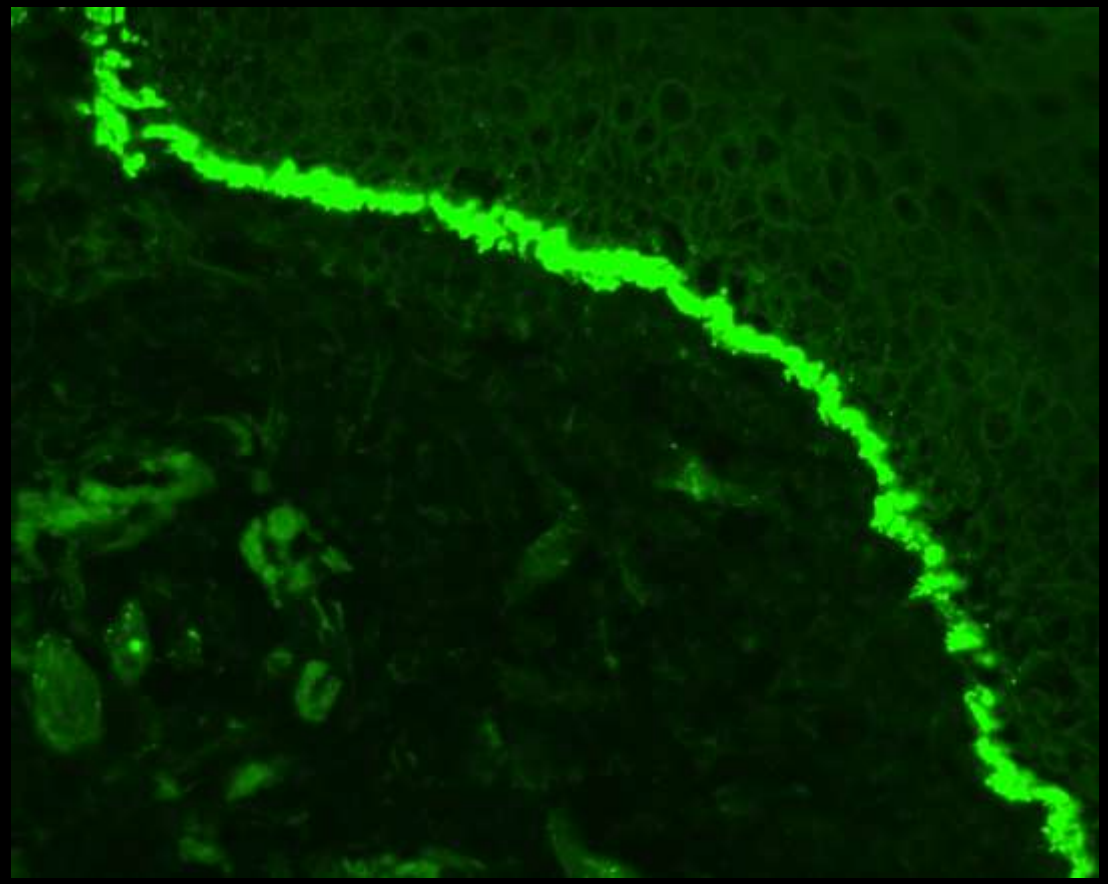
- Direct immunofluorescence of skin biopsy
  - Strong linear C3 and IgG at the dermo-epidermal junction
- Indirect immunofluorescence using monkey oesophagus
  - Strong positive junctional anti-skin antibodies
- Positive IgG anti-BP180 antibodies by ELISA



IgG



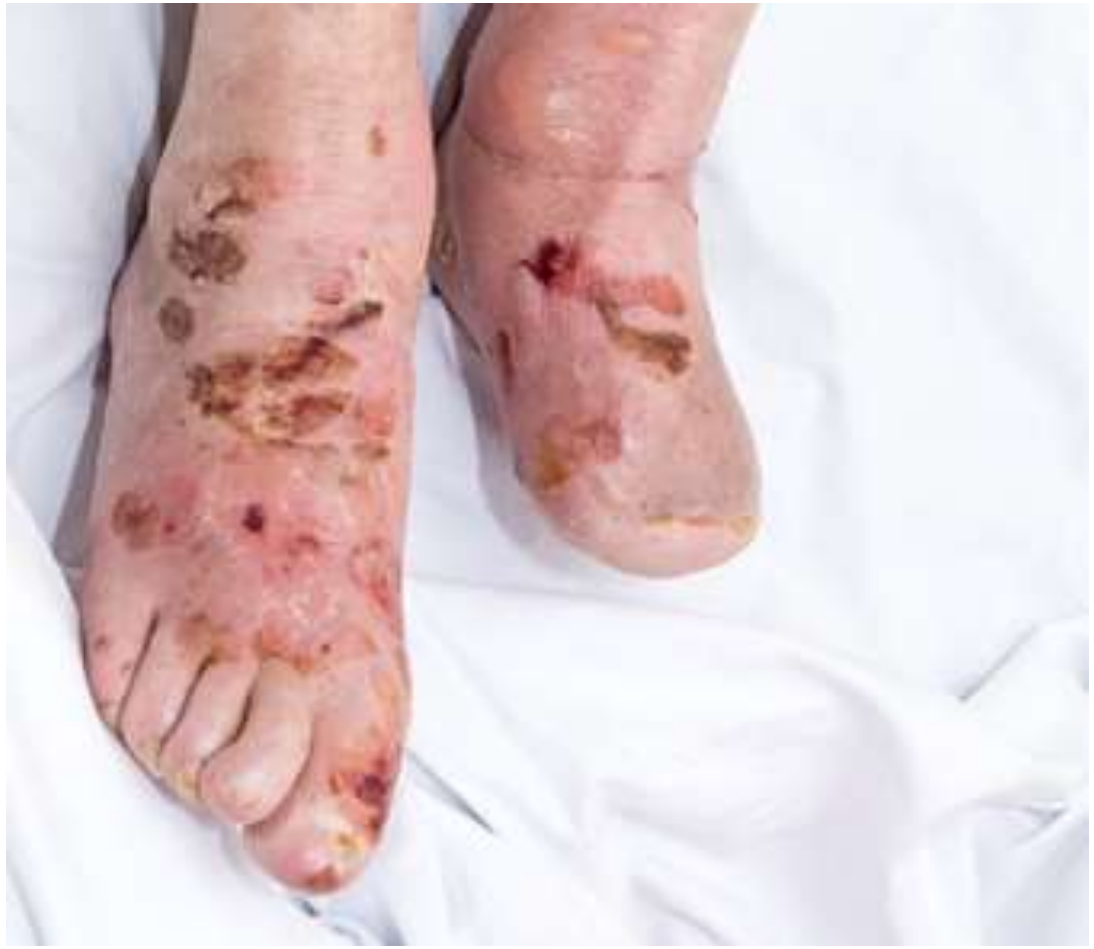
C3



Progress

- High dose oral prednisolone
  - Not able to be weaned with doxycycline, nicotinamide, topical corticosteroids
  - Diabetic control worsened
    - HbA1c 9.6 within 2 months
  - Forefoot amputation for non-healing ulcers
- IVIg
- Rituximab

Time to check the literature!

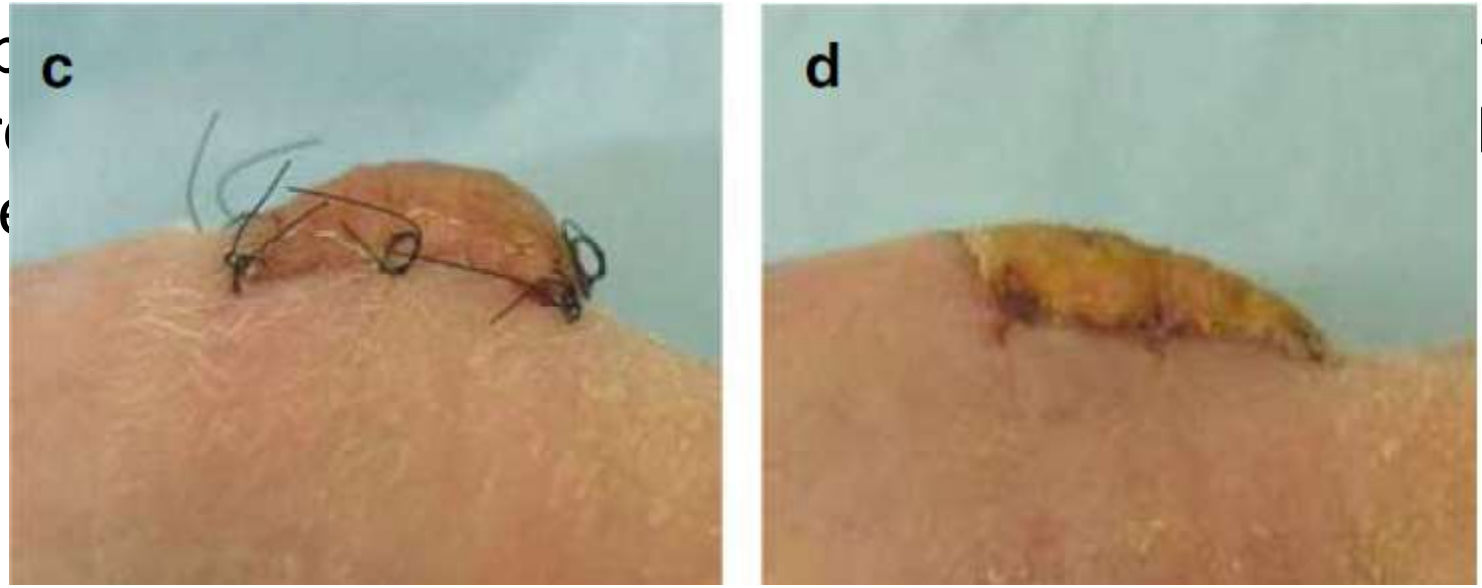


Experimental evidence for role of IgE

- Previously observed that total IgE levels elevated in 70% of untreated BP patients.
- 90% of these patients had IgE directed against BP180 antigen.
- Basophils from these patients would degranulate when exposed to recombinant BP180. [1,2]
- Mouse models using disease specific IgG did not replicate some of the disease features – urticarial plaques, blistering, eosinophil recruitment.

Experimental evidence for role of IgE

- First demonstration of pathogenicity of IgE antibodies:
- Injection of disease specific IgE (isolated from BP patients) in human skin grafted onto athymic mice resulted in urticarial plaques with histological separation of the epidermis. Eosinophil recruitment along with disease specific IgE also seen on degranulated mast cells. [3]
- Disease sp ocyte in vitro in pr BP pathogene

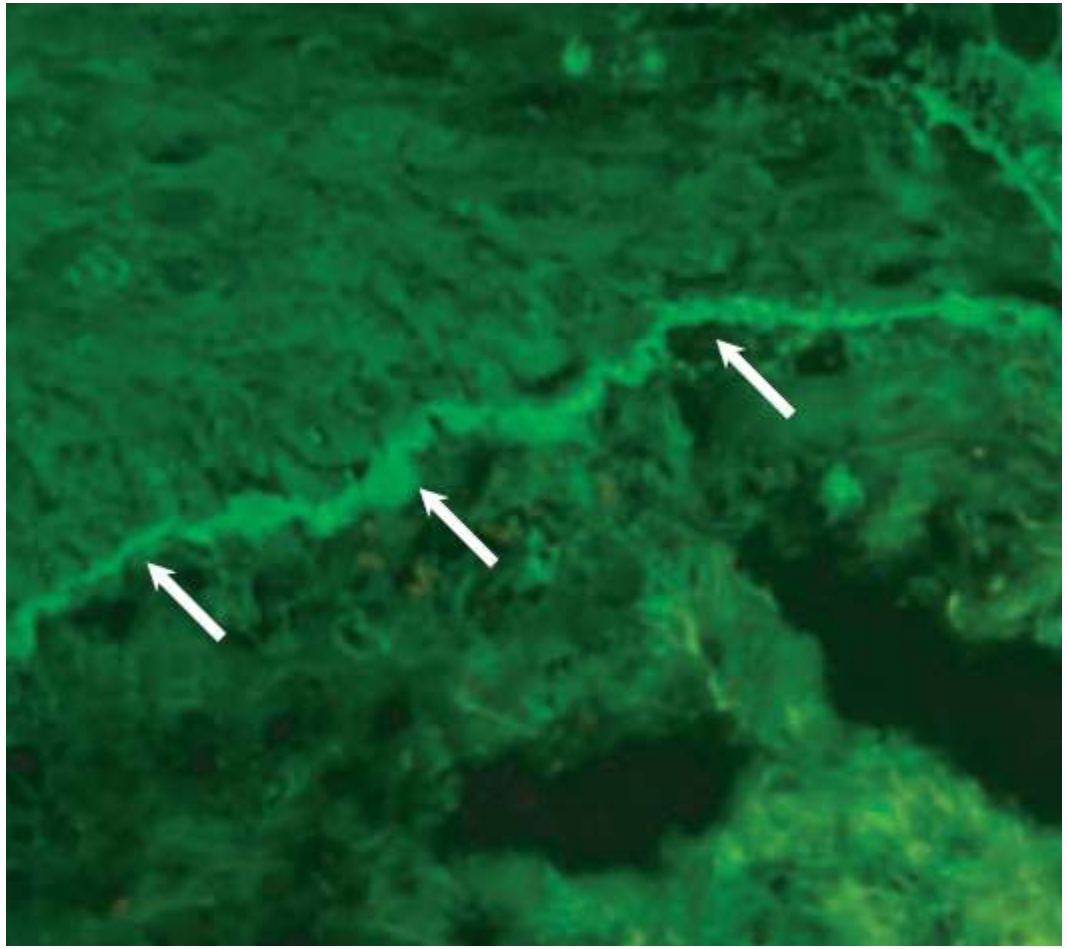


Experimental evidence for role of IgE

- Expression of high affinity IgE receptor, FcεRI, on peripheral and tissue eosinophils in patients with BP providing a potential mechanism for BP IgE. [5]
  - Eosinophil expression of FcεRI is minimal, does not activate eosinophils, and is of unclear functional significance. [6]
- Mouse model with human antigen used to demonstrate anti-hNC16a IgE purified from patients are pathogenic through their interaction with eosinophils that expressing human FcεR1. The effect was dependent on both hNC16a and eosinophils that express human FcεRI. [7]

Laboratory evidence for role of IgE

- Measurement of anti-NC16a IgE via ELISA in patients demonstrated [8]
  - i) better correlation with disease remission than disease specific IgG and
  - ii) doubled body surface area involvement if positive.
- Linear IgE demonstrated in 40% of biopsies of patients. [9]



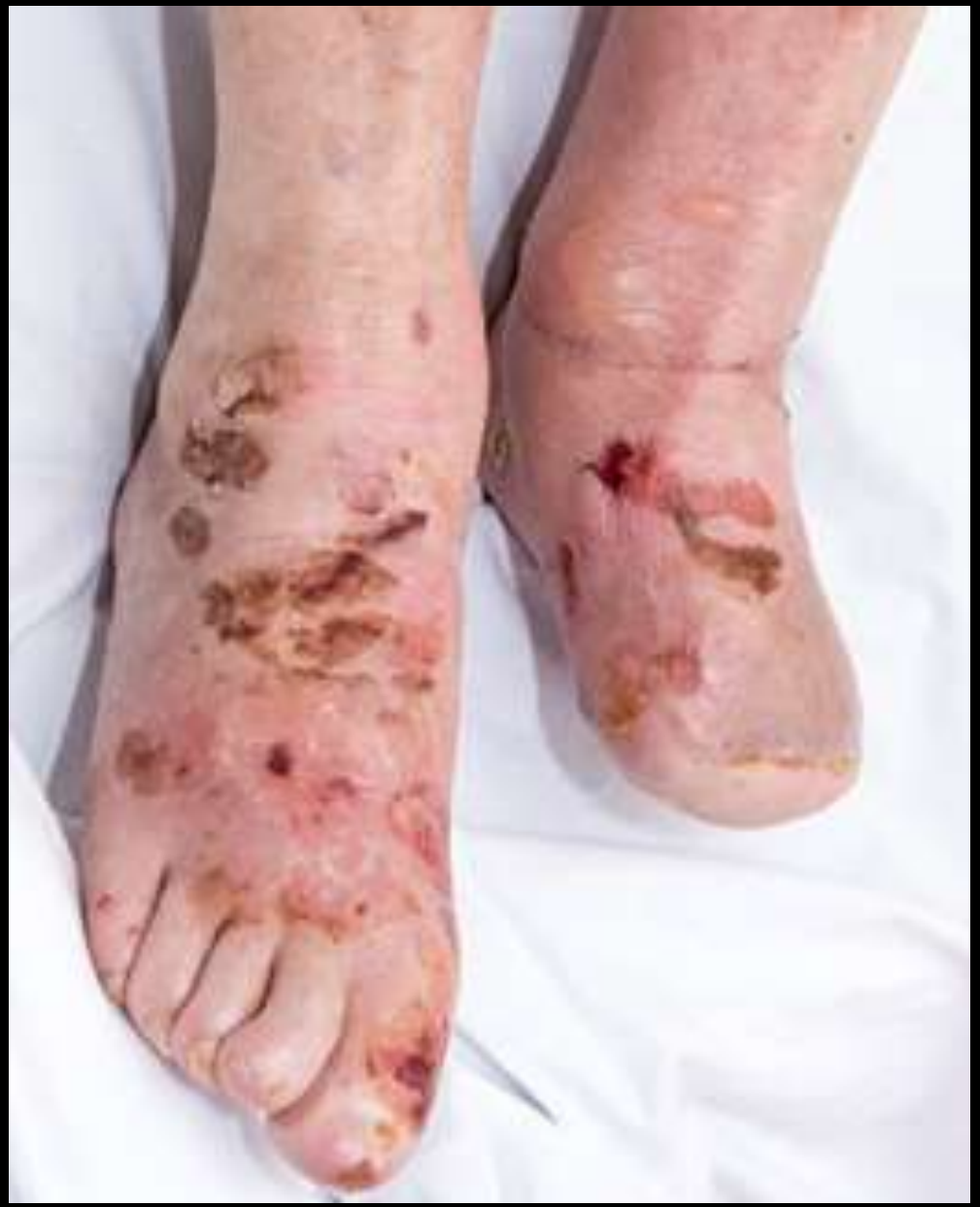
Clinical evidence for role of IgE

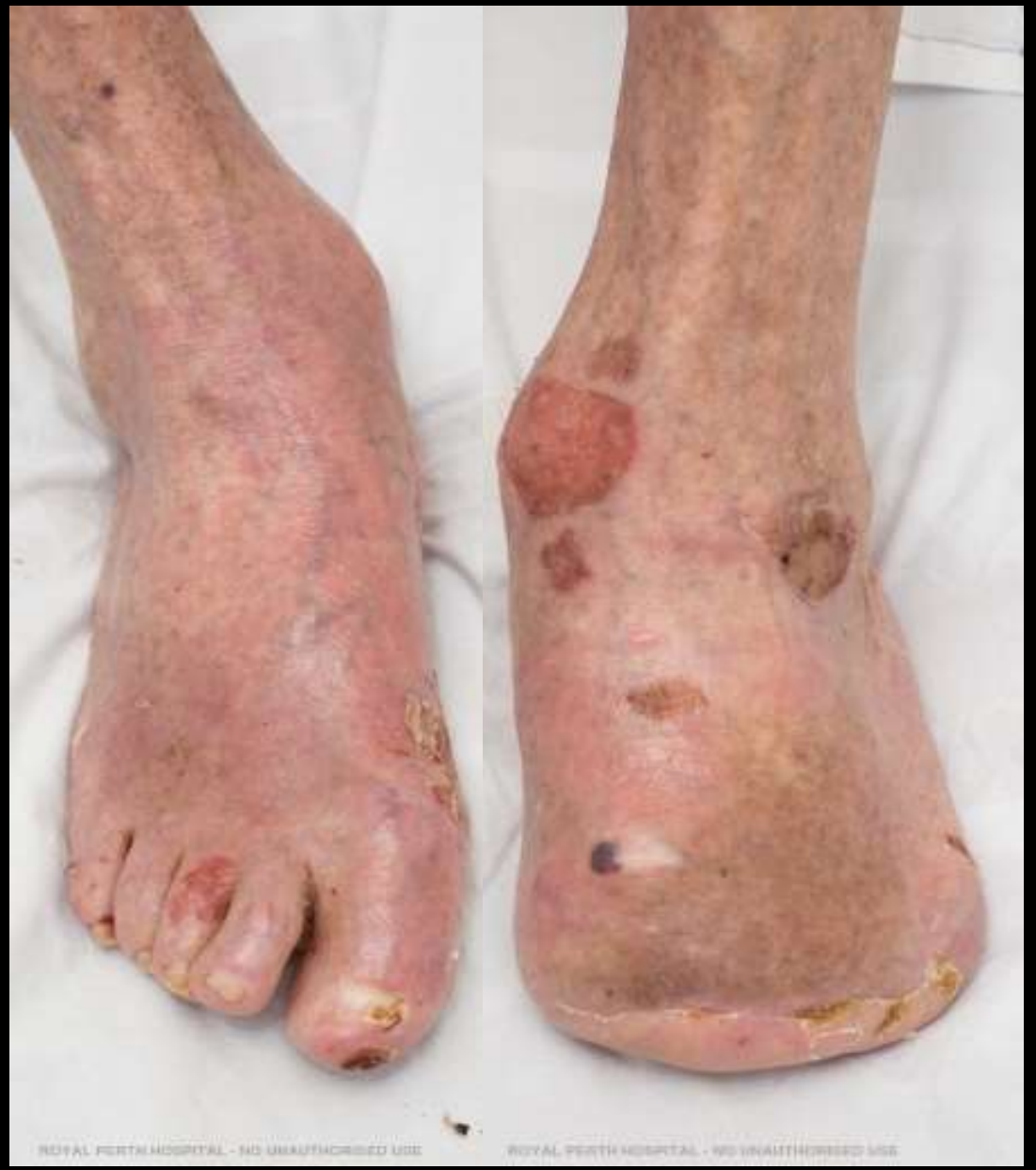
- Yu et al (2014) reported 6 patients with steroid refractory disease who received therapeutic benefit from anti-IgE treatment. [10]
  - Clinical improvement was rapid in all cases.
  - All able to stop steroid therapy within a few months.
- Another 2 cases reported in 2016 with similar clinical responses. [11]

- Back to our case – omalizumab instituted at 300mg every 4 weeks.

Progress

Time relative to first dose	Event
4 days	Resolution of pruritus and cessation of new bullae formation.
8 days	Resolutions of erythematous plaques surrounding bullae and initiation of wound healing.
2 weeks	Eosinophil count normalised and prednisolone was tapered.
3-4 weeks	Mild recurrence of mild pruritus and a few isolated blisters coincided with an increase in blood eosinophil count to 1.85x10*9/L, which subsequently resolved again with a second dose of omalizumab.

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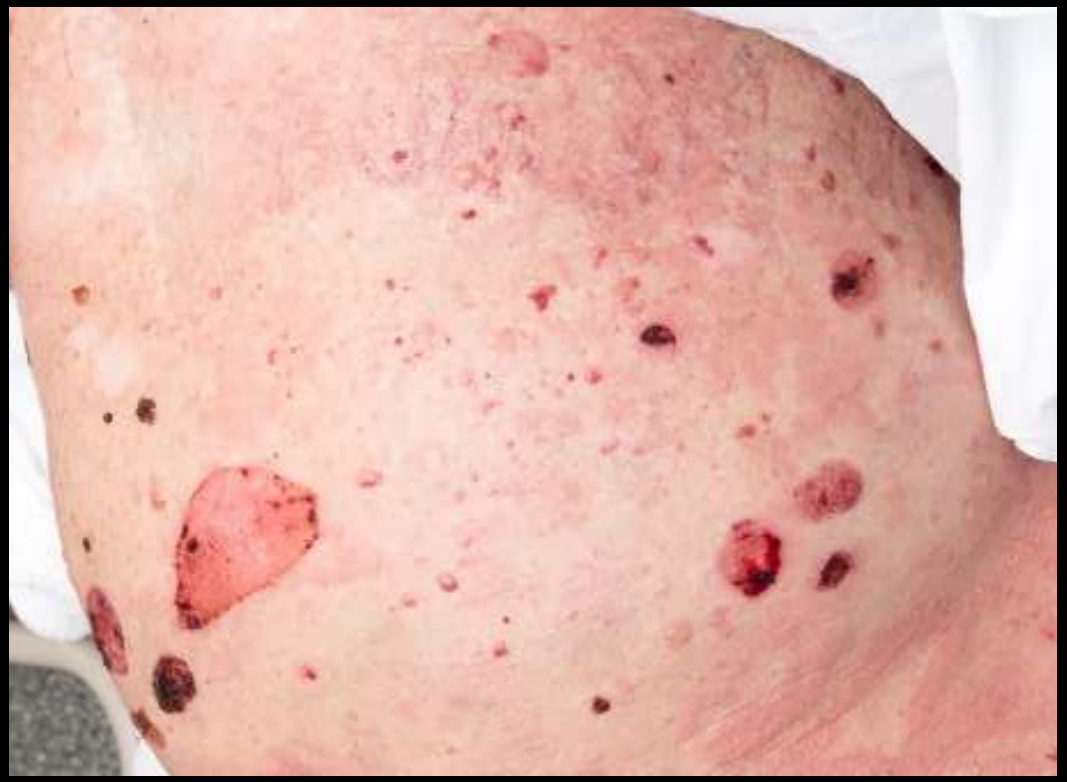
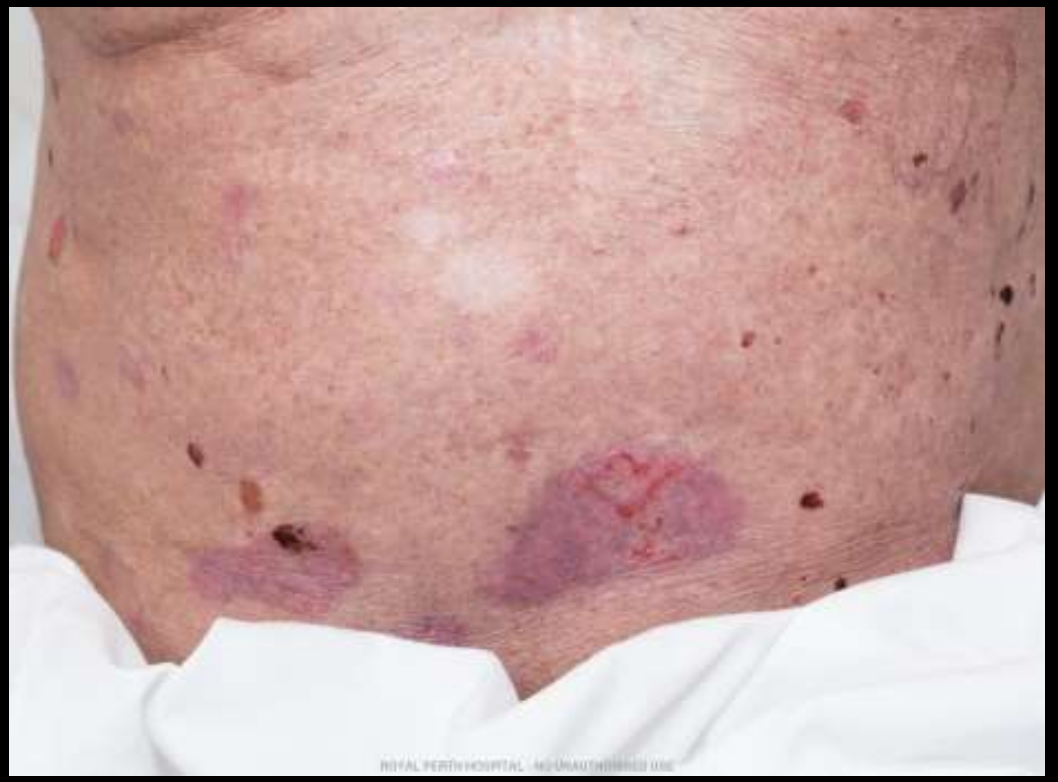




Outcome

- Ongoing disease control with 3 weekly injections
  - Corticosteroids weaned off completely

- Questions yet to be determined
  - Which laboratory test involving testing for IgE autoantibodies might support treatment decisions and/or monitoring in patients?
  - If there is value in detection of IgE autoantibodies above clinical phenotype + current testing (eosinophilia, total IgE)?

Other conditions with autoreactive IgE

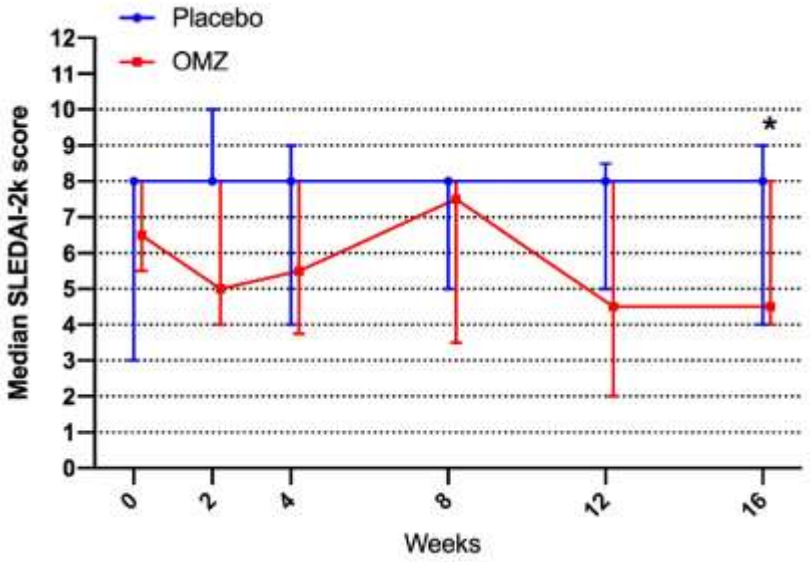
Disease	Antigenic target
Systemic lupus erythematosis	dsDNA, SS-A, Smith
Chronic Spontaneous Urticaria	dsDNA, thyroglobulin, thyroid peroxidase
Uveitis	Retinal S antigen
Rheumatoid Arthritis	Granulocyte- and organ-specific nuclear targets
Mothers with foetal loss	SS-A
Thyroid disease	Thyroid peroxidase
Multiple Sclerosis	myelin-derived peptides

Adapted from [12]

Very early data in SLE

Phase 1b exploratory study [13]

- 15 patients with active SLE with known autoreactive IgE antibodies
- Randomised (2:1) to anti-IgE (omalizumab) or placebo for 16 weeks
- Significant improvement in disease activity scores, although clinical significance questionable.
- Limitations include
  - Small number of patients
  - Mild clinical disease



Thanks for your attention

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DIF IgE