Clinical Vignettes in Allergy and Clinical Immunology

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(No disclosures)

Learning objectives

Case # 1.

Recognize a common **cutaneous disease**, differentiate systemic causes from pure cutaneous involvement, rationale for ordering lab tests and approaches to treatment.

Case # 2.

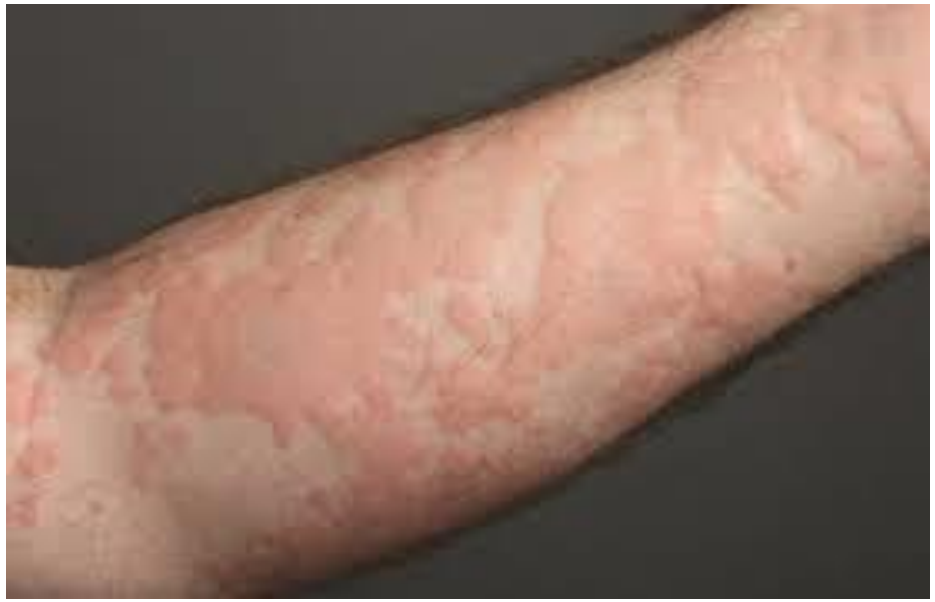
Diagnosis, clinical association, evaluation and management of a patient with **Selective IgA deficiency.**

Case # 3.

Role of Serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE) and serum free light chains in the **diagnoses of B cell monoclonal gammopathies**.

Case # 1

- A 30 year male, noted red , raised, itchy lesions over his torso, arms and legs. They waxed and waned , migrating to different parts of the body. He tried cold showers, hot showers, used his HEPA air filter with no relief. Lotions and creams helped a bit. This persisted for 3 weeks, he avoided sea foods, nuts but the rash got worse. Took Benadryl on and off with minimal relief (but felt very tired and sleepy). A severe episode at week 7 interfered with his life style. He consulted his PCP who captured the rash (see below). PCP remarked that review of systems was normal.



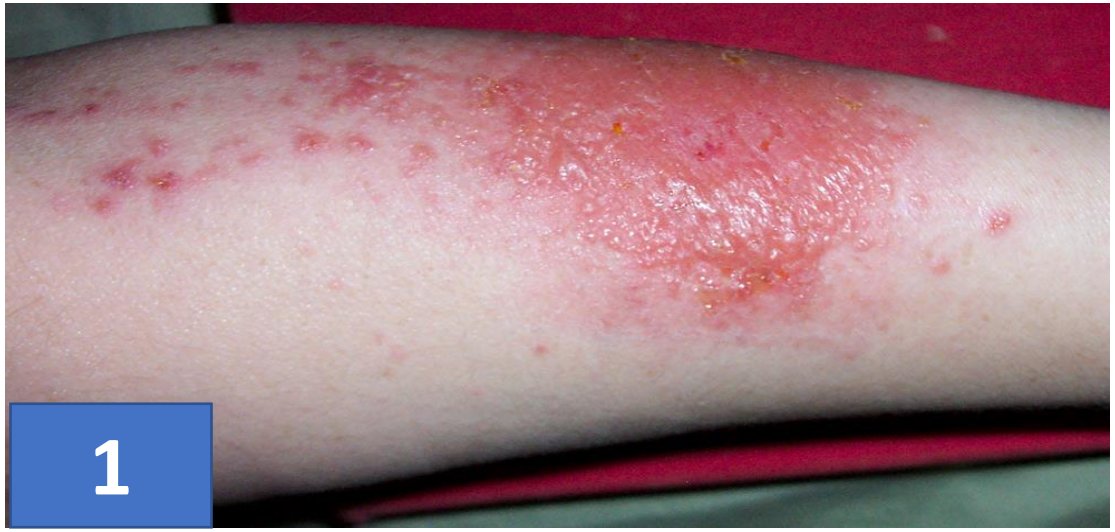
Examination revealed normal vital signs. No lymphadenopathy. No clubbing. No synovitis, arthritis, ecchymosis, pigmentary lesions or skin atrophy. He noted some excoriations from scratching. The chest, abdomen, and joints were normal. No focal neurological deficits.

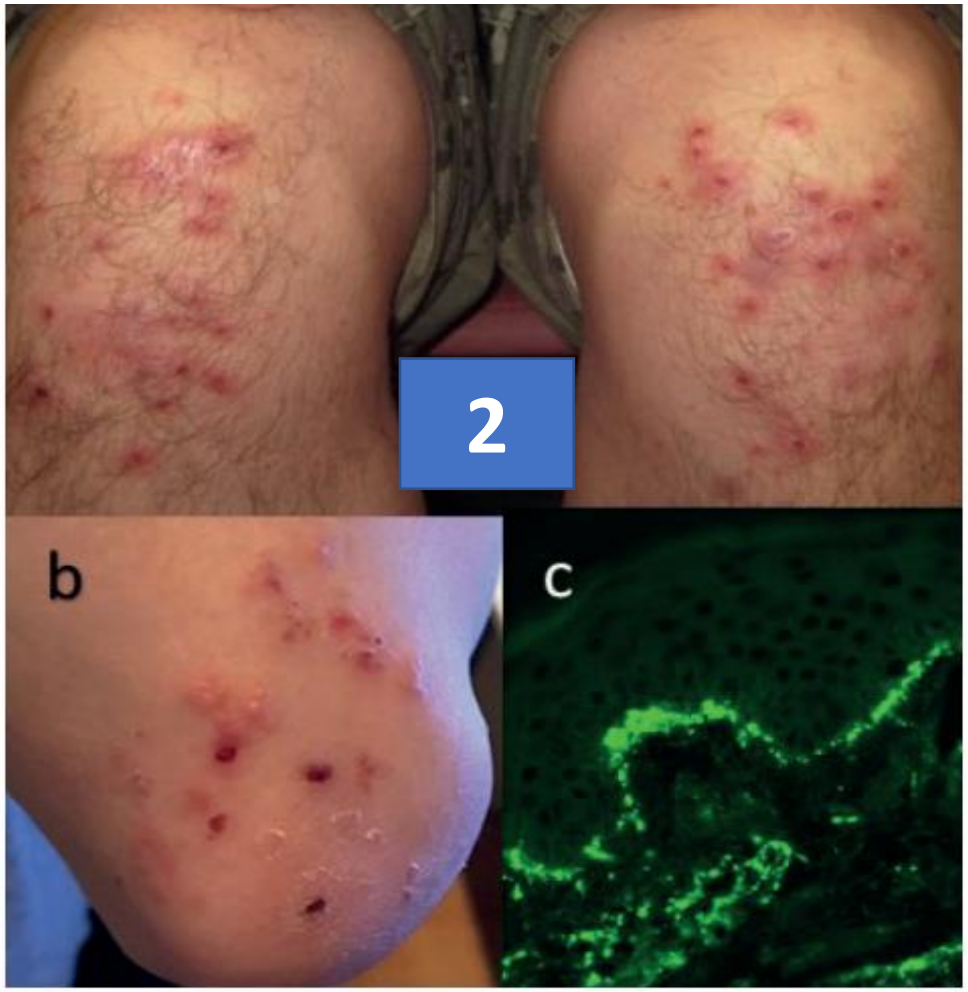
Case # 1 … Continued

Q 1. What is the most likely diagnosis?

a) Allergic contact dermatitis
b) Chronic spontaneous urticaria (chronic idiopathic urticaria)
c) Cutaneous urticarial vasculitis
d) Dermatitis herpetiformis
e) Systemic mastocytosis

Q2. Picture 1 depicts and Picture 2 represents…?



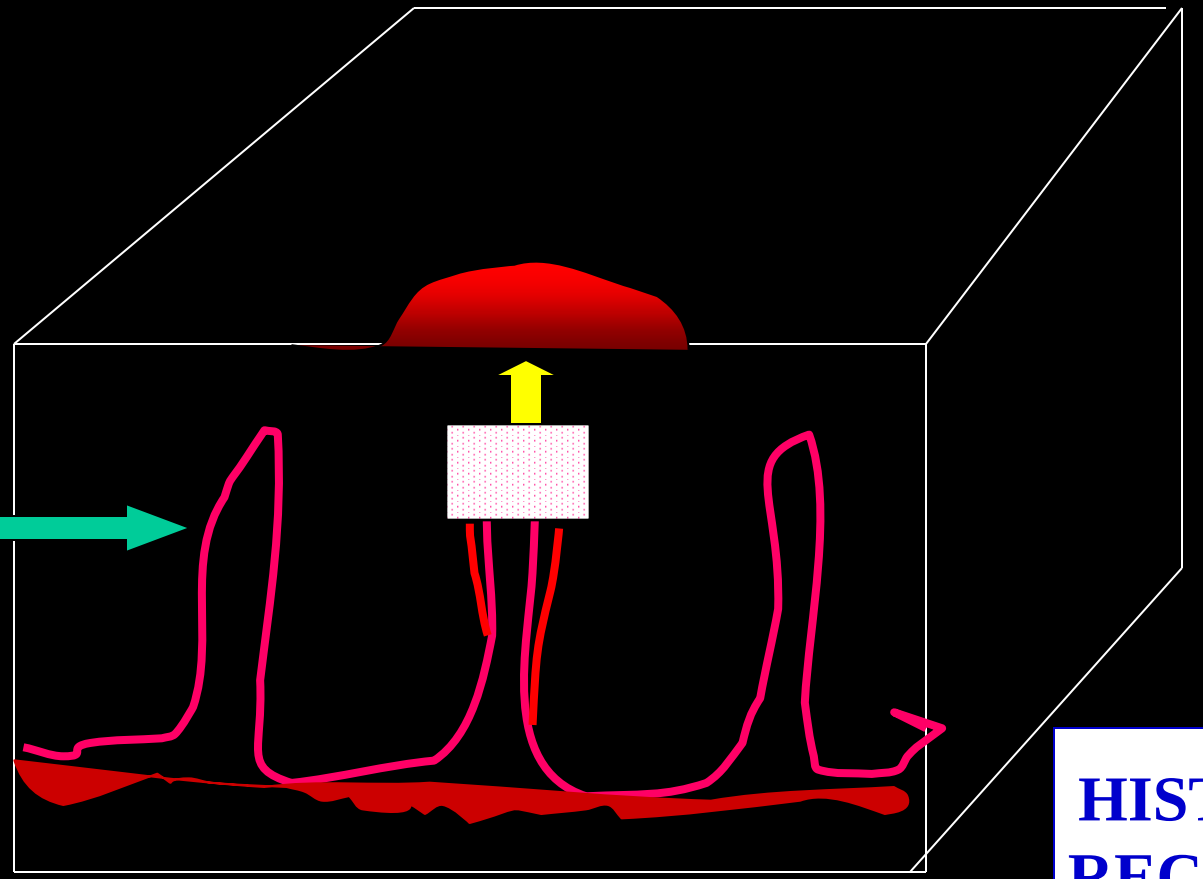


A) Allergic contact dermatitis
B) Chronic spontaneous urticaria (chronic idiopathic urticaria)
C) Cutaneous urticarial vasculitis
D) Dermatitis herpetiformis
E) Systemic mastocytosis

Case # 1 : Genesis of Hives or Urticaria

SUPERFICIAL PLEXUS = HIVES

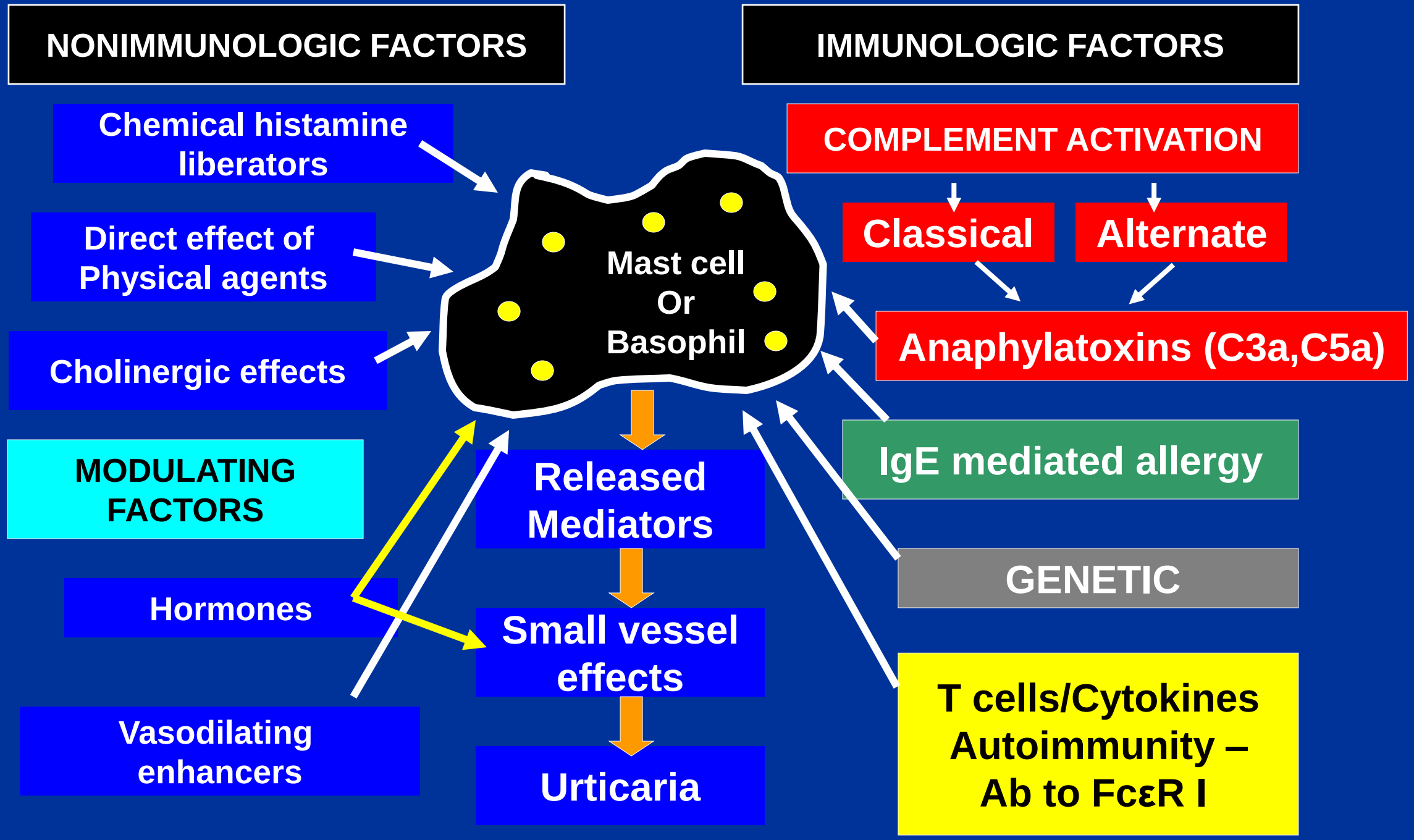
DEEP PLEXUS = ANGIOEDEMA



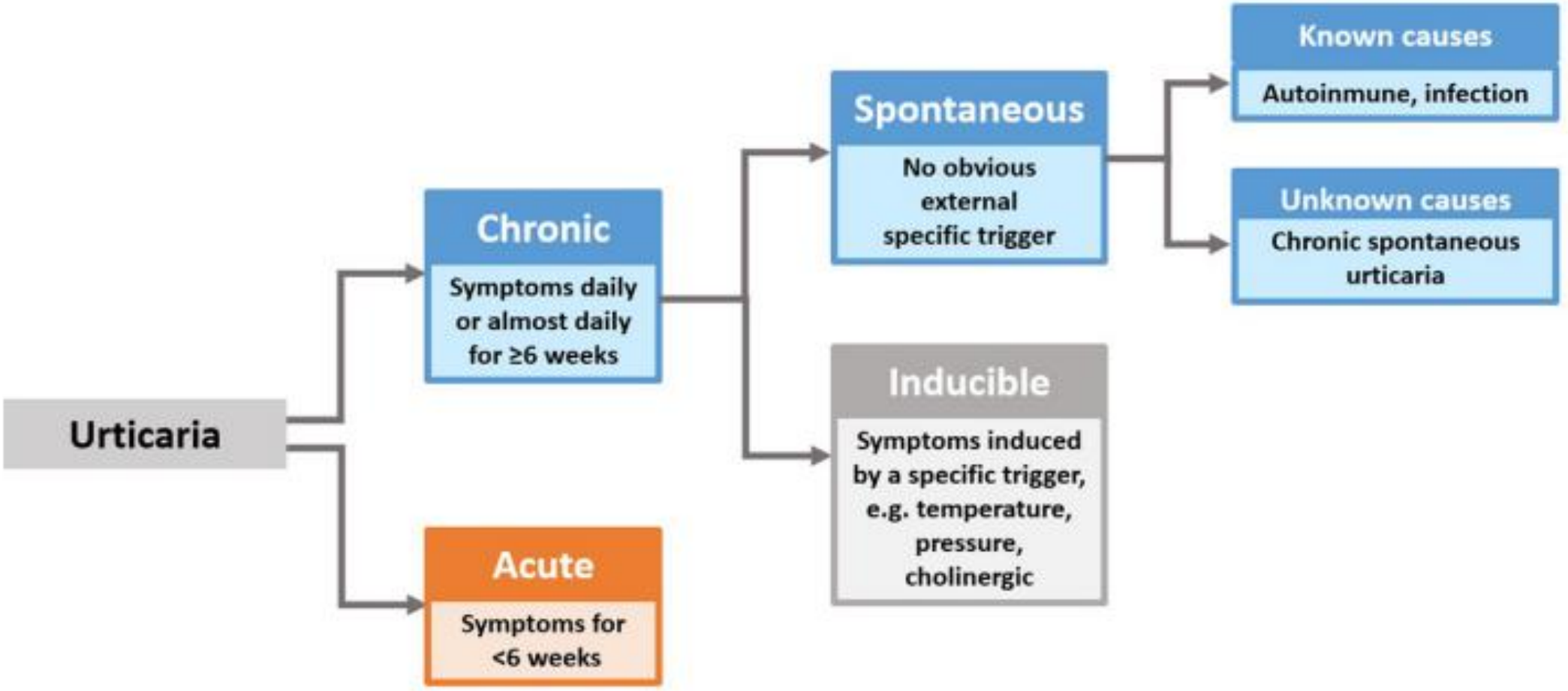
HISTAMINE RECEPTORS

H 1 = 85%

H 2 = 15%


NONIMMUNOLOGIC FACTORS
IMMUNOLOGIC FACTORS
Chemical histamine liberators
Direct effect of Physical agents
Cholinergic effects
MODULATING FACTORS
Hormones
Vasodilating enhancers
Mast cell Or Basophil
Released Mediators
Small vessel effects
Urticaria
COMPLEMENT ACTIVATION
Classical
Alternate
Anaphylatoxins (C3a,C5a)
IgE mediated allergy
GENETIC
T cells/Cytokines Autoimmunity – Ab to FcεR I

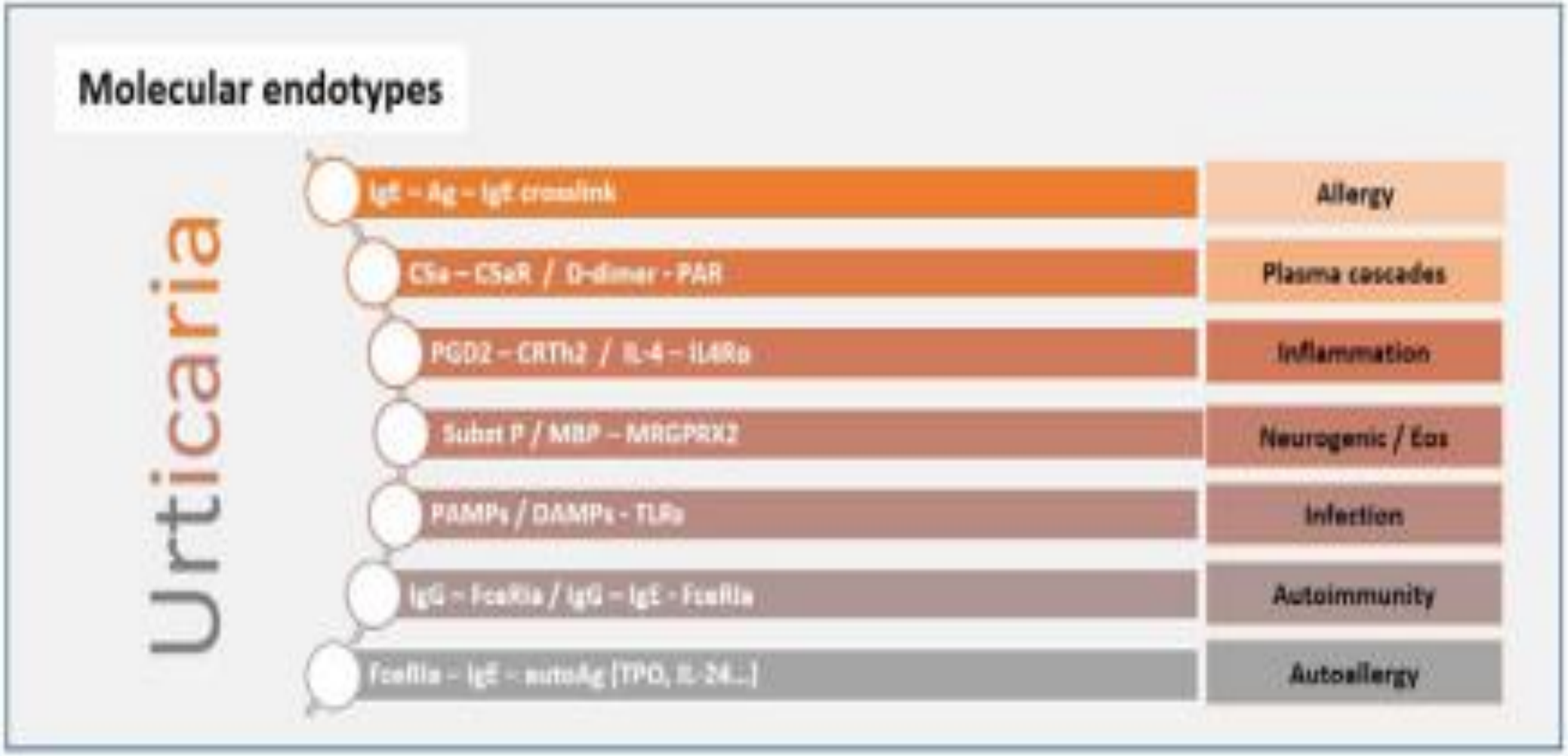
Classification of urticaria



Sánchez-Borges et al. World Allergy Organization Journal (2021) 14:100533

Clinical approach to urticaria

Molecular mechanisms or endotypes



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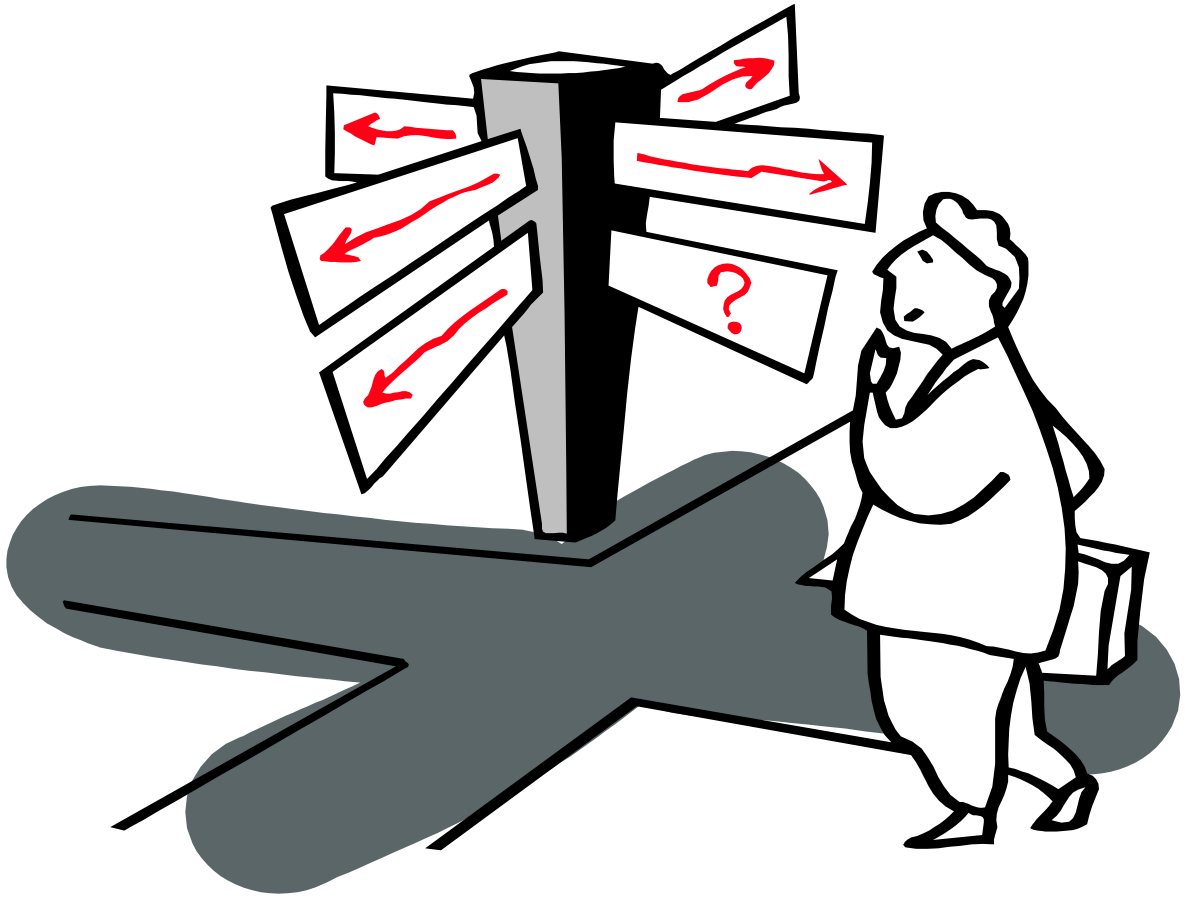
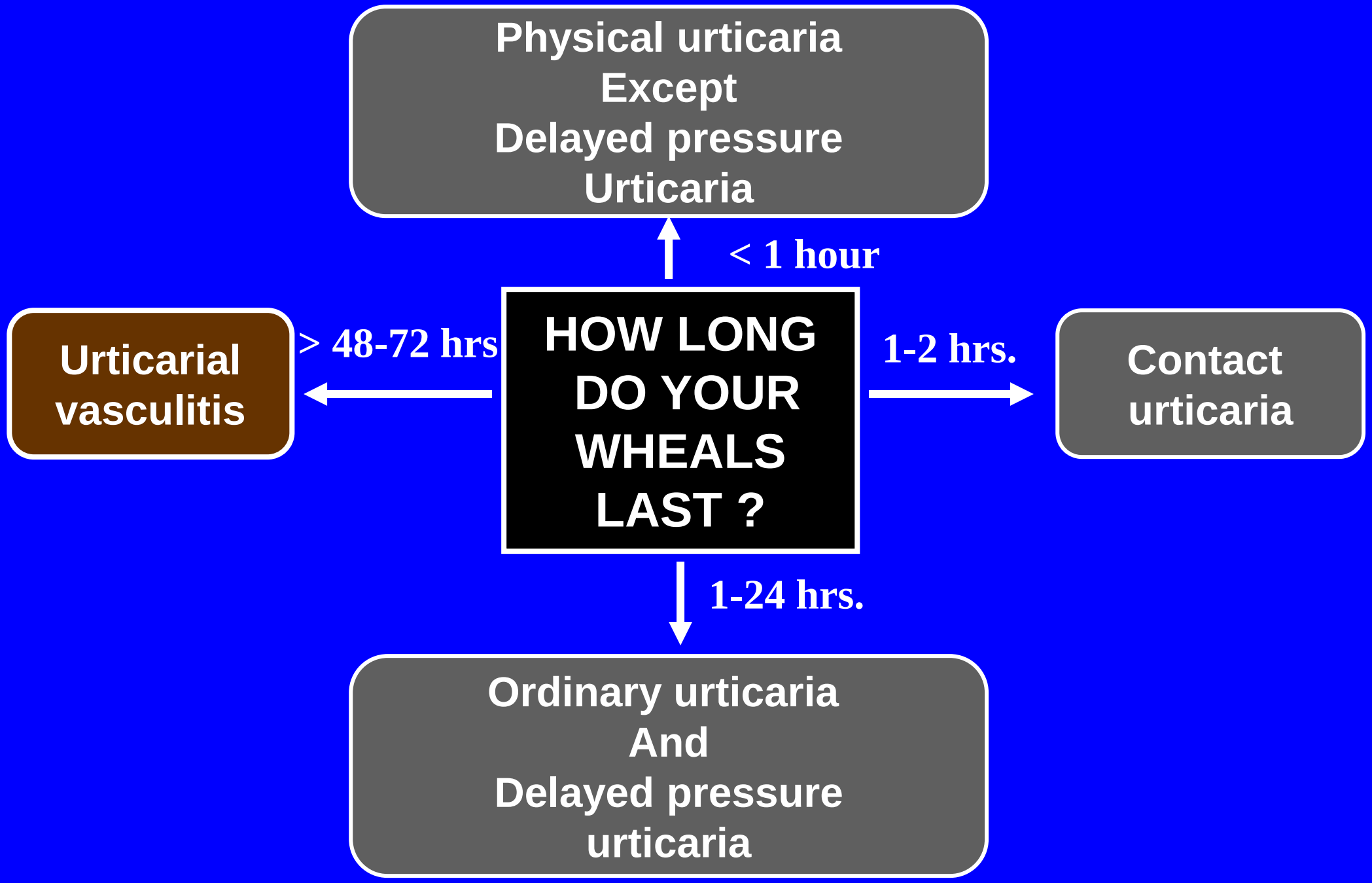
Case # 1 - Clues to diagnosis of Urticaria

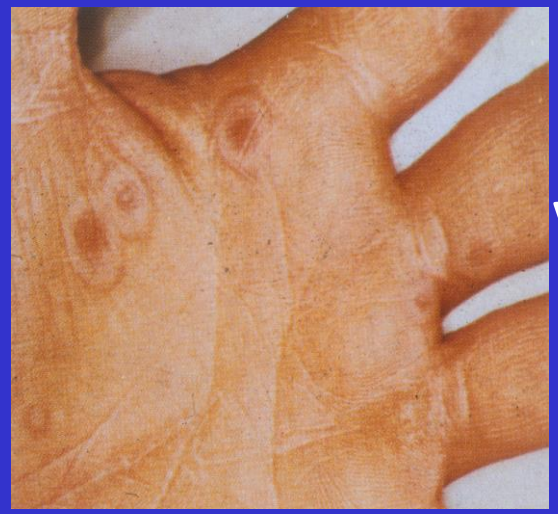
Duration of individual hives




Physical urticaria
Except
Delayed pressure
Urticaria
< 1 hour
Urticarial
vasculitis
> 48-72 hrs
HOW LONG
DO YOUR
WHEALS
LAST ?
1-2 hrs.
Contact
urticaria
1-24 hrs.
Ordinary urticaria
And
Delayed pressure
urticaria

URTICARIAL VASCULITIS

Distinctive dermatological features



Persistence - Wheals > 48 hours

Pigmentation or target lesions

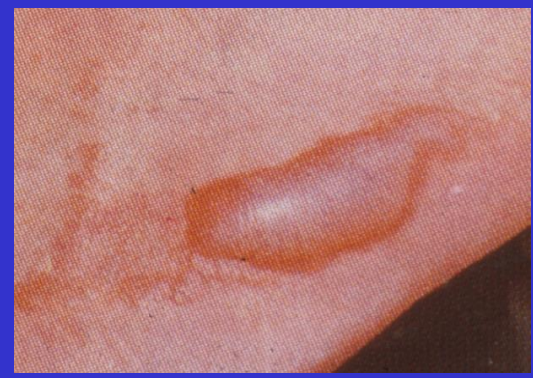
Palpable purpura

Vesiculation and bullae

Induration

Necrosis

Exfoliation



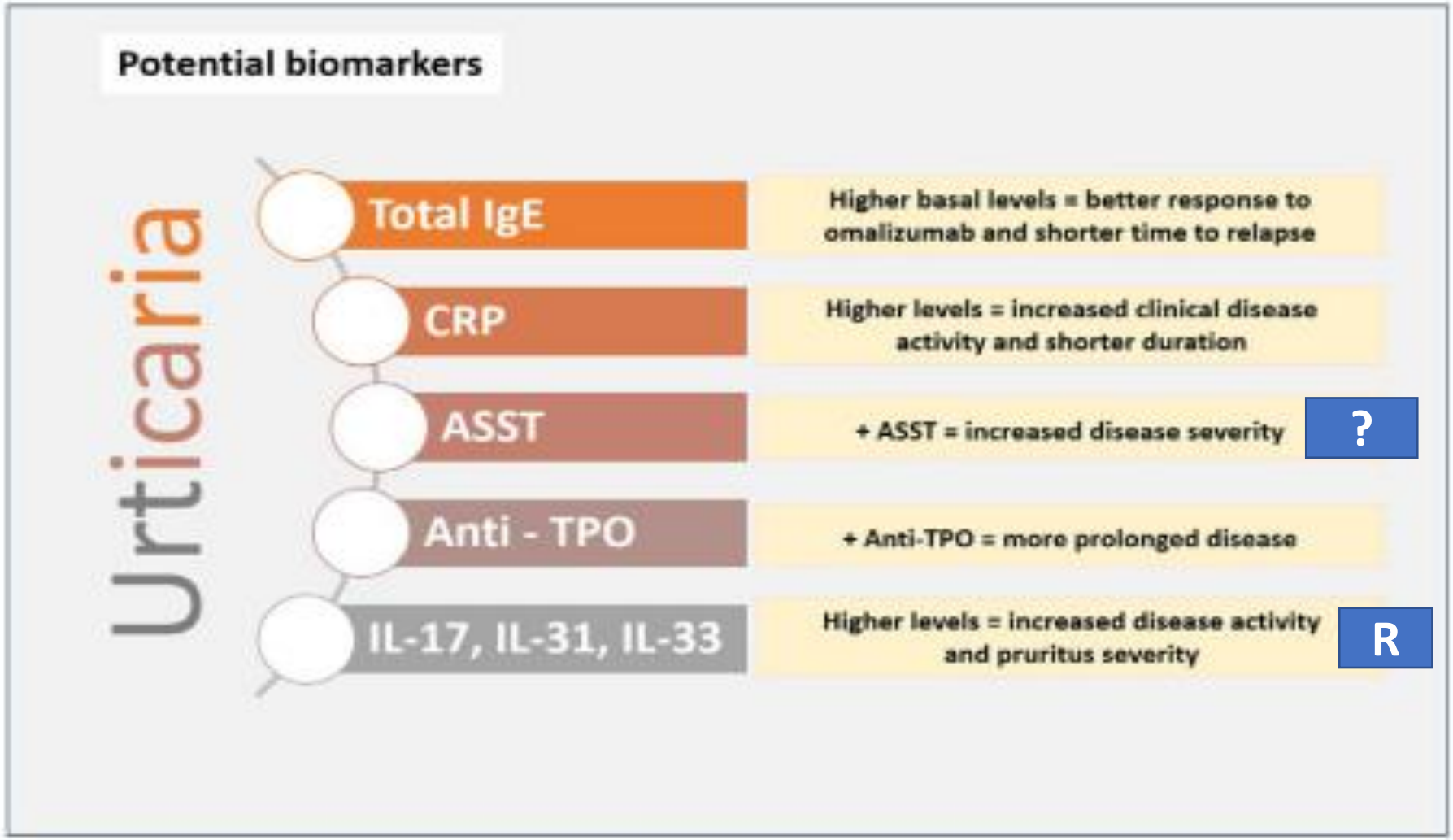
WITH OR WITHOUT SYSTEMIC FEATURES :

Fever, Arthritis, Lymphadenopathy

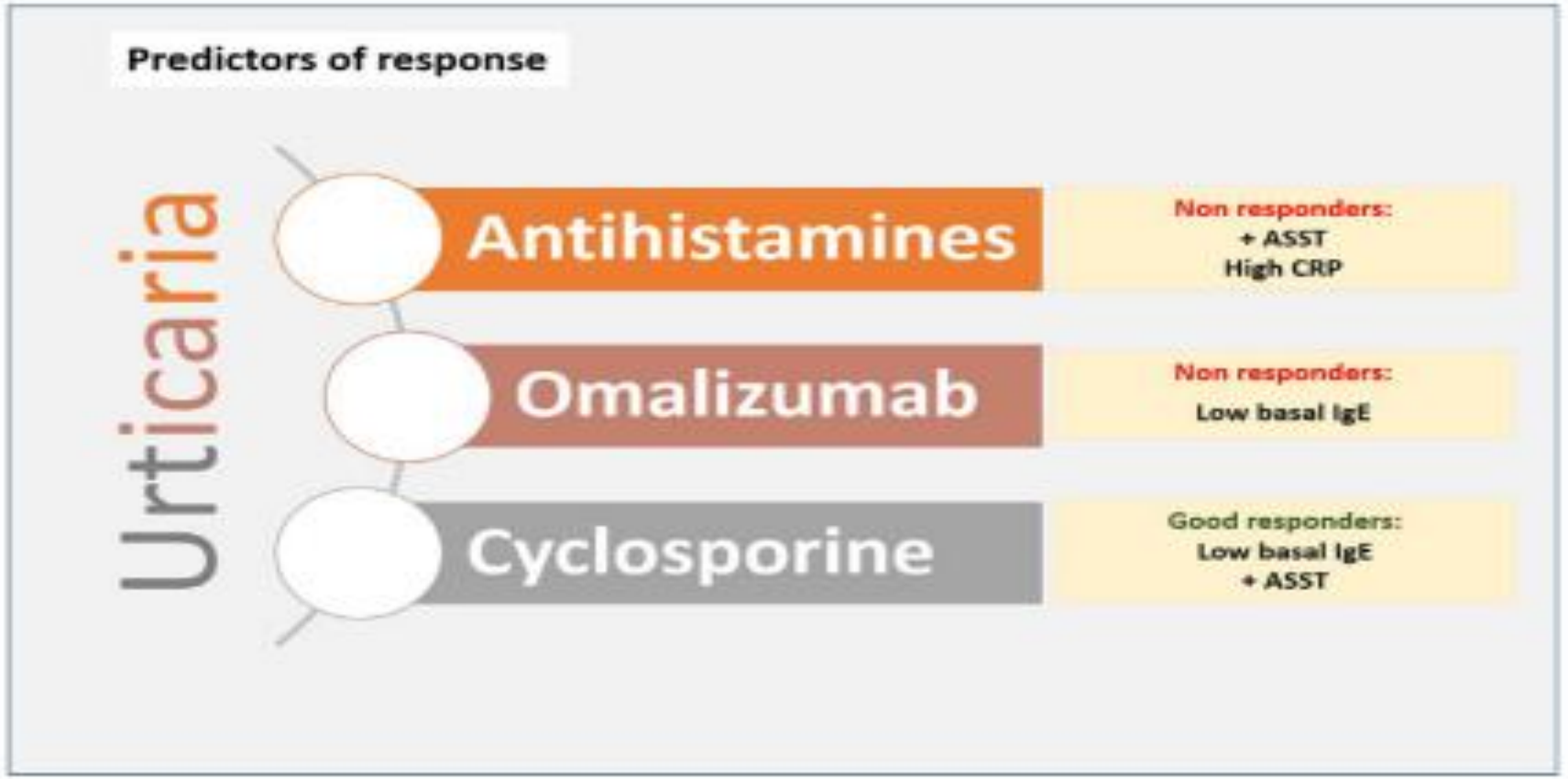
Laboratory Evaluation of Urticarial Syndrome

- Urinalysis
- 24 hour urine for protein and creatinine clearance
- **CBC with diff., ESR and CRP (CSU)**
- Comprehensive metabolic panel
- Serum protein electrophoresis
- C3, C4 and CH50
- Hepatitis B and C antigen
- **Total IgE, TSH, anti-TPO (CSU)**
- Cryoglobulins
- ANA, ENA and ANCA
- Skin biopsy.

Potential Biomarkers for Chronic Spontaneous Urticaria



Biomarkers as predictors of response in CSU



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Therapeutic guidelines

	The EAACI/WAO Guideline	The AAAAI/ACAAI Guideline
Basic treatment: Avoidance of triggers and relevant physical factors if physical urticaria/angioedema is present.		
STEP 1	Monotherapy with sgAH	Monotherapy with sgAH
	If inadequate control: After 2-4 weeks or earlier, if symptoms are intolerable	assess for patient's tolerance and efficacy
STEP 2	Increase sgAH dose (up to 4x)	One or more of the following: - Dose advancement of sgAH used in Step 1 - Add another sgAH - Add H_2-antagonist - Add LTRA - Add fgAH to be taken at bedtime
	If inadequate control: After 2-4 weeks or earlier, if symptoms are intolerable	assess for patient's tolerance and efficacy
STEP 3	Add on to sgAH: Omalizumab	Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated
	If inadequate control: Within 6 months or earlier, if symptoms are intolerable	assess for patient's tolerance and efficacy
STEP 4	Add on to sgAH: Ciclosporin*	Add an alternative agent - Omalizumab or cyclosporine* - other anti-inflammatory agents, immunosuppressants, or biologics

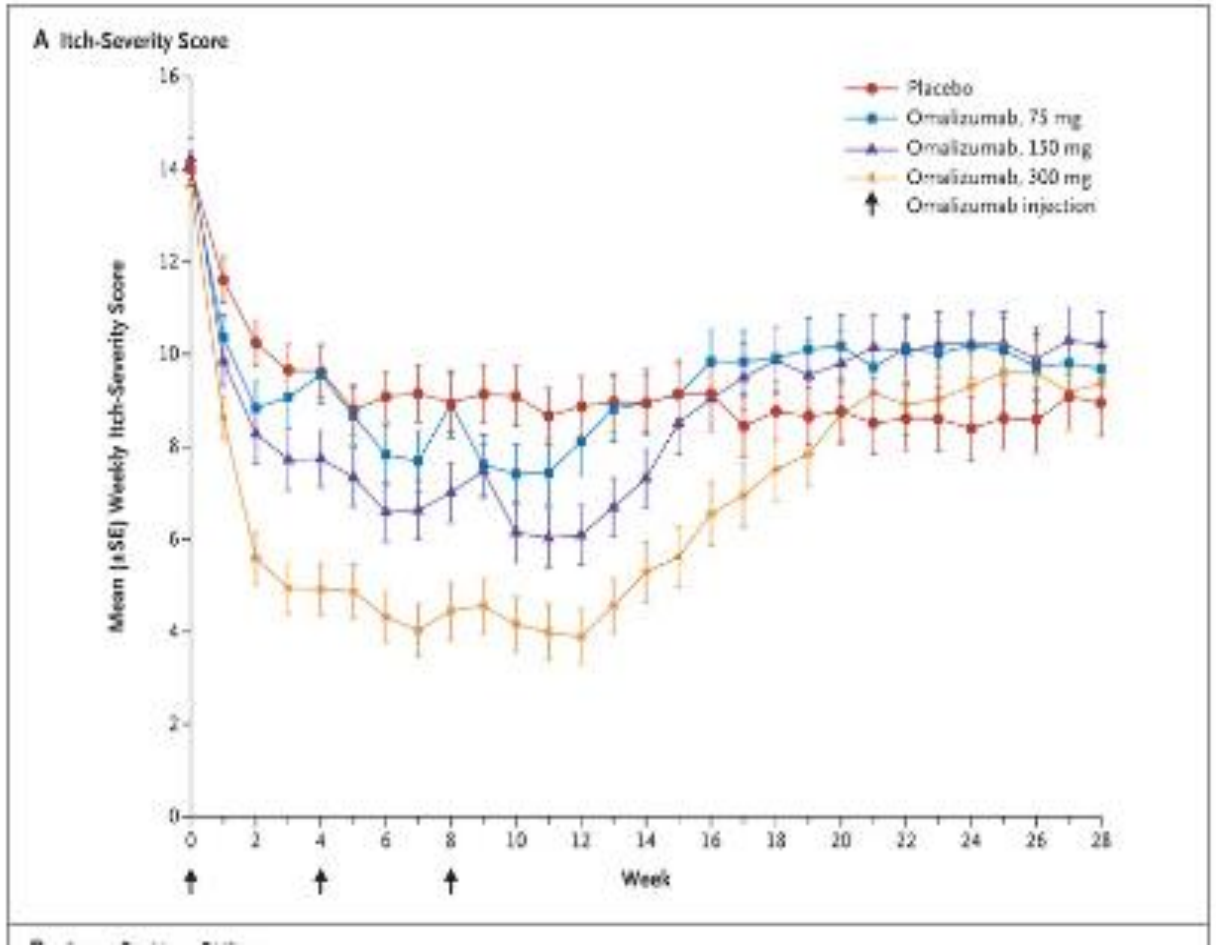
Follow up care for case #1

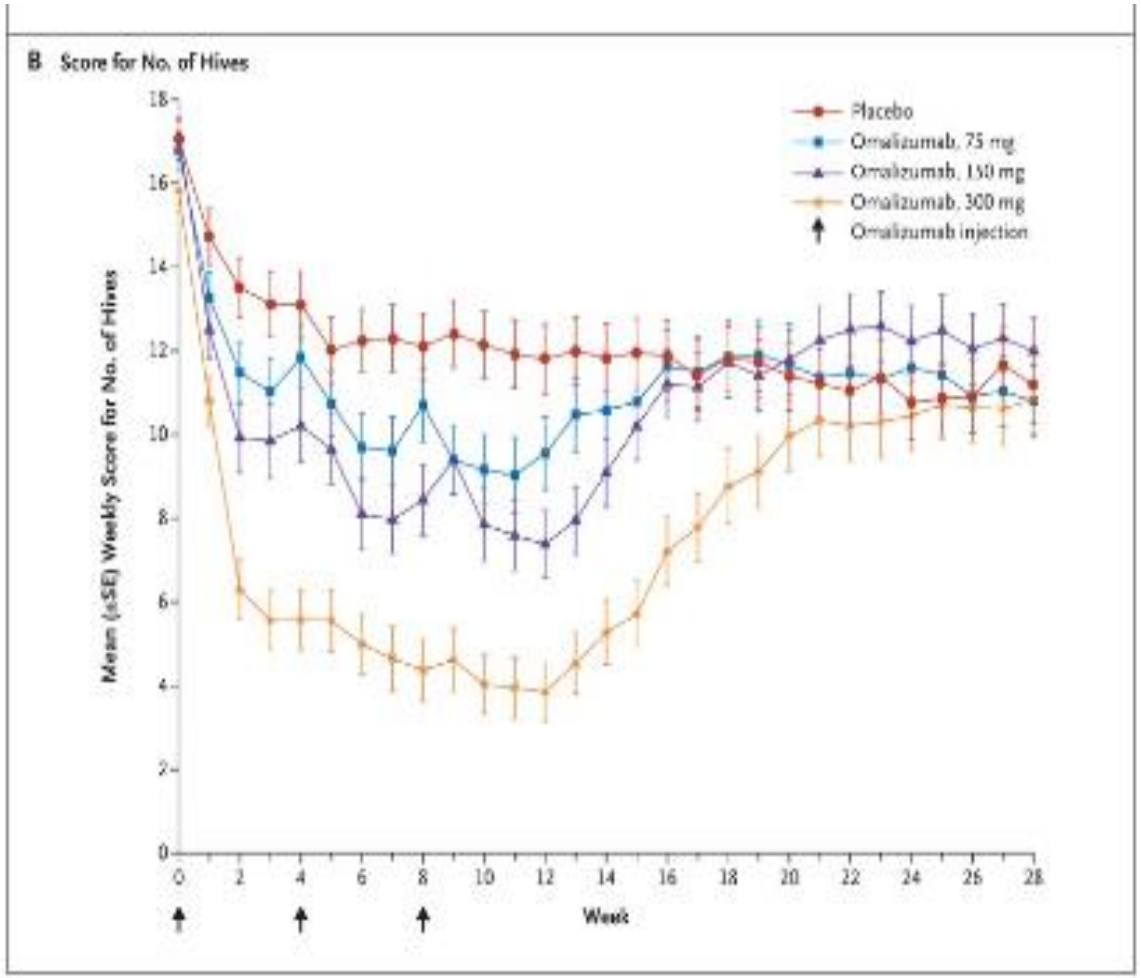
- Despite 360 mg of fexofenadine in AM, 20 mg of cetirizine in PM and again at night the hives were persistent and QOL poor after 3 weeks. The **TPO Ab was positive**. He was euthyroid. ESR and CRP normal. Total IgE increased **410 I.U.** Skin biopsy revealed perivascular **lymphocytes,** sparse eosinophils.

Q 3. The treatment of choice at this stage will be

A. Add a H2 blocker bid and hydroxyzine 50 mg at night
B. Consider cyclosporin 2.5 to 4mg/Kg to above regimen
C. Prednisone 40mg daily for 7 days and taper over 4 weeks to above Rx
D. Consider sulphasalazine or Dapsone
E. Consider anti - IgE monoclonal antibody – Omalizumab

Omalizumab in chronic spontaneous urticaria





N Engl J Med 2013; 368:924-935

Case # 2

- A 27 year old Caucasian research scientist, working on a murine model of arthritis, presents with an upper respiratory tract infection that escalated to acute purulent bacterial sinusitis that responded to nasal lavage and antibiotics.
- Past history was significant for chronic, allergic rhino-sinusitis poorly controlled on nasal fluticasone and antihistamines. He avoids wheat products as he notices abdominal bloating and at times loose stools.
- Exam revealed pale, violaceous nasal mucosa, prominent turbinates and possible nasal polyps. No lymphadenopathy. Normal tonsils. Has vitiligo over the chest. Cardiac, pulmonary, abdominal, musculoskeletal and neurological exam were normal. The chest X ray was normal. CT scan of paranasal sinuses confirmed presence of polyps in middle meatus.

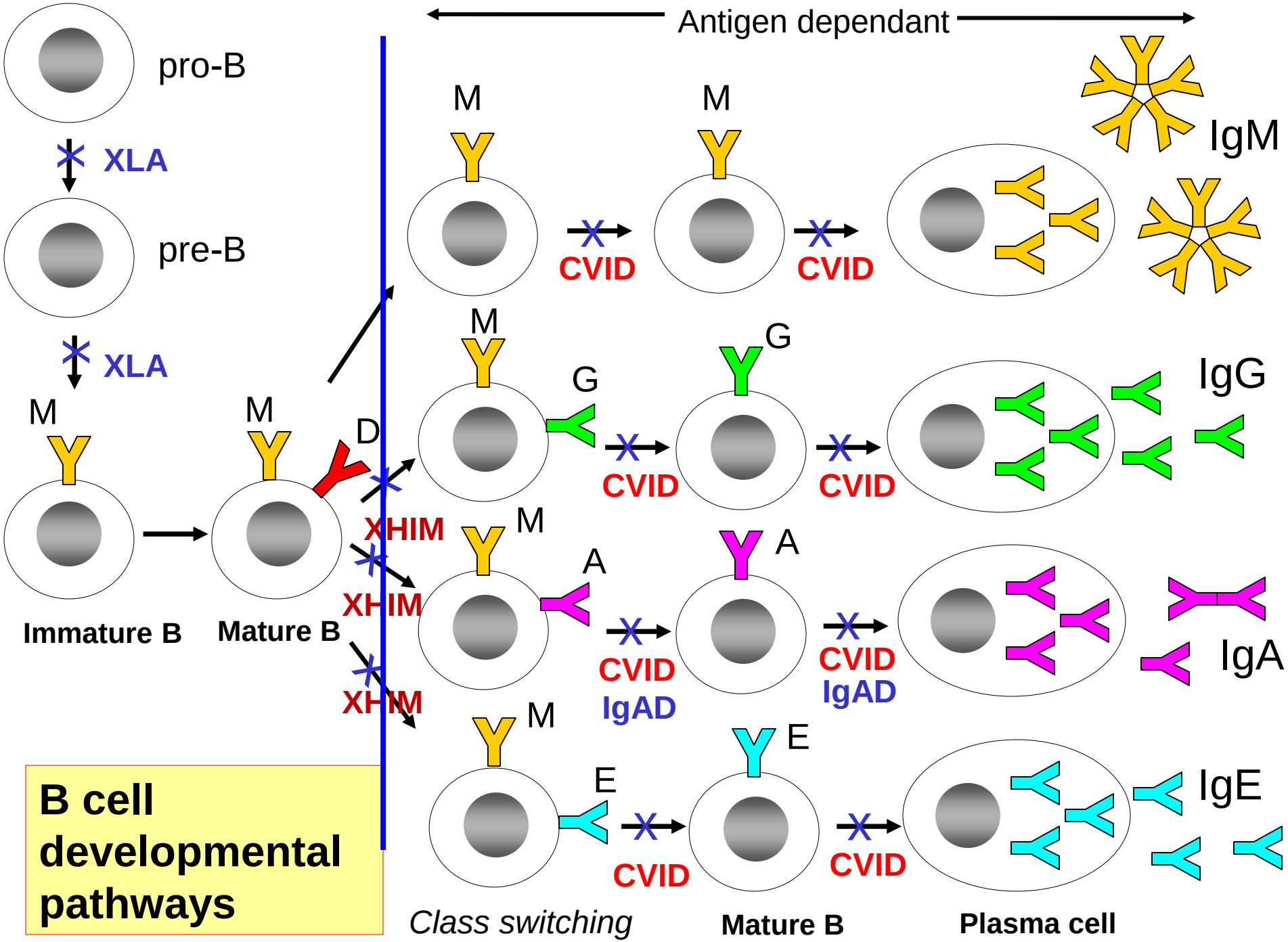
Case # 2 … continued

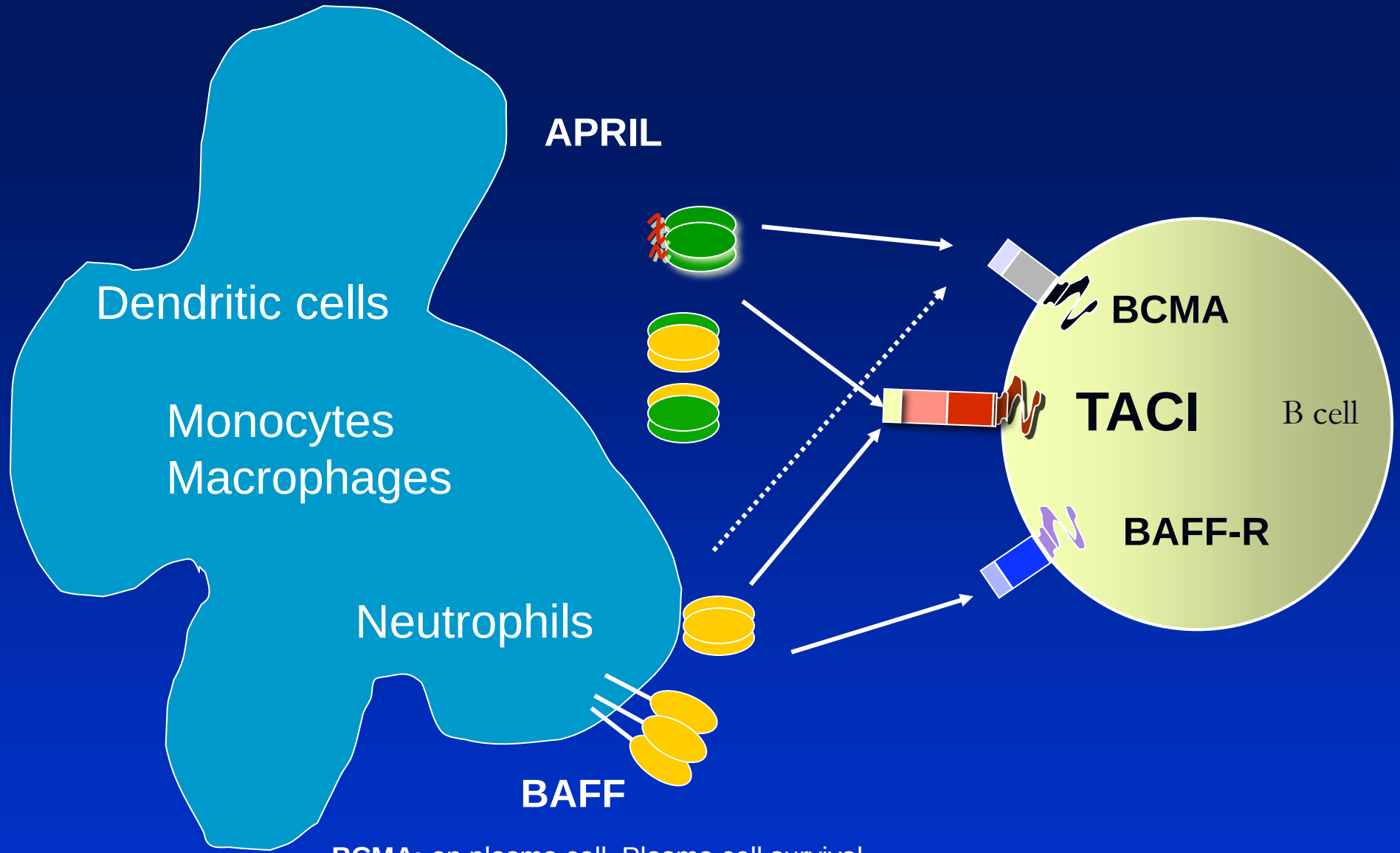
- CBC revealed a WBC of 12K with 6% eosinophils. ESR, CRP and CMP was normal. Total IgE was 510 I.U. He had positive skin prick tests to molds, dust mite and mice epithelium and negative for wheat and gliadin. Serum IgG was 920 mg/dL (normal 614-1295) IgA < 7 mg/dL (normal 67-309), IgM 310 mg/dL (normal 56-309). The SPEP was normal.

Q 4-8.

The tests necessary for management are: Comment **A for Yes and B for No**

4) Obtain IgG subclass
5) Obtain pre and post pneumococcal vaccine and tetanus toxoid responses
6) Order tTG and DGP IgG antibody
7) Order tTG and DGP IgA antibody
8) Order HLA-DQ2 and HLA-DQ8 testing


Antigen dependant
pro-B
XLA
pre-B
XLA
M
M
D
Immature B
Mature B
XHIM
XHIM
XHIM
M
M
CVID
CVID
IgM
M
G
G
CVID
CVID
IgG
M
A
A
CVID
IgAD
CVID
IgAD
IgA
M
E
E
CVID
CVID
IgE
B cell developmental pathways
Class switching
Mature B
Plasma cell



BCMA: on plasma cell. Plasma cell survival
TACI: mostly on germinal centers. Isotype switching and B homeostasis (NFAT, NFkb)
BAFF-R: naïve and transitional B cells. Isotype switching and plasma, B cell survival

Rachid et al : Curr Allergy Asthma Rep. 2006 Sep;6(5):357-62.

Follow up data ….

- The IgG subclasses were normal and his antibody responses to pneumococcal and tetanus antigens were normal. He has selective IgA deficiency only without functional antibody deficiency syndrome.
- The anti tTG IgA antibody was positive and he had the HLA-DQ2 and HLA DQ-8 haplotype.
- He has selective IgA deficiency with symptomatic allergic disease and celiac disease with vitiligo
- Further, his allergic rhinosinusitis and nasal polyposis was interfering with his productivity and QOL.

Management paradigms

1) He is not a candidate for IVGG replacement therapy
2) Should he need transfusion of blood, only washed RBC must be used. Alternatively, blood cells from an IgA deficient donor is a choice
3) He must adhere to a gluten free diet
4) Given he has nasal polyposis and poor response to nasal steroids and antihistamines, biologics are indicated. Dupilimab, by blocking the alpha chain of IL-4 and IL-13 receptor is a superior choice compared to anti IgE therapy or anti IL-5 or anti-IL5R therapy.
5) Efficacy of allergen immunotherapy to mouse antigens has not been studied.
6) Surveillance for emergence of other autoimmune diseases is necessary.

Case # 3

- 56 year old male presents with fatigue, swelling of feet, and oliguria of 15 days duration. Denies orthopnea, shortness of breath or chest pain.
- Healthy thus far with no hypertension or diabetes
- Exam reveals normal vital signs, normal JVP, bilateral pitting edema of feet, no lymphadenopathy. Normal cardiac, chest, abdominal and neurological exam.
- Urinalysis : 4+ proteinuria, no cells. Few fatty casts present.
- 24 hour urinary protein was 6 g .
- Normocytic normochromic anemia. Normal diff and platelets.
- BUN 52 mg%, creatinine 2.8 mg with decreased GFR. Albumin 2.0 g/dL
- ANA, C3, C4, CH50 normal
- Renal ultrasound – normal sized kidney and no obstruction uropathy.

Q 9.

The most likely diagnosis is

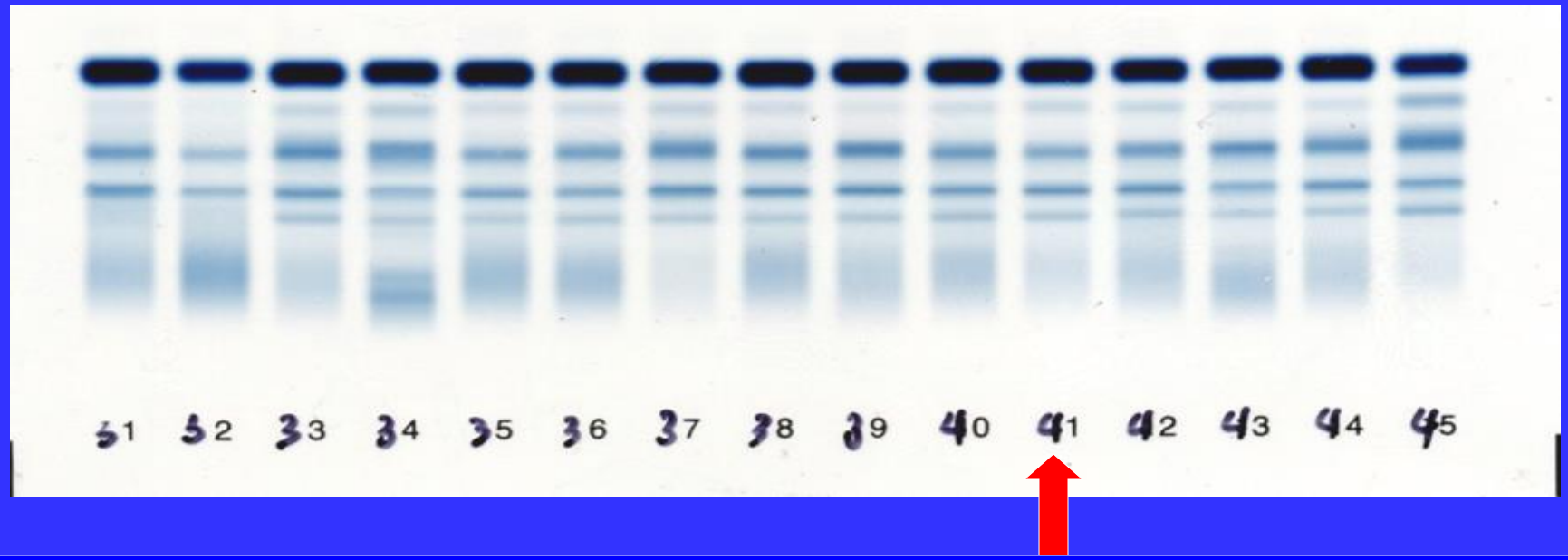
A) IgA nephropathy

B) Mesangiocapillary glomerulonephritis

C) Minimal change disease

D) Secondary nephrotic syndrome

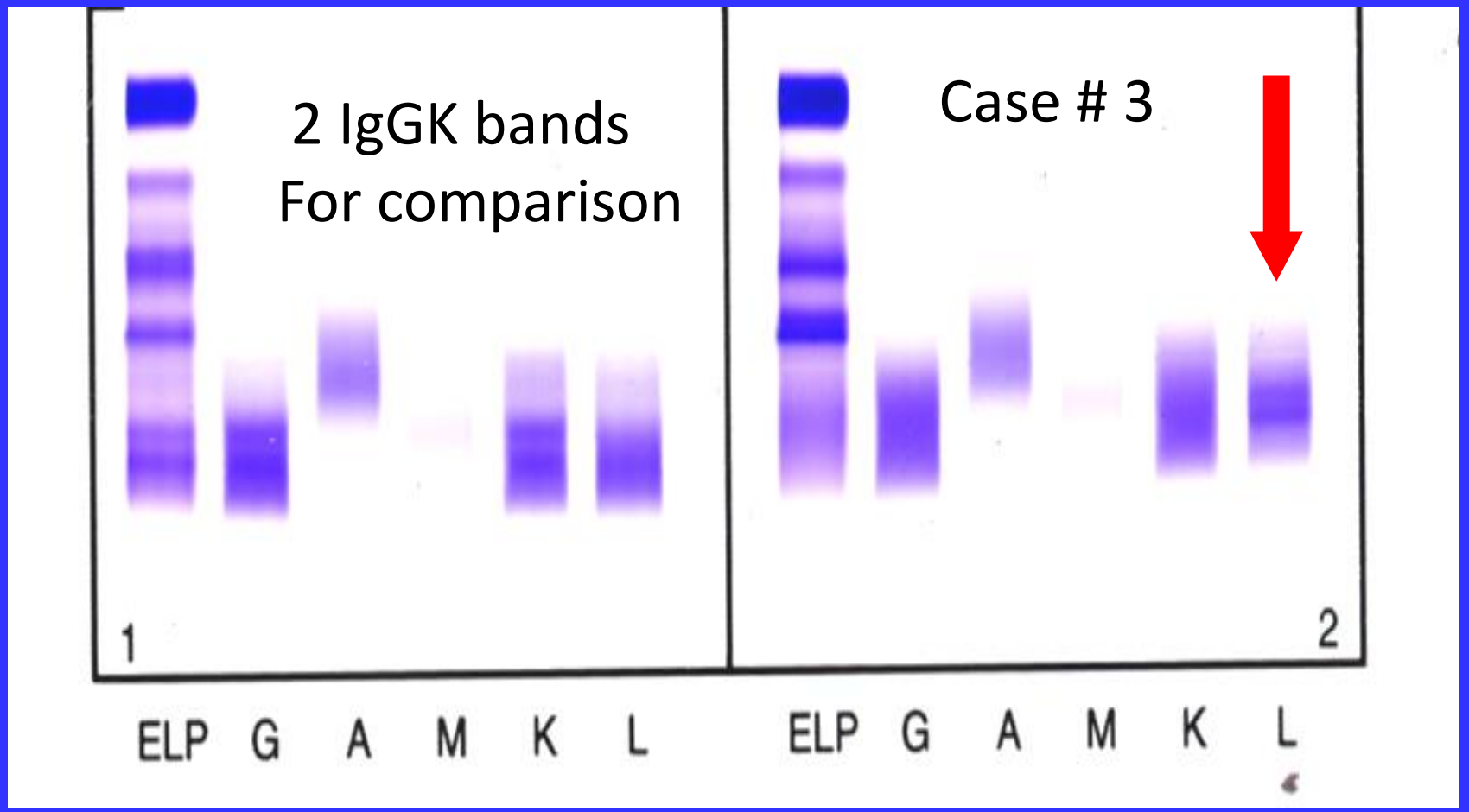
SPEP profile – Case #3 (Lane 41)



IgG is 498, IgA is 126 and IgM is 53
(Normal values IgG 614-1295, IgA 67-309 and IgM 56- 339)
sFκLC is 11.2 (3.3 -19.4) and sFλLC (5.3 to 26.3) is 550 and ratio 0.01

Immunofixation sample # 41

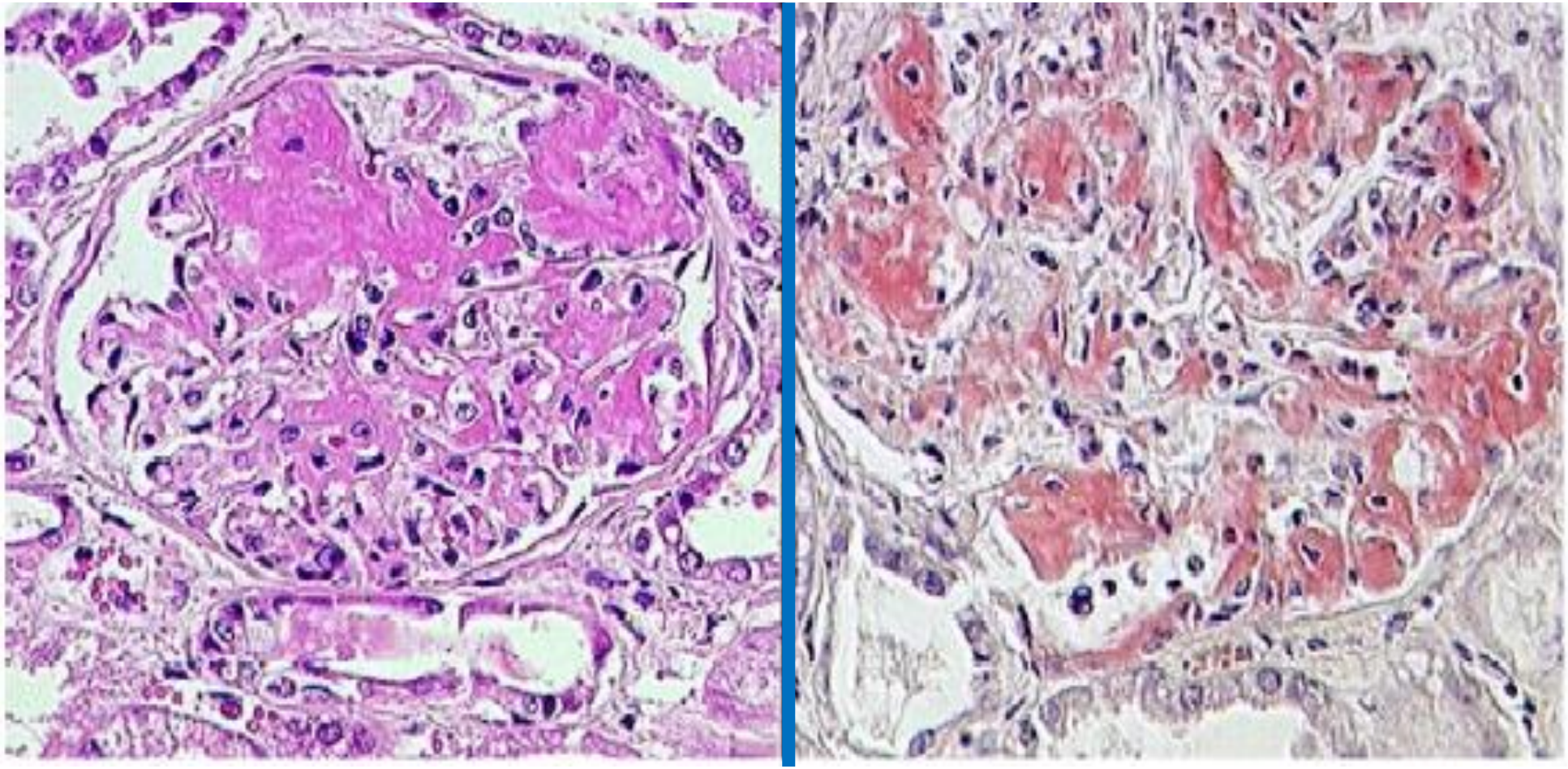
sFKLC is 11.2 and sFLLC is 550 K/L ratio = 0.01



Bone marrow biopsy

- Large clusters of atypical plasma cells
- Monotypic lambda expression
- Flow cytometry : CD138+ CD19- population with monotypic cytoplasmic lambda light chains (only 2% of cells)
- Diagnosis: Lambda light chain myeloma

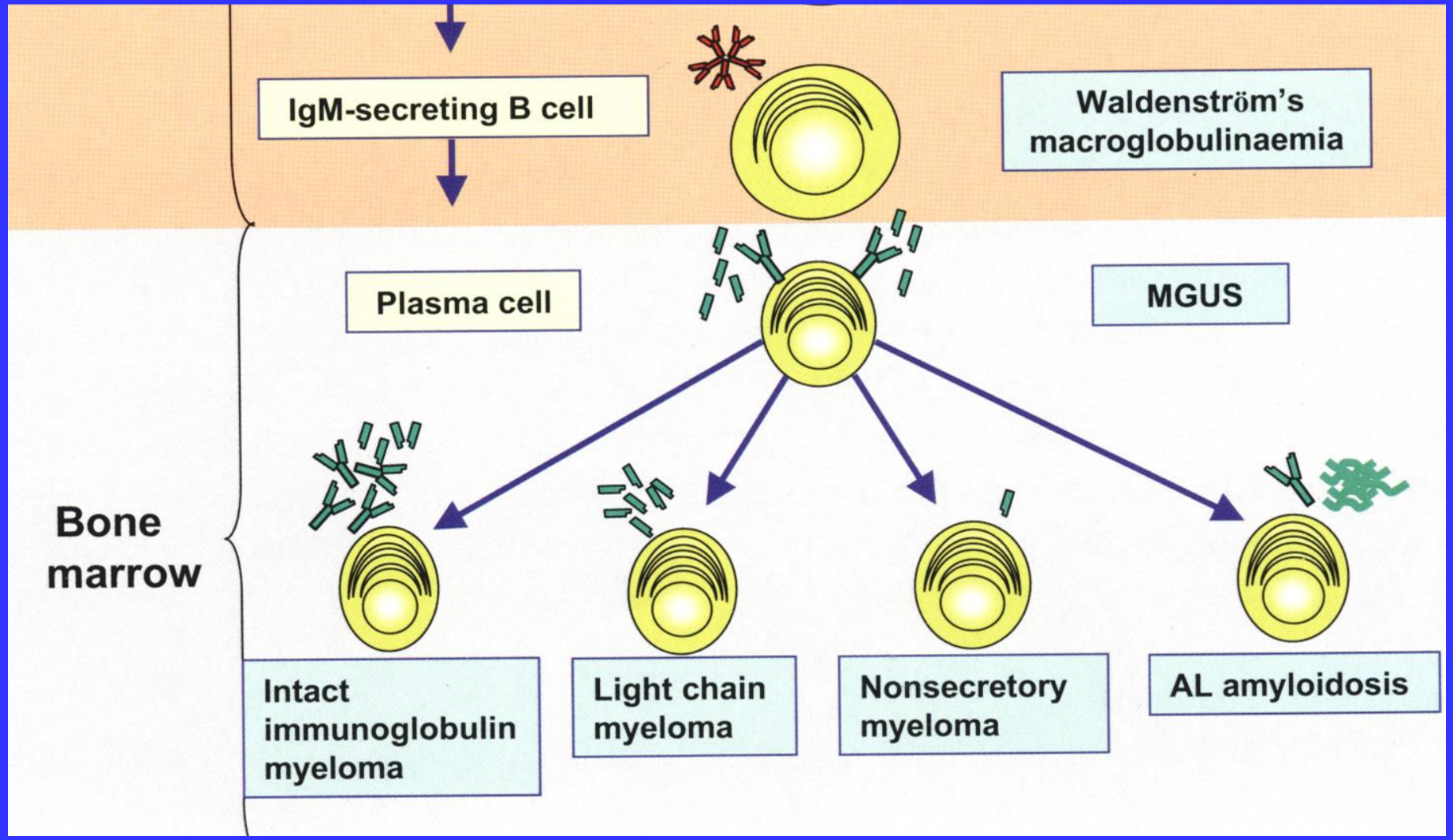
Renal Biopsy of case # 3



H and E stain

Congo Red stain

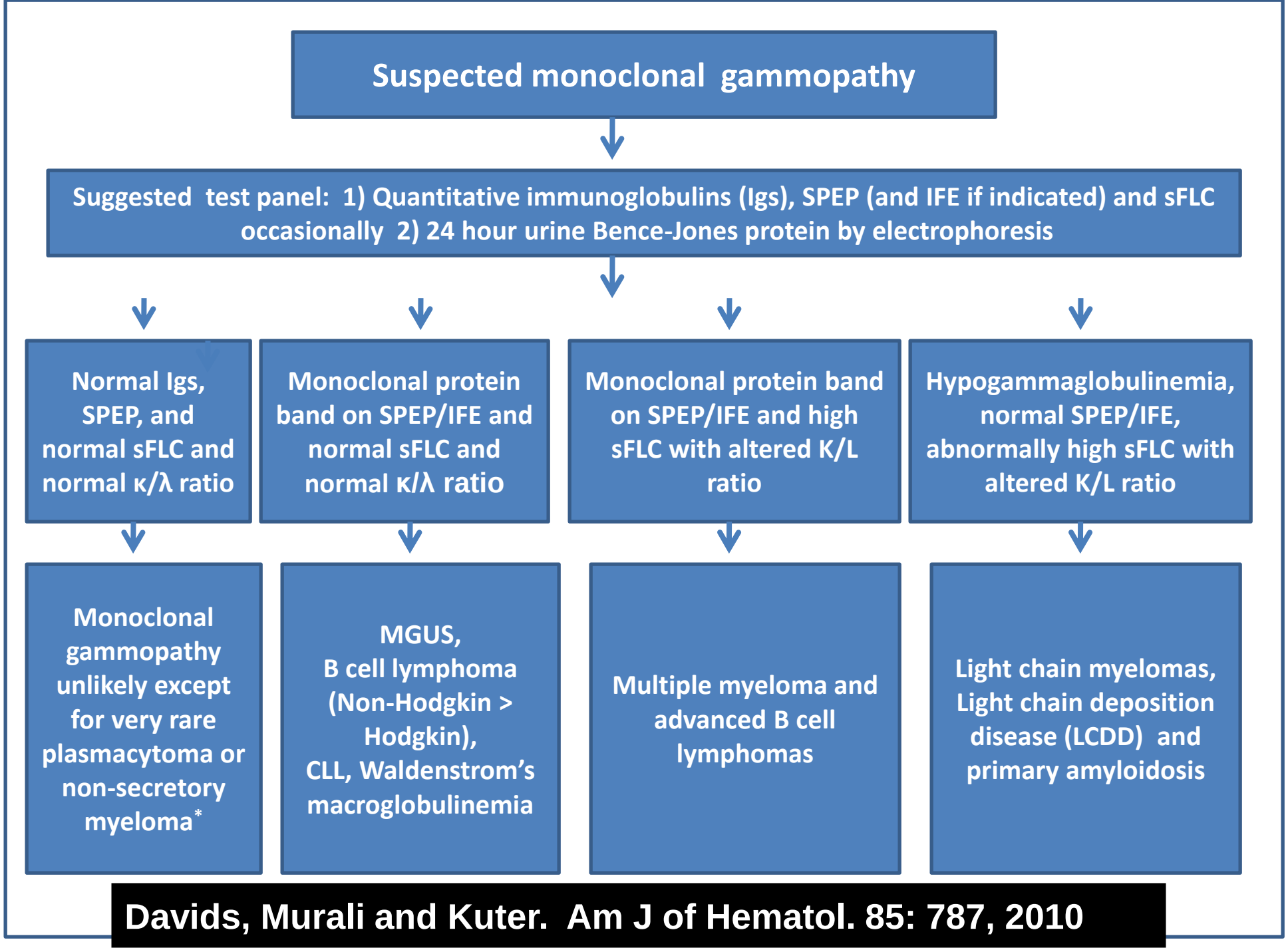
Unbalanced production of H and L chains results in altered FLC kinetics



Case # 3 - Summary

- Nephrotic syndrome secondary to renal amyloidosis, due to lambda light chain myeloma or primary renal amyloidosis.
- The same clinical scenario without a definable hematological malignancy is known as Monoclonal Gammopathy of Renal Significance (MGRS)

N Engl J Med (2021) 384: 1931-1941



Davids, Murali and Kuter. Am J of Hematol. 85: 787, 2010

Take home messages – case # 3

- Hypogammaglobulinemia does not always reflect primary B cell deficiency
- B cell clonal dyscrasia can present as symptomatic or asymptomatic hypogammaglobulinemia
- A normal SPEP and even a normal IFE does not exclude a monoclonal gammopathy – Need sFLC and uBJP to unravel the spectrum of B cell monoclonal gammopathies

Learning objectives - revisited

Case # 1.

Identify systemic causes of hives from chronic spontaneous urticaria, understand pathogenesis, rationale for lab tests and approaches to treatment.

Case # 2.

Highlights the features and evaluation of Selective IgA deficiency. Clinical associations and principles of therapy and surveillance are alluded.

Case # 3.

Diagnostic value of Serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE) and serum free light chains in the **diagnoses of B cell monoclonal gammopathies** in a patient with **nephrotic syndrome.**

Rx: Antihistamines and ? Anti-leukotrienes

- Use one potent second generation antihistamine
- Combine fexofenadine 180 -360 mg in a.m. or desloratidine 5 -10 mg in a.m. with cetirizine 10 -20 mg mid-day and h.s
- Use hydroyxyzine 25-50 mg q.i.d. or comparable dose of doxepin 10-25 mg h.s.
- H2 blockers synergize with H1 blockers. No role for monotherapy
- In meta analysis leukotriene receptor antagonists alone or with H1 and H2 blocker did not improve clinical outcomes