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Lupus Syndromes

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Lupus Syndromes

- LE-associated syndromes
- LE-like syndromes

LE-Associated Syndromes

Definition

- Fulfill the diagnostic criteria of SLE
  - 1997 American College of Rheumatology
  - 2012 Systemic Lupus International Collaborating Clinics Criteria
- Typical skin manifestations of CLE with compatible histopathology
- Concurrence of other diseases

LE by itself is a heterogenous syndromic disorder!

RheumTutor.com

SLICC† Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

Histopathology of Cutaneous LE

- Similar histological features in different subtypes of CLE
- Superficial and deep perivascular and periadnexal lymphocytic infiltrate
- Interface-dermatitis with vacuolar degeneration of the dermoepidermal junction and necrotic keratinocytes in the lower epidermal layers
- Thickening of the basement membrane as a late consequence
- DLE: prominent ortho- and parahyperkeratosis, follicular plugging, and epidermal atrophy
- LE panniculitis: lobular lymphocytic panniculitis
- LE tumidus: abundant mucin deposition between collagen bundles
- Chilblain lupus: dermal edema and vascular dilatation

Kuhn A et al. J Autoimmun 2014;48-49:14-9

LE-Associated Syndromes

- Aicardi-Goutières syndrome
- Spondyloenchondrodysplasia with immune dysregulation
- Prolidase deficiency
- …

Aicardi-Goutières Syndrome

- Aicardi J, Goutières F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol 1984;15:49–54
- Aicardi–Goutières syndrome (AGS 1-8)
- Acral chilblain lesions are seen in > 40% of cases
- AGS-1:
  - OMIM 225750
  - 3p21.31, Mutations in DNA exonuclease TREX1
  - TREX1: *t*hree prime *r*epair *ex*onuclease 1, an endogenous DNA exonuclease depleting damaged DNA to maintain genome integrity and prevent immune activation

Aicardi-Goutières Syndrome-1

Neurologic *Central Nervous System*

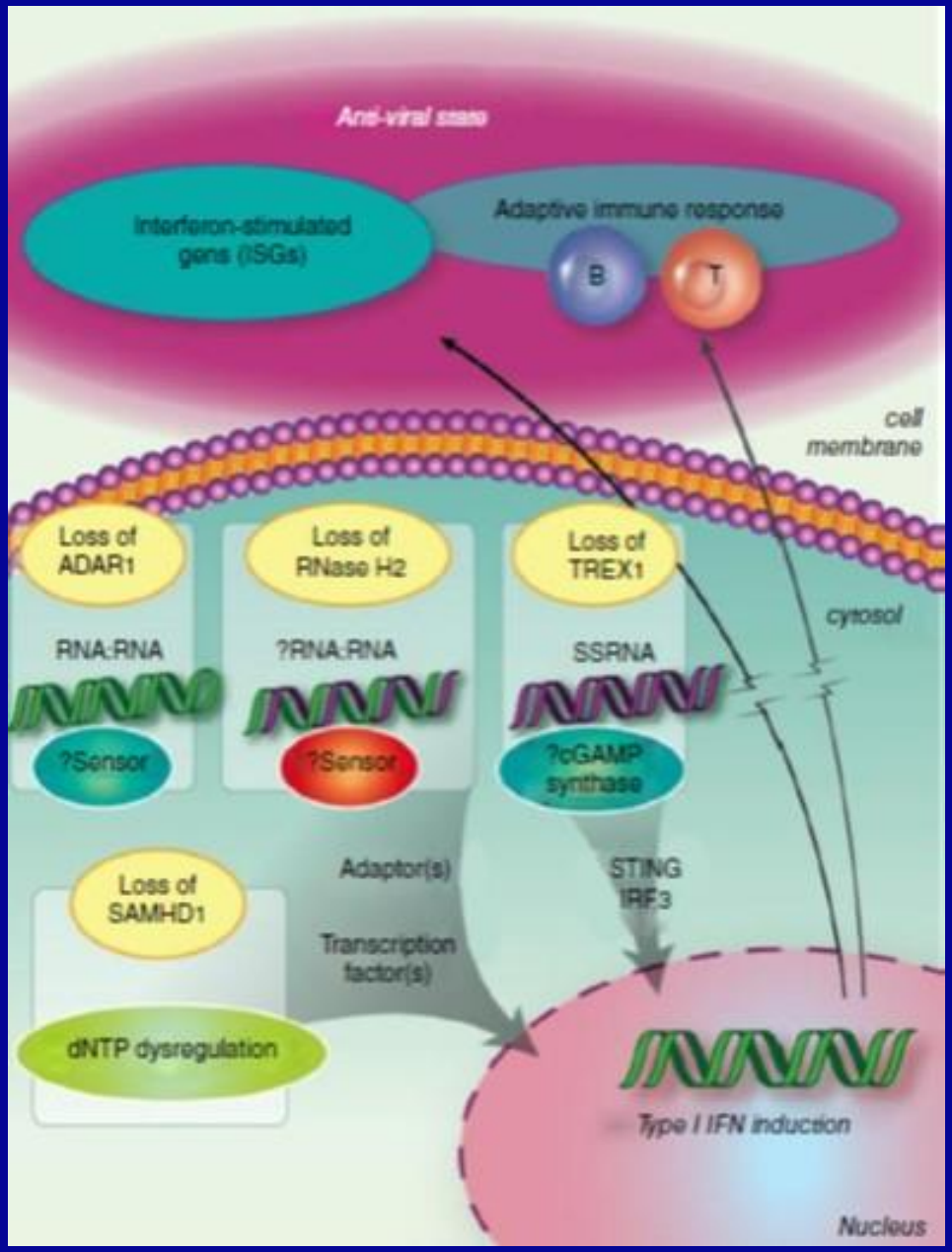
- Encephalopathy, progressive
- Developmental retardation, profound
- Tetraplegic spasticity
- Visual inattention
- Seizures
- Cerebral atrophy, progressive
- Bilateral, symmetric intracerebral calcifications, especially in the basal ganglia and periventricular areas

Aicardi-Goutières Syndrome

- AGS-2: OMIM 610181, 13q14.3, *RNASEH2B* (RNase H2 endonuclease complex)
- AGS-3: OMIM 610329, 11q13.1, *RNASEH2C*
- AGS-4: OMIM 610333, 19p13.13, *RNASEH2A*
- AGS-5: OMIM 612952, 20q11.23, *SAMHD1* (deoxynucleoside triphosphate triphosphohydrolase)
- AGS-6: OMIM 615010, 1q21.3, *ADAR* (double-stranded RNA-editing enzyme)
- AGS-7: OMIM 615846, 2q24.2, *IFIH1* (interferon-induced helicase C domain-containing protein 1, melanoma differentiation-associated protein 5, MDA5)
- AGS-8?: cyclic GMP-AMP synthase (cGAS)

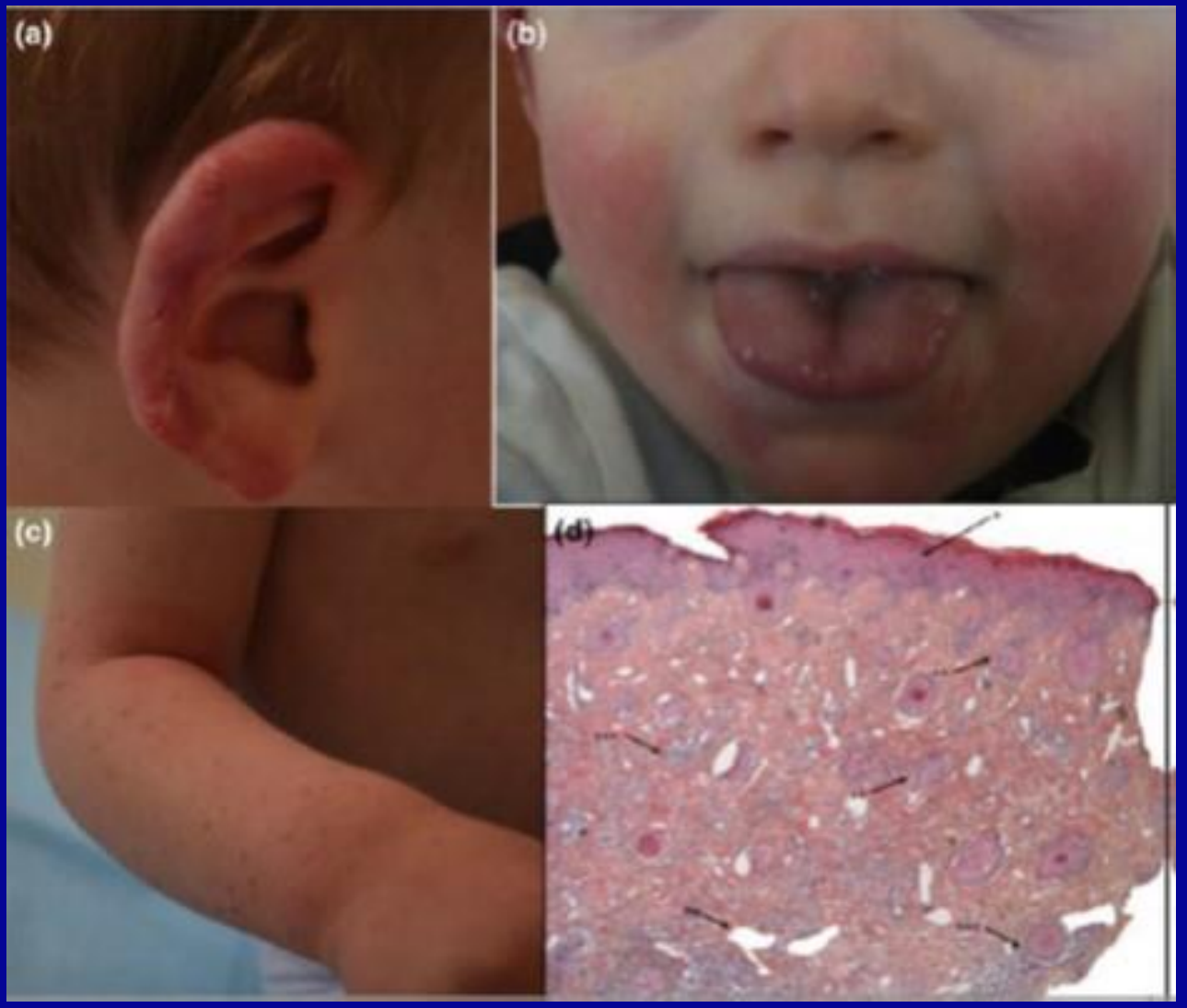
Gao D et al. Proc Natl Acad Sci USA 2015;112:E5699-705

Aicardi-Goutières Syndrome: Pathogenesis



Crow YJ et al. Clin Exp Immunol 2014;175:1-8

Aicardi-Goutières Syndrome-7 with *IFIH1 Mutation*



Bursztejn AC et al. Br J Dermatol 2015;173:1505-13

LE-Like Syndromes

Definition

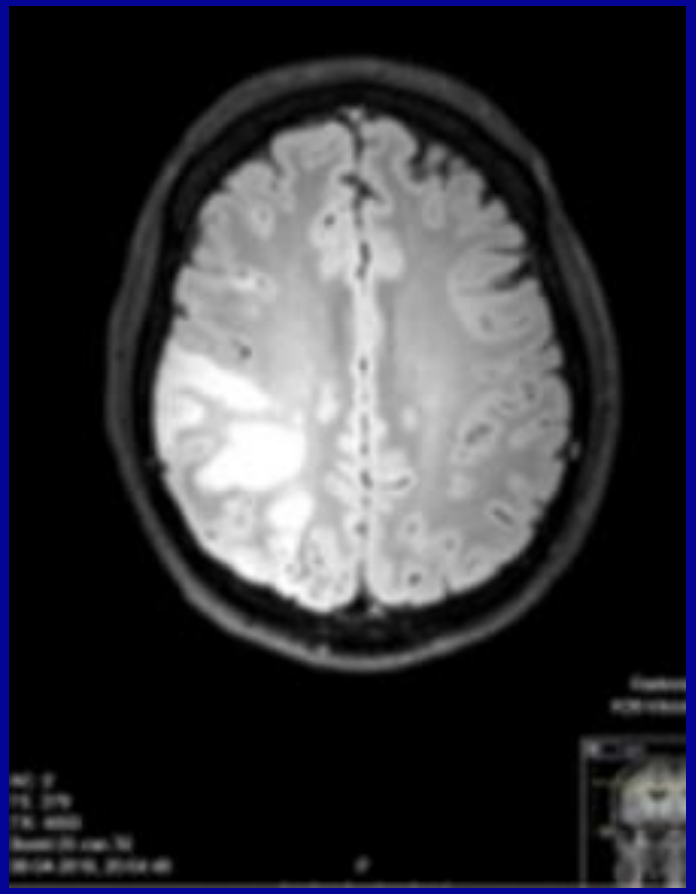
- Clinical manifestations mimicking LE, but
- Do not fulfill the diagnostic criteria of SLE
- Do not display histology of CLE
- Exclusion of monogenic LE
- Exclusion of drug-induced LE
- Exclusion of infections, sarcoidosis and lymphoma

Monogenic LE

- Genetic deficiency of early complement components
  - C1q deficiency: ca. 90% with SLE
  - C2 deficiency: ca. 75% with SLE
  - C4 deficiency: ca. 10% with SLE
- Familial chilblain lupus
- Aicardi-Goutières syndrome (40% with chilblain lupus)
- Spondyloenchondrodysplasia with immune dysregulation
- Prolidase deficiency (ca. 10% with SLE)
- Familial hemophagocytic lymphohistiocytosis
- Autosomal recessive hyper-IgE syndrome
- …

Aggarwal R et al. Lupus 2010;19:52-7; Carneiro-Sampaio M et al. Front Immunol 2015;6:185; Esteban YM et al. Pediatr Ann 2017;46:e309-13

C1q Deficiency with Neuropsychiatric LE

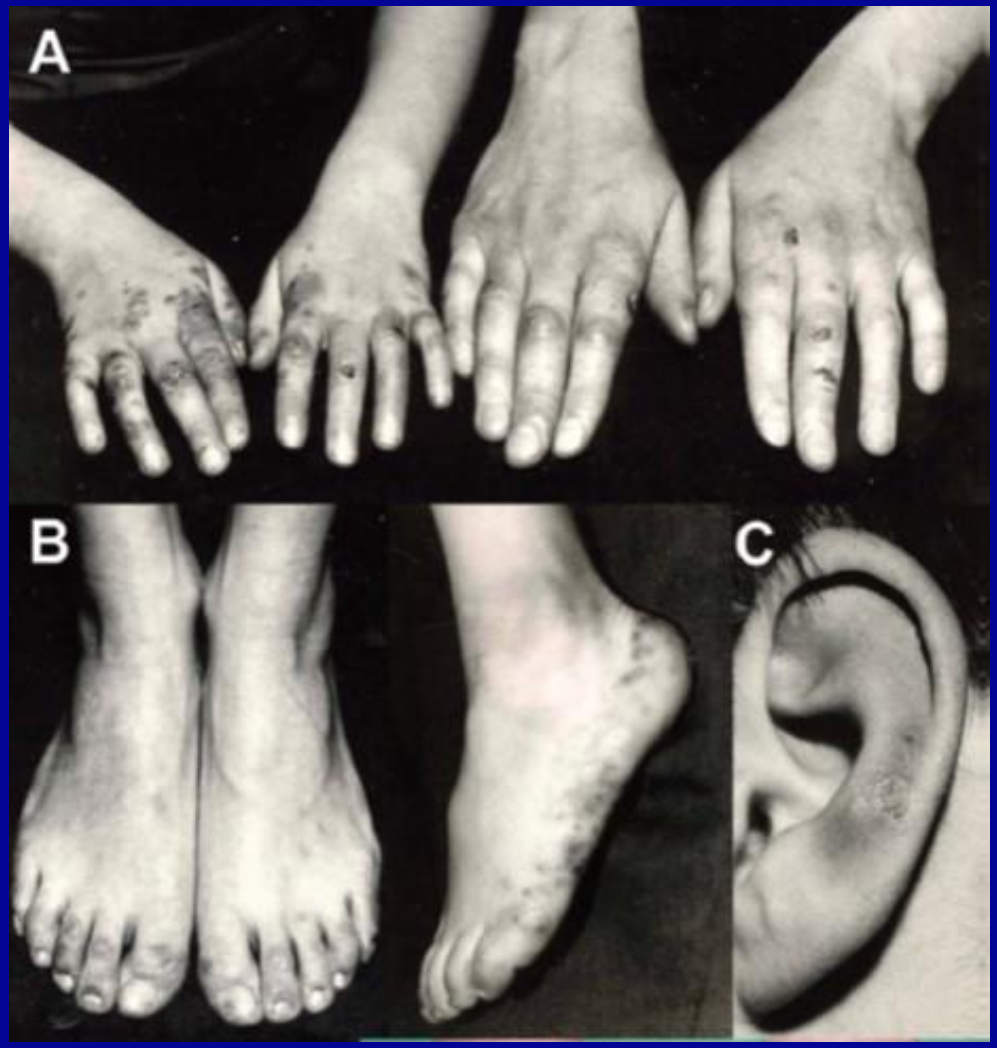


van Schaarenburg RA et al. Front Immunol 2016;7:647

Familial Childblain Lupus-I

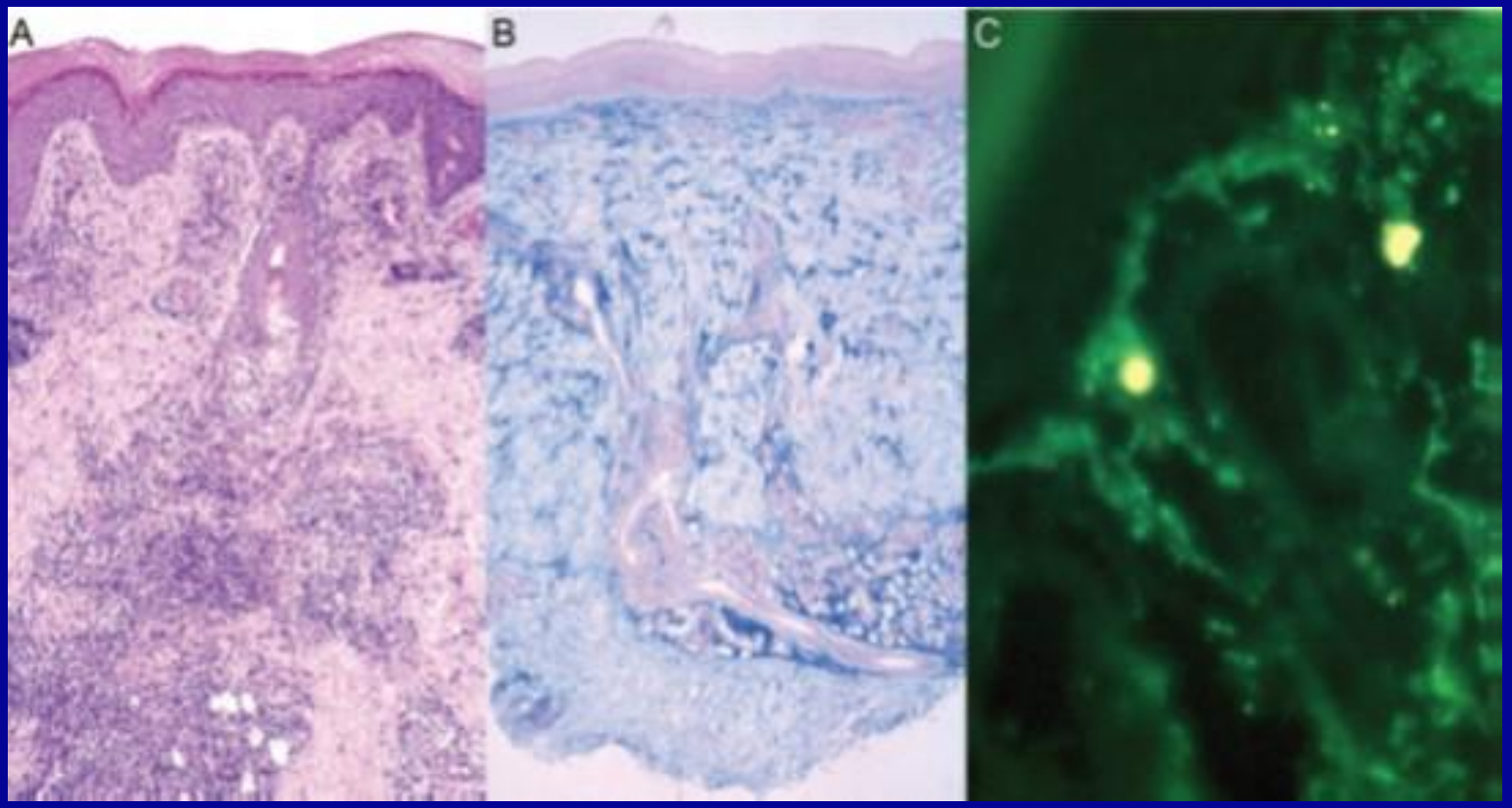
- OMIM 610448, autosomal dominant
- 3p21.31, mutation in 3-prime repair exonuclease-1 gene (TREX1)
- Clinics
  - Onset in early childhood
  - Acral painful bluish-red papules/nodules (fingers, toes, nose, cheek, ears)
  - Cutaneous ulcers, with subsequent atrophic hypopigmented scars
  - No Raynaud phenomenon
  - No cutaneous photosensitivity
  - Arthralgias (knees and shoulders)
  - Antinuclear antibody present (in some patients)

Familial Chilblain Lupus



Lee-Kirsch MA et al. Am J Hum Genet 2006;79:731-7

Familial Chilblain Lupus: Histology



Lee-Kirsch MA et al. Am J Hum Genet 2006;79:731-7

Familial Chilblain Lupus-2

- OMIM 614415, autosomal dominant
- 20q11.23, mutation in SAM domain- and HD domain-containing protein 1 gene (SAMHD1)
- SAMHD1
  - Triphosphohydrolase activity converting deoxynucleoside triphosphates (dNTPs)
  - Blocking HIV-1 replication
  - Aicardi–Goutières syndrome-5
- Clinics
  - Onset in early childhood
  - Arcal painful bluish-red papules/ nodules
  - Persistent angiomatous lesions on the fingers
  - Cutaneous photosensitivity

Familial Chilblain Lupus-3?

- A heterozygous mutation of STING, a signaling molecule in the cytosolic DNA sensing pathway
- Mutant STING enhances homodimerisation in the absence of its ligand cGAMP, resulting in constitutive activation of type I interferon (IFN)
- Treatment of two affected family members with the Janus kinase (JAK) inhibitor tofacitinib led to a marked suppression of the IFN signature

König N et al. Ann Rheum Dis 2017;76:468-72

Drug-Induced LE

- Drug-induced LE
  - Hydralazine, procainamide, isoniazid, minocycline, diltiazem
- Drug-induced SCLE
  - Hydrochlorothiazide
  - Terbinafine (OR 53), TNF-α antagonist (OR 8), anti-epileptics (OR 3.4), proton pump inhibitors (PPI) (OR 2.9)
  - Aromatoase inhibitors, chemotherapeutics (capecitabin, 5-FU, taxanes)
- Novel treatment
  - TNF-alpha antagonists
  - Immune checkpoint inhibitors

Abdel-Wahab N et al. PLoS One 2016;11:e0160221. Ho C et al. StatPearls [Internet]. 2017 Jul 3; Momen SE et al. Br J Dermatol 3 AUG 2017

LE-Like Syndromes

- Mimicking cutaneous LE (CLE)
- Mimicking SLE
- Challenge: overlap and association with LE

CLE-Like Syndromes

- Bloom syndrome
- Rothmund-Thomson syndrome
- …

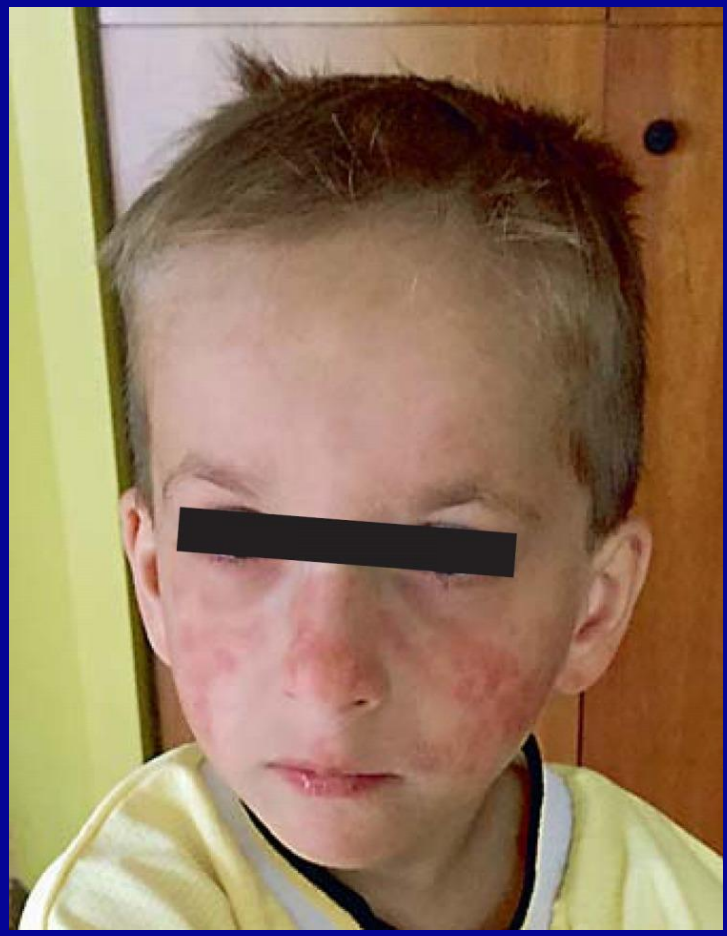
Bloom Syndrome

- Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. AMA Am J Dis Child 1954;88:754–8
- OMIM 210900, autosomal recessive
- 15q26.1, mutations in BLM/RecQ protein-like 3 gene (RECQL3) leading to formation of an abnormal DNA helicase protein and genomic instability
- Prenatal and postnatal growth deficiency
- High-pitched voice
- Facial deformities
- Insulin-resistant diabetes mellitus
- Hypogonadism
- Immunoglobulin deficiency (IgA, IgG, IgM)
- Increased cancer risks: leukemia, squamous cell carcinoma

Bloom Syndrome

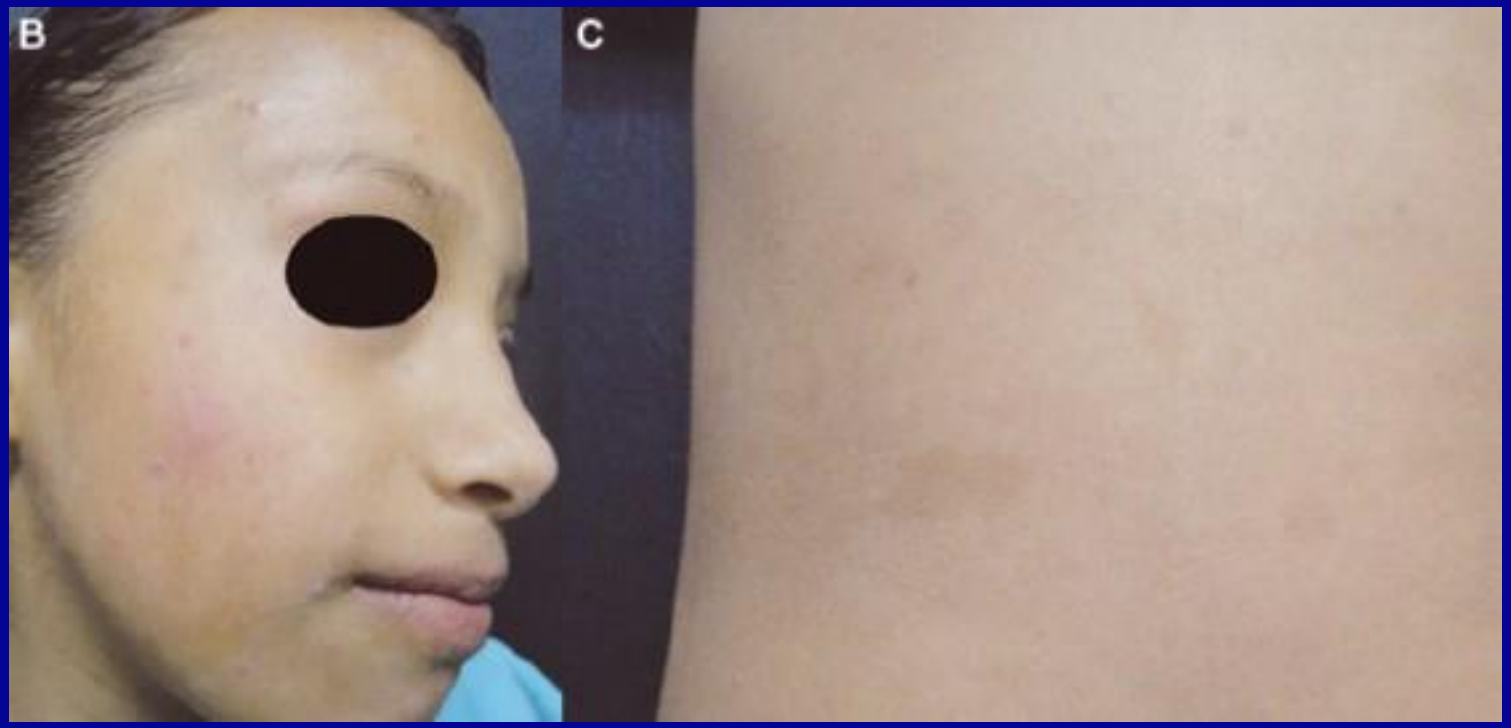
Skin

- Facial telangiectasia in butterfly midface distribution
- Excessive photosensitivity
- Spotty hypopigmentation and hyperpigmentation
- Cafe-au-lait spots
- Hypertrichosis



Cunniff C et al. Mol Syndromol 2017;8:4-23

Bloom Syndrome



Rosales-Solis GM et al. Gac Med Mex 2016;152:747-8

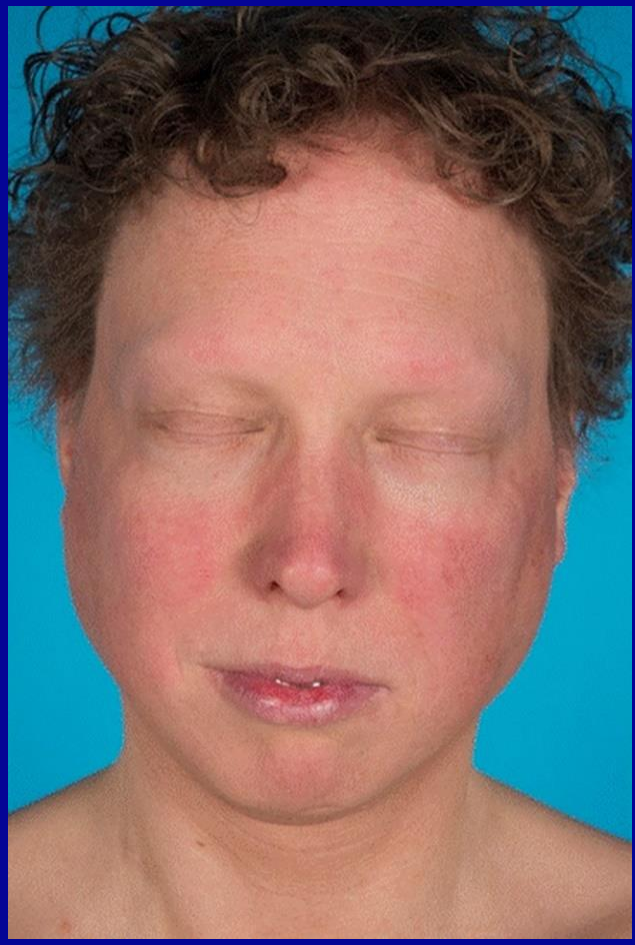
Rothmund-Thomason Syndrome

- Rothmund A. Über Cataracten in Verbindung mit einer eigentümlichen Hautdegeneration. Gräfes Arch Klin Exp Ophthal 1868;14:159-82
- Thomson MS. Poikiloderma congenitale. Br J Dermatol 1936;48:221-34
- OMIM 268400, autosomal recessive
- 8q24.3, Mutations in DNA helicase RECQL4
- Short statue
- Ophthalmologic abnormalities, e.g. Juvenile zonular cataracts
- Skeletal defects
- Mental retardation in 5-13%
- Neoplasia
  - Basal cell carcinoma, squamous cell carcinoma
  - Osteosarcoma

Rothmund-Thomson Syndrome

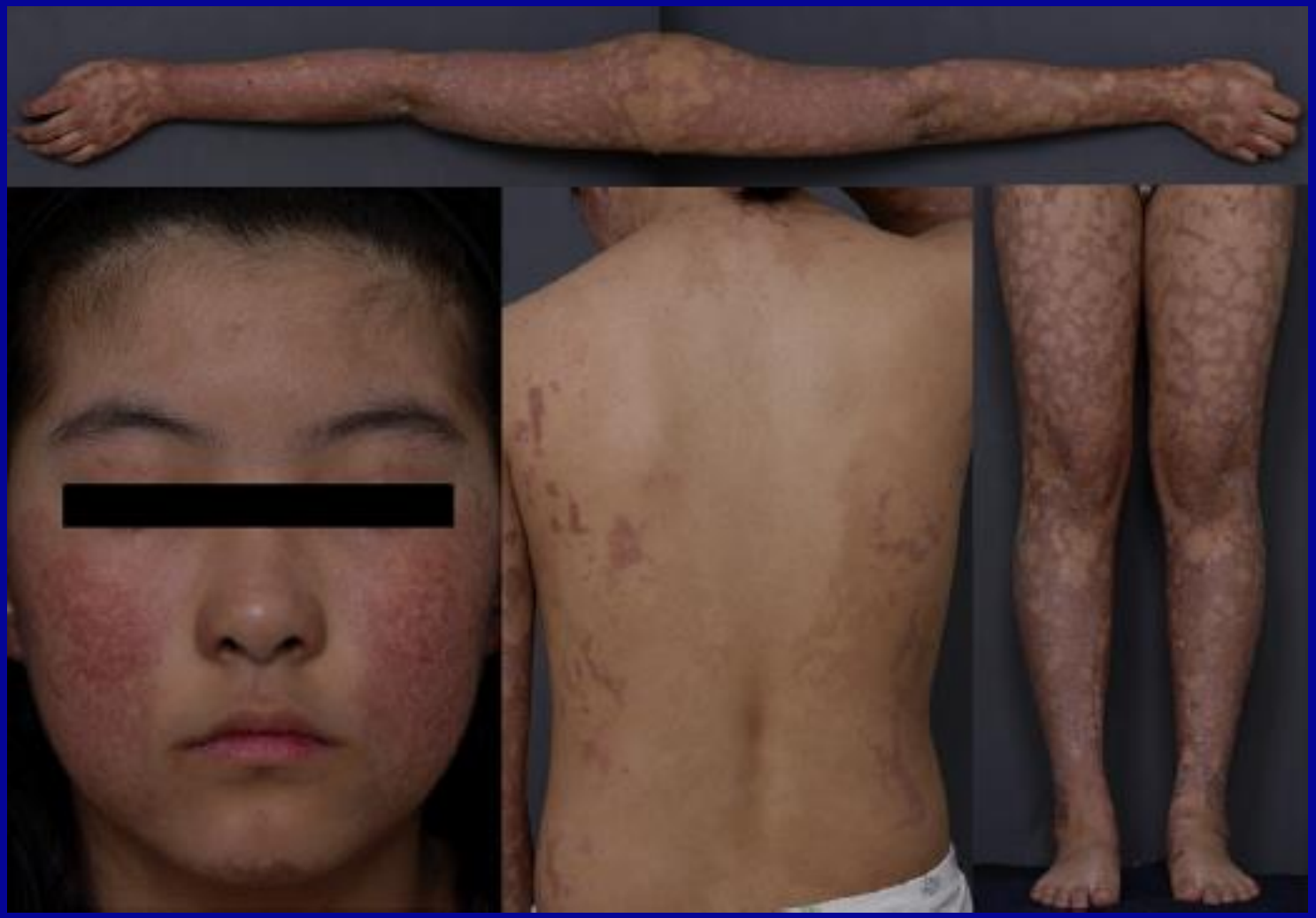
Skin

- Erythematous skin lesions in infancy
- Poikiloderma with telangiectasia, skin atrophy and ulceration
- Excessive photosensitivity
- Atrophic nails
- Hypotrichosis, alopecia, Canities praecox



van Rij MC et al. Eur J Pediatr 2017;176:279-83

Rothmund-Thomson Syndrome



Yang JY et al. JAAD Case Rep 2017;3:172-4

Chromosomal Instability Syndromes

Chromosomal breakage syndromes

- Bloom syndrome
- Rothmund-Thomson syndrome
- Xeroderma pigmentosum
- Ataxia telangiectasia
- Nijmegen breakage syndrome
- Fanconi anemia

SLE-Like Syndromes

- Adult onset Still's disease
- Hemophagocytic lymphohistiocytosis
- Primary immunodeficiency disorders
- Kikuchi-Fujimoto disease
- SAVI Syndrome
- …

Adult Onset Still's Disease: Diagnosis

Yamaguchi criteria ≧ 5 (sensitivity 93%)

- Major criteria ≧ 2
  - Fever ≧ 39°C for at least a week
  - Arthralgia or arthritis for ≧ 2 weeks
  - Evanescent nonpruritic salmon colored rash on trunk/extremities
  - Granulocytic leukocytosis (≧ 10,000/mL)
- Minor criteria
  - Sore throat
  - Lymphadenopathy
  - Hepatomegaly or splenomegaly
  - Abnormal liver function tests
  - Negative tests for RF and ANA

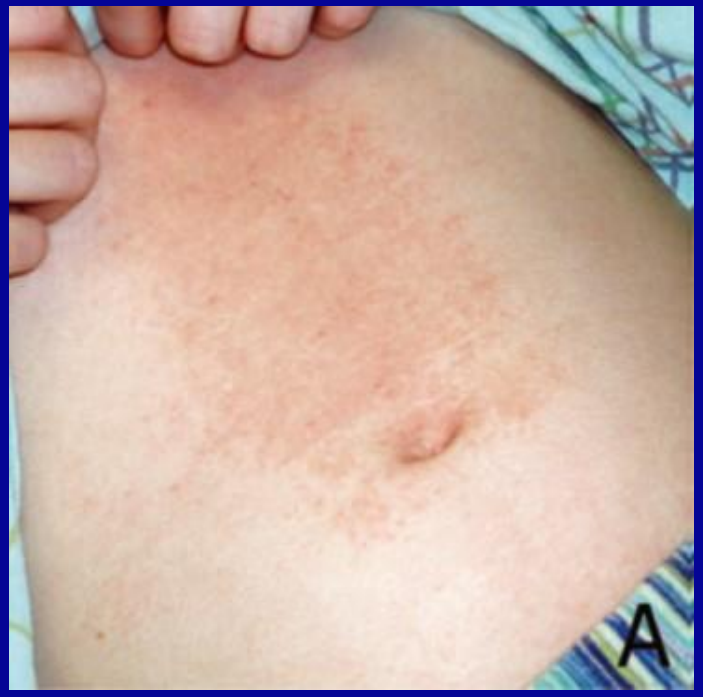
Adult Onset Still's Disease: Diagnosis

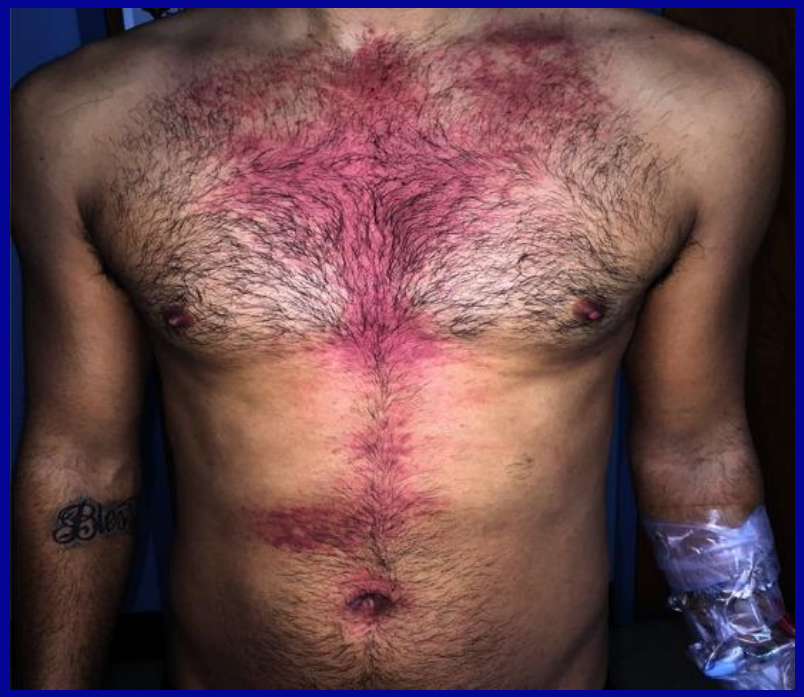
Fautrel criteria (sensitivity/specificity= 80.6%/ 98.5%)

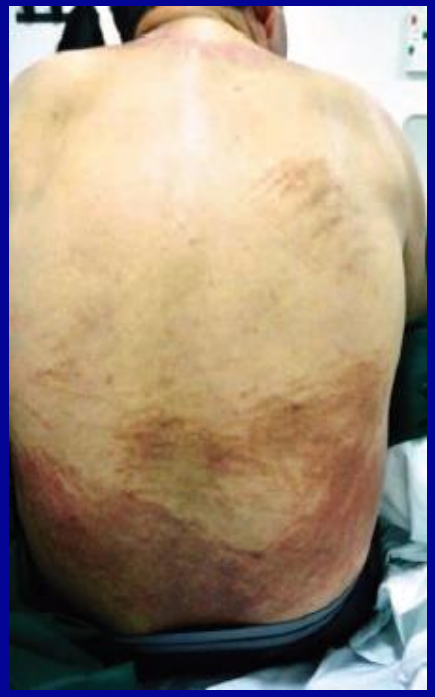
- Major criteria
  - Spiking fever ≥ 39°C
  - Arthralgia
  - Transient erythema
  - Pharyngitis
  - Neutrophilic polymorphonuclear count ≥ 80%
  - Glycosylated ferritin fraction ≤ 20%
- Minor criteria
  - Typical Still's rash
  - Leukocytosis (10,000/mm^3)
- Diagnosis: major criteria ≧4 , or 3 major + 2 minor criteria

Adult Onset Still's Disease

Atypical skin manifestations: persistent pruritic







Michailidou D et al. Auto Immun Highlights 2015;6:39-46; Sun NZ et al. J Am Acad Dermatol 2015;73:294-303; Narváez Garcia FJ et al. Medicine (Baltimore) 2017;96:e6318

Autoinflammatory Diseases Mimicking SLE

- Monogenic
  - Familial Mediterranean fever
  - Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS)
  - Mevalonate kinase deficiency syndrome /Hyper-IgD syndrome
  - Cryopyrin-associated periodic syndrome
- Polygenic
  - Still's disease (Systemic-onset juvenile idiopathic arthritis)
  - Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA)
  - Behçet disease

Hemophagocytic Lymphohistiocytosis (HLH)

- Primary familial HLH
  - Typical onset in infants and children
  - Genetic mutations (perforin 1, syntaxin 11, syntaxin-binding protein-2), affecting the cytotoxic functions of T lymphocytes and natural killer cells
- Secondary HLH (macrophage activation syndrome)
  - Cytopenia, hepatosplenomegaly, liver dysfunction, elevated serum LDH, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia
  - Hemophagocytosis present in 60% of patients
  - Association with infection, pregnancy, malignancy, or autoimmune diseases especially Still's disease & SLE
  - 0.9-2.4% of patients with SLE develop secondary HLH

Cron RQ et al. Expert Rev Clin Immunol 2015;11:1043-53; Schulert GS et al. Annu Rev Med 2015;66:145-59; Liu AC et al. Clin Rheumatol 2017 Apr 13

Diagnosis 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis

- Ferritin > 684 ng/mL

And any 2 of the following

- Platelet count $\leq 181 \times 10^9$/L
- Triglycerides > 156 mg/dL
- Fibrinogen $\leq$ 360 mg/dL
- Aspartate aminotransferase > 48 units/L

Ravelli A et al. Ann Rheum Dis 2016;75:481-9

Primary Immunodeficiency Disorders Mimicking SLE

Primary immunodeficiency may predispose to SLE

- Congenital deficiency in C1q, C1r/s and C4
- Selective IgA deficiency
  - Prevalence ratio 8.9 for SLE (0.57 % vs. 0.06 % in a population-based matched cohort study from Sweden)

Secondary immunodeficiency associated with (chronic) SLE

- Selective IgA deficiency
- Selective IgM deficiency
- X-linked recessive hyper-IgM syndrome
- Common variable immunodeficiency

Takeuchi T et al. Autoimmunity 2001;34:115-22; Torres-Salido M et al. Rheumatol Int 2011;31:537-41; Ludvigsson JF et al. J Clin Immunol 2014;34:444-51; Carneiro-Sampaio M et al. Front Immunol 2015;6:185

Primary Immunodeficiency Disorders

- A genetically heterogenous group of >150 disorders that affect distinct components of the innate and adaptive immune system
- Often associated with autoimmune diseases
- The high concordance of T-regulatory cell defects to organ-specific autoimmune disease
- The absence of central nervous system involvement may reflect immunological privilege

Carneiro-Sampaio M et al. Front Immunol 2015;6:185

Primary Immunodeficiency Disorders

- Immune complex diseases as an autoimmune disease?
  - Autoantibodies may be absent
  - Tissue damage caused by deposition of immune complex
- A causative link between primary antibody deficiencies and autoimmune diseases?
  - Due to a common genetic background?
  - An intense antigen load as a result of recurrent or persistent infections may affect either tolerance or ignorance, e.g. by molecular mimicry or the presence of superantigens

Carneiro-Sampaio M et al. Front Immunol 2015;6:185

Kikuchi-Fujimoto Disease (KFD)

- Histiocytic necrotizing lymphadenitis
- Unilateral painful cervical lymphadenopathy (especially in the posterior cervical triangle) in young Asian women (HLA-DPA1+/HLA-DPB1+), with spontaneous resolution in 1-4 months
- Skin manifestations unspecific
  - Maculopapular/morbilliform/urticarial exanthem, diffuse erythema
- Differential diagnosis to SLE
  - Antinuclear antibodies, antiphospholipid antibodies, anti-dsDNA, and rheumatoid factor are usually negative
  - Histology of lymphadenopathy
- Association between KFD and SLE
  - KFD a forme fruste of SLE?

Baenas DF et al. Int Med Case Rep J 2016;9:163-7

Association Between KFD and SLE

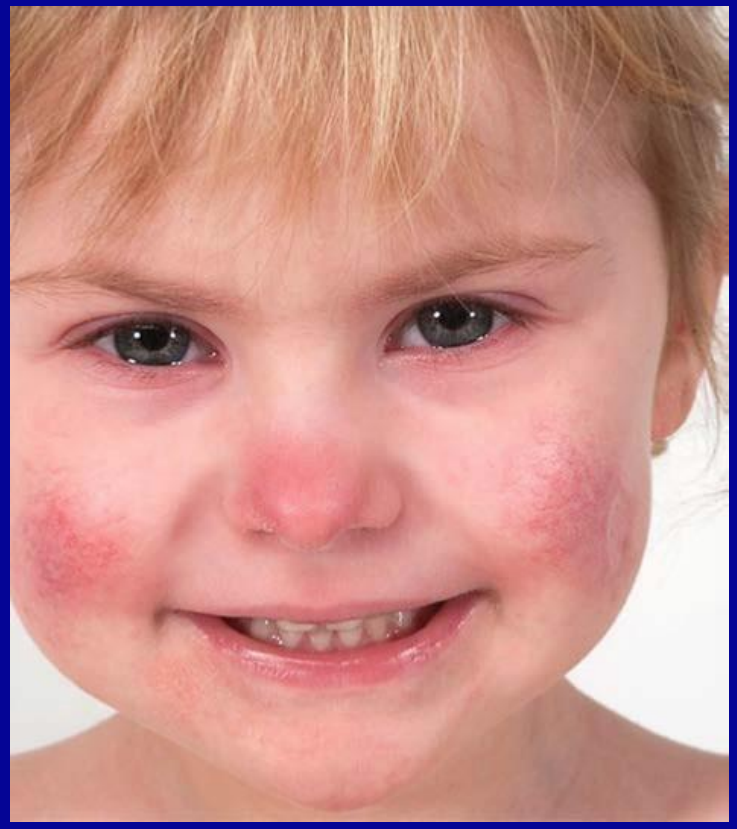
- 158 adults with proven KFD-SLE, with 113 sufficient clinical information
  - Female: male ratio 5.0
  - Mean age at diagnosis 34 years (range 14-56 years)
  - Ethnicity 50.5% Asian, 34% Caucasian, 15% others
  - cf. isolated KFD: a higher frequency of high fever (90%), severe KFD (88%), and extranodal manifestations
  - cf. isolated SLE: a higher frequency of fever and systemic symptoms, a lower frequency of lupus nephritis (22%)
  - KFD preceding (31%), succeeding (18%), or concurring with (51%) SLE as LE-associated syndrome

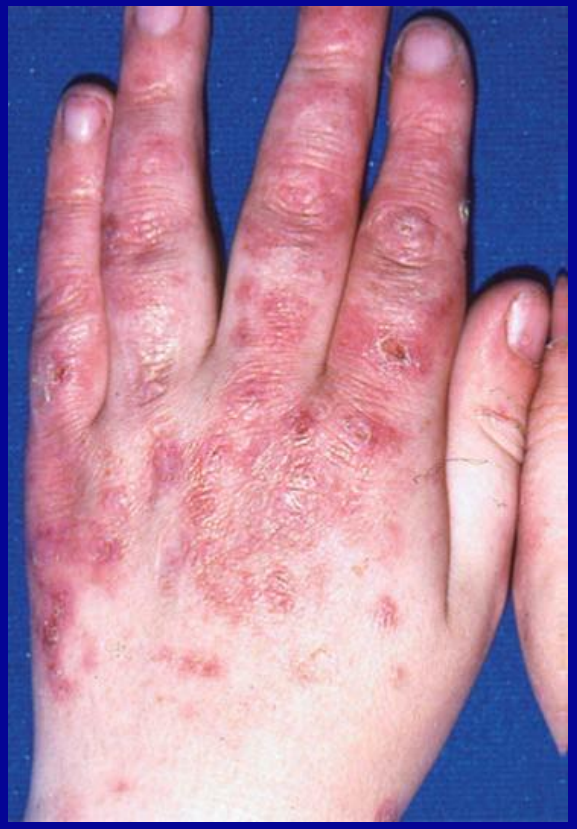
Sopeña B et al. Semin Arthritis Rheum 2017;47:46-52

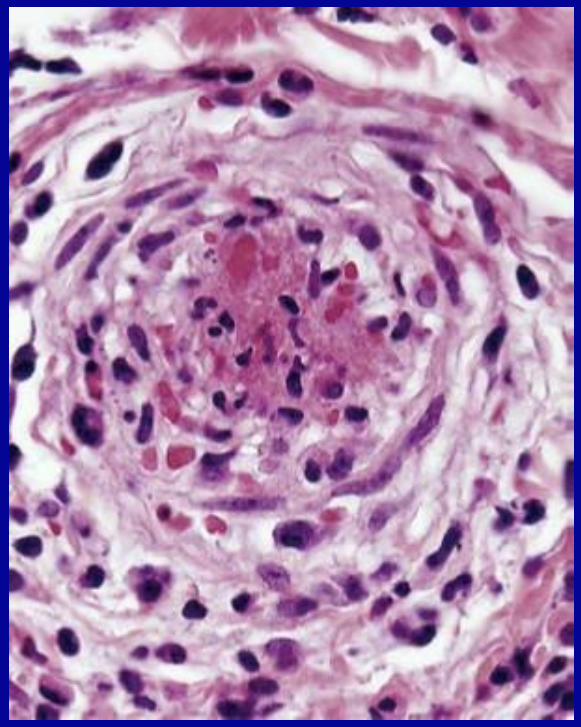
SAVI Syndrome

- Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy
- Liu Y et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014;371:507-18
- An interferonopathy caused by gain-of-function mutations in TMEM173, leading to constitutive action of STING and up-regulation of IFN-β signaling
- Characterized by facial erythema with telangiectasia, acral/cold-sensitive tissue ulceration and amputations, and interstitial lung disease
- Traditional immunosuppressive medications and biologic therapies appear to be of limited benefit, but JAK inhibitors may impact disease progression

SAVI Syndrome

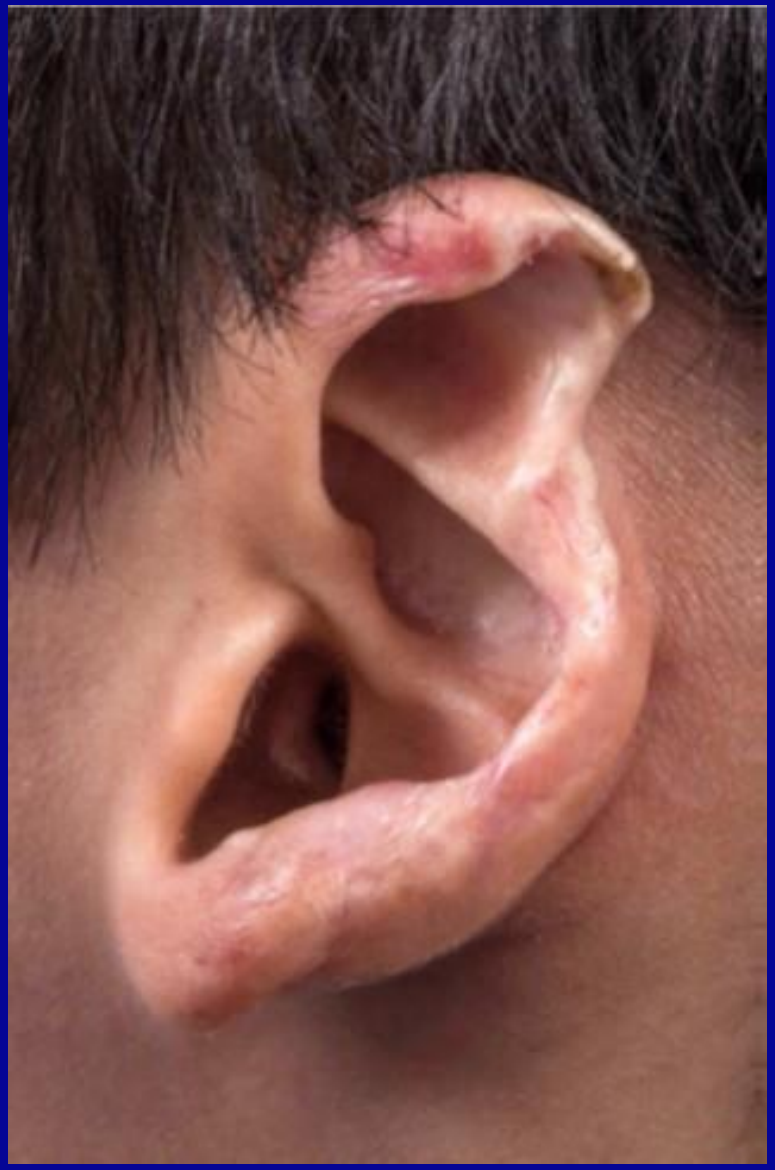


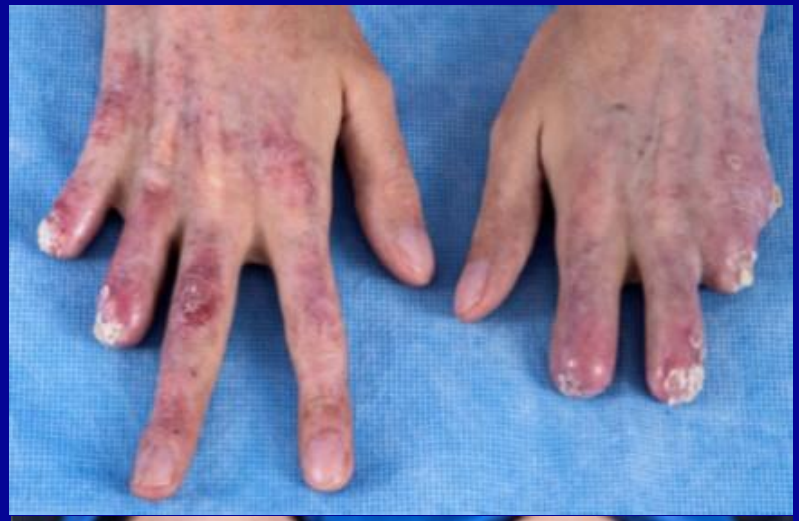


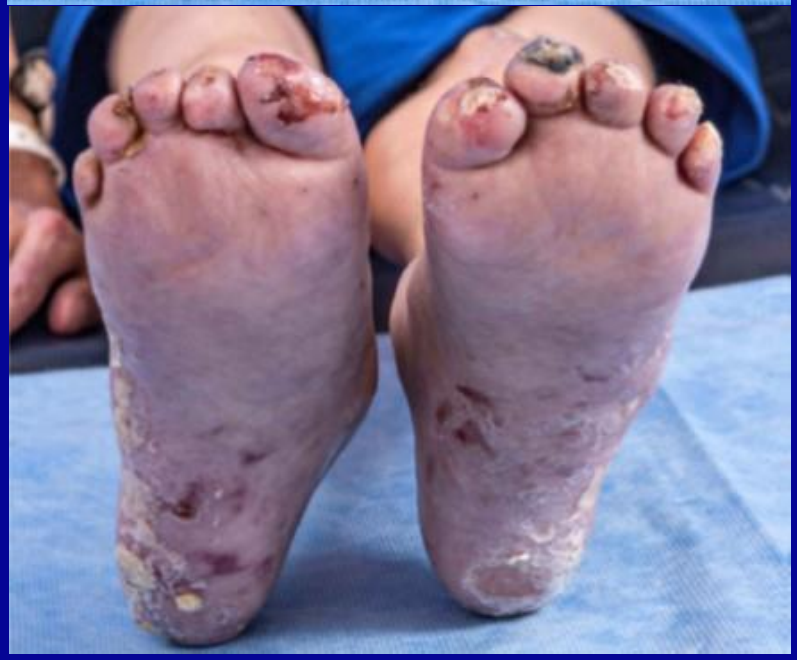


Liu Y et al. N Engl J Med 2014;371:507-18

SAVI Syndrome







Chia J et al. J Am Acad Dermatol 2016;74:186–9

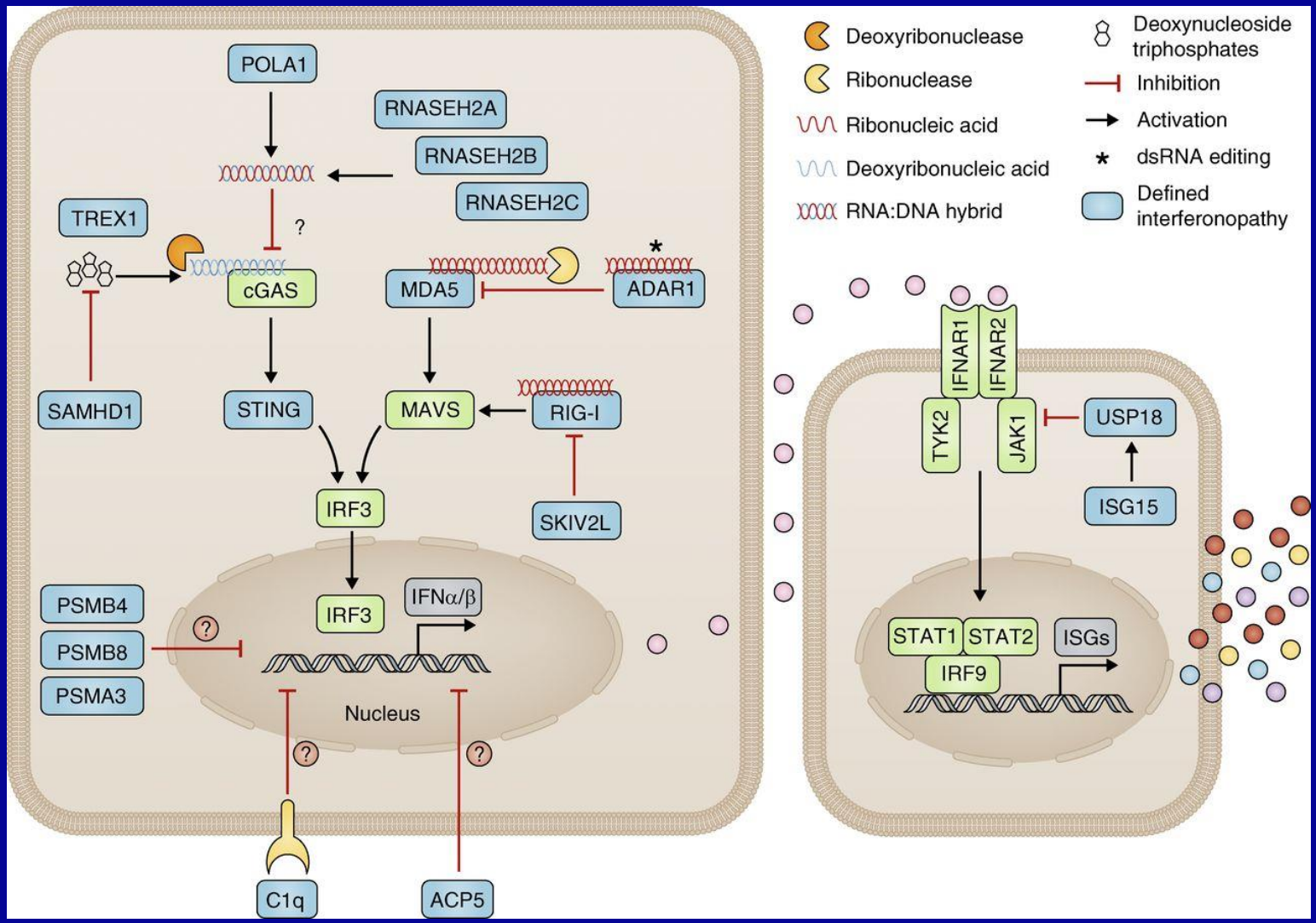
Type I Interferonopathies: The Type I Interferon-Mediated Monogenic Autoinflammation

Monogenic phenotypes, including

- Classic Aicardi-Goutières syndrome (AGS-1)
- Familial chilblain lupus
- Spondyloenchondrodysplasia
- SAVI syndrome
- CANDLE syndrome (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature)

Munoz J et al. JAMA Dermatol 2015;151:872-7

Type I Interferonopathies



Rodero MP, Crow YI. J Exp Med 2016;213:2527-38

Conclusions

- Heterogeneity of SLE and CLE
- LE-like and LE-associated syndromes: Intersection and transformation
- Autoimmune diseases, autoinflammatory diseases, primary immunodeficiency disorders: commonness, difference, overlapping, interaction
- Monogenic vs. polygenic
- Treatment perspective
  - Type I-IFN: high vs. low
  - Small molecule inhibitors: JAK-STAT inhibitors?

Sinicato NA et al. Pharmaceut Med 2017;31:81-8

Thank you very much!