The cross-road between PIDs and allergy

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KEY REVIEW ARTICLE

Attending to Warning Signs of Primary Immunodeficiency Diseases Across the Range of Clinical Practice

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A group of ~ 350 monogenic diseases presenting with: recurrent infections, autoimmunity, inflammation, allergy, neurological disorders, and cancer

All that itches is not always eczema

Eczema is a complex, chronic, relapsing inflammatory skin disorder with a lifetime prevalence in the United States of 17%.[5] Interestingly, 80% have an elevated serum IgE.[6] It is the earliest part of the allergic march toward allergic rhinitis and asthma, with 66% of patients progressing to develop asthma plus at least 1 allergy by 3 years of age.'

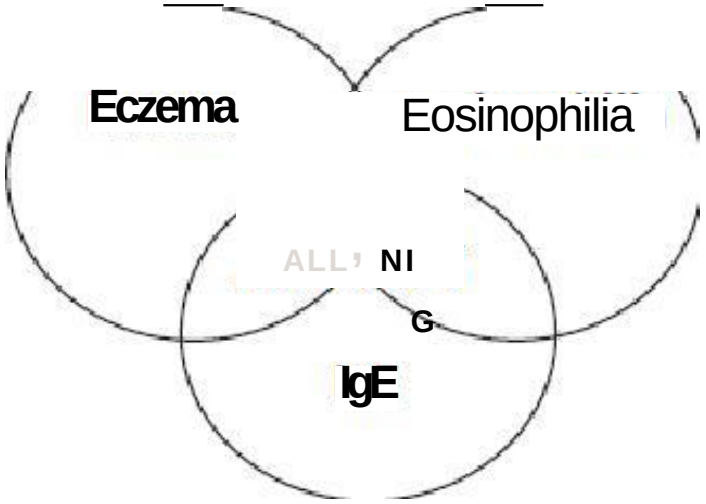


Fig. 1. The allergic triad. Allergic diseases share common factors with primary immunodeficiencies including skin rashes such as eczema, increased immunoglobulin (Ig)E, and eosinophilia.

Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

Allergy and PIDs

Table 1
Phenotypic expression of eczema, eosinophilia, and increased IgE in primary immunodeficiency

Eczema	Eosinophilia	Increased IgE
IPEX	IPEX	IPEX
Omenn	Omenn	Omenn
AD-HIES	AD-HIES	AD-HIES
AR-HIES	AR-HIES	AR-HIES
Wiskott-Adrich		

Various primary immunodeficiencies have a predominance in manifestation of their disease.
Abbreviations: AD-HIES, autosomal-dominant hyper-19E syndrome; AR-HIES, a utosom al recessive hyper-IgE syndrome; 1G, immunoglobulin; 11DEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

Omenn Syndrome

Omenn Syndrome

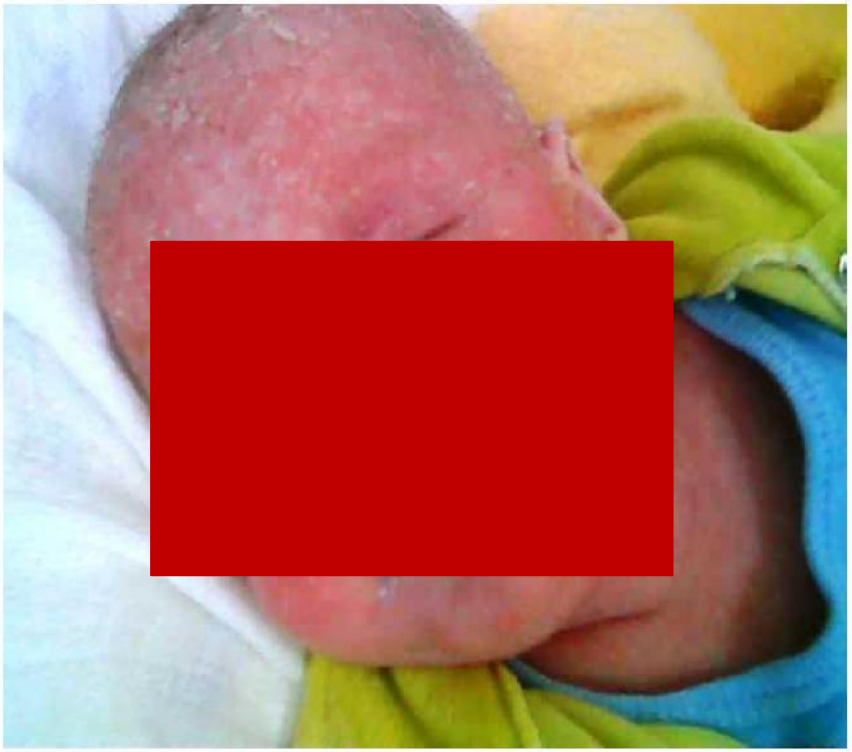
Omenn syndrome is an inflammatory condition characterized by erythroderma, desquamatous alopecia, chronic diarrhea, failure to thrive, lymphedema, and hepatomegaly.[9] It was originally described in 1965 with reticuloendotheliosis and eosinophilia.[1°] The prevalence is estimated at less than 1/1,000,000.[11] It is linked to SCID and presents in the first year of life, but the signs and symptoms evolve over time. These patients are highly susceptible to the infections that are typically seen in SCID patients.

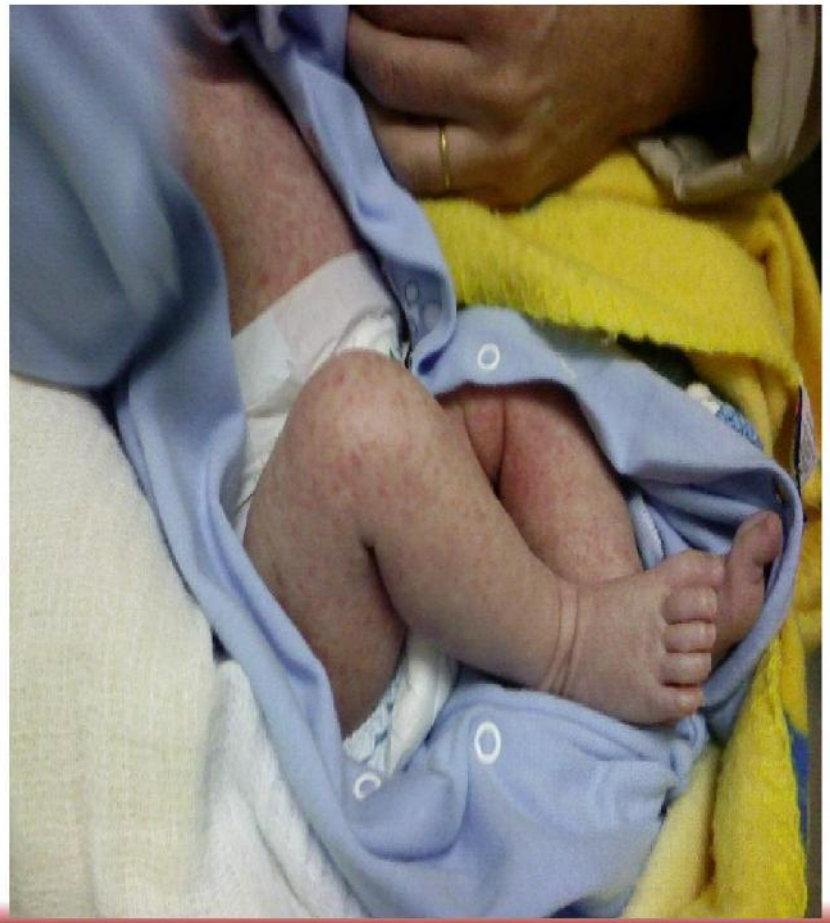
Pathogenesis

There are no specific genetic defects for Omenn syndrome. It is an inflammatory phenotype of SCID that has been linked to mutations in the recombination-activating gene 1 (RAG1) or RAG2, RNA component of mitochondrial RNA processing endoribonuclease, adenosine deaminase, interleukin (IL)-2R, IL-7R, artemis-nuclease-DCLRE1C DNA ligase 4, and 22q11 microdeletion. It usually presents in an autosomal-recessive pattern. This is a "leaky" T/B-SCID phenotype where some T or B cells are present and suggestive of mutations that lead to impairment of the V(D)J DNA recombination involved in generating immunoglobulins as well as T-cell receptors.

Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

Omenn pre-BMT





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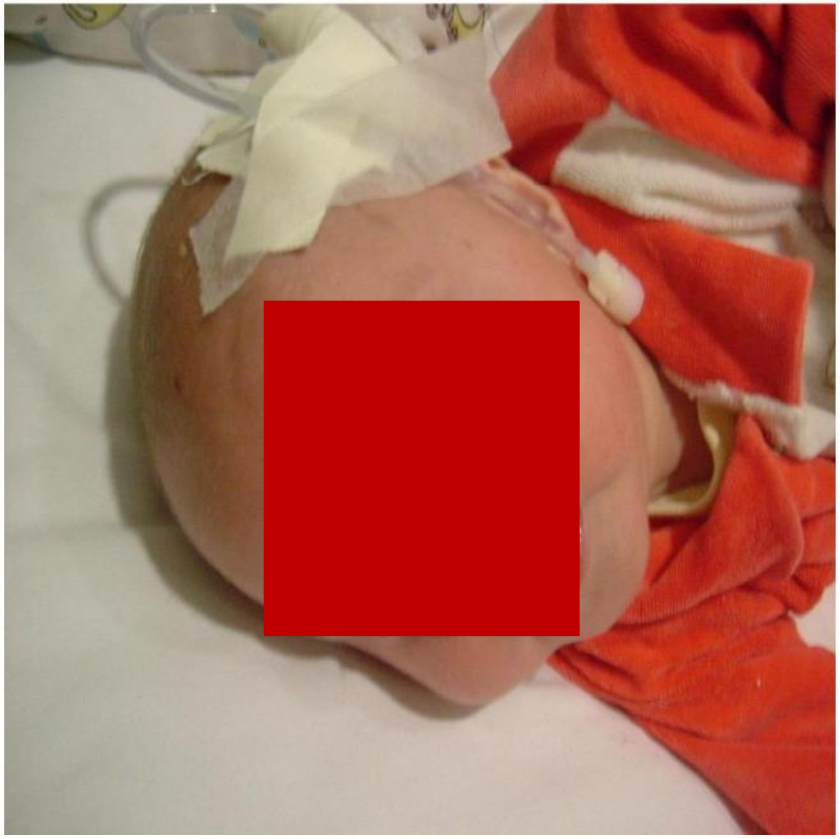
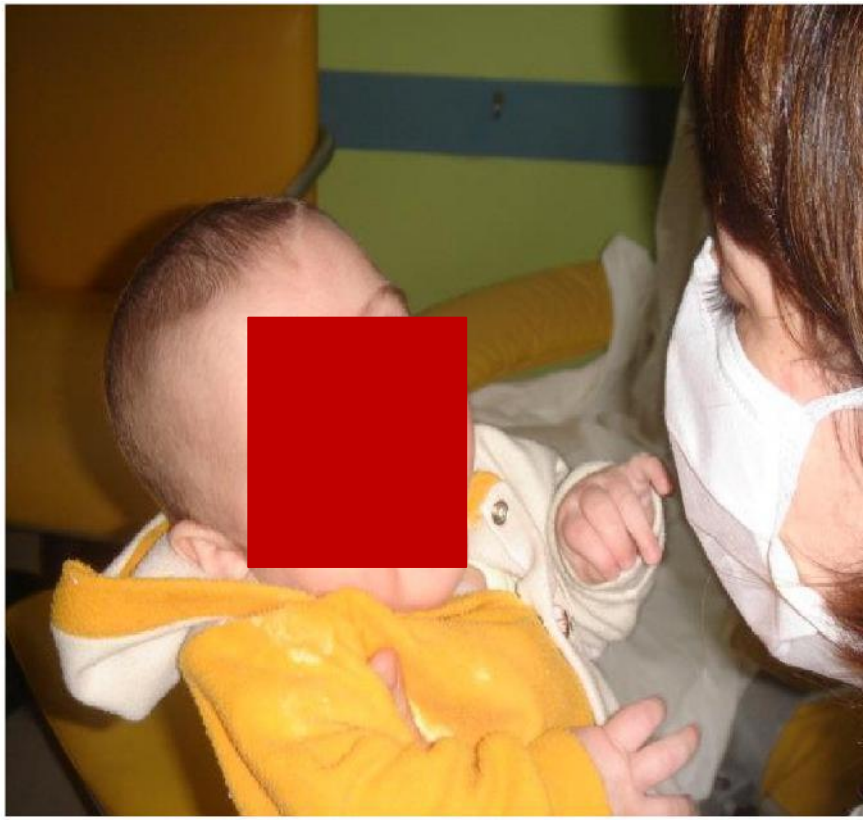
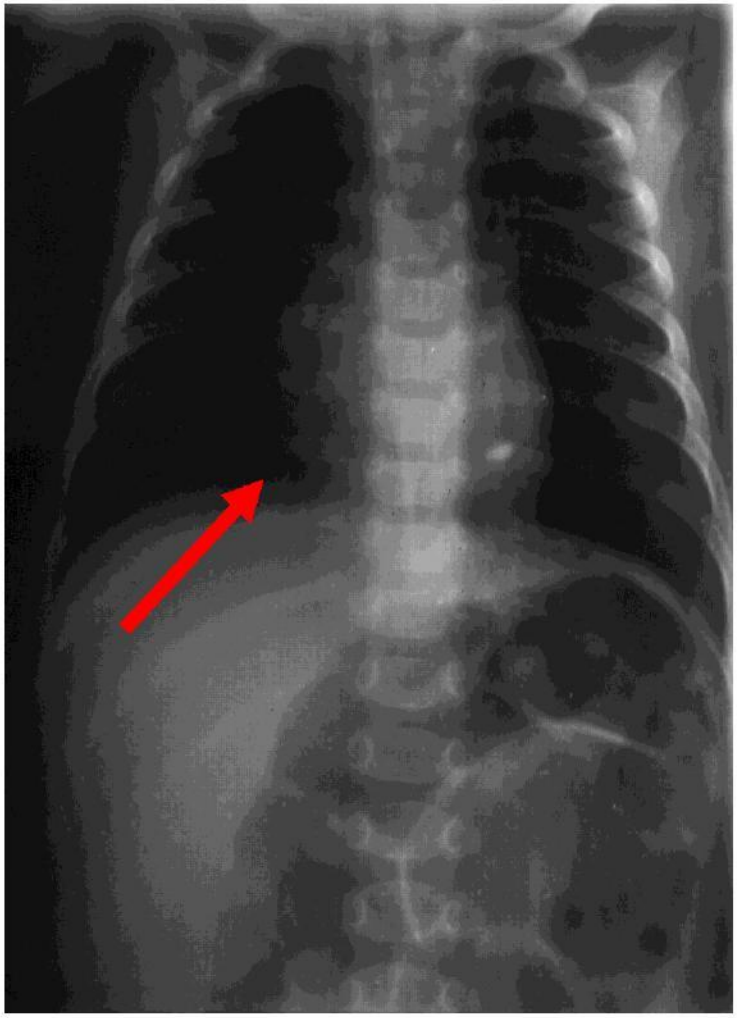
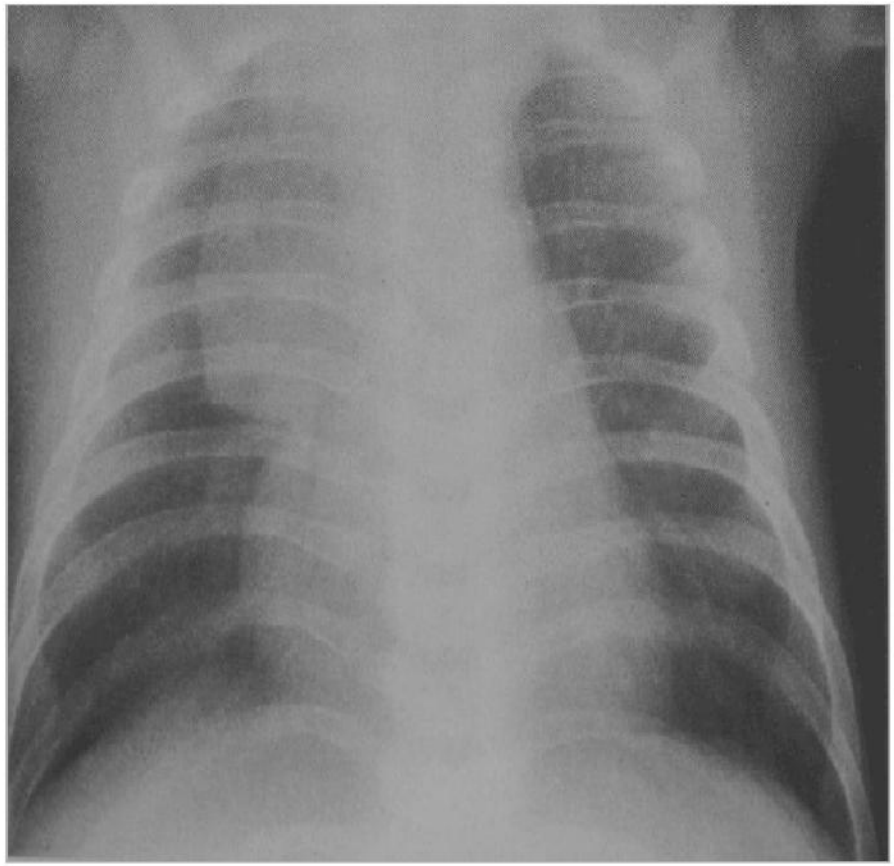
Omenn post-BMT





Omenn pre- and post BMT





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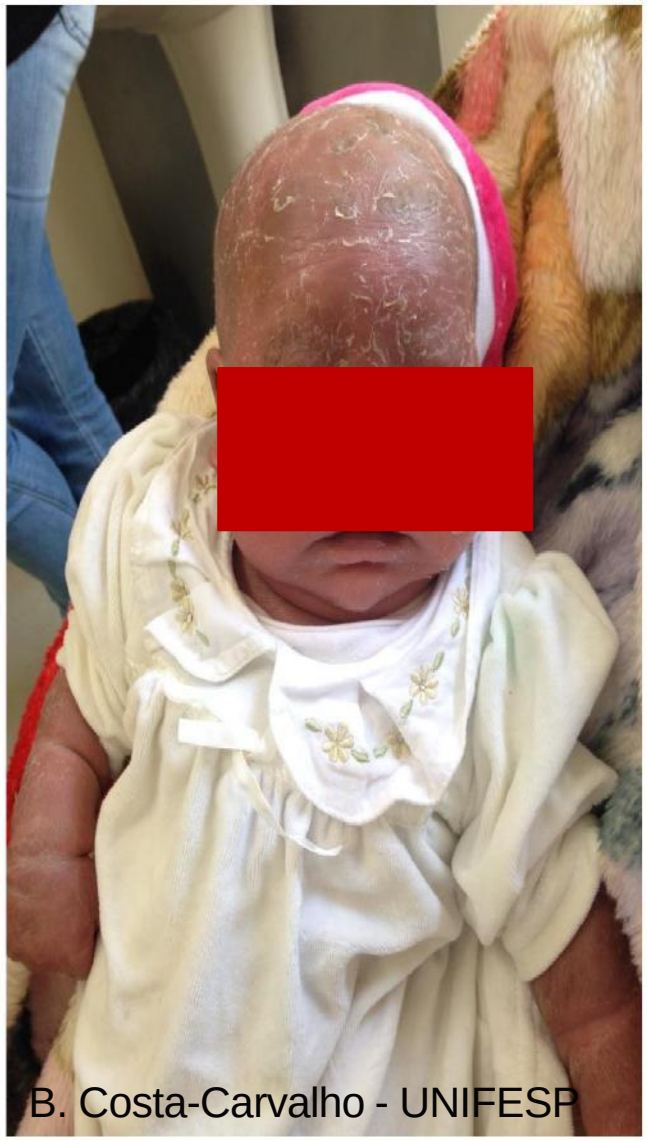
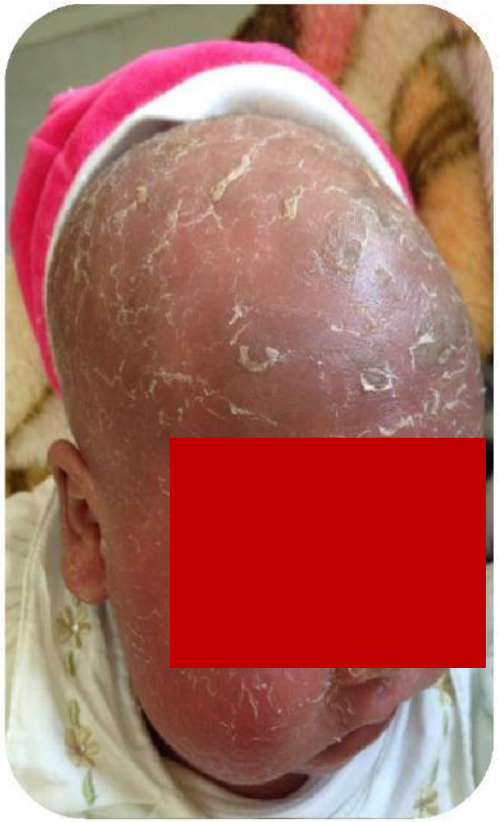
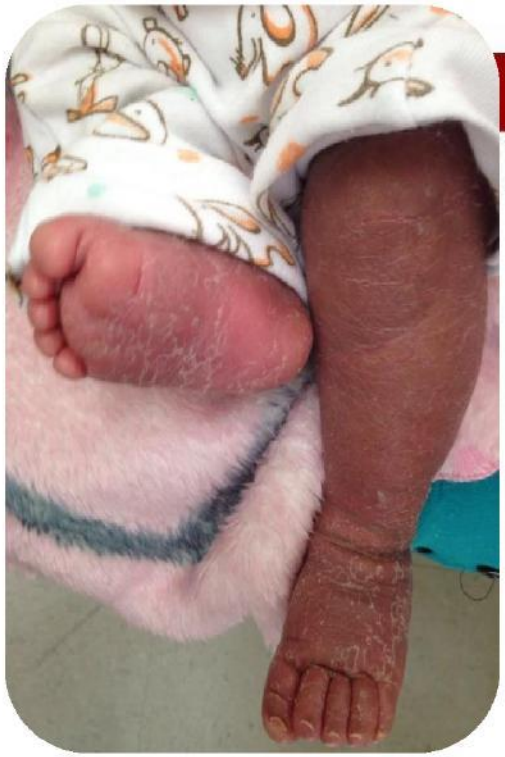
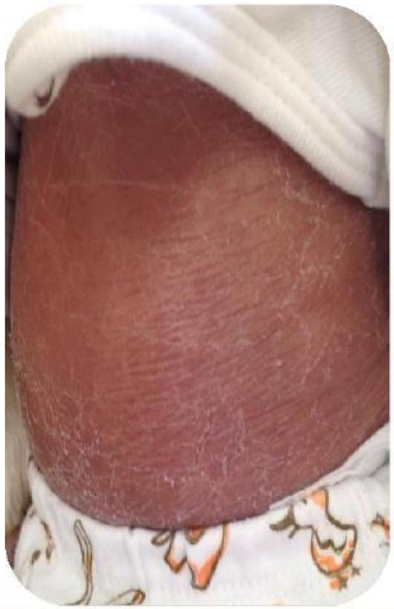
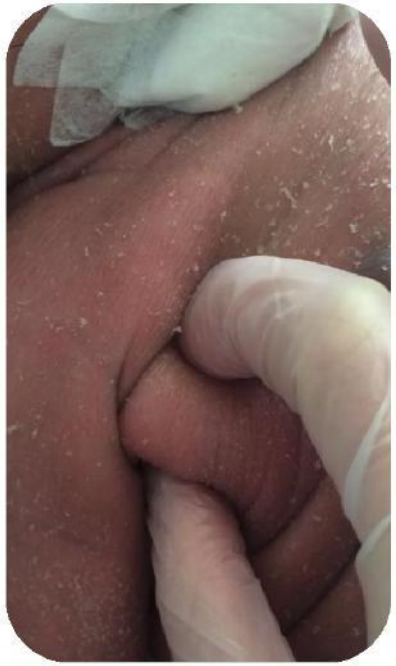
Omenn – Death no BMT











IPEX

X-linked Immunodysregulation, Polyendocrinopathy, and Enteropathy

Infants with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) usually present with severe diarrhea owing to enteropathy, end ocrinopathy usually manifesting as type 1 diabetes mellitus, and dermatitis (eczema, erythroderma). Other features may include hypothyroidism, autoimmune hemolytic anemia, throm bocytopenia, lymphadenopathy, hepatitis, and nephritis. IPEX was originally described in 1982[14] and the prevalence is estimated at less than 1 in 1,000,000[15] with only around 200 cases reported to date. Patients present in the first year of life and severity varies.

Pathogenesis

IPEX is an X-linked recessive disease caused by a mutation in the FoxP3 gene on chromosome Xp11. This transcription factor plays an important role in the development and function of **T** regulatory cells that are actively involved in suppressing the immune system and in self-tolerance.[16] These **T** regulatory cells (CD4+25+) control **T-** and B-cell inflammatory reactions. FoxP3 binds to the FOX-binding site within the IL-2 promoter and suppresses its activity.

Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked (Xp11.23)

1 year, 5.2 kg

Chronic diarreha

Auto-immune entheropathy

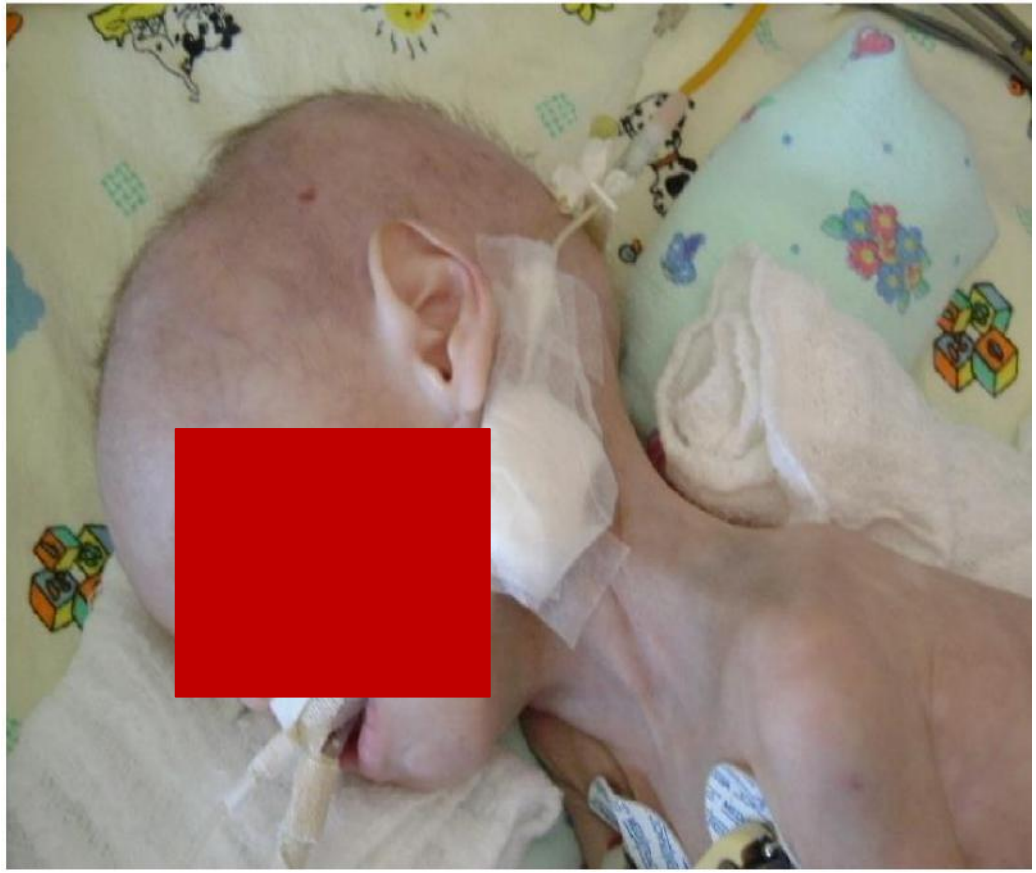
Type I diabetes

Hypothyroidism

Eczema

Hemolitic anemia

Sepsis (4)



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Wiskott-Aldrich Syndrome p-cv

Wiskott-Aldrich Syndrome

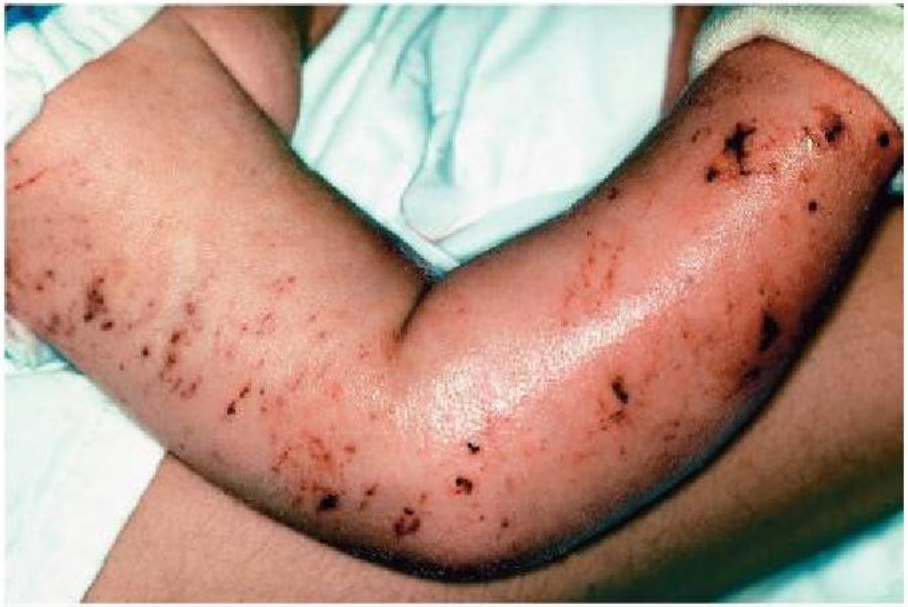
Infant males with severe diarhea, eczema, and thrombocytopenia should be evaluated for Wiskott-Aldrich syndrome. Because of severe thrombocytopenia (which typically causes bloody diarrhea), most cases present with hemorrhagic manifestations of this syndrome yet eczematous skin lesions are readily visible. These males are prone to recurrent infections, with a component of autoimmunity in approximately 40% of cases. It was originally descri bed in 1 954,[22] and the prevalence is estimated at around 4 in 1 ,000,000.[23]

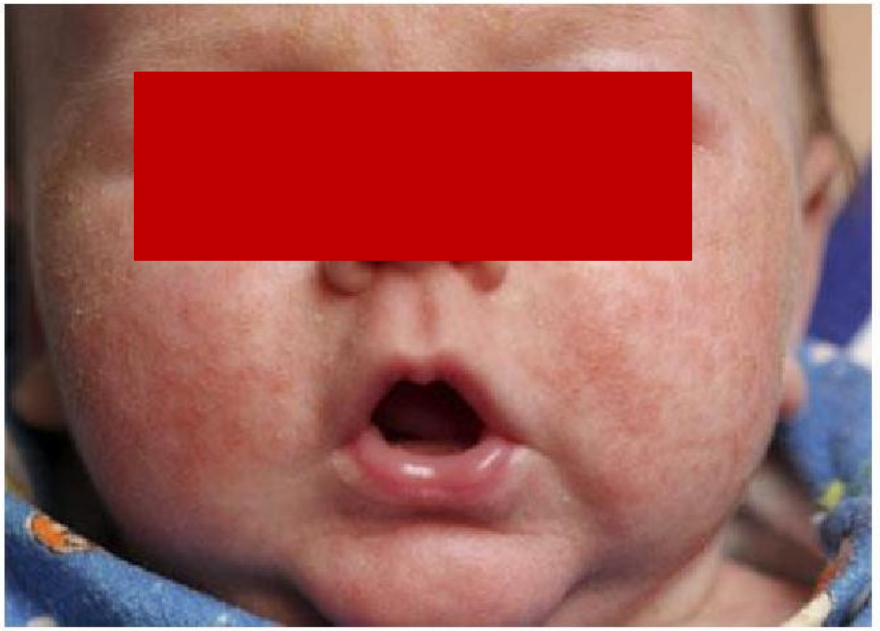
Pathogenesis

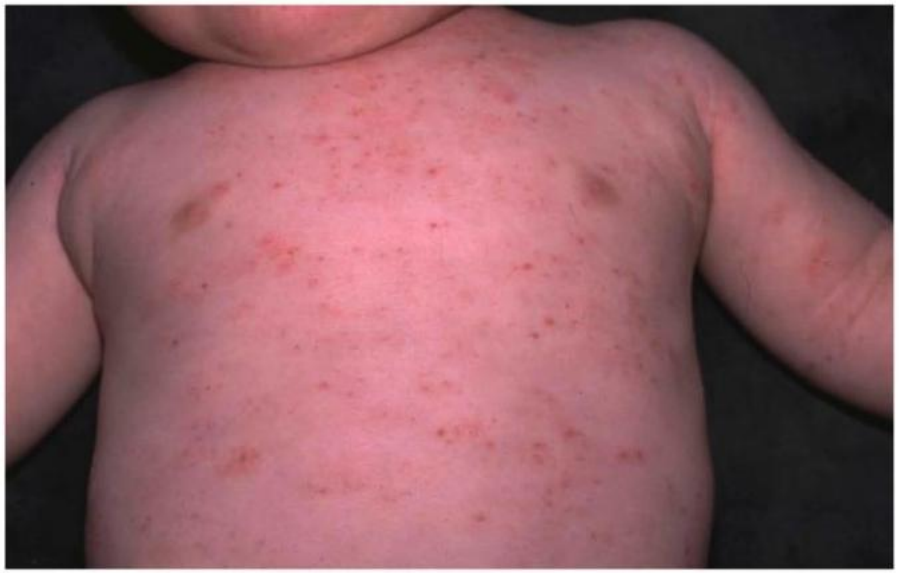
Wiskott-Aldrich syndrome is an X-linked recessive disease owing to hemizygous mutations in the Wiskott-Aldrich syndrome gene (Xp1 1.4-p11.21), coding for the Wiskott-Aldrich syndrome protein (WASp), which is exclusively expressed in hematopoietic cells and plays a critical role in the organization of the actin cytoskeleton. WASp is involved in T-cell actin reorganization,' coupling surface Ig and signal transduction for B-cell activation,' as well as natural killer (NK) cell cytotoxicity. All immune cells, B, NK, and T cells are affected, resulting in a combined phenotype.

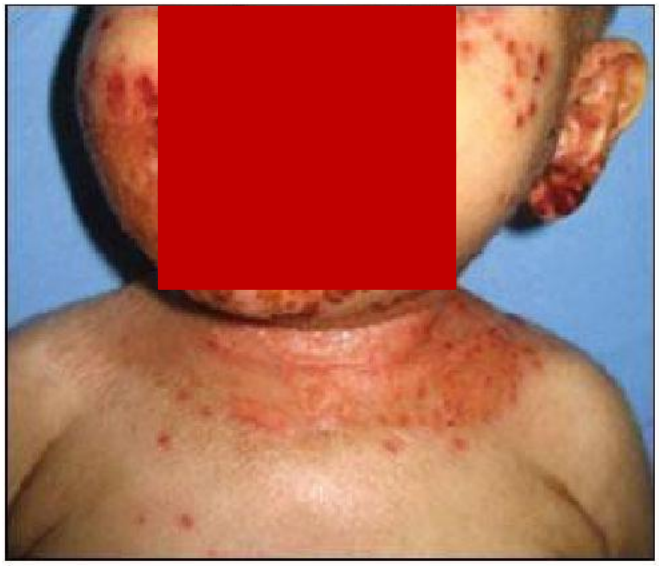
Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

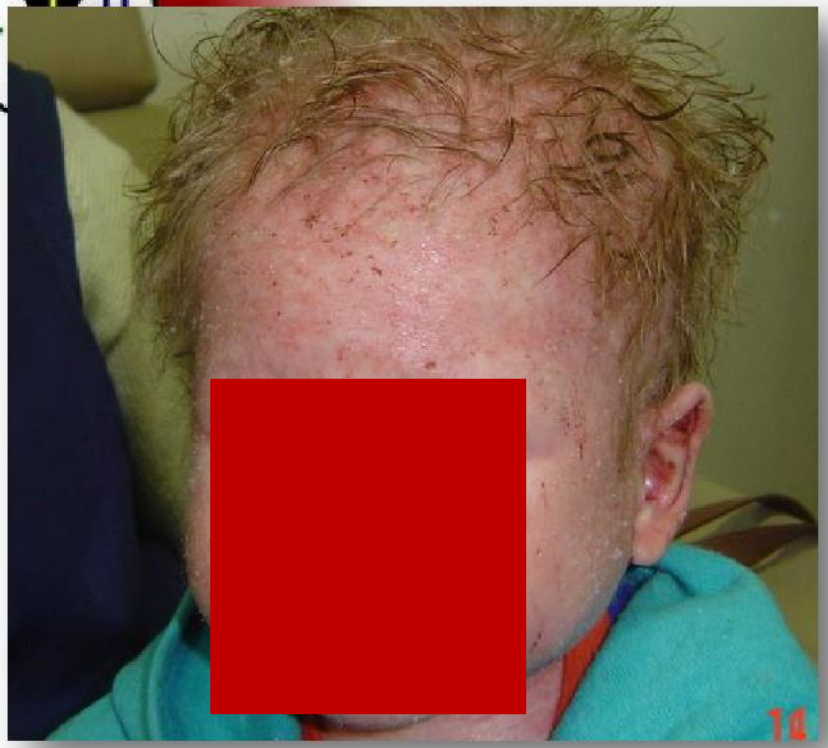
Wiskott-Aldrich Syndrome

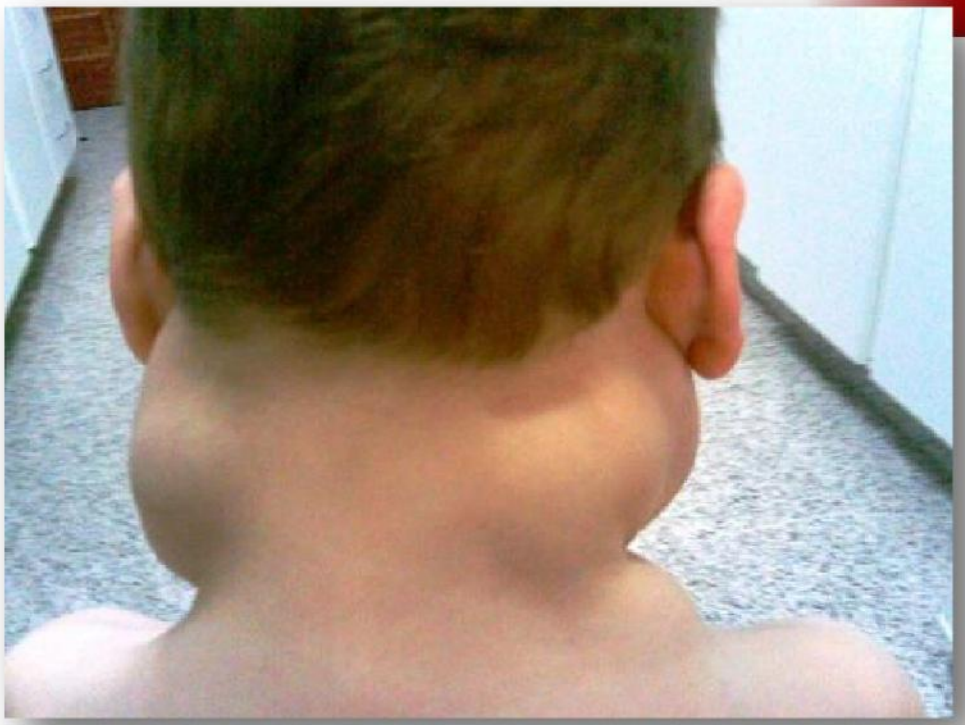


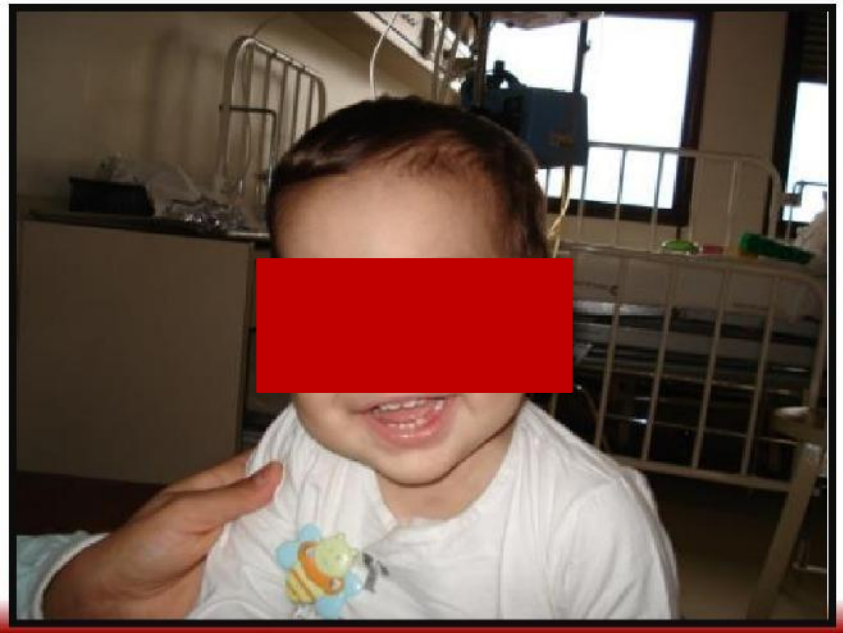










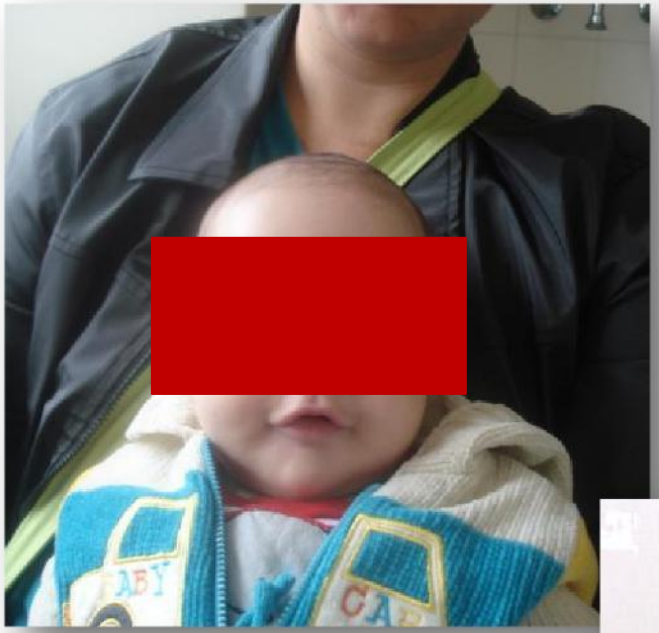


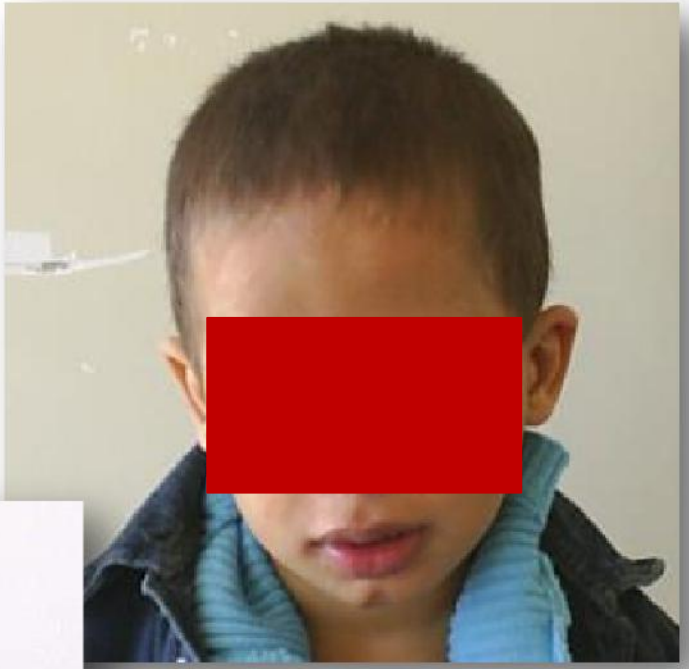
WAS pre- & post-BMT

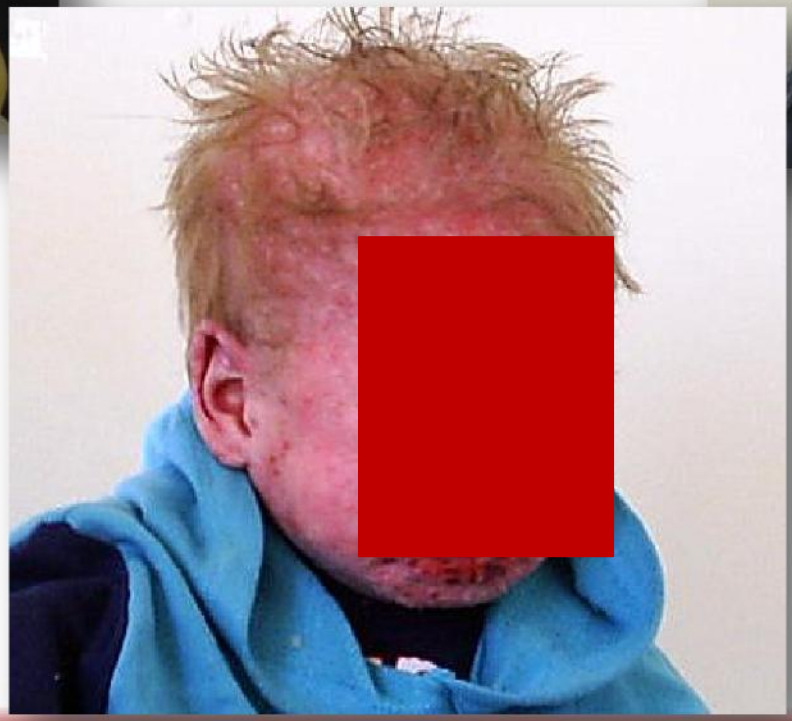
Carmem Bonfim UFPR

WAS 3 brothers : “Allergy or Autoimmunity

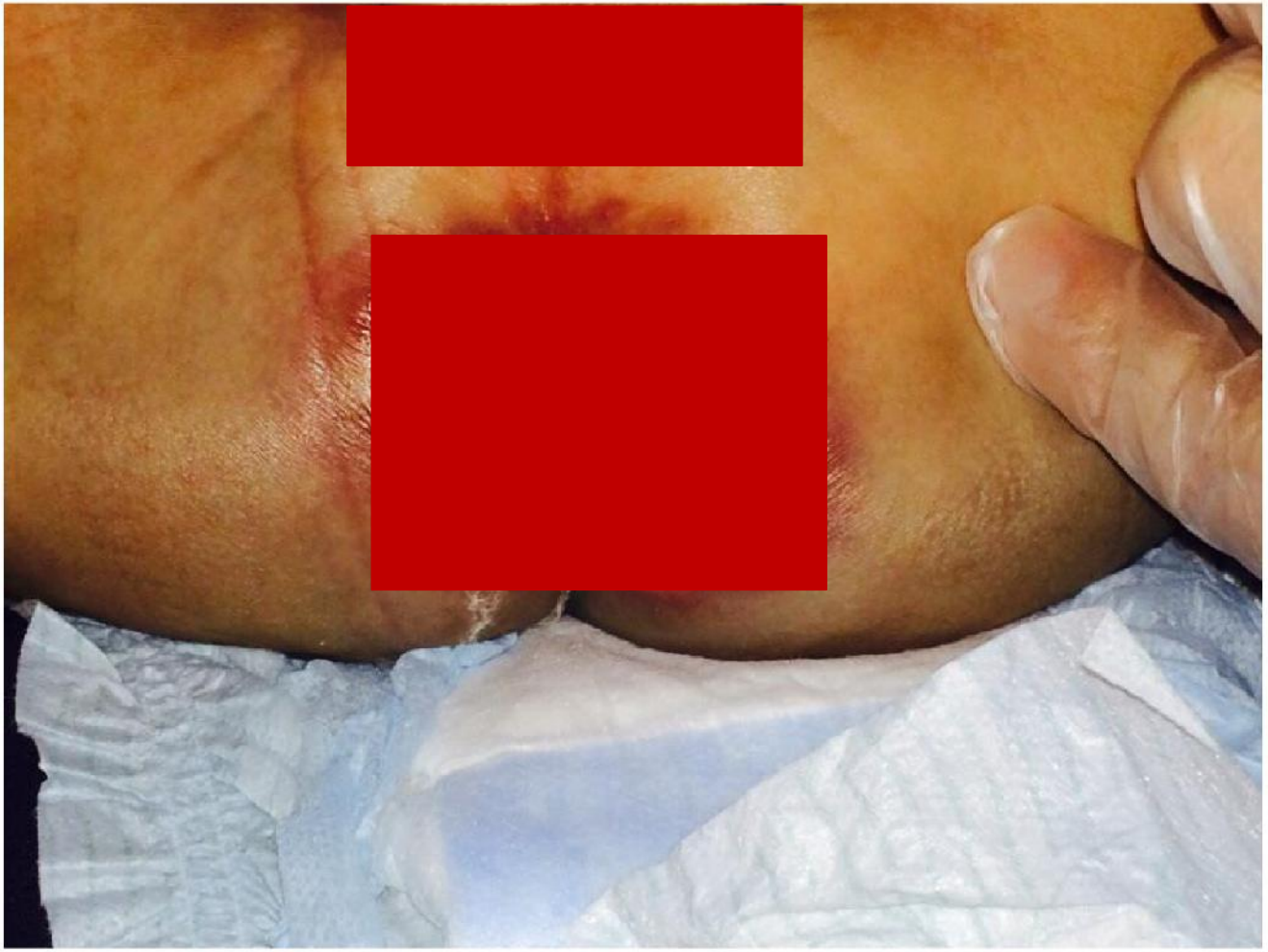
Carmem Bonfim UFPR

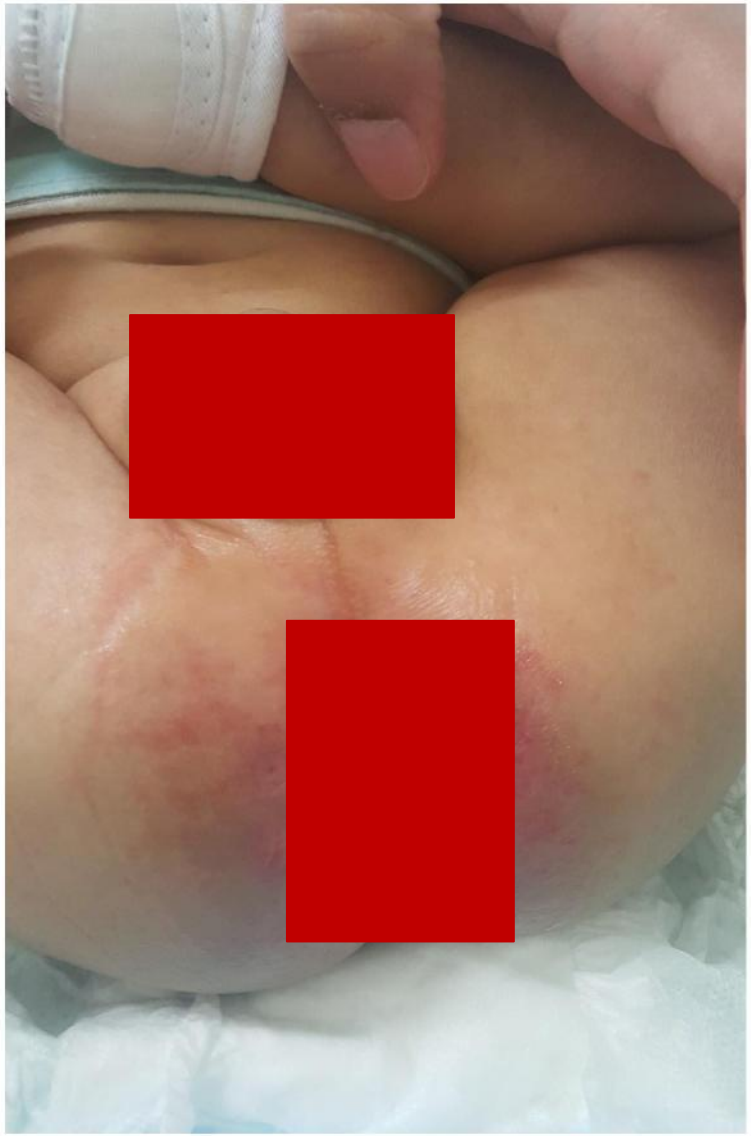






Wiskott-Aldrich Syndrome





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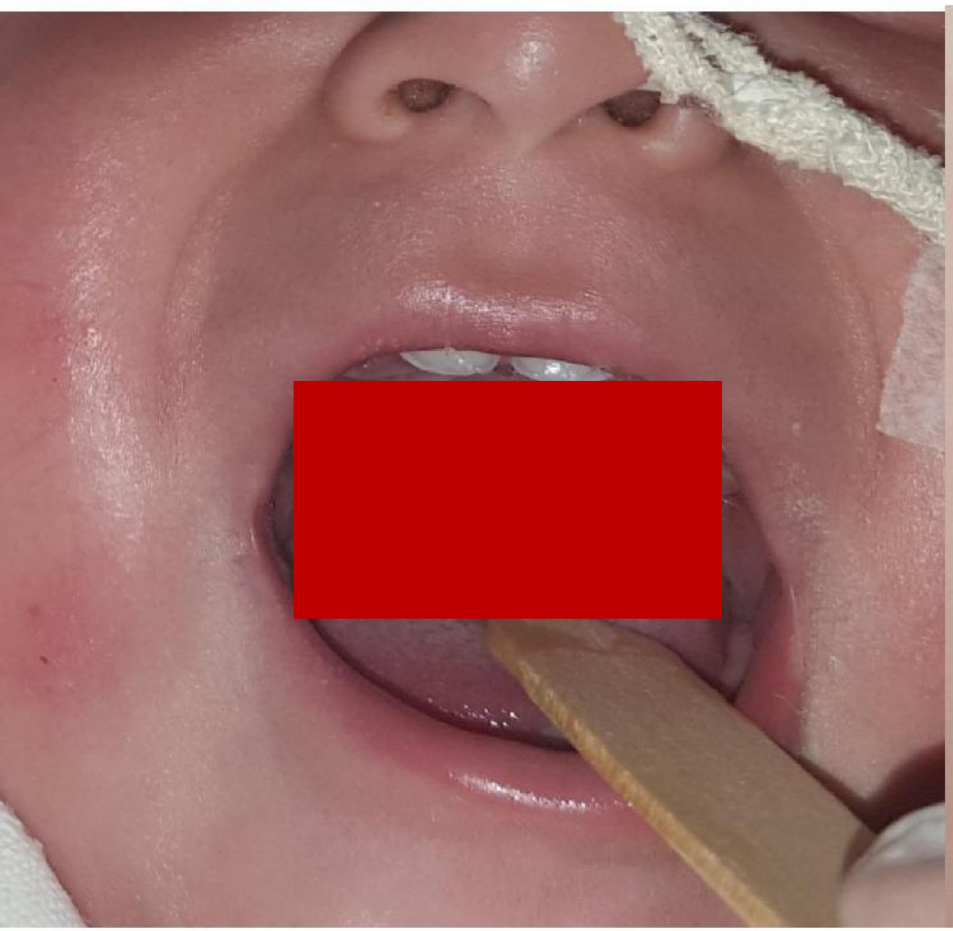
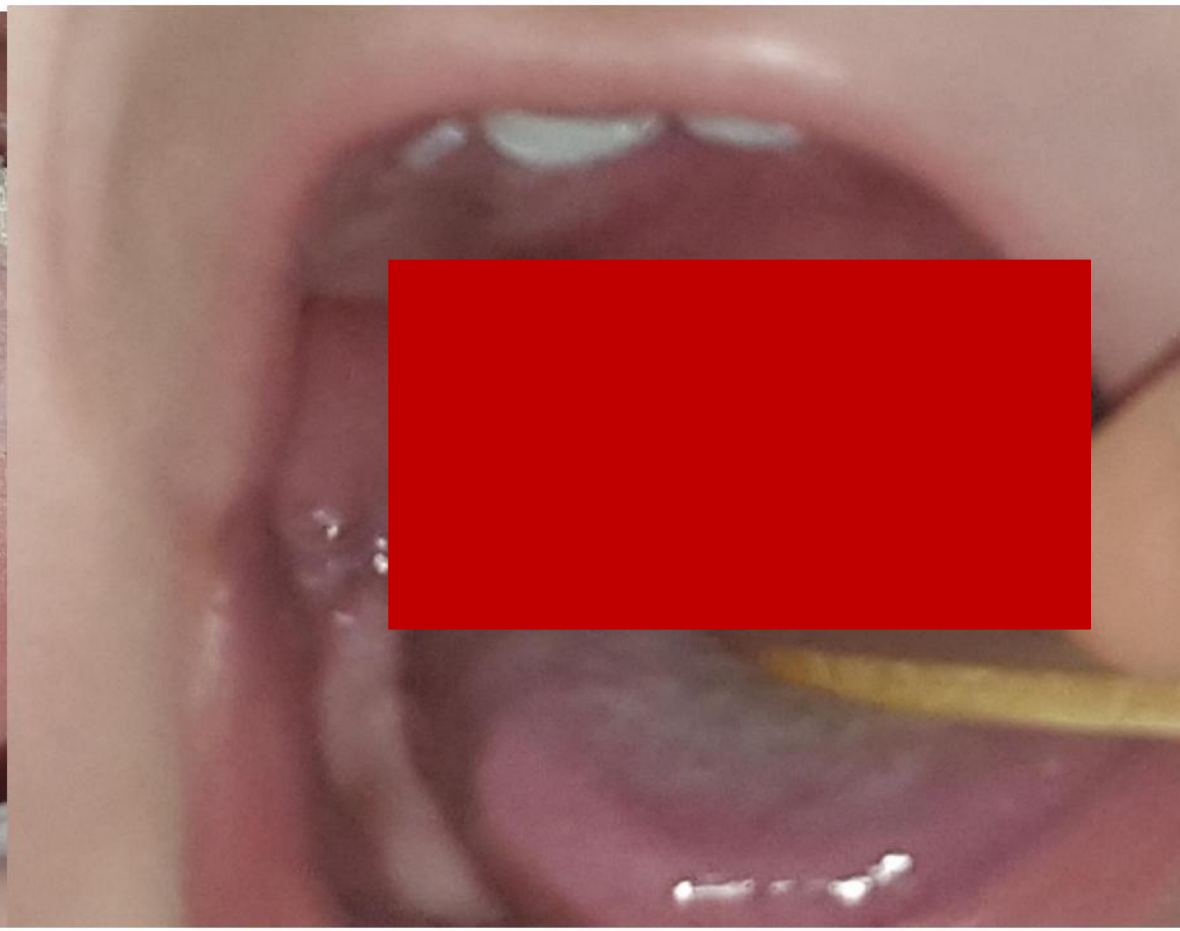
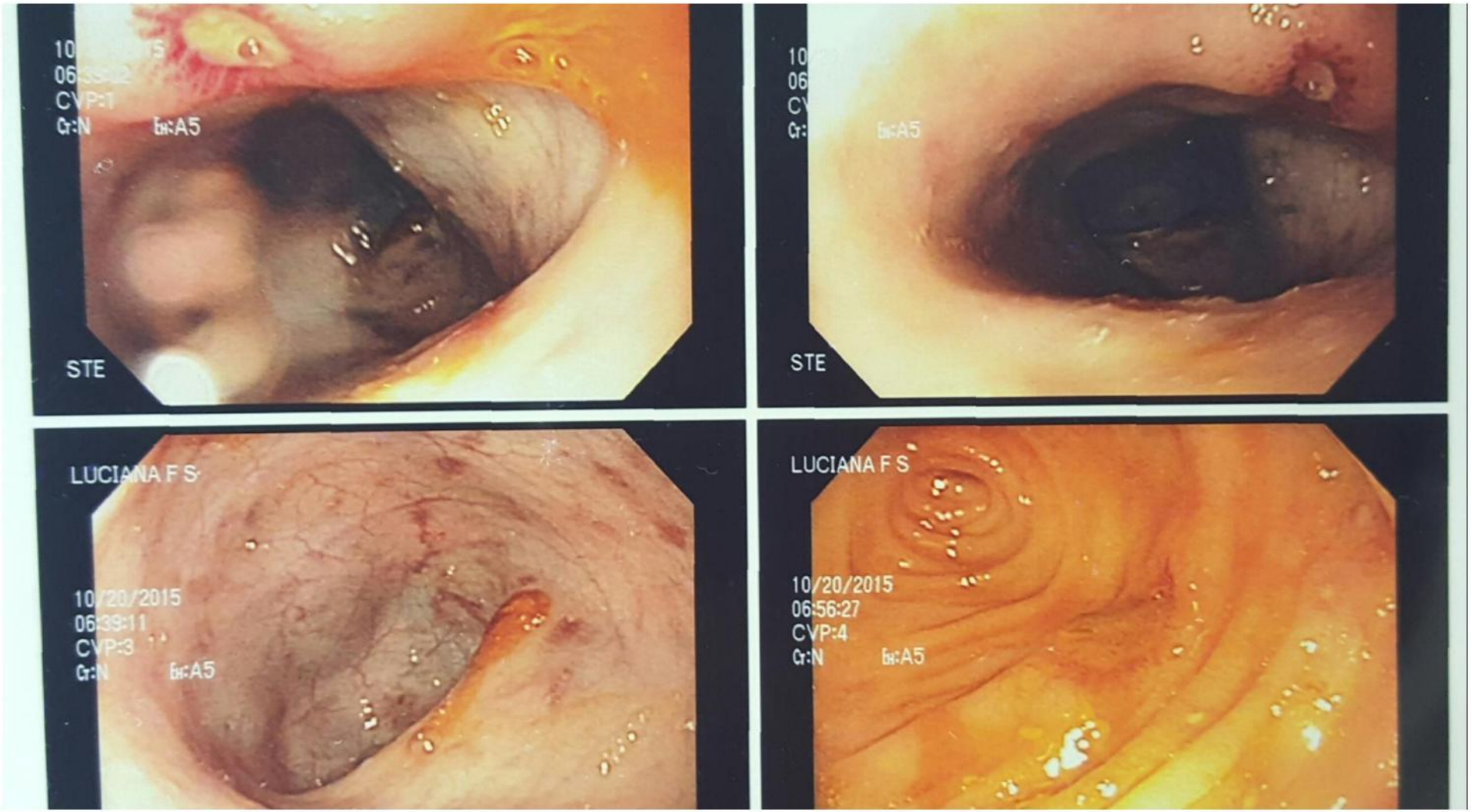
Wiskott-Aldrich Syndrome

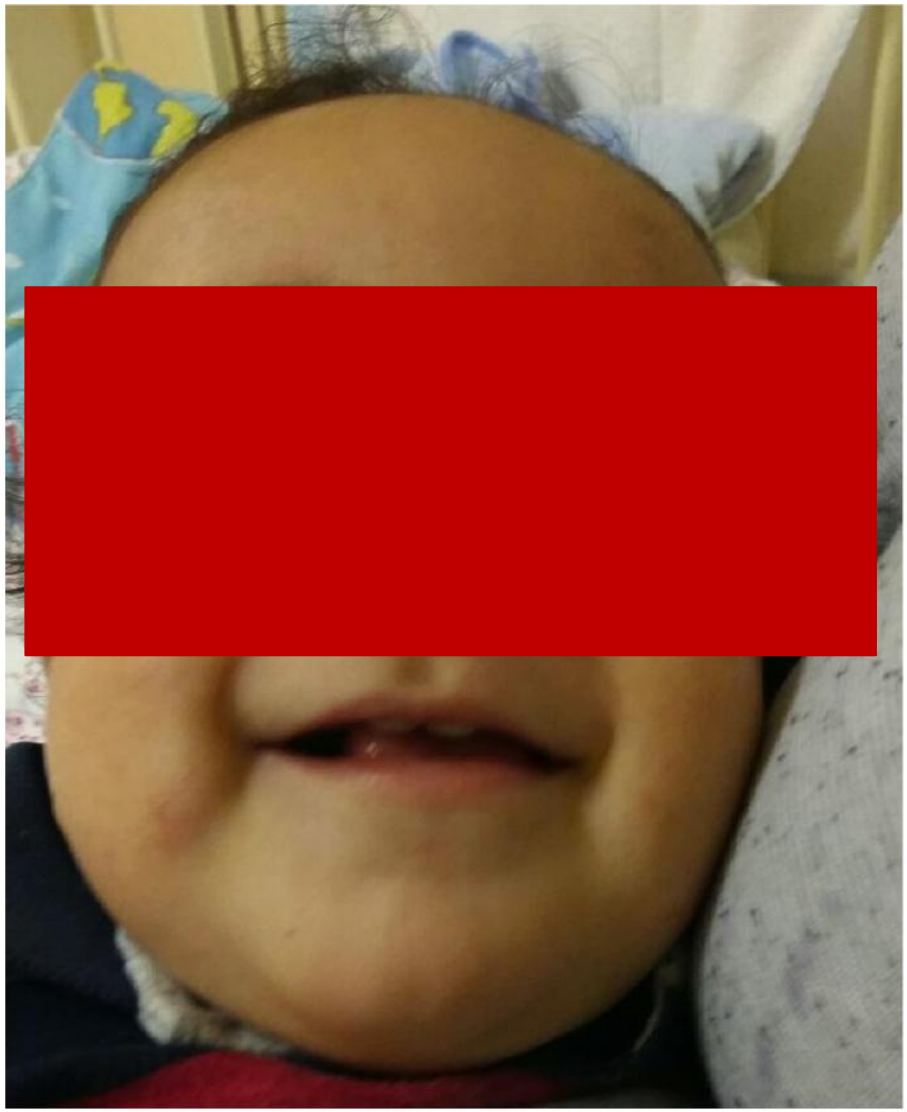




Wiskott-Aldrich Syndrome



WAS post-BMT



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HIGE, Eosinophilia, Eczema

[KS?

Table 2
AD-HIES and AR-HIES

	AD-HIES	AR-HIES	
Gene Association	STAT3	DOCK8	TYK2
Mostly de novo mutations	X		
Increased IgE	X	X	X
Eczema	X	X	X
Eosinophilia	X	X	X
Coarse facies	X		
Skeletal abnormalities	X	—	—
Retained primary teeth	X	—	—
Hyperextensible joints	X	—	—
Pulmonary pneumatocele	X	-	—
Viral skin infections	X		X
Asthma	X		—
Food allergies	X		—
Decreased IgM	X		—
Mycobacterium susceptibility	X		
Difficulty handling herpes simplex virus and Molluscum	X	X	
CNS manifestations	X	X	
Cerebral vascular malformations	X	X	

Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

AD-HIES STAT3

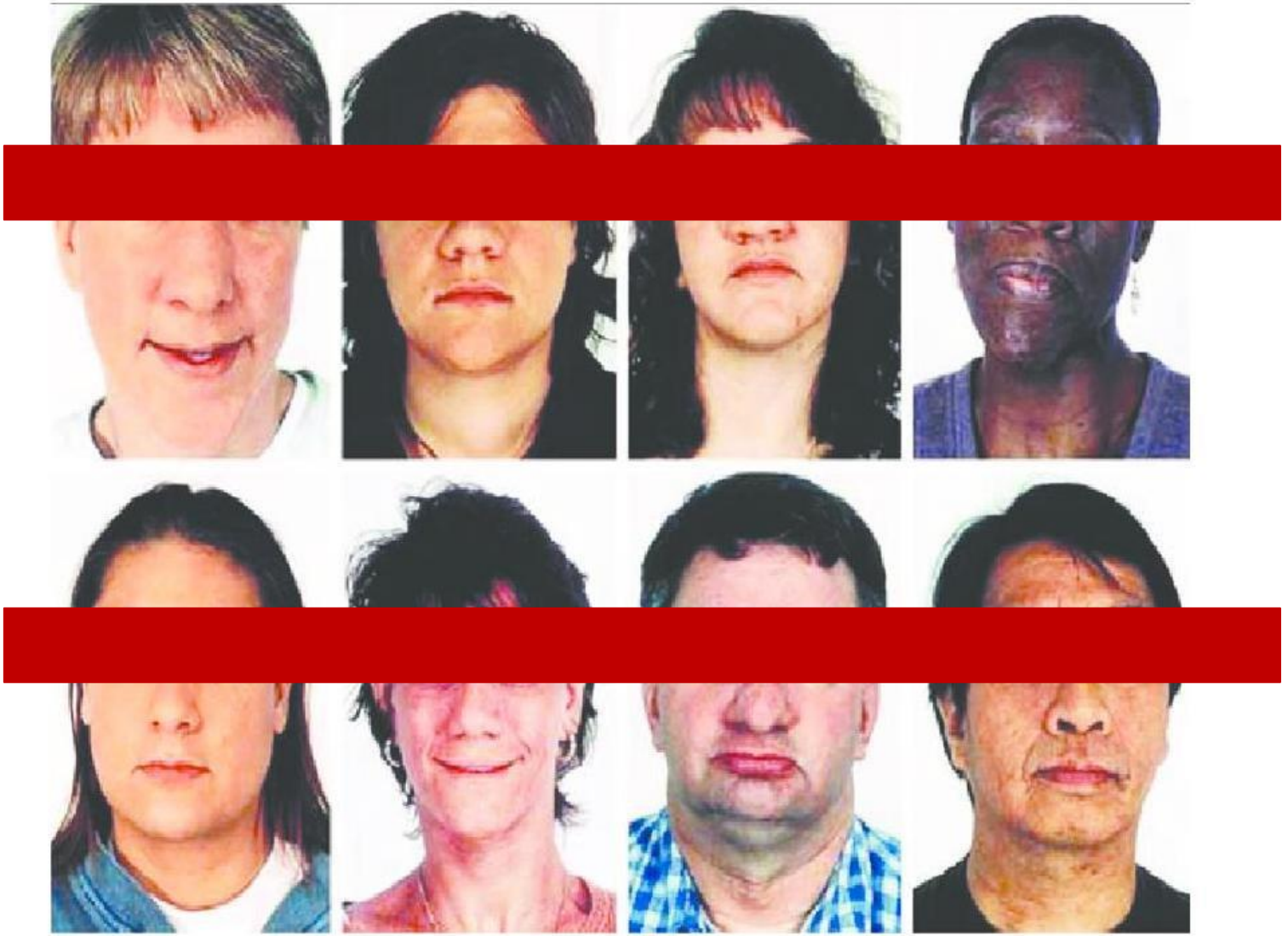
Pathogenesis

A dominant-negative heterozygous mutation in STAT3 leads to AD-HIES. STAT3 is located at 17q21.31 and is critical in the signal transduction of a broad range of cytokines that act as transcription activators. Phosphorylation of tyrosine 705 leads to activation and the formation of homodimers or heterodimers, which then translocate to the cell nucleus. They respond to cytokines and growth factors including: interferons, epidermal growth factor, IL-5, IL-6, hepatocyte growth factor, leukemia inhibitory factor, bone morphogenetic protein 2, IL-10, and leptin. The loss of function results in the failure of cells to respond appropriately to normal signaling.

There is a decrease in central memory (CD4- and CD8-positive T cells expressing CD27 and CD45R0) not due to apoptosis or cell turnover and stimulation of naive T cells with IL-7 or IL-15 failed to restore memory cell generation.' Defects in STAT3 decreases signaling through the T helper 1 pathway and skews toward T helper 2 cytokine production. Most cases are caused by de novo mutations.

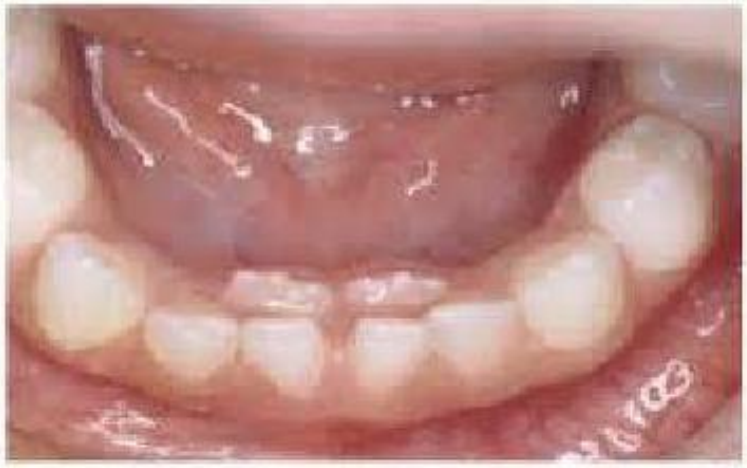
Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

AD-HIES STAT3

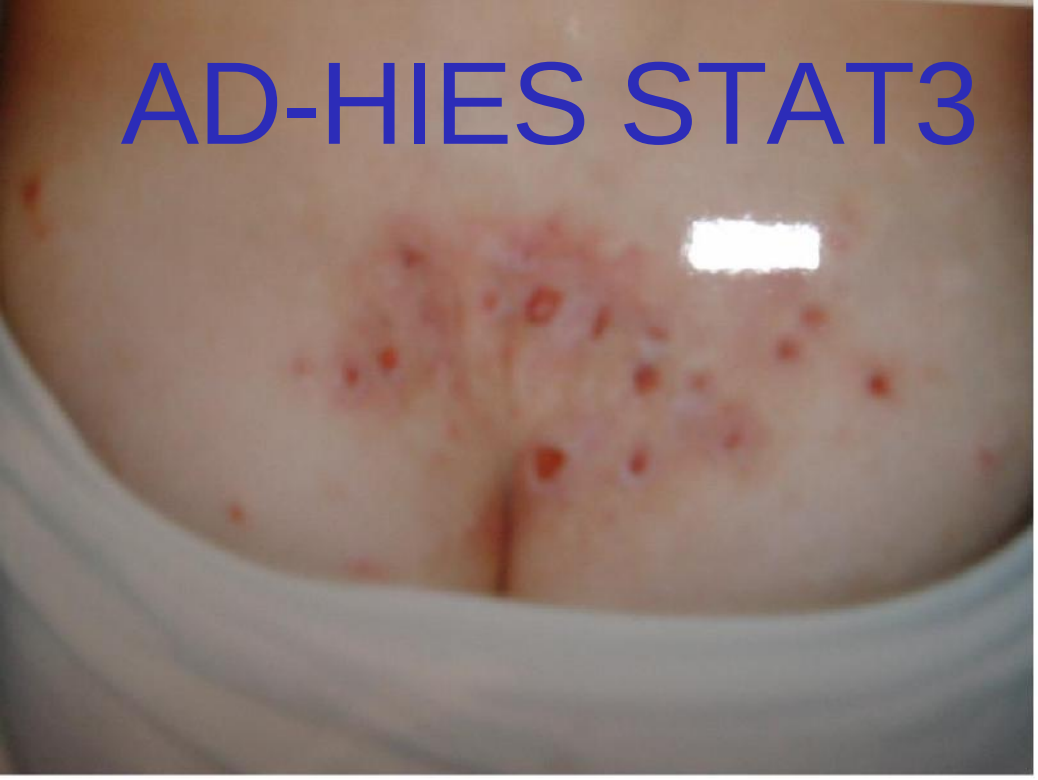


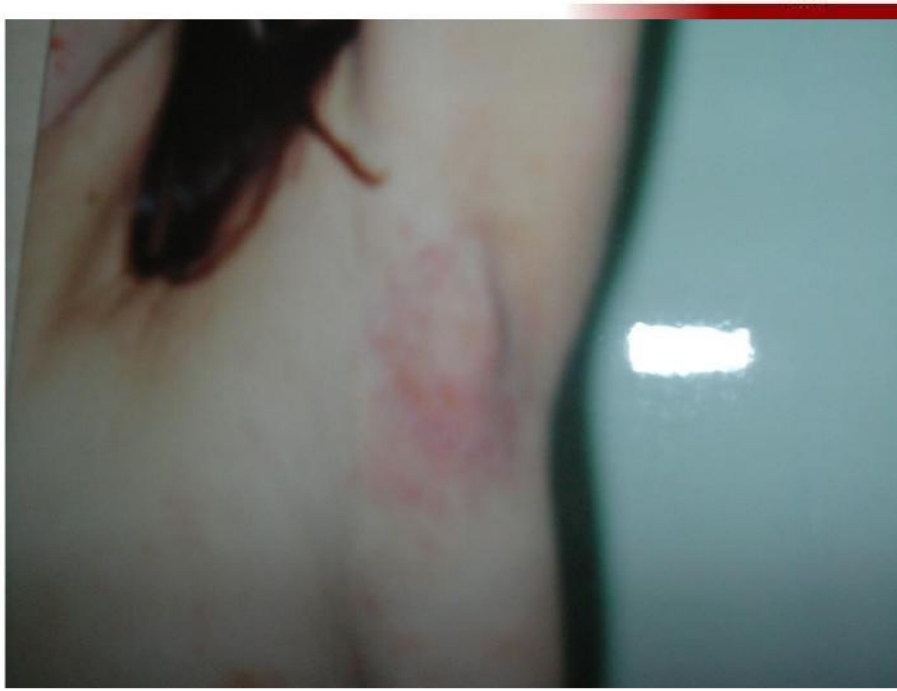
Grimbacher , NEJM 1999, 340:692-702

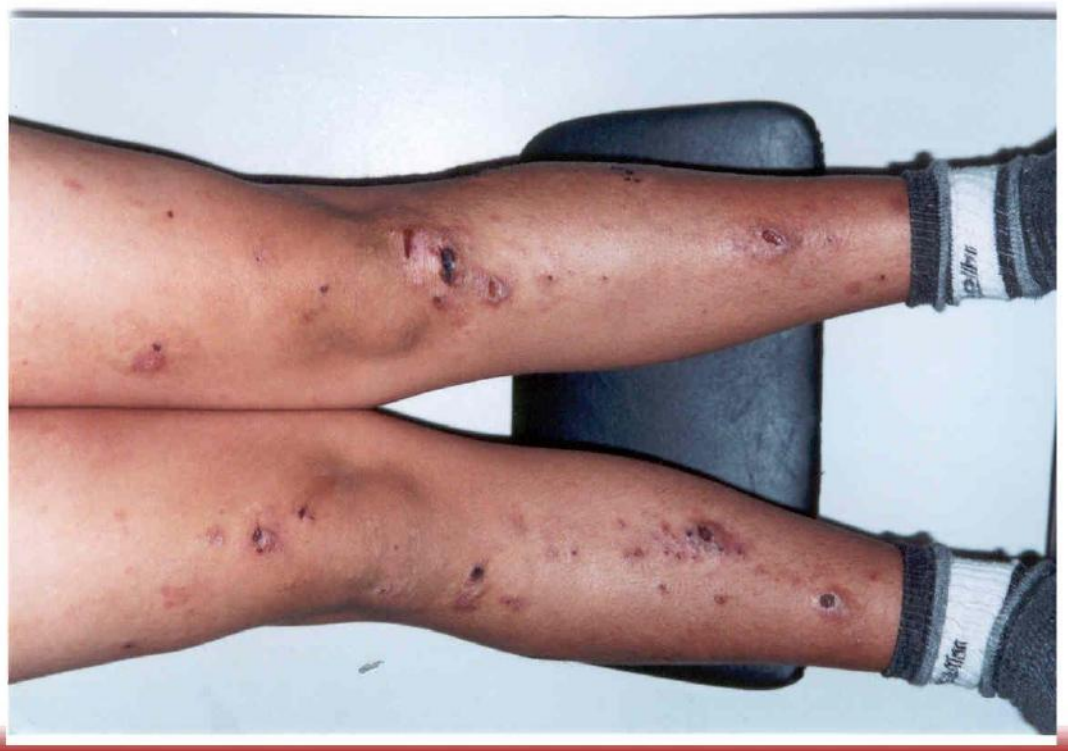
AD-HIES STAT3



AD-HIES STAT3







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AD-HIES STAT3

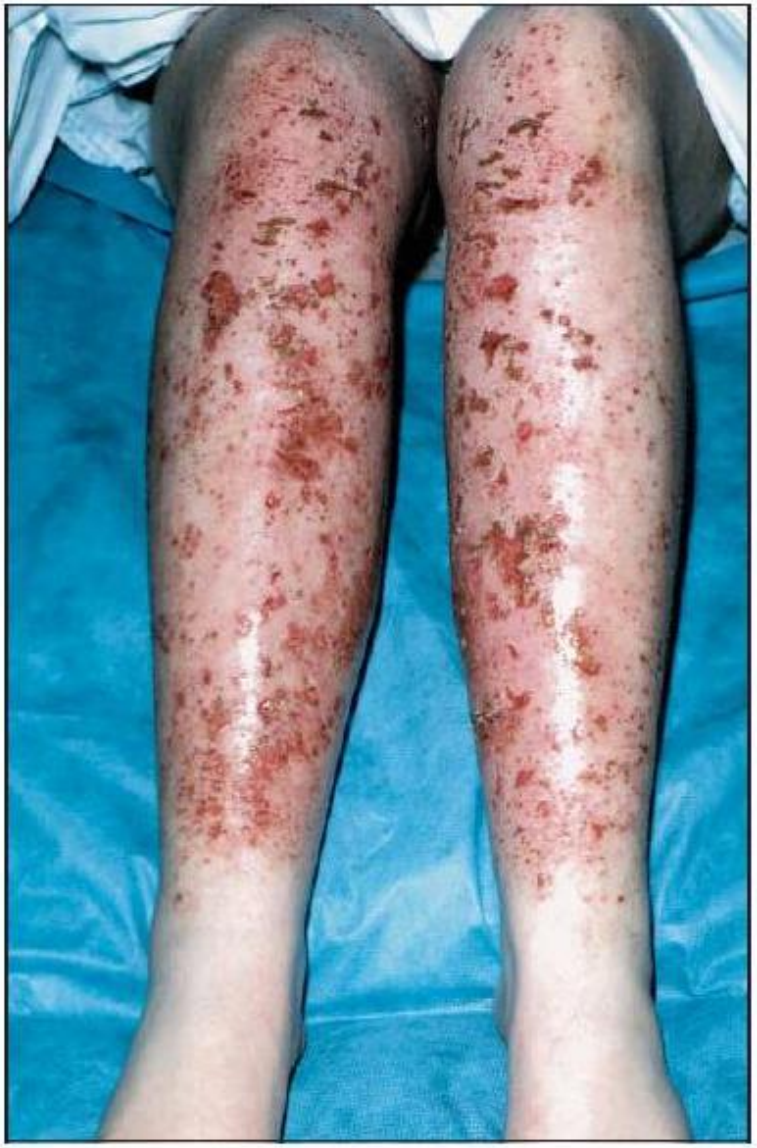


Figure 4. The dermatitis pictured here, on the same patient as shown in Figure 3, is diffuse and affects atypical areas for atopic dermatitis, sparing the areas usually covered by the patient's socks.

Eberting CL et al Arch Dermatol. 2004 Sep;140(9):1119-25

AD-HIES STAT3

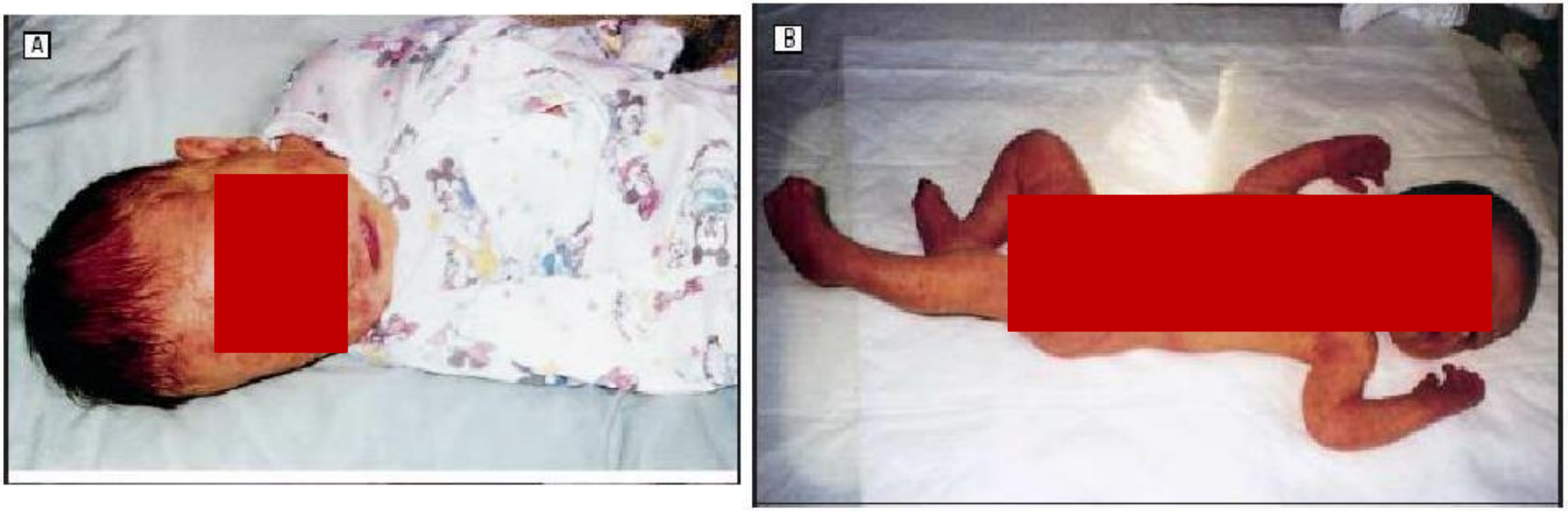
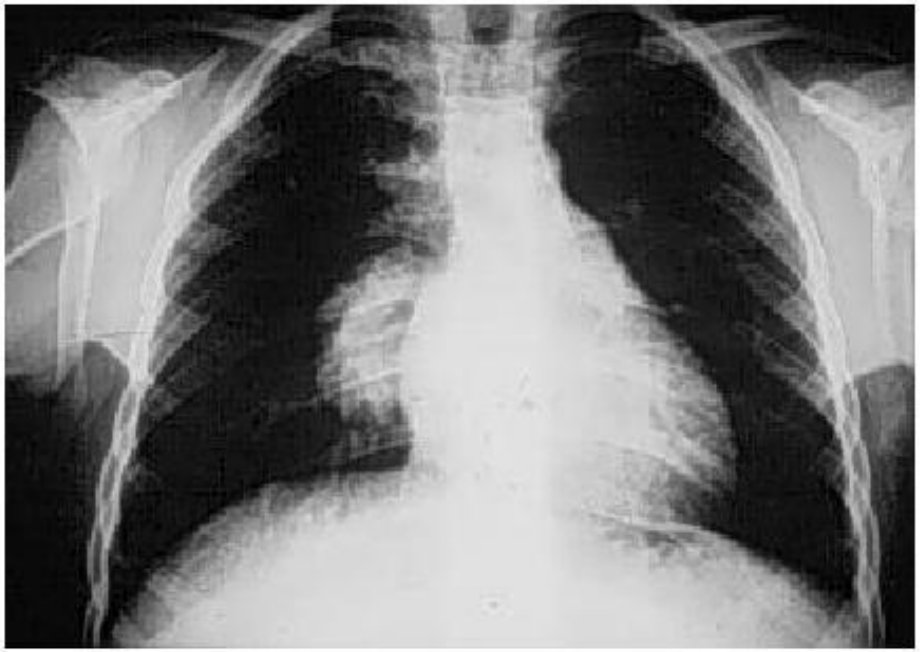
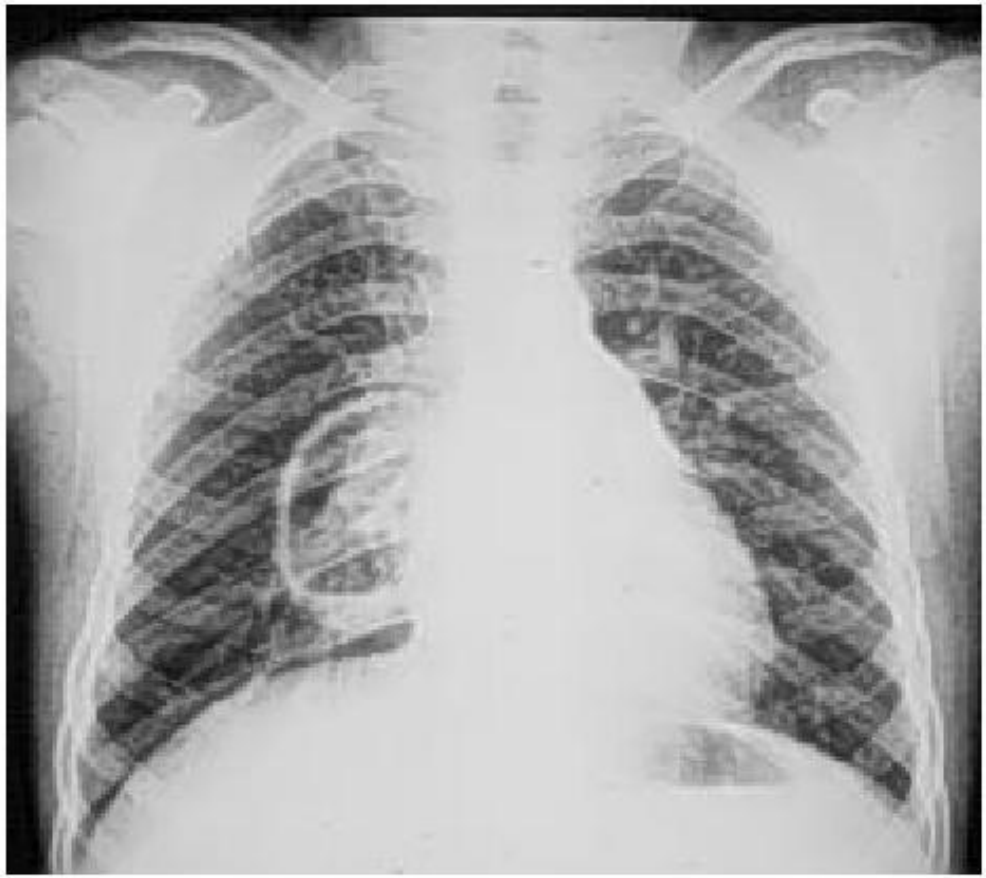


Figure 2. The newborn rash of hyper-IgE syndrome began on the face of this 5-day-old infant (A) and progressed to involve most of the body by age 2 weeks (B).

Eberting CL et al Arch Dermatol. 2004 Sep;140(9):1119 25

AD-HIES STAT3





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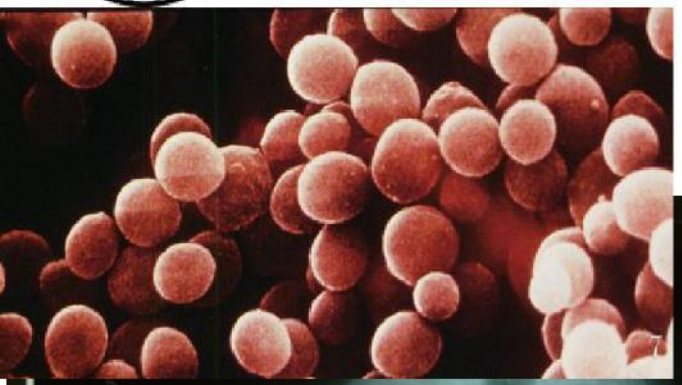
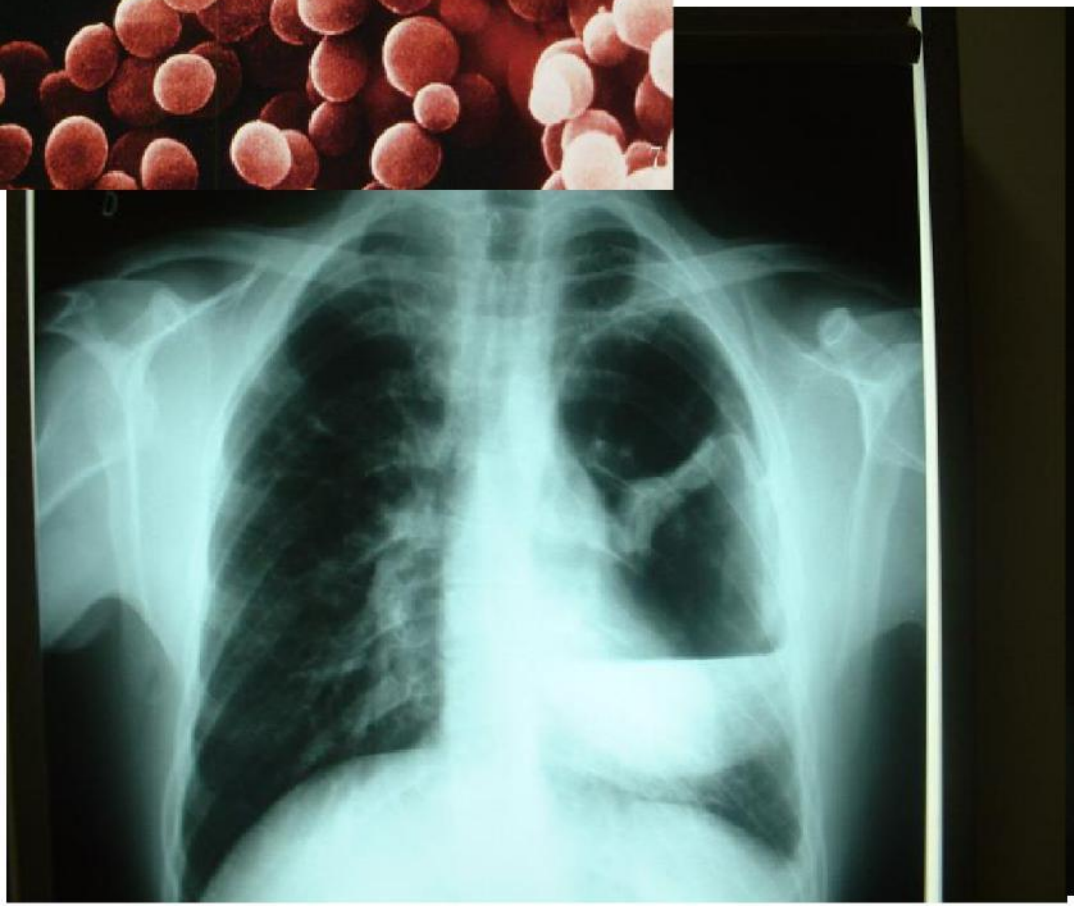
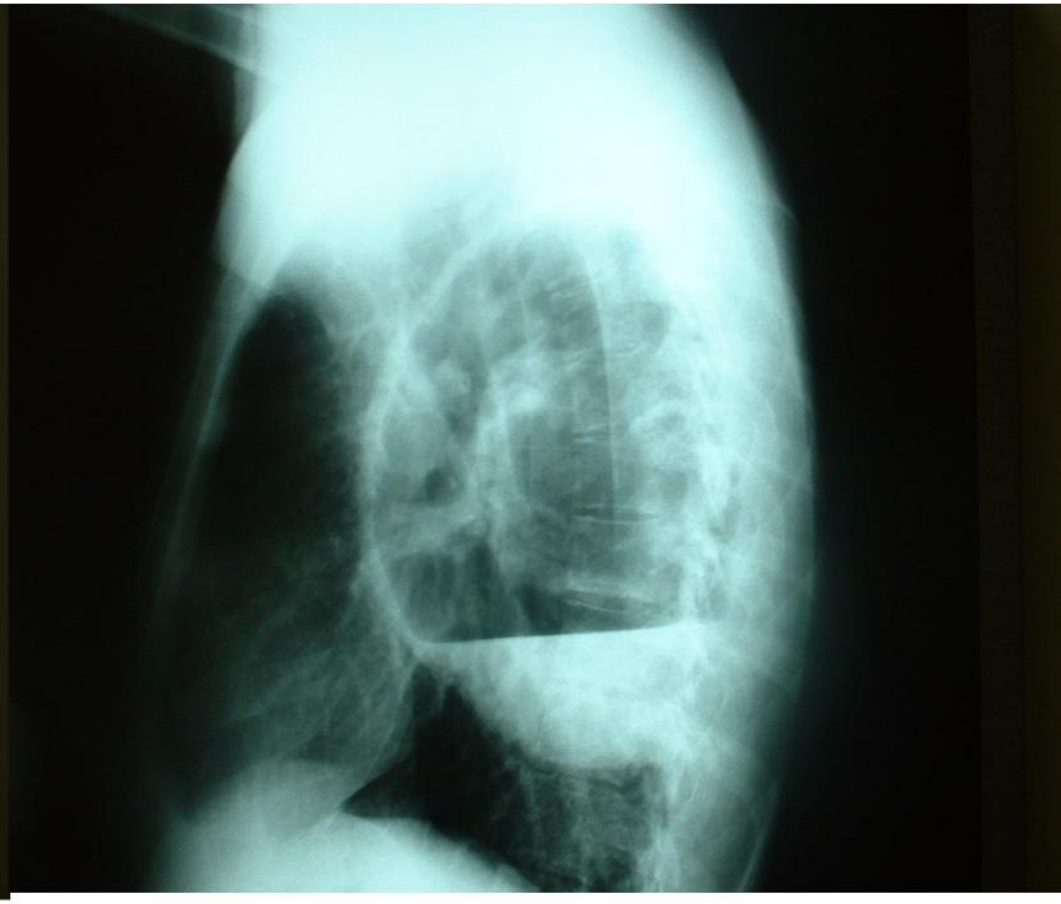
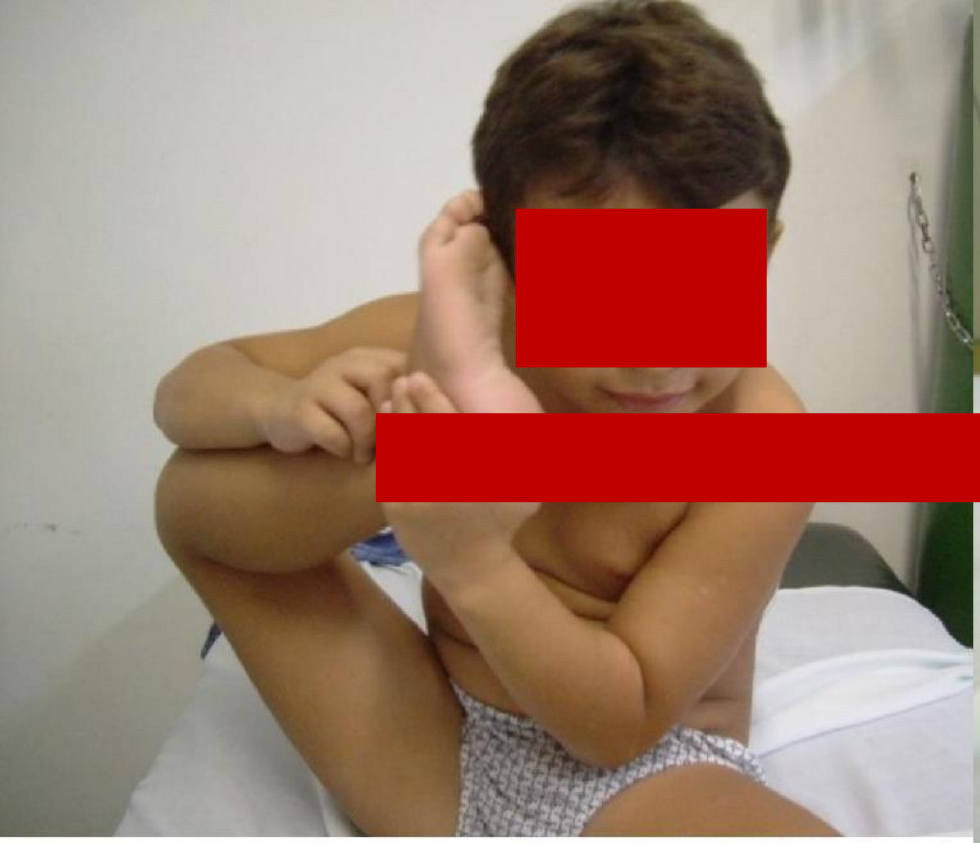
AD-HIES STAT3

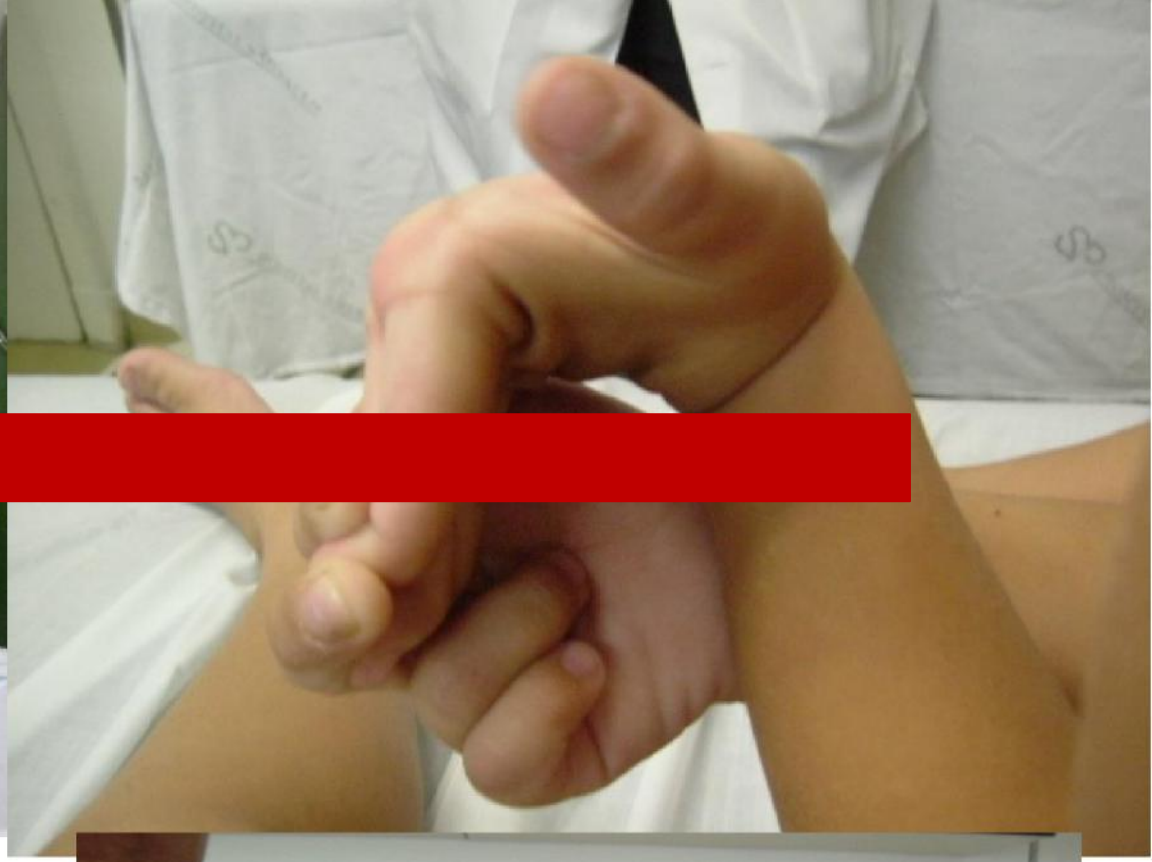


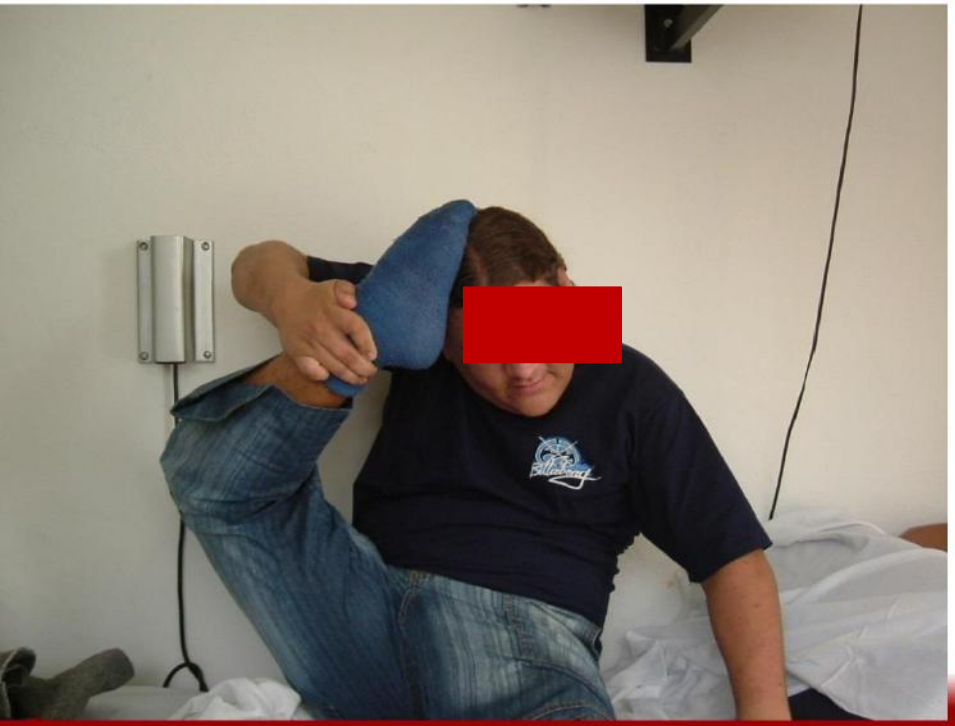




Fonte: Ambulatório de Imunologia Clínica – UNIFESP-EPM

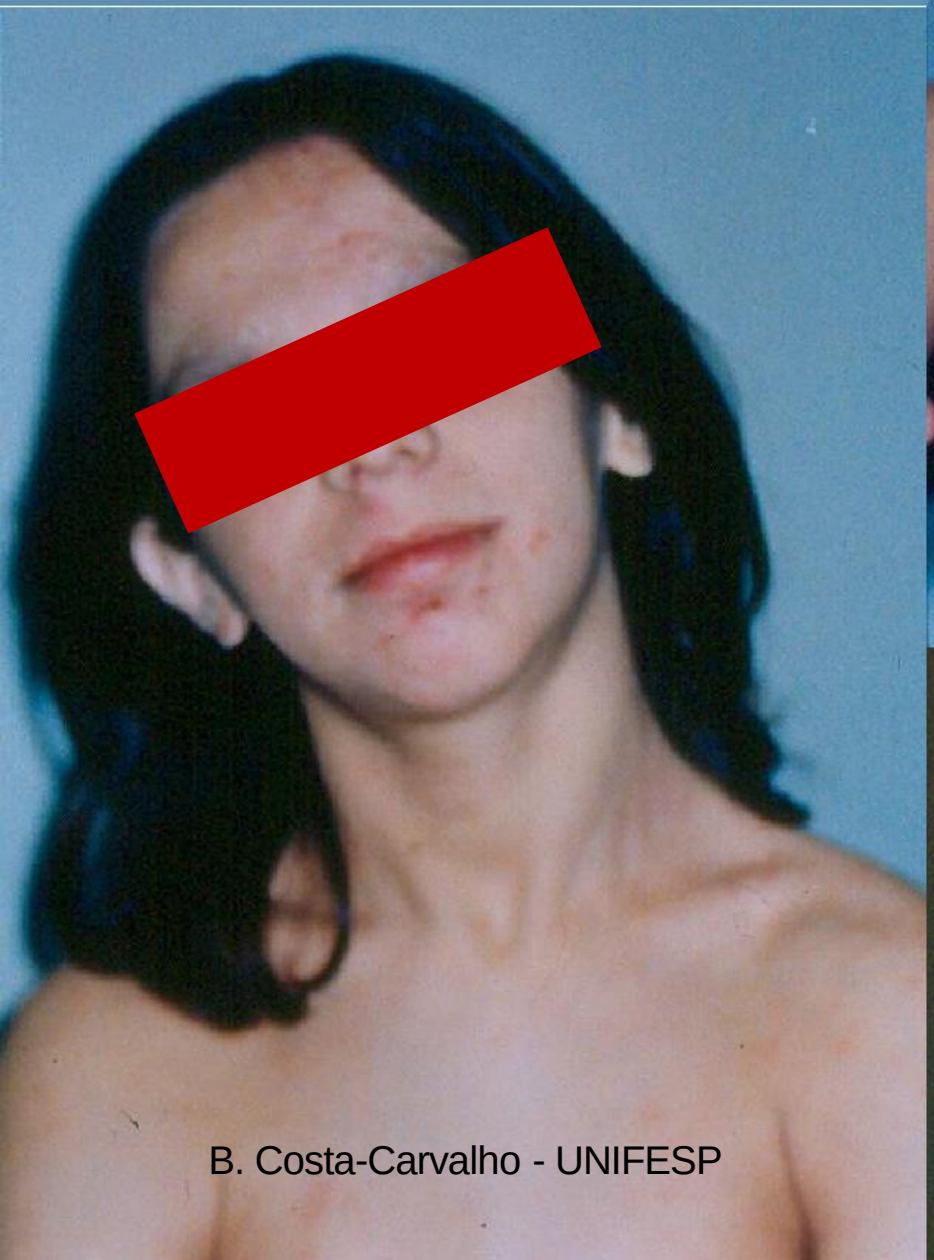


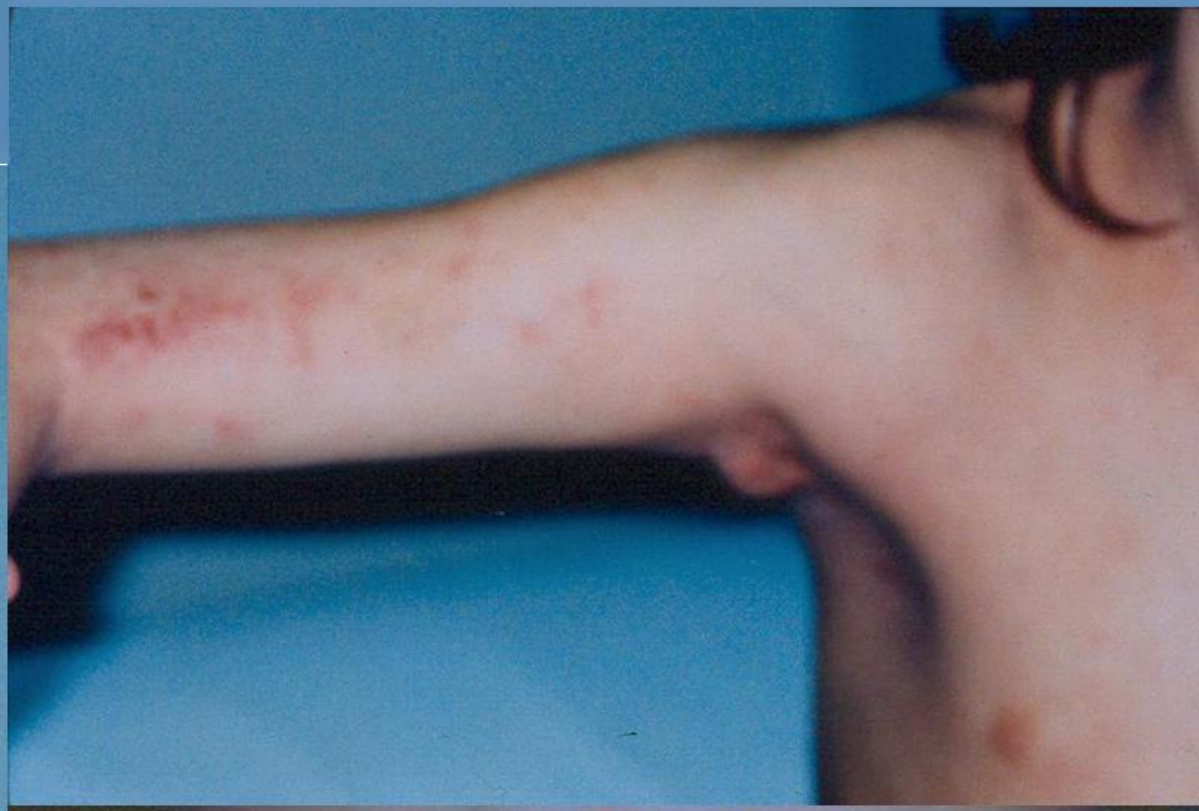


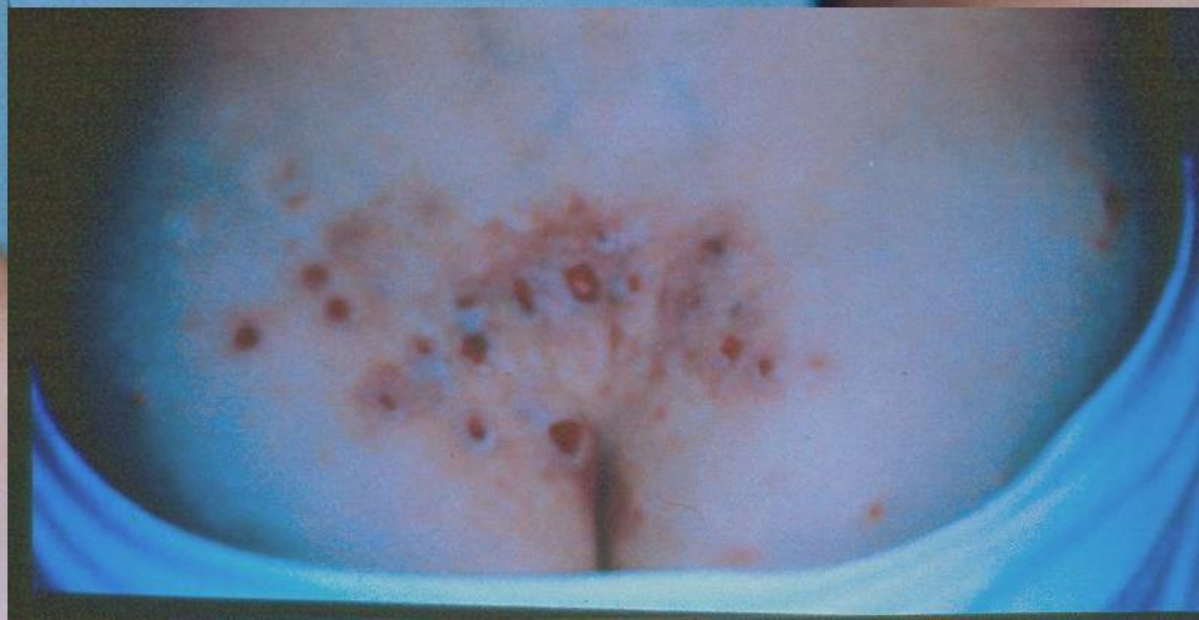


B. Costa-Carvalho - UNIFESP

15 year-old boy with Hyper-IgE syndrome







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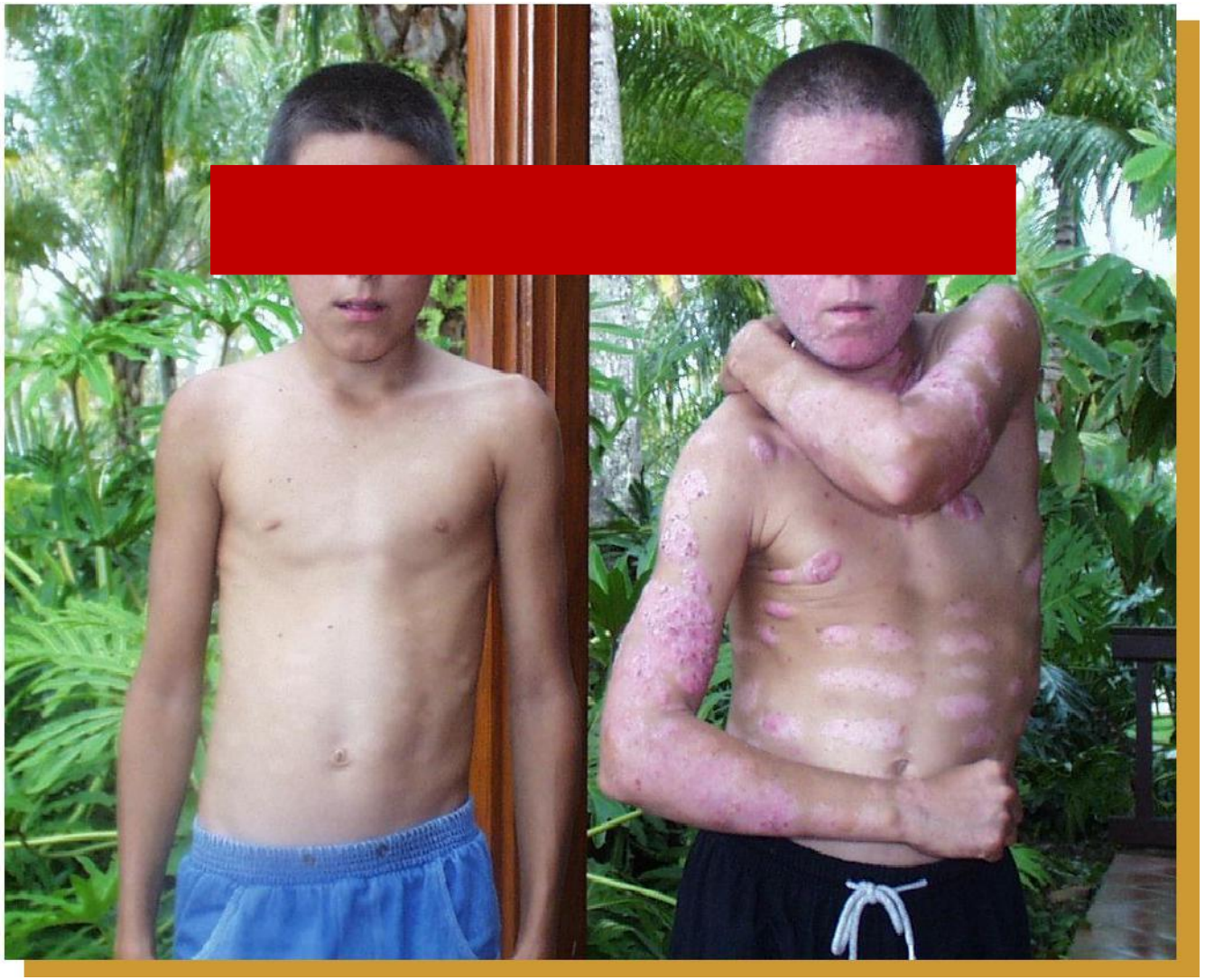
AR-HIES

Pathogenesis

AR-HIES is a combined immune deficiency where DOCKS or TYK2 mutations affect CD4 and CD8 proliferation, B cells, and memory cells. Homozygous mutations of DOCKS (9p24.3) result in its loss of function. DOCK8 belongs to a subfamily of guanine nucleotide exchange factors, which have multiple roles, including signal transduction and activation of small G proteins. Recent evidence suggests that, although T and NK cells home and migrate into human tissue normally, the cytoskeletal defects in DOCK8-deficient **T** and NK cells lead to an unusual form of cell death —"cytothripsis" (cell shattering).[41] The inability of effector T cells and the absence of memory CDS^{+} T cells leave patients without protective immunity and a sensitivity to viral infection. Homozygous mutations in TYK2 (19p13) interrupt cytokine-controlled survival, proliferation, differentiation, and function of immune cells as well as others. This member of the JAK signaling family associates with the cytoplasmic domain of types 1 and 2 cytokines including interleukins, interferons, and hemopoietins by phosphorylating receptor subunits. Disruption of antiviral types 1 and 3 interferon signaling pathways lead to an increased susceptibility to viruses and mycobacterium.

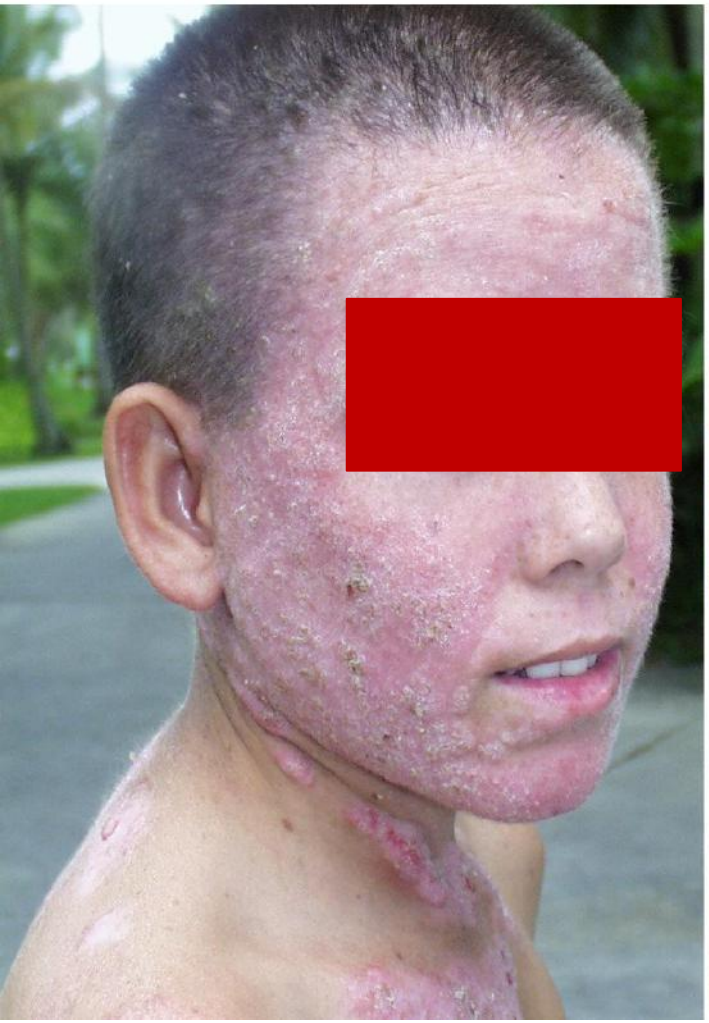
Chan & Gelfand, Immunol Allergy Clin North Am. 2015 Nov;35(4):767-78

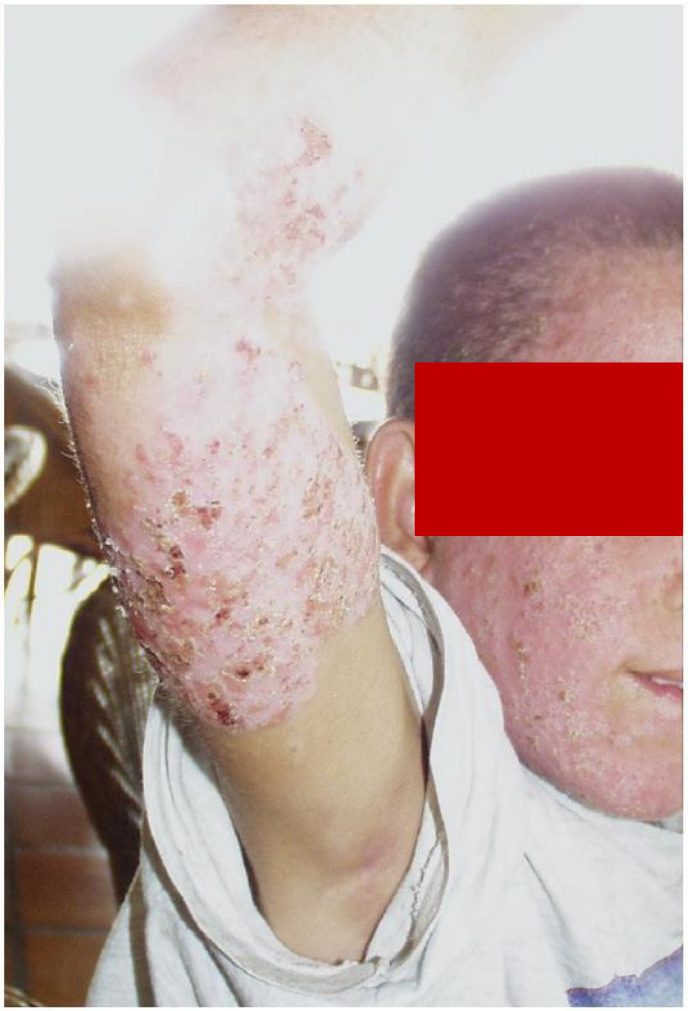
AR-HIES

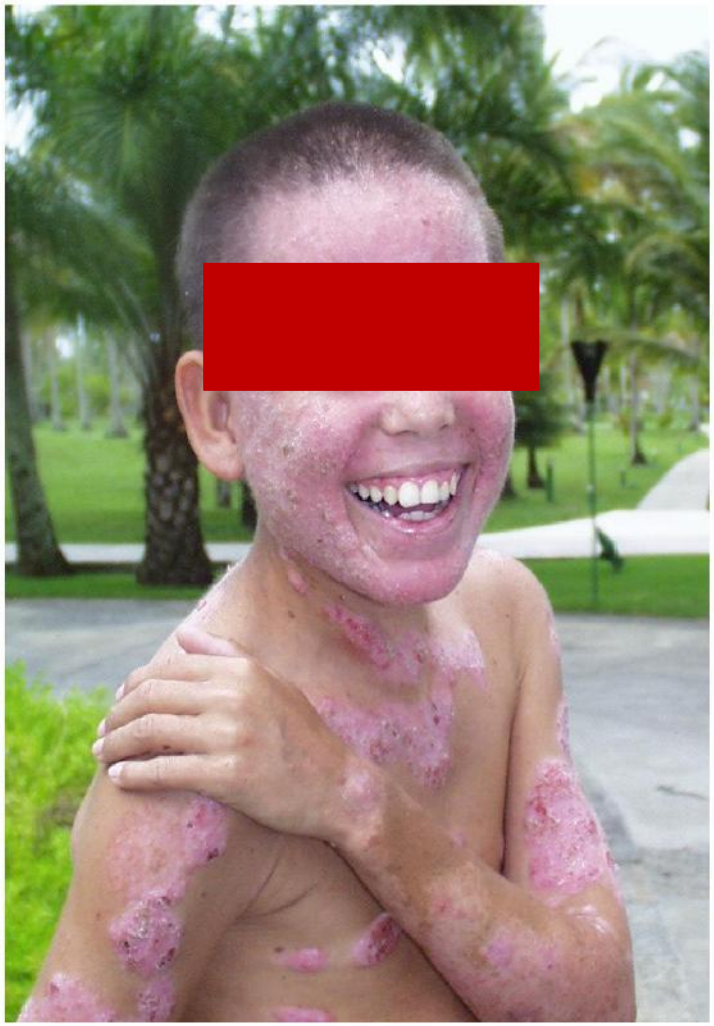


Grumach , FM-ABC

AR-HIES







Grumach , FM-ABC

DOCK8 deficiency

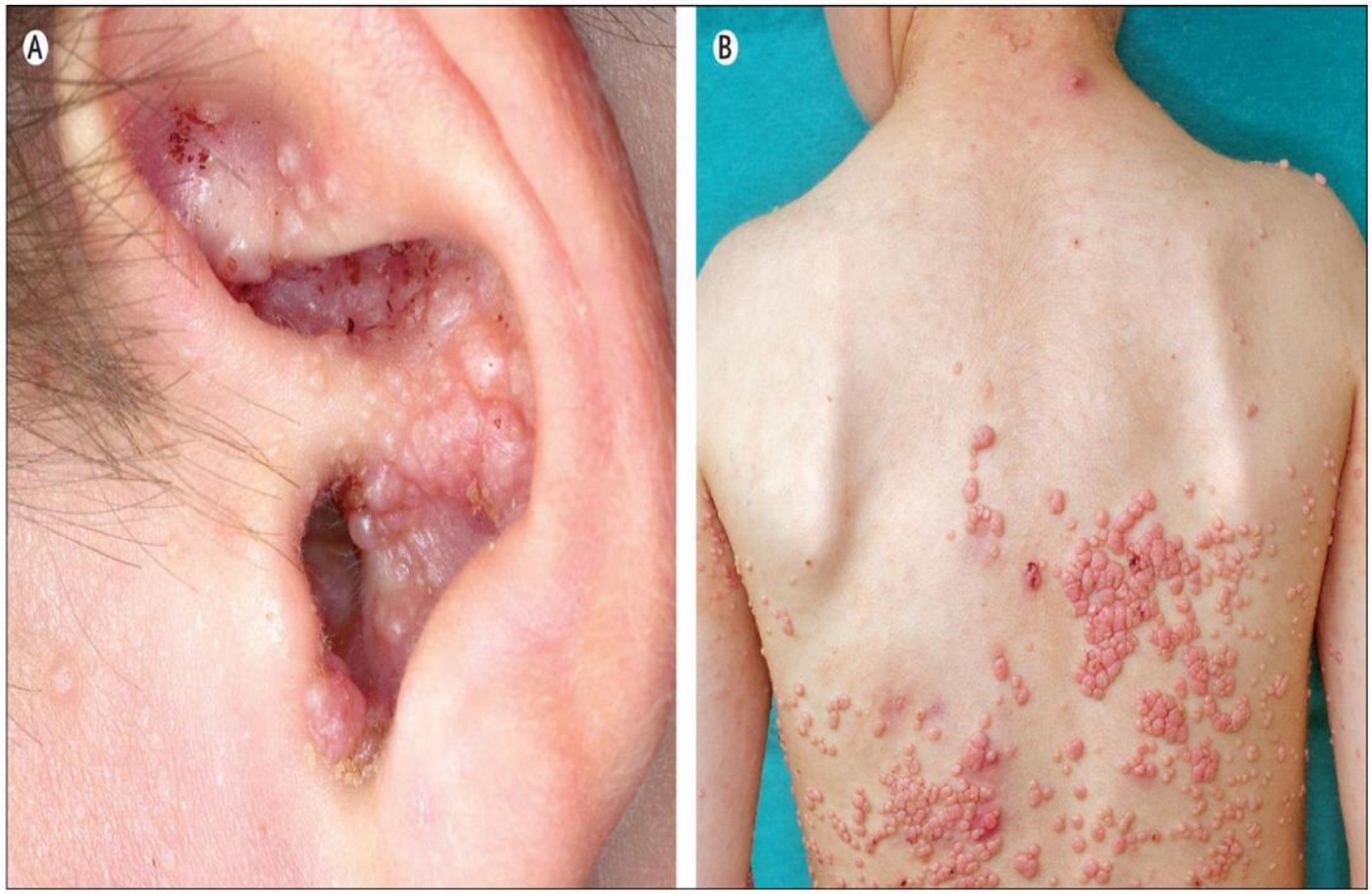
- AD, eczema, recurrent upper and lower respiratory tract infections
- Parenchymal lung abnormalities, pneumatocele formation have not been observed
- Severe fungal and viral cutaneous infections: HSV, herpes zoster, molluscum contagiosum, HPV
- Food and environmental allergies

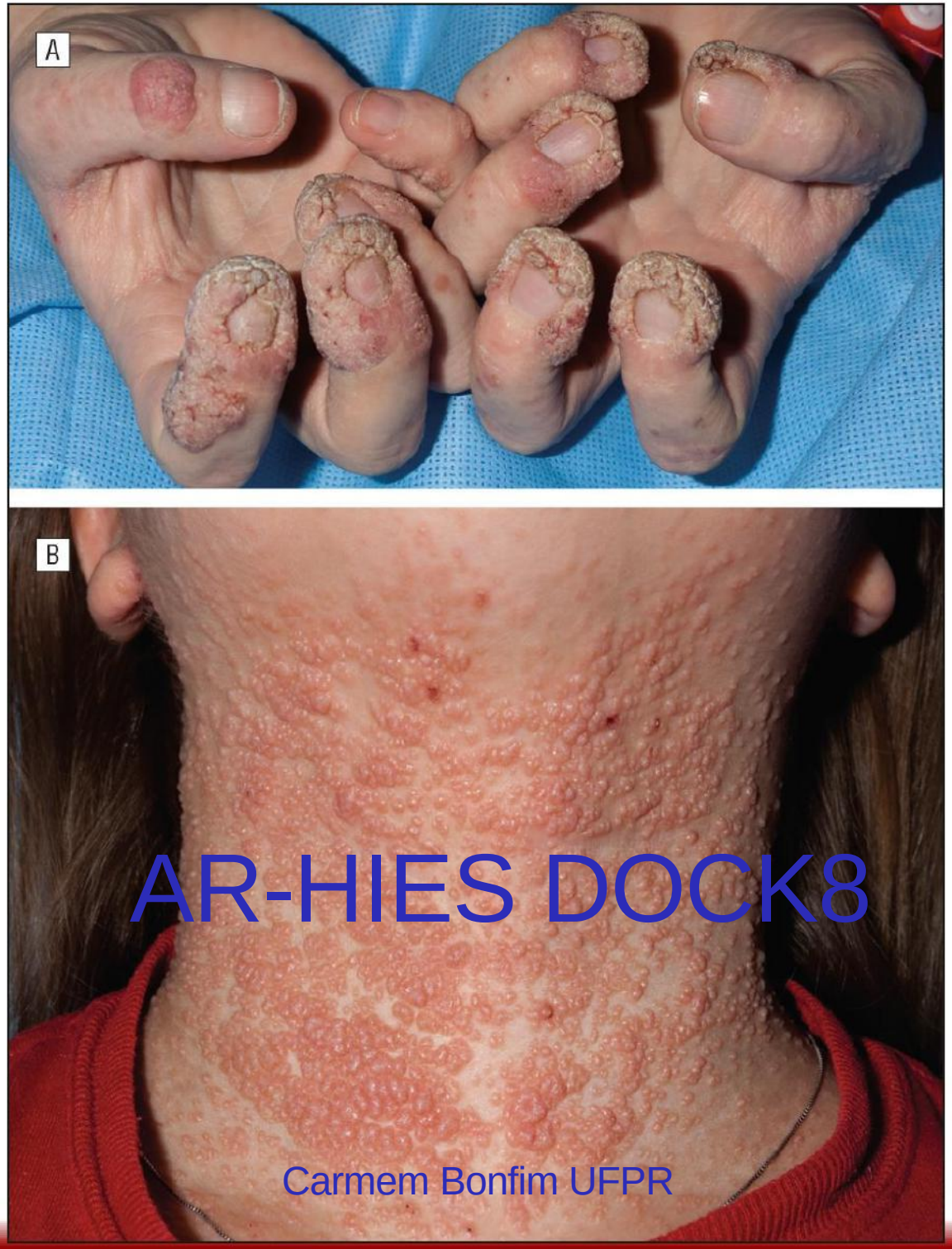
Rael E. et al. WAO Journal 2012; 5:79-87
Freeman AF, Holland SM. Disease Marker& 2010.123-130 Szczawinska-Poplanyk A., el al. Orphanel Journal of Rare Diseases 2011.6:76

Combined Immunodeficiency Associated with *DOCK8* Mutations

Zhang Q, et al. NEJM 2009;361:2046-55.

AR-HIES DOCK8





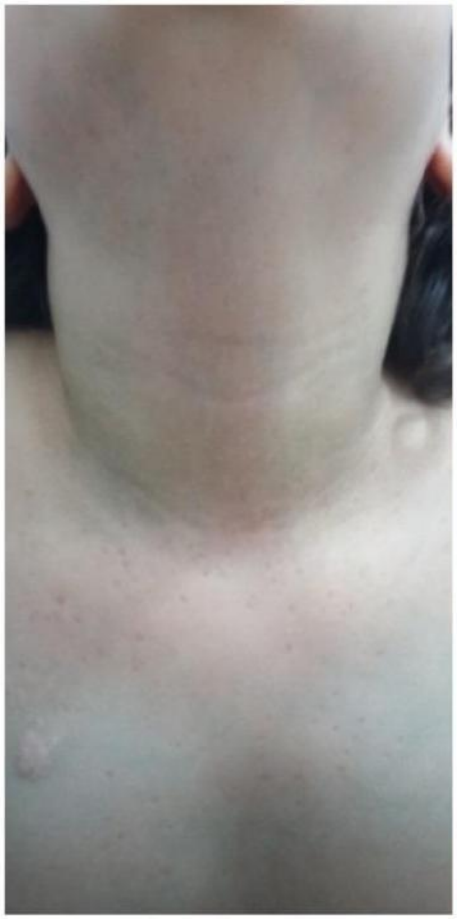
AR-HIES DOCK8

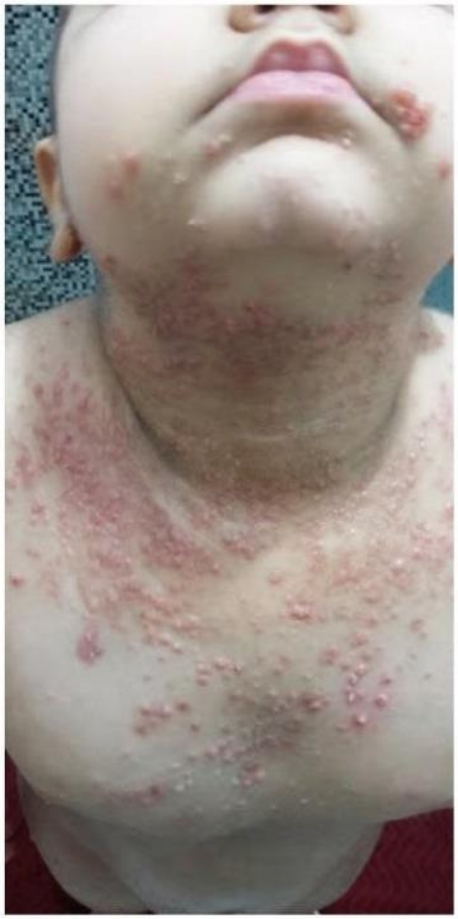
Carmem Bonfim UFPR

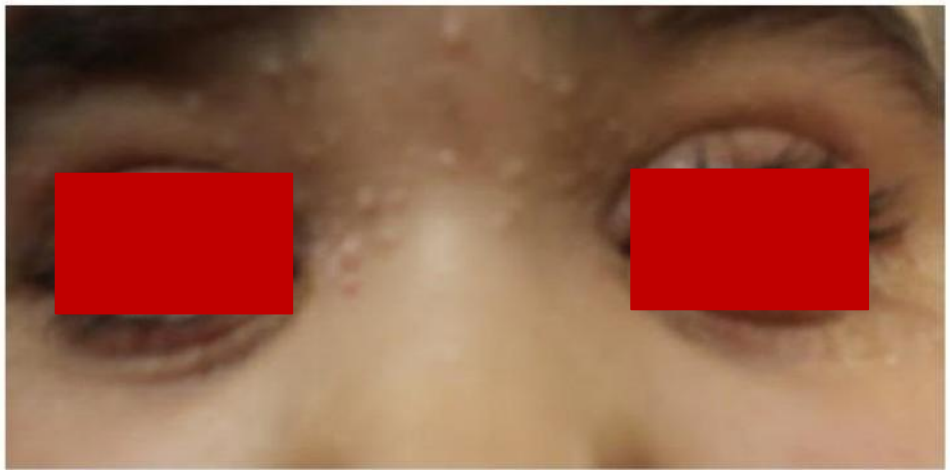
AR-HIES DOCK8

Carmem Bonfim UFPR

AR-HIES DOCK8







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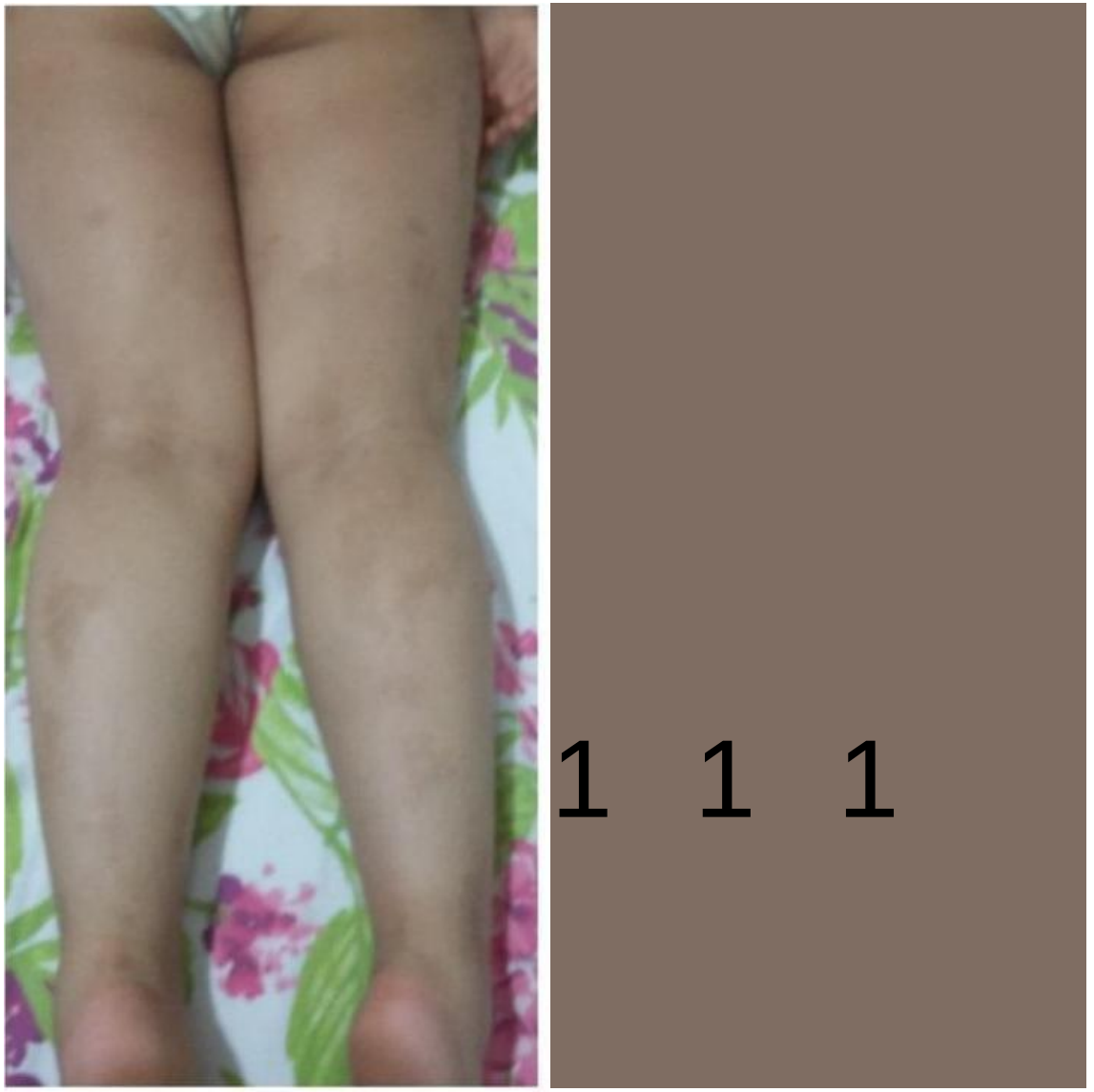
AR-HIES DOCK8



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AR-HIES DOCK8

ICB

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