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Primary immunodeficiency update I: Syndromes associated with eczematous dermatitis

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Abstract

In the past decade, the availability of powerful molecular techniques has accelerated the pace of discovery of several new primary immunodeficiencies (PID) and revealed the biologic basis of other established PID. These genetic advances, in turn, have facilitated more precise phenotyping of associated skin and systemic manifestations and provide a unique opportunity to better understand the complex human immunologic response. These continuing medical education articles will provide an update of recent advances about PID that may be encountered by dermatologists through their association with eczematous dermatitis, infectious, and non-infectious cutaneous manifestations. Part I will discuss new primary immunodeficiencies that have an eczematous dermatitis. Part II will focus on primary immunodeficiencies that greatly increase susceptibility to fungal infection and the noninfectious presentations of PID.

INTRODUCTION

Eczematous dermatitis is a common finding among several primary immunodeficiencies (PID) and may be the presenting clinical manifestation to the dermatologist. However, atopic dermatitis is also common in the general population, thus recognition of additional features of immunodeficiency can facilitate earlier diagnosis. In a series of 75 patients with severe dermatitis with no known underlying primary immunodeficiency, Aghamohammadi *et al*.[1] identified 5 patients with hyper-immunoglobulin (Ig) E syndrome (HIES) and one patient with Wiskott-Aldrich syndrome (WAS) (mean age at diagnosis: 5 years old). This underscores the importance of eliciting a history of recurrent infections or family history suggestive of immunodeficiency in patients with severe atopic dermatitis. In this continuing

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medical education article we provide an update on primary immunodeficiencies associated with dermatitis.

HYPER-IGE SYNDROMES

The first HIES to be described was Job's syndrome. This multisystem PID was initially described in 1966 as a disorder of recurrent cold abscesses, eczematous dermatitis, and lung disease.[2, 3] Autosomal dominant hyper-IgE syndrome (AD-HIES) shares several clinical features with dedicator of cytokinesis 8 (DOCK8) deficiency, also known as autosomal recessive (AR)-HIES, but also has several key differences, which result in distinct phenotypes and prognoses. In addition, there are two other rare autosomal recessive diseases associated with HIES. The first is caused by mutations in phosphoglucomutase-3 (*PGM3*). The second disorder, associated with a mutation in tyrosine kinase 2 (*Tyk2),* was reported in one patient with elevated IgE, eczema, and susceptibility to viral, fungal, and bacterial infections including mycobacteria.[4, 5] A subsequently reported patient with a mutation in *Tyk2* also had a susceptibility to mycobacterial infections, but did not have HIES, making the link between *Tyk2* mutation and AR-HIES uncertain.[6, 7] Although elevated serum IgE and eczematous skin disease is a known presentation among the aforementioned HIES immunodeficiencies, Wiskott-Aldrich syndrome and Netherton syndrome may also present with similar skin and laboratory findings. Figure 1 reviews PIDs associated with eczematous dermatitis and distinctive features of each syndrome. Below we review in greater detail AD-HIES and DOCK8 deficiency, as well as recently described PGM3 deficiency.

Autosomal dominant hyper-IgE syndrome

Key points

- Early onset dermatitis
- Cold abscesses and lung infections
- Multisystem disease with skeletal and connective tissue abnormalities

In 2007, AD-HIES was found to be caused by dominant negative mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene, a key transcription factor which regulates a diverse number of biologic processes including cell growth regulation and inflammation.[8, 9]

The majority of patients with AD-HIES develop a neonatal papulopustular eruption (Fig 2, *A*), often within the first week of life that typically starts on the face and scalp, but can generalize. The rash often changes into an eczematous morphology within the first year.[10] Chronic dermatitis (Fig 2, *B*) in AD-HIES is strongly associated with *Staphylococcus aureus* skin colonization and infection. Control of *S aureus* through prophylactic systemic antimicrobials and topical antiseptics limits eczematous disease, but recurrences throughout life are common. Exacerbations of dermatitis are often due to resistant *S aureus* strains or poor antimicrobial adherence. Dilute sodium hypochlorite baths, as used in atopic dermatitis, may be effective, but further clinical study in this population is needed.[11] Recommended therapy is a half-cup of household bleach in a full tub of water with exposure for 15 minutes three days weekly. For those who are not able or willing to use dilute bleach

baths, chlorhexidine or sodium hypochlorite containing washes may be helpful.[12] In contrast to DOCK8 and atopic patients with high serum IgE levels, anaphylaxis is rare and food allergies are not a major concern in AD-HIES, although the latter is more prevalent in AD-HIES than in the general population.[13, 14]

S aureus is also the major pathogen responsible for recurrent cold skin abscesses and sinopulmonary infections in AD-HIES. Pulmonary infection results in abscess formation and pneumatocele development (Fig 3, *A*), which predispose patients to subsequent *Pseudomonas*, *Aspergillus*, and nontuberculous mycobacterial (NTM) infections and additional morbidity. Prophylactic anti-staphylococcal antibiotics are recommended to decrease risk of pneumonia and staphylococcal abscesses.[3] Chronic mucocutaneous candidiasis (CMC) occurs in 83% of patients, and many patients require long-term antifungal treatment.[3, 10] STAT3 is integral for the differentiation of Th17 cells. AD-HIES patients lack Th17 cells, thereby leading to impaired interleukin (IL)-17/IL-22 signaling and this high risk of CMC.[15] STAT3 is also important for production of other proinflammatory cytokines and $CD8^+$ T cell memory maintenance, which likely contributes to the risk of reactivation of varicella-zoster virus (VZV) and Epstein-Barr virus (EBV).[16] Memory B cell differentiation is also impaired, leading to variable specific antibody production; therefore, some patients require chronic immune globulin replacement in addition to prophylactic antimicrobials.[17]

As the name implies, elevated serum IgE is seen in all AD-HIES patients, with peak IgE levels above 2000 IU/mL in 97% of patients and eosinophilia in 93%.[3] However, IgE levels may diminish over time and may be within the normal range in adulthood. Craniofacial, musculoskeletal, and vascular abnormalities are also common and help distinguish AD-HIES from other PID associated with eczematous dermatitis and skin infection. A characteristic facial appearance emerges in childhood comprised of facial asymmetry, large bulbous nose, prominent chin, and prominent skin pores (Fig 2, *C*). Craniosynostosis, Chiari I malformations, retained primary teeth (Fig 3, *C*) and midline oropharyngeal anomalies are also common, particularly high-arched palate (Fig 2, *D*) and midline sagittal cleft of the tongue. Musculoskeletal abnormalities, including scoliosis (Fig 3, *B*), develop in approximately three quarters of patients, minimal trauma fractures occur in more than 50% patients, and joint hyperextensibility is also common (Fig 2, *F*).[7, 18] Patients with AD-HIES have decreased bone mineral density (BMD) and increased osteoclast activity. Studies in *STAT3* knock out mice confirm an important role for STAT3 in bone homeostasis[19]; however, a recent study did not demonstrate a relationship between BMD, as measured on dual-energy x-ray absorptiometry (DEXA) scan or serum markers of osteoclastic activity, and fracture risk in AD-HIES.[19–21] Another new finding is that STAT3 is also involved in the regulation of matrix metalloproteinases (MMP) and plasma levels of MMP8 and MMP9 are elevated, while MMP3 is lower in patients with AD-HIES and may be responsible for impaired tissue remodeling.[22]

A newly identified systemic manifestation of AD-HIES is vascular anomalies, including lacunar infarcts in the brain, coronary aneurysms (37%), and coronary dilation and tortuosity (70%). The coronary abnormalities have been associated with risk of myocardial infarction.[23–25] AD-HIES is also associated with an increased risk of malignancy, most

commonly non-Hodgkin's lymphoma.[26] Life expectancy for patients with AD-HIES is the fifth to sixth decade. Mortality is most commonly from infection.[7]

DOCK8 deficiency

Key points

- Autosomal recessive
- Elevated IgE and multiple allergies
- Eczematous dermatitis
- Severe human papillomavirus (HPV), molluscum contagiosum virus (MCV), and herpes viral infections

In 2009, mutations in *DOCK8* were identified as the genetic basis of the majority of cases of AR-HIES, a syndrome now commonly referred to as DOCK8 deficiency.[27, 28] Both DOCK8 deficiency and AD-HIES are characterized by elevated serum IgE, eosinophilia, eczematous dermatitis, and recurrent sinopulmonary and staphylococcal skin infections. Unlike AD-HIES, DOCK8 deficiency is also characterized by severe cutaneous viral infections due to herpes simplex virus (HSV) (Fig 4, *A*), HPV, MCV, and varicella-zoster virus (VZV). Widespread HPV and MCV infection (Fig 4, *B, C,* and *D*) may be disfiguring and resistant to standard treatments. Interferon (IFN)3 has been used to treat the mucocutaneous viral infections, with improvement in HPV infection and, in one case, HSV infection.[29, 30] Patients are at elevated risk of squamous cell carcinoma at sites of HPV infection (Fig 4, *E*), and cutaneous T cell lymphoma has also been reported.[28, 31] Malignancy is a frequent cause of death in the second and third decade of life.[7, 32]

DOCK8 deficiency is associated with impaired natural killer (NK) cell development and survival, which likely contributes to the profound susceptibility to cutaneous viral infections.[33] In addition, $CD4^+$ and $CD8^+$ T cells are frequently reduced and often diminish further with age. Further, plasmocytoid dendritic cells are profoundly decreased. This cell population is critical for production of IFN3 in response to the cutaneous viral infections through the toll like receptor (TLR)-9 signaling pathway.[29, 30] Consistent with an elevated risk of recurrent sinopulmonary infections, memory B cells are often reduced in number, and, although total serum IgG may be within normal range, specific antibody production is frequently impaired.[17, 34, 35] Mucocutaneous candidiasis is less common in DOCK8 deficiency as compared to AD-HIES. Differentiation of Th17 cells and IL-17 production is impaired, albeit to a lesser degree than seen in AD-HIES.[36] The mechanism is not yet understood, but may be related to general T cell deficiency.

Patients with DOCK8 deficiency present with variable severity of dermatitis (Fig 4, *F* and *G*). Signs begin in the first several months of life with a classic atopic dermatitis distribution and appearance.[31] In contrast, most patients with AD-HIES present with a neonatal pustular eruption that eventually progresses to an eczematous dermatitis.[10] Additionally, patients with DOCK8 deficiency frequently have multiple food allergies and asthma. Treatment of the atopic dermatitis is often difficult due to concurrent cutaneous viral infections and a predilection for bacterial infections that can worsen with the use of topical or systemic

corticosteroids. Skin superinfection with *Staphylococcus aureus* is frequent and antiseptic measures, including dilute sodium hypochlorite baths and systemic antibiotics, are recommended based on studies in the general atopic dermatitis population as well as our experience with dermatitis in the PID setting.[11, 37]

Given the risk of malignancy (squamous cell carcinoma and lymphoma) and the reduced life expectancy associated with DOCK8 deficiency, allogeneic hematopoietic stem cell transplant (HSCT) is the treatment of choice.[38–40] Cutaneous viral infections and dermatitis have shown dramatic improvement in the first 6 months after transplant.[31, 40]

PGM3 deficiency

Key points

- Autosomal recessive
- Elevated IgE levels with dermatitis, multiple allergies, and asthma
- Neurologic abnormalities

PGM3 deficiency was described in 2014 as a novel autosomal recessive PID associated with atopic dermatitis, recurrent infections, and elevated IgE.[41, 42] PGM3 is a protein that catalyzes the conversion of N-acetylglucosamine-6-phosphate (GlcNAc-6-P) into GlcNAc-1-P in the synthesis of uridine diphosphate (UDP)-GlcNAc, a critical component of the glycosylation pathway, thereby affecting a wide range of diverse proteins. Atopic dermatitis was a universal feature in all 17 patients described.[41, 42] Similar to DOCK8 deficiency, patients with *PGM3* mutations frequently have other prominent atopic features, including asthma and allergies. These patients tended to have susceptibility to viral infections, including cutaneous HSV and MCV, as seen in DOCK8 deficiency. Much like in AD-HIES, patients with PGM3 deficiency have sinopulmonary infections, with bronchiectasis and pneumatocele development, skin and soft tissue bacterial infections. Mucocutaneous candidiasis can also develop, although it is not a consistent feature. One unique cutaneous finding in PGM3 deficiency is leukocytoclastic vasculitis seen in numerous patients. Distinguishing features of AD-HIES, DOCK8 deficiency, and PGM3 deficiency are shown in Table I. In contrast to AD-HIES and DOCK8 deficiency, neurologic impairment is a prominent feature in patients with PGM3 deficiency, and include developmental delay and low IQ (88%), ataxia (88%), dysarthria (63%), myoclonus (63%), sensorineural hearing loss (50%), and electroencephalography (EEG) abnormalities (38%).[41] Hypomyelination is seen on brain magnetic resonance imaging (MRI). Common hematologic manifestations include cytopenias, mostly lymphopenia and neutropenia.

IMMUNE DYSREGULATION, POLYENDOCRINOPATHY AND ENTEROPATHY, X-LINKED (IPEX) SYNDROME

Key points

- X-linked recessive
- Early onset dermatitis

- Multi-organ autoimmune disease due to loss of peripheral tolerance

Immune dysregulation, polyendocrinopathy and enteropathy, X-linked syndrome, is an X-linked recessive condition due to loss of function mutations in forkhead box protein 3 (*FOXP3*). It is characterized by a decreased or absent T regulatory (Treg) cell population and multi-organ autoimmune disease. There is considerable phenotypic variation in patients with IPEX syndrome without an obvious genotype-phenotype correlation.[43] Affected males develop autoimmune enteropathy in infancy that can be life threatening. Patients may also develop insulin-dependent diabetes mellitus (IDDM) and thyroid dysfunction early in life.[44] Antibodies to organ specific antigens have been demonstrated in patients with IPEX, explaining autoimmune manifestations such as IDDM, thyroiditis, cytopenias, hepatitis, and nephritis.[45] The most common cutaneous finding is eczematous dermatitis.[46] Other less frequent presentations include psoriasiform dermatitis, erythroderma, urticaria, pemphigoid nodularis, cheilitis, onychodystrophy, and alopecia universalis.[44, 47, 48] Elevated IgE and eosinophilia are common, as are food allergies. Infections are likely due to both the immune suppressive drugs employed to manage the autoimmune disease and impaired skin barrier and gut epithelium. Severe disease may lead to mortality in early childhood. HSCT is currently the only curative treatment, although gene therapy is being investigated.[49, 50]

MAMMALIAN STERILE 20-LIKE 1(MST1) DEFICIENCY

Key Points

- Autosomal recessive
- Bacterial, viral, and candidal cutaneous infections
- Structural cardiac anomalies

Mammalian sterile 20-like 1 deficiency, previously known as serine/threonine protein kinase 4 (STK4) deficiency, is an autosomal recessive PID associated with bacterial and viral infections (HSV, HPV, MCV, EBV) as well as mucocutaneous candidiasis. *MST1* encodes a serine-threonine kinase that is ubiquitously expressed but has increased levels in cells of hematopoietic origin.[51] First reported in 2012, four consanguineous affected families with MST1 deficiency have now been described.[51–53] Systemic findings include structural cardiac anomalies (atrial septal defects and patent foramen ovale) and valvular disease.[52, 53] Eczematous dermatitis has been reported, but is poorly characterized.[53] Additionally, multiple autoantibodies including antinuclear, anticardiolipin, and antineutrophil cytoplasmic antibodies, and autoimmune hemolytic anemia has been described.[51–53] *Mst1* and *Mst2* were recently found to be important regulators of *Foxp3* expression and Treg development, providing a biologic rationale for the autoimmune manifestations of this condition.[54, 55] Affected patients have a peripheral neutropenia with normal bone marrow maturation, as well as T and B cell lymphopenia. The primary therapeutic intervention for this condition is infection control. Three patients with MST1 deficiency have undergone HSCT, but 2 died within 6 months due to graft-versus-host disease and infectious complications.[53]

CONCLUSION

Genetic advances have identified several novel primary immunodeficiencies and allowed better characterization of their cutaneous phenotypic presentation. In Part 1, we reviewed the clinical characteristics, genetic basis, and immunologic abnormalities in PID associated with eczematous dermatitis, including several newly described syndromes. In Part 2, we will provide an update on other recently described PID that are not associated with eczematous dermatitis.

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ABBREVIATION AND ACRONYM LIST

AD	autosomal dominant
AD-HIES	autosomal dominant hyper-IgE syndrome
AR	autosomal recessive
BMD	bone mineral density
CMC	chronic mucocutaneous candidiasis
DEXA	dual-energy x-ray absorptiometry
DOCK8	dedicator of cytokinesis 8
EBV	Epstein-Barr virus
EEG	electroencephalography
FOXP3	forkhead box protein 3
GlcNAc-6-P	N-acetlyglucosamine-6-phosphate
HIES	hyper-IgE syndrome
HPV	human papillomavirus
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
IDDM	insulin-dependent diabetes mellitus
Ig	immunoglobulin
IFN	interferon
IL	interleukin
IPEX	immune dysregulation, polyendocrinopathy and enteropathy, X-linked syndrome
MCV	molluscum contagiosum virus

MMP	metalloproteinase
MRI	magnetic resonance imaging
MST1	mammalian sterile 20-like 1
NK	natural killer
NTM	nontuberculous mycobacterial
PGM3	phosphoglucomutase 3
PID	primary immunodeficiency
STAT3	signal transducer and activator of transcription 3
STK4	serine/threonine protein kinase 4
Treg	regulatory T
TLR	toll-like receptor
TYK2	tyrosine kinase 2
UDP	uridine diphosphate
VZV	varicella-zoster virus
WAS	Wiskott-Aldrich syndrome
WHIM	warts, hypogammaglobulinemia, immunodeficiency and myelokathexis
WILD	warts, immunodeficiency, primary lymphedema, and anogenital dysplasia

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Learning objectives

After completing this Journal CME activity, the learner should be able to differentiate primary immunodeficiencies that present with eczematous dermatitis based on infectious and non-infectious manifestations; identify the numerous systemic manifestations of autosomal dominant hyper-IgE syndrome;

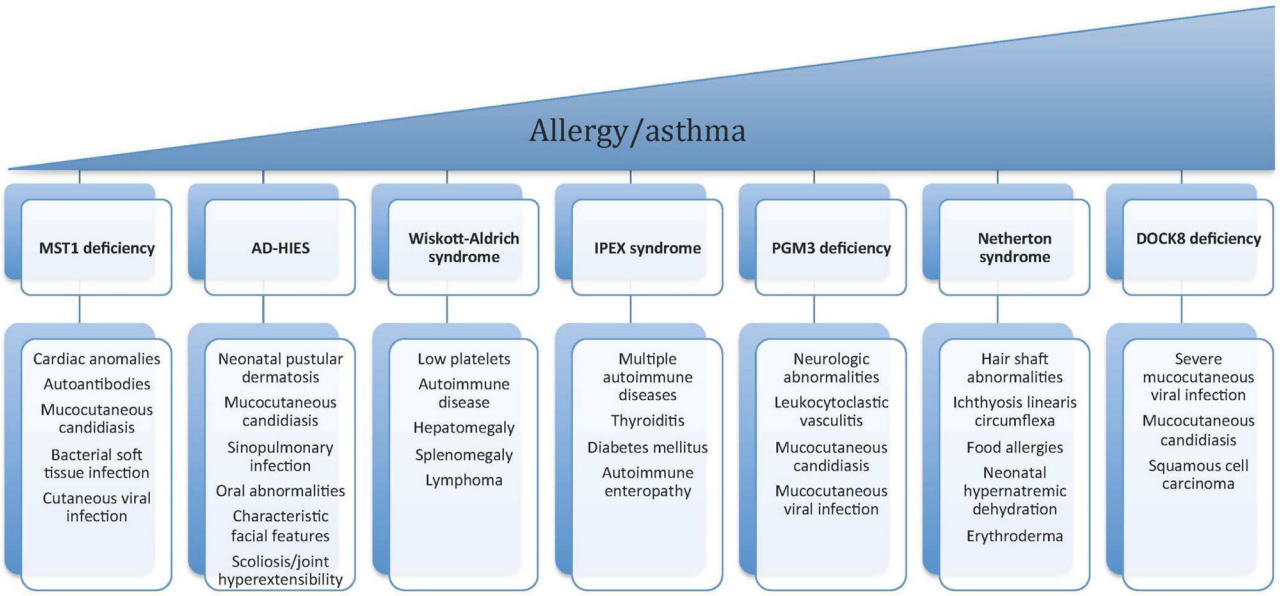


Figure 1.

Clinical features of primary immunodeficiencies with eczematous dermatitis stratified by prevalence of allergies and asthma.

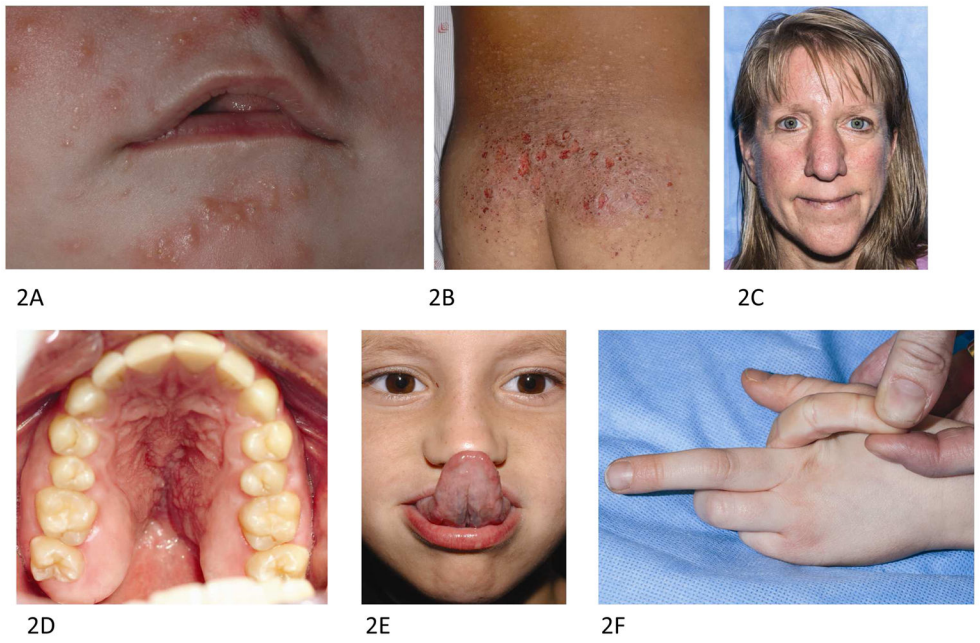
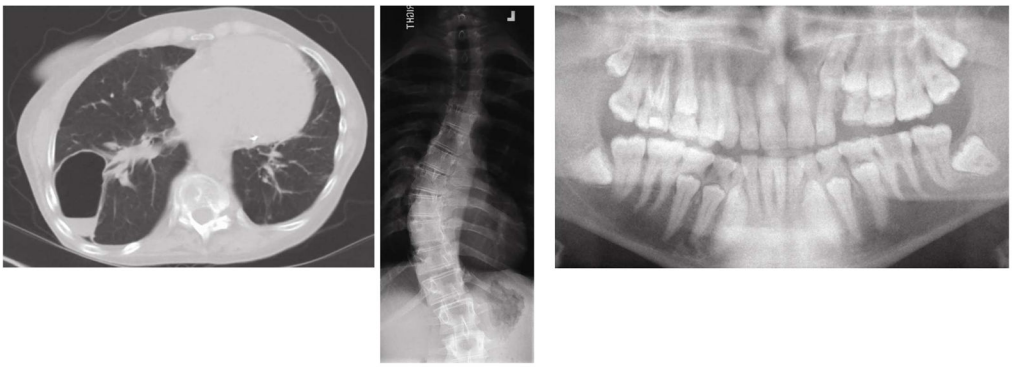


Figure 2.

Cutaneous findings in autosomal dominant hyper-IgE syndrome. A 3 week old infant with neonatal pustular eruption of the (A) face. B. A 7 year old boy with chronic dermatitis on the lower back. C. Characteristic facies with coarse facial features, broad nasal bridge, large bulbous nose, prominent skin pores and prognathism in a 44 year old female. D. High arched palate. E. Gorlin's sign demonstrating hyperextensibility similar to that seen in Ehlers-Danlos syndrome. F. Joint hyperextensibility in a 6 year old boy.



3A 3B 3C

Figure 3.

Autosomal dominant hyper-IgE syndrome radiographic findings. A. 42 year old female with right lung pneumatocele and (B) severe scoliosis. C. Multiple retained primary teeth visualized by panoramic radiograph in 21 year old male.

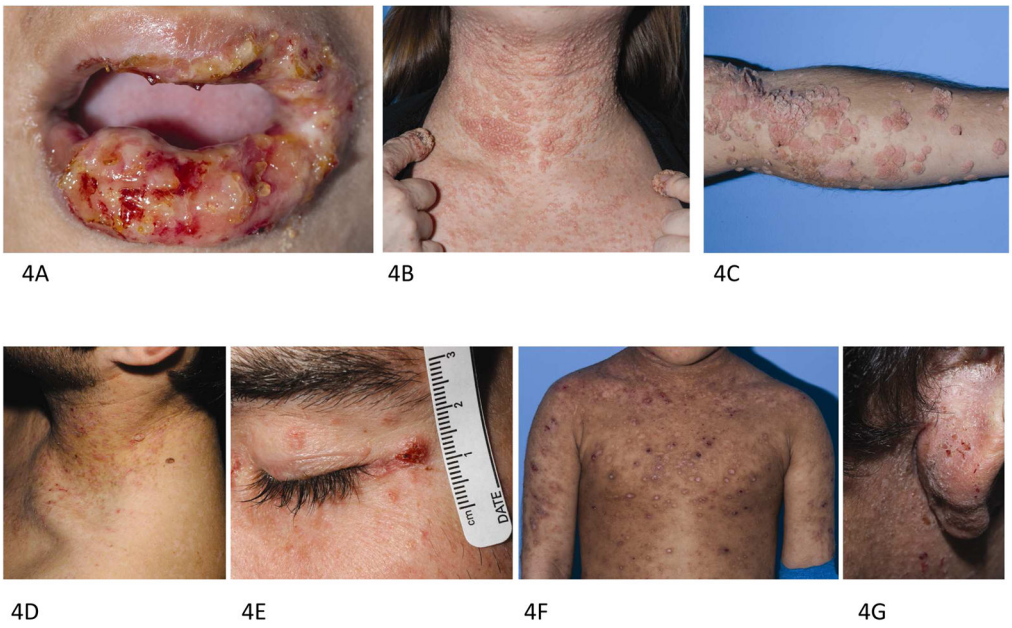


Figure 4.

The spectrum of cutaneous findings in DOCK8 immunodeficiency. A. Severe herpetic stomatitis in a 7 year old girl. B. Generalized molluscum contagiosum with verrucous HPV infection on the distal fingers in a 22 year old female. C. Generalized verrucosis of the arm, extensive pink to red brown thin papules resembling epidermodysplasia verruciformis in a 25 year old male (D), and squamous cell carcinoma on the face (E). Biopsy of the chest revealed coarse keratohyaline granules and abundant pale gray cytoplasm similar to findings seen in epidermodysplasia verruciformis. F. Extensive dermatitis with excoriations and post-auricular crusting (G) in a 5 year old with DOCK8 immunodeficiency.

Table 1

Comparison of hyper-immunoglobulin E syndromes

	STAT3 deficiency (Job's syndrome)	**DOCK8 deficiency**	**PGM3 deficiency**
GENETIC FEATURES			
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Gene	*STAT3*	*DOCK8*	*PGM3*
Protein	Signal transducer and activator of transcription 3	Dedicator of cytokinesis 8	Phosphoglucomutase 3
Function	Mediates cellular responses to interleukins, stem cell factor, and other growth factors	Activates Rho GTPases, cytoskeletal reorganization, cell migration, phagocytosis	Enzyme catalyzing conversion of GlcNAc-6-P into GlcNAc-1-P
IMMUNOLOGIC FEATURES			
Eosinophila	Common	Common	Common
Allergies	Rare	Common	Common
Asthma	Rare	Common	Common
Sinopulmonary infection	Common	Common	Common
Bronchiectasis	Common	Rare	Less common
DERMATOLOGIC FEATURES			
Newborn rash	Cephalic papulopustular eruption	-	-
Eczematous dermatitis	Common	Highly variable	Highly variable
Bacterial skin abscesses	Common	Less common	Common
Leukocytoclastic vasculitis	-	-	Common
Mucocutaneous viral infection	Rare	Very common, severe	Occasional reports
Mucocutaneous candidiasis	Common	Less common	Less common
OTHER FEATURES			
Malignancy	SCC (rare)	SCC (vulvar, facial, anal)	-
Characteristic facial appearance	Coarse features, asymmetry, broad nasal root, hypertelorism, prognathism	-	Narrow palpebral fissures
Oral findings	Retained primary dentition, high-arched palate	-	High-arched palate
Joint hyperextensibility	Very common	Rare	Rare
Minimal trauma fractures	Very common	Rare	-
Scoliosis	Very common	-	Rare
Neurologic symptoms	-	-	Conductive hearing loss, ataxia, myoclonus

DOCK8 – dedicator of cytokinesis 8, *PGM3* - phosphoglucomutase 3, *STAT3* – signal transducer and activator of transcription 3 *GlcNAc-1-P* – N-acetylglucosamine-1-phosphate; *GlcNAc-6-P* – N-acetylglucosamine -6-phosphate