Primary immunodeficiency update

Part II. Syndromes associated with mucocutaneous candidiasis and noninfectious cutaneous manifestations

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Learning Objectives
After completing this learning activity, participants should be able to differentiate the new primary immunodeficiency syndromes based on the noninfectious manifestations (dermatitis, SCC, DFSP, granuloma, cutaneous lupus) that may occur on the skin.

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Several primary immunodeficiencies (PIDs) have recently been described that confer an elevated risk of fungal infections and noninfectious cutaneous manifestations. In addition, immunologic advances have provided new insights into our understanding of the pathophysiology of fungal infections in established PIDs. We reviewed PIDs that present with an eczematous dermatitis in part I. In part II of this continuing medical education article we discuss updates on PIDs associated with fungal infections, their biologic basis in PIDs, and noninfectious cutaneous manifestations. (J Am Acad Dermatol 2015;73:367-81.)

Part I of this continuing medical education article addressed primary immunodeficiencies (PIDs) associated with eczematous dermatitis. In part II, we provide an update on other PIDs, including those associated with mucocutaneous candidiasis and PIDs with noninfectious skin manifestations.

NEW MUCOCUTANEOUS CANDIDIASIS SYNDROMES

Key points

- **Several new monogenic disorders have been associated with chronic mucocutaneous candidiasis**
- **Gain of function *STAT1* mutations cause chronic mucocutaneous candidiasis with a variety of systemic manifestations**
- **CARD9 mutations predispose to chronic mucocutaneous candidiasis, invasive fungal infections, and deep dermatophytosis**

The innate immune response is the host's first line of defense against fungal infection (Fig 1). Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and C-type lectin receptors, recognize components of pathogens, termed pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved. TLR2 and TLR4 recognize

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Abbreviations used:

ADA:	adenosine deaminase
AIRE:	autoimmune regulator
AML:	acute myeloid leukemia
APECED:	autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia
APLAID:	autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation
APS-1:	autoimmune polyendocrine syndrome type 1
AR:	autosomal recessive
CARD9:	caspase-associated recruitment domain
CLEC7A:	C-type lectin domain family 7, member A
CMC:	chronic mucocutaneous candidiasis
COL1A1-PDGFB:	collagen type I, alpha-1-platelet-derived growth factor subunit beta
CXCL12:	chemokine CXC motif ligand 12
CXCR4:	chemokine CXC motif receptor 4
DFSP:	dermatofibrosarcoma protuberans
DOCK8:	dedicator of cytokinesis 8
EBV:	Epstein–Barr virus
GATA2:	GATA-binding protein 2
GOF:	gain of function
HPV:	human papillomavirus
HSCT:	hematopoietic stem cell transplant
IL:	interleukin
MDS:	myelodysplastic syndrome
MonoMAC:	monocytopenia and mycobacterial infection
MST1:	mammalian sterile 20-like 1
mTEC:	medullary thymic epithelial cell
NIH:	National Institutes of Health
NF-κB:	nuclear factor-kappa B
NK:	natural killer
OS:	Omenn syndrome
PAMPs:	pathogen-associated molecular patterns
PID:	primary immunodeficiency
PLAID:	PLCγ2-associated antibody deficiency and immune dysregulation
PLCG2:	phospholipase C, gamma 2
PRR:	pattern recognition receptor
RAG:	recombination activating gene
SCID:	severe combined immunodeficiency disease
SDF-1:	stromal cell-derived factor-1
STAT3:	signal transducer and activator of transcription 3
Treg:	T regulatory
TLR:	Toll-like receptor
TNF:	tumor necrosis factor
WHIM:	warts, hypogammaglobulinemia, immunodeficiency and myelokathexis
WILD:	warts, immunodeficiency, primary lymphedema, and anogenital dysplasia

O-linked mannan on the fungal cell wall and activate nuclear factor-kappa B (NF-κB) through the adaptor protein MyD88. Dectin-1, a C-type lectin receptor, recognizes beta-glucans, leading to NF-κB induction through the adaptor protein caspase recruitment domain family, member 9 (CARD9). This results in transcription of proinflammatory cytokines that bind to receptors on T_H17 cells. The discovery of T_H17 cells in 2005 and, subsequently, mucocutaneous candidiasis syndromes associated with specific T_H17 signaling defects, highlights the importance of this pathway in host defense to fungi.[1,2] This has also provided new insight into the pathogenesis of other established PIDs with chronic mucocutaneous candidiasis (CMC; Table I).[3]

Gain of function *STAT1* mutations

Gain of function (GOF) mutations in signal transducer and activator of transcription 1 (*STAT1*) are associated with autosomal dominant CMC, likely because of a STAT1-dependent increase in the production of interferons (IFNs) that inhibit T_H17 development.[3-5] GOF mutations in *STAT1* result in diminished interleukins (IL)-17A and -22 and an enhanced response to type I IFNs.[4,6] In addition to CMC, patients are at risk for other fungal infections (eg, disseminated coccidioidomycosis and histoplasmosis), bacterial sinopulmonary infections, mycobacterial, and Herpesviridae family infections.[7-9] The clinical severity of this syndrome is highly variable (Fig 2); some patients manifest only CMC, but other patients develop multiple endocrine, dental, gastrointestinal, and autoimmune abnormalities, including early-onset diabetes, enteropathy, hypothyroidism, hemolytic anemia, and autoimmune hepatitis.[4,10] Cerebral aneurysms and malignancy (oral and esophageal) have also been described.[4,11]

Dectin-1 mutations

In 2009, Ferwerda et al[12] identified a family with autosomal recessive (AR) CMC associated with mutations in *Dectin-1*. Dectin-1, also known as C-type lectin domain family 7, member A (CLEC7A), is a PRR expressed by phagocytes that recognizes beta-glucans on the fungal cell wall. This protein, along with CARD9, is vital to antifungal immunity via induction of the STAT3 pathway and release of T_H17-differentiating cytokines.[13,14] Affected patients develop vulvovaginal candidiasis most commonly, followed by oral and esophageal candidiasis, but do not appear to be susceptible to invasive candidal infection. Variants in the *Dectin-1* gene are fairly common; however, the functional significance of these polymorphisms remains unclear.