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Primary immunodeficiency update II: Syndromes associated with mucocutaneous candidiasis and non-infectious cutaneous manifestations

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Abstract

Several primary immunodeficiencies (PID) have recently been described which confer elevated risk of fungal infections as well as non-infectious cutaneous manifestations. In addition, immunological advances have provided new insights into our understanding of the pathophysiology of fungal infections in established PID. We reviewed PID that present with an eczematous dermatitis in Part I. In Part II, we will discuss updates on PID associated with fungal infections and their biological basis in PID as well as non-infectious cutaneous manifestations.

INTRODUCTION

In Part I of this two part continuing medical education series we discussed primary immunodeficiencies (PID) associated with eczematous dermatitis. In Part II we provide an update on other PID, including those associated with mucocutaneous candidiasis and PID with non-infectious skin manifestations.

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NEW MUCOCUTANEOUS CANDIDIASIS SYNDROMES

Key points

- Several new monogenic disorders have been associated with chronic mucocutaneous candidiasis (CMC)
- Gain of function *STAT1* mutations cause CMC with a variety of systemic manifestations
- *CARD9* mutations predispose to CMC, 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 (PRR), such as toll-like receptors (TLR) and C-type lectin receptors, recognize components of pathogens, termed pathogen-associated molecular patterns (PAMPs), that are evolutionarily conserved. TLR2 and TLR4 recognize O-linked mannan on the fungal cell wall, and activate nuclear factor-kappa B (NF- κ B) through the adaptor protein MyD88. Dectin-1, a C-type lectin receptor, recognizes β -glucans, leading to NF- κ B induction through the adaptor protein caspase recruitment domain family, member 9 (*CARD9*). This results in transcription of proinflammatory cytokines which bind to receptors on Th17 cells. The discovery of Th17 cells in 2005 and, subsequently, mucocutaneous candidiasis syndromes associated with specific Th17 signaling defects, demonstrate 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 CMC (Table 1).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 due to a *STAT1*-dependent increase in production of interferons (IFN) that inhibit Th17 development.^{3–5} GOF mutations in *STAT1* result in diminished interleukin (IL)-17A and IL-22, and enhanced response to type I IFNs.^{4, 6} In addition to CMC, patients are at risk for other fungal infections (e.g. 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, A and B)—some patients manifest only CMC, whereas 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 β -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 Th17 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.

CARD9 deficiency

Mutations in *CARD9* are also responsible for a new monogenic autosomal recessive CMC. However, unlike Dectin-1 deficiency, *CARD9* deficiency is also associated with invasive fungal infection and deep dermatophytosis.^{15, 16} Neutrophil dysfunction may account for the invasive potential of fungal infections in *CARD9* deficiency, particularly candidal meningitis.^{17, 18} Drewniak *et al.*¹⁷ demonstrated that production of IL-6 and IL-1 β in response to *Candida albicans* is dependent on *CARD9*. Failure of monocytes or dendritic cells to produce these cytokines results in naïve T cells unable to differentiate into Th17 cells. Recommended therapy for superficial dermatophyte involvement is systemic terbinafine or posaconazole.¹⁹ The addition of GM-CSF to standard antifungal therapy may improve therapeutic response to invasive infections.^{20, 21}

IL-17RA, IL-17, and ACT1 associated CMC

Three additional recently identified inborn errors of immunity associated with CMC further demonstrate the importance of Th17 cytokines in CMC: autosomal recessive mutations in the *IL-17RA* and *ACT1* genes, and autosomal dominant mutations in the *IL-17F* gene. In 2011, Puel *et al.*²² described a boy born to consanguineous parents who developed CMC as well as superficial skin infection with *S aureus* in infancy. Gene sequencing identified a homozygous mutation in the *IL17RA* gene, which encodes the receptor IL-17RA. The same report described a second family with 5 affected family members who developed CMC due to a heterozygous missense mutation in the *IL17F* gene, which encodes IL-17F, one of 6 known IL-17 cytokines. Lastly, in 2013 a novel mutation was identified in *ACT1* which results in CMC due to loss of response to IL-17.²³ Two siblings were reported with oral thrush and onychomycosis from *Candida* as well as superficial *S aureus* skin infections. Genetic screening identified biallelic missense mutation in *ACT1*, also known as NF- κ B activator 1 or *TRAF3IP2*, encoding an adaptor molecule that interacts with the IL-17 receptors to allow downstream activation of pathways including NF- κ B.

AUTOIMMUNE POLYENDOCRINOPATHY, CANDIDIASIS, AND ECTODERMAL DYSPLASIA (APECED)

Key points

- Autosomal recessive
- Triad of hypoparathyroidism, Addison's disease, and CMC
- Autoimmune manifestations common due to loss of central tolerance

APECED is characterized by the triad of CMC, hypoparathyroidism, and Addison's disease.¹⁴ Clinical diagnosis requires 2 of these 3 findings; however, additional autoimmune manifestations in the skin and other organs are common. This syndrome, also known as autoimmune polyendocrine syndrome type 1 (APS-1), is a rare autosomal recessive

condition caused by biallelic mutations in the autoimmune regulator (*AIRE*) gene.²⁴ *AIRE* is expressed in medullary thymic epithelial cells (mTECs) and is essential for deletion of autoreactive T cells. Mutations in *AIRE* render the AIRE protein undetectable in mTECs, and allow survival of autoreactive T cells.^{25, 26} APECED is associated with autoimmune dysfunction of the parathyroid and adrenal glands in early adolescence, hypothyroidism, autoimmune hepatitis, and pernicious anemia.²⁷ Dermatologic manifestations of autoimmunity in APECED include vitiligo and alopecia areata/universalis (Fig 3, A). CMC, often present by age 6, is the primary infectious manifestation in APECED (Fig 3, B). In 2010, autoantibodies against Th17 cytokines (IL-17A, IL-17F, and IL-22) were discovered in patients with APECED, suggesting a causative link to CMC in these patients.^{26, 28, 29} A similar susceptibility to CMC due to autoantibodies to IL-17 and IL-22 has been described in patients with thymoma.²⁶

GRANULOMATOUS SKIN DISEASE IN PID

Noninfectious granulomatous skin inflammation is an important cutaneous clue to the diagnosis of PID. Phospholipase C, gamma 2 (*PLC γ 2*)-associated antibody deficiency and immune dysregulation (PLAID) and severe combined immunodeficiency (SCID) due to hypomorphic recombination-activating gene (*RAG*) mutations, are recent additions to the differential diagnosis of PID associated with noninfectious granulomas (Table 2).

PLAID

Key points

- Autosomal dominant
- Evaporative cold urticaria in all patients, granulomas in a subset of patients
- Neonatal nasal and acral inflammatory lesions

Familial atypical cold urticaria was first described in 2009 in three families.³⁰ In 2012, three additional unrelated families with evaporative cold urticaria were identified and found to have a genomic deletion in *PLCG2* leading to gain of function of the protein, PLC γ 2, a syndrome termed PLAID.³¹ This is an autosomal dominant condition associated with urticaria induced by evaporative cooling or contact with cold air. Cold urticaria develops in early childhood and persists into adulthood. In this syndrome, PLC γ 2 enzyme activity increases with cold temperature, leading to increased mast cell degranulation. A subset of patients with PLAID also develop neonatal skin lesions on the fingers, toes, and nasal tip. Although the nature of the lesions is not yet fully characterized, nasal lesions have progressed to nasal destruction in two cases.³² In addition, a minority of patients with neonatal skin lesions progress to granulomatous skin disease later in life (Fig 4). Patients also develop allergic disease (56%), recurrent sinopulmonary infections (44%), and autoimmune disease (26%) including vitiligo, thyroiditis and arthritis. Elevated ANA titers were found in 62% among patients with PLAID who were tested. Immune abnormalities in PLAID include elevated immunoglobulin (Ig)E, decreased IgA and IgM, and decreased circulating B cells and natural killer (NK) cells. B cells in PLAID have reduced class switched antibody production, but increased mature B cell compartment.³¹

Autoinflammation and $PLC\gamma 2$ -associated antibody deficiency and immune dysregulation (APLAID), also reported in 2012, is associated with a missense mutation, rather than deletion, in the same gene, *PLCG2*.³³ Patients with APLAID have a more pronounced inflammatory syndrome than PLAID, with recurrent sinopulmonary infections, interstitial pneumonitis and respiratory bronchiolitis, eye inflammation, colitis, and arthralgias. Skin features include epidermolysis bullosa-like blistering in infancy that develops into vesiculopustular lesions and erythematous plaques following heat exposure. The immunophenotype of APLAID demonstrates an absence of class switched memory B cells, as seen in PLAID, with normal naïve and memory T cells and NK cells.³³

SCID

Key points

- Most common cause is a mutation in *IL-2R γ*
- Hypomorphic *RAG* mutations are associated with granulomatous skin disease, autoimmunity, and a less severe infection profile than null *RAG*-associated SCID
- Adenosine deaminase deficient SCID patients are at risk of single or multiple dermatofibrosarcoma protuberans (DFSP) tumors

SCID is a group of disorders characterized by B and T cell immunodeficiency and multiple known genetic defects. The most common form is X-linked recessive SCID, caused by mutations in the *IL-2R γ* gene. This produces a $T^{-}B^{+}NK^{-}$ immunophenotype with early onset infection and risk of death; however, many other phenotypes have recently been described with variable presentations.

Null mutations in *RAG1* or *RAG2* are responsible for about 20% of cases of SCID. These genes play a critical role in recombination of V(D)J segments of immunoglobulins and T cell receptors. This is important both for antigen recognition as well as for maturation of lymphocytes.³⁴ It has long been recognized that null mutations of this gene are responsible for classic autosomal recessive $T^{-}B^{-}NK^{+}$ SCID. This leads to severe early-onset viral and bacterial infections, usually within the first month of life, requiring hematopoietic stem cell transplant (HSCT) for survival.

In contrast to patients with null mutations, patients with hypomorphic *RAG* mutations have residual V(D)J recombination with variable clinical presentations.³⁵ The clinical spectrum of hypomorphic *RAG* SCID now includes (1) Omenn syndrome (OS), (2) early onset autoimmunity, (3) immunodeficiency with granulomas, (4) isolated $CD4^{+}$ lymphopenia, and (5) cytomegalovirus infection with $\gamma\delta$ T cell expansion.^{36–40} OS was the first characterized syndrome associated with hypomorphic *RAG* mutations, and presents similar to classic SCID with infections early in infancy. The immunophenotype is $T^{+/-}B^{-}NK^{+}$. Patients develop erythroderma in infancy, lymphadenopathy, hepatosplenomegaly, and alopecia. Laboratory evaluation in OS shows eosinophilia, elevated serum IgE, an absence of B cells, and expansion of oligoclonal T cells that infiltrate organs.^{34, 36, 41} This condition may be fatal despite early HSCT.³⁶

In 2008, Schuetz *et al.*³⁶ reported a new presentation of hypomorphic mutations in *RAG1* or *RAG2*, characterized by granulomatous skin disease early in life, but a less severe immunodeficiency than null mutation RAG SCID. The immunophenotype in these patients is T⁺/B⁺/NK⁺, with low lymphocyte counts and low immunoglobulin levels, including IgE.³⁶ Destructive granulomas developed in the skin and visceral organs, and responded poorly to treatments including corticosteroids, antibiotics, and immunosuppressants.^{35, 36, 42, 43} It has been postulated that these destructive granulomas are a result of a dysregulated hyperinflammatory response to viral antigen.

Adenosine deaminase (ADA) deficiency is the most common cause of autosomal recessive SCID. The immunophenotype is notable for profound lymphopenia of T, B, and NK cells as well as impairment of both cellular and humoral immunity. ADA plays a key role in the purine salvage pathway, and ADA deficiency leads to accumulation of toxic metabolites and eventual chromosomal breakage.⁴⁴ ADA-SCID is associated with high mortality and most patients present in the neonatal or infantile period with severe fungal, viral, and bacterial infections.⁴⁵ However, the use of pegylated ADA enzyme replacement and gene therapy has dramatically altered the life expectancy in this severe immunodeficiency.

Recently, an association between ADA-SCID and dermatofibrosarcoma protuberans has been reported. Kesserwan *et al.*⁴⁶ found that 8 of 12 patients with ADA-SCID followed at National Institutes of Health (NIH) had one or more DFSP lesions (including 15 lesions in one patient). The majority of tumors presented as atrophic plaques located on the trunk and extremities (Fig 5, A and B). Patient age at the time of biopsy ranged from 2–22 years. ADA-SCID associated DFSP lesions demonstrate a proliferation of CD34⁺ spindle cells but often lack the prototypic storiform histologic appearance (Fig 5, C-E). In this cohort, lesions were confirmed by molecular testing to harbor the characteristic collagen type I, alpha-1-platelet-derived growth factor subunit beta (COL1A1-PDGFB) fusion gene found in DFSP tumors. The natural history of ADA-SCID DFSP is unknown and the optimal management strategy is also unclear. Given the multiplicity of lesions in affected patients, wide excision of lesions would require numerous potentially disfiguring surgical procedures. The potential role of imatinib mesylate for management of ADA-SCID DFSPs has not been studied in this setting.

PID ASSOCIATED WITH HUMAN PAPILLOMAVIRUS

Cutaneous viral infections such as human papillomavirus (HPV) are a common presentation of numerous recently described PID: DOCK8 deficiency and MST1 deficiency (see Part I), GOF STAT1 mutation, as well as GATA2 deficiency and WHIM syndrome, which will be discussed below (Table 3). A history of widespread or treatment-refractory disease and careful family history can identify those patients at risk for an underlying PID who may require close surveillance for HPV-related dysplasia and malignancy.

GATA2 deficiency

Key points

- Autosomal dominant

- HPV infection with frequent progression to dysplasia
- Variable age of onset of infections
- High risk of myelodysplasia/acute myeloid leukemia

In 2011, loss of function mutations in GATA-binding protein 2 (*GATA2*) were found to be responsible for four syndromes: (1) monocytopenia and mycobacterial infection (MonoMAC) syndrome, (2) dendritic cell, monocyte, B lymphocyte, and NK lymphocyte deficiency, (3) familial myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), and (4) Emberger syndrome (primary lymphedema and MDS) (Table 4).^{47–52} *GATA2*, one of six known mammalian GATA factors, is a zinc-finger transcription factor expressed in hematopoietic stem cells. The variety of functions of this gene, including regulation of other transcription factors, lymphatic development, endothelial cell activation, and proliferation, explains the diverse clinical findings of *GATA2* deficiency (Fig 6).⁴⁷ In 2014, a cohort of 57 patients with *GATA2* deficiency was reported from the NIH, demonstrating remarkable disease heterogeneity in age of onset (early childhood to late adulthood) and disease severity.⁵³ Kindred studies have shown that affected family members may manifest limited signs and symptoms. Therefore, genetic screening is recommended for all family members so that appropriate clinical screening can be performed.

Infection and myelodysplasia are often the presenting signs of *GATA2* deficiency and were found in 82 and 84% of the patients in the NIH cohort, respectively.⁵³ The most common infection is HPV, reflecting the profound NK lymphocytopenia and dysfunction characteristic of *GATA2* deficiency. HPV infection usually presents by the second decade of life and manifests as generalized verrucosis with persistent cutaneous and genital disease that can rapidly progress to cervical, vulvar, and anal dysplasia (Fig 7, A).⁴⁹ Other common infections include disseminated nontuberculous mycobacteria (NTM) (Fig 7, B), severe cutaneous and systemic bacterial infections, *Herpesviridae* family infections, and fungal infections. Mycobacterial and fungal infections generally present in the third decade of life.⁴⁹ HPV infection is often recalcitrant to treatment, but IFN α and IFN γ have been successful in several patients.^{54, 55} Azithromycin is recommended as prophylaxis against NTM infection and early HPV vaccination should be considered, although no studies on the efficacy of vaccination have been performed in the setting of *GATA2* deficiency.⁵³

Patients with *GATA2* deficiency develop autoimmunity through mechanisms not yet fully understood. Autoimmune thyroid disease is most frequent, and was found in 8 of 57 patients followed at the NIH (14%).⁵³ Decreased regulatory T (Treg) cells may promote autoimmunity. In addition, CD56^{bright} NK cells play an immunoregulatory role, and therefore absence of this NK subtype may predispose patients with *GATA2* deficiency to autoimmunity.^{55, 56}

GATA2 deficiency is also associated with pulmonary alveolar proteinosis (18%), which can lead to pulmonary arterial hypertension (9%). Panniculitis, including erythema nodosum (Fig 7, C), develops in one-third of patients with *GATA2* deficiency and is frequently associated with underlying infection, particularly mycobacterial infection. Eleven percent of

patients in the NIH cohort also developed unilateral or bilateral lymphedema, and one-quarter developed venous thromboses.⁵³

Malignancy is a major cause of morbidity and mortality in GATA2 deficiency. One third of patients develop HPV-related dysplasia and 11% of patients in the NIH cohort developed melanoma or nonmelanoma skin cancer.⁵³ Breast cancer and other solid tumors were also identified in the NIH cohort; however, the greatest risk of death for patients with GATA2 deficiency is progression of MDS to AML and chronic myelomonocytic leukemia. Patients with GATA2 deficiency have approximately 50% risk of developing MDS or leukemia in early adulthood, so early diagnosis can be life saving.^{50, 57} Myelodysplasia, present in 84% of GATA2 patients in the NIH cohort, results in multilineage cytopenia of B cells, NK cells, monocytes, and dendritic cells. In addition, there is variable CD4⁺ lymphocytopenia and neutropenia.^{53, 58} In one recent study of patients carrying a clinical diagnosis of idiopathic cyclic neutropenia or CD4⁺ lymphocytopenia, *GATA2* mutations were found in 6 of 14 patients screened.⁵⁹ HSCT offers the only cure for GATA2 deficiency.^{53, 57}

WILD syndrome, an acronym for a syndrome of disseminated warts, immunodeficiency, primary lymphedema, and anogenital dysplasia, was proposed by Kreuter *et al*⁶⁰ in 2008. This group identified one previously reported case with similar findings to their patient.⁶¹ However, given the similarity between the clinical features between these presentations, it is suspected that the reported patients with WILD syndrome may have GATA2 deficiency.⁶²

WHIM syndrome

Key points

- Autosomal dominant
- HPV infections with variable severity
- Recurrent bacterial infections
- Plerixafor offers a potential targeted therapy for WHIM syndrome

The syndrome of warts, hypogammaglobulinemia, immunodeficiency and myelokathexis (WHIM syndrome) is a rare autosomal dominant PID initially described in 1964 in a 10 year old girl with recurrent infections and granulocytopenia.⁶³ This patient also had a characteristic bone marrow abnormality of WHIM syndrome, myelokathexis, which is retention of neutrophils in the marrow. In 2003, gain of function mutations in the gene encoding chemokine C-X-C motif receptor 4 (CXCR4) were found to be responsible for this condition.⁶⁴ CXCR4 is the receptor for chemokine (C-X-C motif) ligand 12 (CXCL12), which regulates hematopoiesis and peripheral trafficking of neutrophils and lymphocyte subsets.⁶⁴

WHIM syndrome manifests with peripheral neutropenia, hypogammaglobulinemia, and HPV infection.⁶⁵ HPV manifestations range from mild disease with multiple verrucae on the genitals, hands, and feet to severe involvement (Fig 8) with HPV-associated oral and cervical carcinoma. Despite peripheral neutropenia, there is appropriate release of neutrophils from the bone marrow in response to acute infection; therefore, serious bacterial infections are rare. However, hypogammaglobulinemia can lead to recurrent sinopulmonary

infections. Unlike many primary immunodeficiencies, autoimmunity and malignancy are infrequent in WHIM syndrome and are limited to a few reports of B cell lymphoma, Epstein-Barr virus (EBV)-associated lymphoproliferative disorder, and cutaneous T cell lymphoma.^{66–68} Other reported systemic findings include tetralogy of fallot, double aortic arch, radius hypoplasia, and phalangeal dysgenesis.⁶⁹

The immunodeficiency of WHIM syndrome is primarily a consequence of myelokathexis. Other immunologic abnormalities include lymphocytopenia, affecting B cells more than T cells, delayed antibody class switching to IgG, and hypogammaglobulinemia.⁷⁰ Reduced plasmacytoid and myeloid dendritic cells at the site of HPV infection may result in reduction of IFN α production in response to viral infection in patients with WHIM syndrome.^{71, 72} CXCR4 is expressed by hematopoietic cells and has been extensively studied as a co-receptor for HIV entry. Both CXCR4 and its ligand, CXCL12 (also known as stromal cell-derived factor-1 or SDF-1) are necessary for the development and trafficking of myeloid cells and B lymphocytes.^{64, 71} Plerixafor is a small molecule antagonist of CXCR4 that is FDA-approved for hematopoietic stem cell mobilization in patients with non-Hodgkin lymphoma or multiple myeloma. In 2010, two Phase I trials demonstrated that plerixafor can effectively mobilize leukocytes from the bone marrow and increase the peripheral absolute lymphocyte, monocyte, and neutrophil counts in patients with WHIM syndrome.^{73, 74} These trials, as well as a more recent study in 2014, suggest that this targeted therapy may decrease bacterial infections and HPV burden in patients with WHIM syndrome.^{73–75}

Prophylactic antibiotic coverage for encapsulated bacteria and *Staphylococcus* is recommended for patients with WHIM syndrome.⁷¹ The effectiveness of HPV vaccination in WHIM patients is unknown, but given the burden of HPV infection and risk of dysplasia, our recommendation is to offer HPV vaccination early. Replacement gammaglobulin may be needed as well as G-CSF for neutropenia. Although mortality in WHIM syndrome is lower than other primary immunodeficiencies, early diagnosis can lead to appropriate prophylactic and treatment strategies to minimize infections and HPV-related dysplasia and malignancy.

CONCLUSION

The use of powerful molecular tools has ushered in an exciting new era of understanding of the genetic basis of PID. This has allowed clear characterization of distinct disease phenotypes, including specific susceptibility to viral and fungal infections and the cutaneous manifestations of PID, both infectious and non-infectious. Hopefully, these advances will also continue to advance our ability to effectively manage these rare but potentially devastating conditions.

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ABBREVIATION AND ACRONYM LIST

ADA	adenosine deaminase
AIRE	autoimmune regulator
AML	acute myeloid leukemia
APECED	autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia
APLAID	autoinflammation and PLC γ 2-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
Ig	immunoglobulin
IFN	interferon
IL	interleukin
MDS	myelodysplastic syndromes
MonoMAC	monocytopenia and mycobacterial infection
MST1	mammalian sterile 20-like 1
mTECs	medullary thymic epithelial cells
NIH	National Institutes of Health
NF-κB	nuclear factor-kappa B
NK	natural killer

NTM	nontuberculous mycobacterial
OS	Omenn syndrome
PAMPs	pathogen-associated molecular patterns
PID	primary immunodeficiency
PLAID	PLC γ 2-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
VZV	varicella-zoster virus
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 mucocutaneous candidiasis based on the other infectious and the noninfectious manifestations; identify primary immunodeficiencies that have noninfectious granulomas; identify the numerous presentations of GATA2 deficiency; identify the targeted therapy for WHIM syndrome

Part II CME

A 28 year-old female with a history of treatment refractory HPV infection of the hands, genitalia and face is evaluated for the first time in your office. She has a history of cervical dysplasia (Grade II) and cutaneous mycobacterial infection. Laboratory work-up reveals severe monocytopenia.

1. What additional clinical feature is most suggestive of a diagnosis of GATA2 deficiency?
 - A. **Lymphedema**
 - B. Joint hyperextensibility
 - C. High-arched palate
 - D. Scoliosis
 - E. Retained primary teeth

2. What malignancy is this patient at highest risk of developing?
 - A. Endometrial cancer
 - B. Glioblastoma multiforme
 - C. Breast cancer
 - D. Lung cancer
 - E. **Acute myelogenous leukemia**

A 7 year old boy with adenosine deaminase-associated severe combined immunodeficiency is seen in clinic for 3 depressed 3–6mm round brown plaques on the torso. The lesions have been slowly enlarging over the past 2 years.

3. What is the most likely diagnosis/next step in management?
 - A. Anetoderma/reassurance
 - B. Morphea/topical steroids
 - C. **Dermatofibrosarcoma protuberans/biopsy**
 - D. Tinea versicolor/topical antifungal therapy
 - E. Disseminated granuloma/biopsy
4. Biopsy reveals a spindle cell infiltrate in the reticular dermis extending into the fat. What immunohistochemical stain is most helpful to confirm the diagnosis?
 - A. **CD34**
 - B. CD20
 - C. CD68
 - D. Factor XIIIa

E. PAS

5. What is the molecular abnormality associated with this lesion?

A. c-kit

B. STAT1

C. STAT3

D. Ras

E. Col1A-PDGFR

Figure 1.

Immune response to fungal infection. A. Pattern recognition receptors such as toll-like receptors (TLR) and C-type lectin receptors (*e.g.* Dectin-1) present on macrophages, dendritic cells, activate independent pathways. TLR2 and TLR4 use the adaptor protein MyD88 to activate nuclear factor kappa B (NF- κ B). This transcription factor translocates into the nucleus and facilitates transcription of pro-inflammatory cytokines. Dectin-1 signals through the adaptor protein caspase recruitment domain family, member 9 (CARD-9), also activating NF- κ B. Binding of interferon- γ (IFN) to its receptor on macrophages allows for homodimerization of signal transducer and activator of transcription 1 (STAT1). This transcription factor produces interferons and proinflammatory cytokines that inhibit Th17 cell development. B. Th17 cells, which produce cytokines critical for antifungal immunity, signal through STAT3. C. IL-17 receptors are expressed on numerous nonhematogenous cells. IL-17 binds its receptor allowing for activation of NF- κ B through the adaptor protein ACT1, producing pro-inflammatory chemokines and cytokines that are important to the host defense against fungal organisms.

A

B

Figure 2. Multiple cutaneous fungal infections associated with *STAT1* gain of function mutation. A. *Trichophyton tonsurans* dermatophyte infection on the thigh and extensive nail dystrophy (B) due to chronic fungal infection in an 18 year old female. Nail clippings identified septate hyphae.

A

B

Figure 3.

Autoimmune polyendocrinopathy candidiasis, and ectodermal dysplasia. A. 38 year old male with alopecia universalis, vitiligo and nail dystrophy (B) secondary to recurrent candidal infection beginning at age 3.

Figure 4. Granuloma formation in PLAID syndrome. Widespread granulomatous disease in 21 year old with PLAID syndrome. Histopathology demonstrated sarcoid-like granulomas without central necrosis as well as diffuse, superficial dermal granulomatous inflammation.

A

B

C

D

E

Figure 5.

Multiple dermatofibrosarcoma protuberans in ADA-SCID. A. Irregularly shaped red-brown plaque on the upper chest in 17 year old male with ADA-SCID. B. A depressed atrophic plaque with poorly-defined margins is seen on close examination. C. Histopathological analysis from 3 similar appearing lesions on this patient a revealed spindle-cell infiltrate, primarily in the reticular dermis (D). E. Immunohistochemistry demonstrates the spindle cell infiltrate strongly expresses CD34; RT-PCR testing from the specimen demonstrated the presence of COL1A1/PDGFB fusion transcripts. (C and D, Hematoxylin-eosin stain, original magnification: C, x40; D, x100; E, CD34 stain; original magnification x200.)

Figure 6. Cutaneous and systemic findings in GATA2 syndrome. Reprinted, with permission, from Spinner MA *et al.*⁸

Figure 7. Cutaneous findings in GATA-2 deficiency. A. Extensive HPV infection with vulvar and anal intraepithelial neoplasia, cutaneous mycobacterial infection (B), and erythema nodosum-like panniculitis (C) in a 40 year old female with GATA2 deficiency.

Figure 8. WHIM syndrome. Confluent perianal condyloma and scattered verrucous papules on the buttock and perineum of a 4 year old with WHIM syndrome.

Table 1

Primary immunodeficiencies associated with chronic mucocutaneous candidiasis

PID (inheritance)	Infections (in addition to CMC)	Immunologic abnormalities	Other findings
STAT3/Autosomal dominant hyper-IgE syndrome (AD)	Recurrent cold skin abscesses Sinopulmonary infections Lower respiratory tract infections Dermatomal herpes zoster	Th17 cell deficiency Memory B and T cell differentiation impaired Elevated serum IgE level Eosinophilia	Neonatal papulopustular eruption Eczematous dermatitis Non-Hodgkin's lymphoma Craniofacial abnormalities Retained primary teeth Scoliosis Minimal trauma fracture Joint hyperextensibility Cerebral/coronary artery aneurysms
Gain of function STAT1 mutation (AD)	Sinopulmonary infections Mycobacterial infections <i>Herpesviridae</i> family infections	Diminished Th17 cells Enhanced response to Type I IFNs	Insulin dependent DM Enteropathy Dental enamel abnormalities Hypothyroidism Hemolytic anemia Autoimmune hepatitis Cerebral aneurysm Oral, esophageal cancer
Dectin-1 mutation (AR)		Undetermined	Squamous cell carcinoma
CARD9 deficiency (AR)	Invasive fungal infections Deep dermatophytosis	Impaired Th17 differentiation	
IL-17RA deficiency (AR)	Superficial bacterial skin infections	Abolished response to IL-17A and IL-17F	
IL-17F deficiency (AD)		Impaired IL-17 signaling	
ACT1 deficiency (AR)	Superficial bacterial skin infections	Abolished response to IL-17A and IL-17F	
APECED (AR)		Autoantibodies to IL-17, IL-22 Autoantibodies to Type I IFN	Vitiligo Alopecia areata/ universalis Hypoparathyroidism Addison's disease Hypothyroidism Autoimmune hepatitis Pernicious anemia

AD – autosomal dominant, *APECED* – autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia, AR – autosomal recessive, CMC – chronic mucocutaneous candidiasis, DM – diabetes mellitus, IFN – interferon, Ig – immunoglobulin, IL – interleukin, PID - primary immunodeficiency

Table 2

Primary immunodeficiencies associated with granuloma formation

Common variable immunodeficiency
Chronic granulomatous disease
Nijmegen breakage syndrome
PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID)
Hypomorphic <i>RAG</i> mutation

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Table 3

New primary immunodeficiencies associated with viral infections

Immunodeficiency	Non-infectious cutaneous manifestation	Infection predisposition	Immunologic abnormalities	Other associated findings
GATA2 deficiency	Panniculitis Congenital lymphedema Melanoma Nonmelanoma skin cancer	HPV, HSV, VZV, NTM infection Severe C. difficile infection	Monocytopenia B and NK cell lymphopenia Dendritic cell cytopenia Variable CD4 lymphopenia Variable neutropenia Normal immunoglobulins	MDS Leukemia Thromboembolic disorder PAP Sensorineural hearing loss Thyroid disease
WHIM syndrome		Bacterial pneumonia, sinusitis, skin/soft tissue infection HPV, HSV, EBV, VZV	Neutropenia B and T cell lymphopenia Decreased IgG and IgA Normal IgM and antibody response	B cell lymphoma EBV-lymphoproliferative disorder Structural cardiac anomalies Upper limb anomalies
DOCK8 deficiency	Ecematous dermatitis Squamous cell carcinoma	Bacterial pneumonia, sinusitis, skin/soft tissue infection HPV, HSV, MCV, VZV	Variable B, T, and NK cell lymphopenia Eosinophilia Elevated IgE Normal/elevated IgG and IgA Decreased IgM Variable antibody response	Asthma, allergies Lymphoma EBV-lymphoproliferative disorder
MST1 deficiency	Ecematous dermatitis	Bacterial pneumonia, sinusitis, skin/soft tissue infection HPV, HSV, MCV, EBV, VZV	Neutropenia B and T cell lymphopenia	EBV-lymphoproliferative disorder Structural cardiac anomalies Autoimmunity
Gain of function STAT1 mutation		Bacterial sinopulmonary Mycobacterial infection HSV, EBV, VZV, CMV Mucocutaneous candidiasis Disseminated fungal infection	Diminished Th17 cells Enhanced response to Type I interferons	Endocrine abnormalities Dental enamel abnormalities Autoimmunity Cerebral aneurysm Oral and esophageal malignancy

CMV, cytomegalovirus; DOCK8, dedicator of cytokinesis 8; EBV, Epstein-Barr virus; GATA2, GATA-binding protein 2; HPV, human papillomavirus; HSV, herpes simplex virus; Ig, immunoglobulin; MCV, molluscum contagiosum virus; MDS, myelodysplastic syndrome; MST1, Mammalian sterile 20-like 1; NK, natural killer; NTM, nontuberculosis mycobacteria; PAP, pulmonary alveolar proteinosis; STAT1, signal transducer and activator of transcription 1; VZV, varicella zoster virus; WHIM, Warts, Hypogammaglobulinemia, Immunodeficiency and Myelokathexis

Table 4

Syndromes associated with *GATA2* mutations

GATA2-related syndrome	Immunologic findings	Infections	Other clinical findings
Monocytopenia and mycobacterial infection (MonoMac) syndrome	Monocyte, B, and NK cell lymphopenia	Mycobacterial Fungal Viral	Pulmonary alveolar proteinosis Erythema nodosum Lymphedema Myelodysplasia Myeloid leukemia
Dendritic cell, monocyte, B, and NK lymphocyte (DCML) deficiency	Dendritic cell, monocyte, B and NK cell lymphopenia	Mycobacterial Viral	Pulmonary alveolar proteinosis Myelodysplasia Myeloid leukemia
Familial myelodysplastic syndrome/acute myeloid leukemia	Multilineage cytopenia		Myelodysplasia Myeloid leukemia
Emberger syndrome	Variable multilineage cytopenia	Viral	Congenital sensorineural hearing loss Lower limb and genital primary lymphedema Anogenital dysplasia Myelodysplasia Myeloid leukemia

DCML, dendritic cell, monocyte, B and NK lymphoid; *MonoMac*, monocytopenia and mycobacterial infection; *NK*, natural killer