Published in final edited form as:

Clin Pediatr (Phila). 2018 June ; 57(7): 874–878. doi:10.1177/0009922817738347.

What Is the Cause of the Chronic Erythematous Scaling Plaques on This 22-Month-Old Girl and Her Family?

Teresa Ro, MD¹, Amika Sood, MD¹, Kevin J. Kelly, MD¹, and Dean S. Morrell, MD¹

¹University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Case Report

A 22-month-old female with a past medical history significant for cutaneous candida infections, thrush, pneumonia, otitis media, and bronchitis presented with a primarily skin fold eruption associated with intense pruritus that has been worsening over the past 6 months. She was born full-term to healthy, nonconsanguineous parents. Per parents, the patient has been sick “all the time.” She started having cutaneous candida infections shortly after birth, 2 episodes of thrush in infancy, pneumonia requiring hospitalization for intravenous antibiotics and supplemental oxygen at 6 months, and multiple episodes of otitis media, and bronchitis. She was up-to-date with her vaccinations and has had normal growth and development since birth.

Family history was significant for similar findings in her 2 older sisters, mom, maternal aunt, and 3 cousins. Her mom also experienced episodes of thrush, primarily in her childhood, cutaneous candida infections, esophageal strictures, and nail dysplasia. The mother denied history of endocrine disorders in herself or family members who have similar cutaneous candida infections. Prior to our patient’s birth, her 2 sisters and mother underwent genetic evaluation, but had been lost to follow-up in another city after redeployment in the military.

On examination, patient was happy, interactive, and overall healthy-appearing. Erythematous plaques with pearl white scales were identified on her plantar surfaces bilaterally as well as in the skin folds of the axilla and perineum (Figure 1). In addition, the patient had multiple individual flesh-colored dome-shaped papules with surrounding erythema. Her 2 female siblings had similar findings while her mother was noted to have hyperkeratotic nails and generalized erythroderma (Figure 2).

Reprints and permissions: sagepub.com/journalsPermissions.nav

Corresponding Author: Dean S. Morrell, Department of Dermatology, University of North Carolina at Chapel Hill, 410 Market Street, Suite 400 CB#7715, Chapel Hill, NC 27516, USA. morrell@med.unc.edu.

Author Contributions

All authors have contributed equally towards making the concept and design of the manuscript, drafting/revising the manuscript and approve the final version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Final Diagnosis

Chronic mucocutaneous candidiasis.

Clinical Course

The potassium hydroxide (KOH) test from a skin scraping of the patient's inguinal fold revealed pseudohyphae and budding yeast cells, indicative of cutaneous infection with *Candida albicans* (Figure 3). Laboratory testing of complete blood cell count, immunoglobulin levels, flow cytometric assessment of T-cell and B-cell populations, neutrophil function, and mitogen stimulation were all within normal limits. Specific lymphocyte proliferation response to *C. albicans* was absent. An abnormal low response to tetanus toxoid was observed; however, antibody titer response to tetanus vaccination was normal. Genetic sequencing identified a heterozygous R274Q mutation in *STAT1*. Prior records revealed that her mother and sisters also had gain-of-function mutations in the signal transducer and activator of transcription 1 (*STAT1*) gene.

The patient's disease manifestation was primarily cutaneous in her intertriginous regions. Her course was also complicated by superficial infections with methicillin-sensitive *Staphylococcus aureus* and molluscum contagiosum as well as scabies. She did not have any autoimmune abnormalities. Her cutaneous fungal infection was treated with oral itraconazole, clotrimazole 1% cream, and triamcinolone 0.1% cream while oral ivermectin was required for eradication of scabies. For her superficial staphylococcal infection, she received 2 courses of cephalexin followed by prophylactic dosing with sulfamethoxazole/trimethoprim. She clinically improved with the above therapeutic regimens with subsequent yeast screens remaining negative.

Discussion

Chronic mucocutaneous candidiasis (CMC) describes a highly heterogeneous group of disorders characterized by recurrent infections in mucous membranes, skins, and nails caused by *Candida*.^{1,2} A common immunologic finding seen in these patients is deficient T-cell mediated cytokine production to provide cell-mediated immunity to *Candida*. Early evidence for this immunologic basis of CMC came from observations of patients with DiGeorge syndrome and severe combined immunodeficiency (SCID). These patients commonly had chronic candidiasis of their oral mucosa, skin, and nails and were found to have low numbers of circulating T lymphocytes as well as poor lymphocyte proliferation to stimulation with *Candida*.² CMC is associated with both acquired and inherited conditions. Examples of acquired medical conditions that result in CMC include human immunodeficiency virus (HIV), diabetes mellitus, and use of antibiotics or immunosuppressants.¹ Oral candidiasis in HIV-infected patients is in fact thought to be a significant prognostic marker for progression to acquired immunodeficiency syndrome.²

CMC is also seen as part of various inherited clinical conditions associated with gene defects leading to deficient T-cell mediated production of interleukin-17 (IL-17) (Table 1). Patients with autosomal dominant hyper IgE syndrome (AD-HIES), associated with a mutation in the signal transducer and activator of transcription 3 (*STAT3*) gene, present with CMC and

increased susceptibilities to cutaneous and pulmonary staphylococcal diseases.³ Patients with autoimmune polyendocrinopathy candidiasis ectodermal dysplasia (APECED), an autosomal recessive disorder associated with mutations in the autoimmune regulator (*AIRE*) gene, present with CMC and multiple autoimmune endocrinopathies, such as hypoparathyroidism, adrenal insufficiency, and type 1 diabetes mellitus.⁴ Patients with homozygous caspase recruitment domain-containing protein 9 (*CARD9*) deficiency have CMC and increased susceptibilities to dermatophytoses and Candidal meningitis.⁵

As in the case of our patient, CMC can also be seen as a part of CMC disease (CMCD), an autosomal dominant disorder associated with a point mutation of *STAT1*. CMCD presents with primarily CMC without other overt clinical manifestations.^{6,8} Individuals with *STAT1* GOF mutations however also have increased susceptibilities to viral and bacterial infections, such as molluscum contagiosum and *S aureus*, failure to thrive, dysphagia/esophageal stenosis, autoimmune diseases such as hypothyroidism, cerebral aneurysms, and carcinomas.⁶ Some of the associated phenotypes, such as cerebral aneurysm, can lead to poor outcomes and even early death. Hence, these patients should be cared for at multidisciplinary centers with familiarity in the diagnosis and management of CMC.⁶ Our patient presented with mucocutaneous fungal infections with *Candida albicans* and superficial infections with *S aureus* and molluscum contagiosum. Patient's mother had esophageal stenosis and nail dysplasia, which are also findings associated with CMCD. She and her family members did not manifest noninfectious phenotypes associated with CMCD such as autoimmune conditions or failure to thrive.

Our patient's specific genetic mutation, R274Q, was first characterized in 2011 as one of the *STAT1* mutant alleles resulting in CMCD. The mutation affects the coiled-coil domain involved in nuclear dephosphorylation and dimerization of unphosphorylated *STAT1*.⁹ Further experiments suggested that the hyperphosphorylated state of the mutant *STAT1* inhibits IL-12R/IL-23R signaling, leading to decreased Th1/Th17 responses and thus, an increased susceptibility to fungal infections.¹⁰ Patients confirmed to have the mutation to this point were found to have clinical features of CMC and the most common nonfungal phenotype seen within the group was thyroid autoimmunity, which is consistent with what has been reported for the general population of patients carrying the *STAT1* GOF mutation.⁶

When evaluating patients with recurrent infections with *Candida*, secondary immunodeficiencies due to underlying disease states, such as HIV or diabetes mellitus, should be considered. Additionally, immunologic work-up should be performed to assess for immune dysfunction and to identify any primary or secondary immune abnormalities.² Genetic testing for known genes associated with CMC, such as *STAT3*, *AIRE*, *CARD9*, and *STAT1*, may also be valuable in elucidating other CMC-associated clinical conditions. For certain genetic disorders associated with CMC, endocrinopathies are common and therefore, should be screened for regularly.² As CMCD is one of the genetic disorders associated with endocrinopathies, our patient will be referred to endocrinology for screening.⁶ She will also continue to be co-managed with Pediatric Dermatology, Allergy and Immunology, and Pediatric Infectious Disease.

The first-line therapy for patients with CMC is long-term treatment with antifungals, such as ketoconazole, fluconazole, itraconazole, and terbinafine, and prompt identification and treatment of any associated comorbid conditions.² Our patient has had negative yeast screens on oral itraconazole and clotrimazole cream. The high rate of azole resistance may however necessitate use of alternative antifungals such as amphotericin B and echinocandin.⁶ Prophylactic antibiotic therapy may also be required for recurrent bacterial infections, particularly with *S aureus*. Treatment with granulocyte colony stimulating factors (GM-CSF) and Ruxolitinib, an oral Janus kinase (JAK) inhibitor, have been shown to be beneficial in some patients with difficult-to-treat CMC.^{11,12} Bone marrow transplantation has been attempted but is not considered a standard treatment option at this present time.¹¹

Conclusion

Chronic mucocutaneous candidiasis is a heterogeneous clinical entity caused by deficiencies, acquired or inherited, affecting T-cell mediated production of cytokines, namely IL-17. We discussed the case of a 22-month-old female who presented with a flare of her cutaneous candidiasis with superimposed cutaneous infections with *S aureus* and molluscum contagiosum found to have an R274 variant of the *STAT1* gene, indicative of chronic mucocutaneous candidiasis disease. Her sisters and mother had similar clinical phenotypes and genetic findings. Our patient is currently doing well with oral itraconazole, oral sulfamethoxazole/trimethoprim, and clotrimazole cream and will continue to have close follow-up from multidisciplinary teams for management of the various facets of CMCD.

Acknowledgments

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Glocker E, Grimbacher B. Chronic mucocutaneous candidiasis and congenital susceptibility to *Candida*. *Curr Opin Allergy Clin Immunol*. 2010; 10:542–550. [PubMed: 20859203]
2. Kirkpatrick CH. Chronic mucocutaneous candidiasis. *Pediatr Infect Dis J*. 2001; 20:197–206. [PubMed: 11224843]
3. Freeman AF, Holland SM. Clinical manifestations, etiology, and pathogenesis of the hyper-IgE syndromes. *Pediatr Res*. 2009; 65:32R–37R.
4. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med*. 1990; 322:1829–1836. [PubMed: 2348835]
5. Glocker EO, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009; 361:1727–1735. [PubMed: 19864672]
6. Toubiana J, Okada S, Hiller J, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. *Blood*. 2016; 127:3154–3164. [PubMed: 27114460]
7. Puel A, Picard C, Cypowyj S, Lilic D, Abel L, Casanova JL. Inborn errors of mucocutaneous immunity to *Candida albicans* in humans: a role for IL-17 cytokines? *Curr Opin Immunol*. 2010; 22:467–474. [PubMed: 20674321]
8. van de Veerdonk FL, Plantinga TS, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011; 365:54–61. [PubMed: 21714643]

9. Liu L, Okada S, Kong XF, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 2011; 208:1635–1648. [PubMed: 21727188]
10. Smeekens SP, Plantinga TS, van de Veerdonk FL, et al. STAT1 hyperphosphorylation and defective IL12R/IL23R signaling underlie defective immunity in autosomal dominant chronic mucocutaneous candidiasis. *PLoS ONE*. 2011; 6:e29248. [PubMed: 22195034]
11. van de Veerdonk FL, Netea MG. Treatment options for chronic mucocutaneous candidiasis. *J Infect*. 2016; 72(suppl):S56–S60. [PubMed: 27161991]
12. Mössner R, Diering N, Bader O, et al. Ruxolitinib induces interleukin 17 and ameliorates chronic mucocutaneous candidiasis caused by STAT1 gain-of-function mutation. *Clin Infect Dis*. 2016; 62:951–953.

Figure 1.
Erythematous plaque with yellowish scale on the patient's elbow.

Figure 2.
Thickened, hyperkeratotic nails with erythematous periungual skin in the mother's right hand.

Figure 3.
Ten percent KOH mount showing pseudohyphae and budding yeast cells in a skin scraping of the patient's inguinal fold.

Table 1

Pathogenesis, Clinical Features, and Outcomes of Patients With *STAT1*, *STAT3*, and *AIRE* Mutations Found in the Literature.

Condition	Gene Defect (Inheritance)	Pathogenesis	Infectious Phenotypes	%	Noninfectious Phenotypes	%
CMCD ^{6,7}	STAT1 (AD)	Impaired production of IL-17 secondary to defects in certain T helper cells	Mucocutaneous fungal infections	98	Autoimmune/inflammatory	37
			<i>Candida albicans</i>		Thyroid disease	22
			Dermatophytes	10	Other endocrine diseases	4
			Invasive fungal infection		Skin disease	10
			<i>Candida</i> spp		Aneurysm	6
			<i>Pneumocystis jirovecii</i>		Cerebral	5
			<i>Aspergillus</i> spp	74	Extracerebral	1
			Bacterial infections		Tumor	6
			<i>Staphylococcus aureus</i>		Benign	0.7
			<i>Streptococcus</i> spp		Squamous cell carcinoma	4
			<i>Pseudomonas aeruginosa</i>	17	Gastrointestinal carcinoma	0.7
			Mycobacterial infections		Other clinical features	
			<i>Mycobacterium tuberculosis</i>		Asthma/eczema	20
			BCG strain	38	Bone fragility	2
			Viral infections		Clinical outcomes	
			Varicella zoster		Failure to thrive	12
			Herpes simplex		Dysphagia/esophageal stenosis	11
			Molluscum contagiosum		Bronchiectasis	21
					Death	12
AD-HIES ^{3,6}	STAT3 (AD)	Low proportions of IL-17 producing T-cells	Recurrent pneumonias	87	Moderate-severe eczema	95
			<i>S aureus</i>		Eosinophilia	90
			<i>Streptococcus pneumoniae</i>		Lymphoma	5
			<i>Haemophilus influenzae</i>		Characteristic face	85
			Parenchymal lung abnormalities	70	Hyperextensibility	70
			Boils	87	Retained primary teeth	70
			<i>S aureus</i>	85	Minimal trauma fractures	65
			Mucocutaneous candidiasis	80	Scoliosis >10 degrees	60
			Recurrent sinusitis or otitis		Coronary vascular anomalies	60

Condition	Gene Defect (Inheritance)	Pathogenesis	Infectious Phenotypes	%	Noninfectious Phenotypes	%
APS-I/APECED ^{4,6}	AIRE (AR)	Decreased IL-17 cytokine levels due to high amounts of neutralizing antibodies against IL-17	Early-onset CMC (mean age = 3.7 y)	90	Arnold Chiari I malformation	40
					Focal hyperintensities on brain MRI	75
					Endocrine components	
					Hypoparathyroidism	79
					Adrenal failure	72
					Insulin-dependent diabetes mellitus	12
					Parietal-cell atrophy	13
					Hypothyroidism	4
					Ovarian failure	60
					Testicular failure	14
					Nonendocrine components	
					Alopecia	29
					Vitiligo	13
					Keratopathy	35
					Hepatitis	12
					Intestinal malabsorption	18
					Enamel hypoplasia	77
					Tympanic-membrane calcification	33
					Nail dystrophy	52

Abbreviations: CMCD, chronic mucocutaneous candidiasis disease; AD-HIES, autosomal dominant hyper IgE syndrome; APS-I, autoimmune polyendocrine syndrome type I; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia.