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CASE SERIES

Chinese Chronic Mucocutaneous Candidiasis: A Case Report Series

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Abstract: Chronic Mucocutaneous Candidiasis (CMC) is a rare immunodeficiency disease characterized by chronic or recurrent superficial *Candida* infections on the skin, nail, and mucous membranes. Here, we present four Chinese patients with CMC who manifested oral mucosal leukoplakia and nail thickening during early childhood, all displaying fissured tongue lines. The causative pathogens isolated from their oral mucosa and nails were identified as *C. albicans* and *C. parapsilosis* through morphology and molecular sequencing. Notably, among the four patients, one presented with vitiligo, while another had hypothyroidism. We have also conducted a review of reported cases of CMC in China and worldwide over the last five years, highlighting potential approaches for diagnosis and treatment. The current molecular evidence in the literature suggests potential for the development of early diagnosis methods, such as screening genetic variables on *STAT1* and *STAT3*. Additionally, potential treatment avenues, including gene-targeted analogues and GM-CSF analogues, could be explored in conjunction with traditional antifungal therapy.

Keywords: chronic mucocutaneous candidiasis, *Candida spp*., diagnosis, treatment

Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare primary immunodeficiency disease characterized by chronic or recurrent superficial *Candida* infections on the skin, nails, and mucosal membranes.[1] The development of CMC is believed to be associated with genetic or acquired T-cell immunodeficiency.[2] The mucosal antifungal T-cell immune response plays a crucial role in clearing *Candida spp*., primarily through the release of IL-17.[3] An impaired Th17 cell response, resulting in decreased IL-17 secretion, is a common trigger for CMC. A genetic factor commonly associated with an impaired IL-17 immune response is the presence of gain-of-function (GOF) mutations in signal transducer and activator of transcription 1 (STAT1).[2]

CMC typically manifests early in life, with antifungal agents being the first-line treatment. However, a significant portion of patients exhibit poor response to antifungal treatment, and prolonged use may contribute to the emergence of drug-resistant strains.[4] Given its rarity and complexity, CMC necessitates careful attention.

In this report, we present four patients diagnosed with CMC. Among them, a 6-year-old child and a 40-year-old male had a family history of the disease. We conducted screening for common reported mutations, including *CARD9, STAT1, IL-17R, STAT3, IL-12R*, and *IL-6R*, using Sanger sequencing technology, yet found no identical mutation across all four patients. Furthermore, through a comprehensive literature review of CMC cases globally over the past five years, coupled with our findings from these four patients, we analyzed the association between mutation sites and clinical manifestations and complications.

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The current molecular evidence in the literature suggests potential for the development of early diagnosis methods, such as screening genetic variables on *STAT1* and *STAT3*, as well as potential treatment avenues, including gene-targeted analogues and GM-CSF analogues, in conjunction with traditional anti-fungal therapy.

Patient No.1

A 6-year-old child presented with a 5-year history of oral mucosal leukoplakia and a 2-year history of thickened fingernails. The child developed a white pseudomembrane in the oral mucosa 8 months after birth. The child was initially diagnosed with "thrush" at a local hospital. Although "thrush" recurred intermittently, it was effectively relieved following antifungal treatment. Three months ago, when the patient turned 6 years old, the father noticed that the middle nail thickening of the child's right hand, prompting them to seek medical attention. Physical examination revealed white patches and slight striae-like changes in the child's oral mucosa, while the right index finger appeared brittle and discolored. All blood test results were normal with no increases in immunoglobulin and neutrophil levels. Examination of oral mucosa samples under a light microscope, revealed the presence of hyphae (Figure 1). A portion of the sample was also inoculated onto Sabouraud Dextrose Agar (SDA) and cultured at 37°C for 3 days. The isolated colonies were then identified as *C. albicans* through fungus-specific primer (ITS1: TCCGTAGGTGAACCTGCGG; ITS4: TCCTCCGCTTATTGATATGC) amplification and sequencing matching in NCBI database. Gene sequencing analysis of the patient's blood sample did not reveal any exon mutations reported in genes such as *CARD9, STAT1, IL-17R, STAT3, IL-12R*, and *IL-6R*. Based on the clinical and fungal identification, the patient was then diagnosed with CMC. The patient's father (patient No. 2) had a similar medical history.

Patient No.2

During the consultation, the father of patient No. 1 drew our attention by discussing his son's medical history. The father complained of a 30-year history of white spots and 25-year history of nail thickening. Approximately 29 years ago, white spots initially appeared on his oral mucosa when he was one year old. The patient was diagnosed with "thrush", and received oral treatment with sodium bicarbonate solution, itraconazole and fluconazole. The patient responded well to antifungal treatment and the lesion completely disappeared. Approximately 25 years ago, when the patient was 5–6 years old, the nails on both hands became thickened, discolored, and brittle. Antifungal treatment provided significant relief and improved the condition of the nail. However, nail issues recurred when treatment was discontinued. Three years ago, despite receiving oral and topical antifungal agents, the nail lesions only partially resolved. Physical examination revealed white patches and deep cracks in the oral mucosa, as well as brittle fingernails (Figure 2). Whole blood test results were normal, with no elevated white blood cell or immunoglobulin levels. Nail crip and the oral mucosa were also inoculated on SDA and blood agar. A yeast colony was isolated after two days and identified as *C. albicans* through morphology and molecular sequencing. The isolated strain showed sensitivities to miconazole (MIC=0.25) and anafraniline (MIC=0.25), but resistance to itraconazole (MIC>8), fluconazole (MIC>64), terbinafine (MIC>8), ketoconazole (MIC>8), amphotericin B (MIC>4), and voriconazole (MIC>4). Additionally, gene sequencing analysis of the patient's

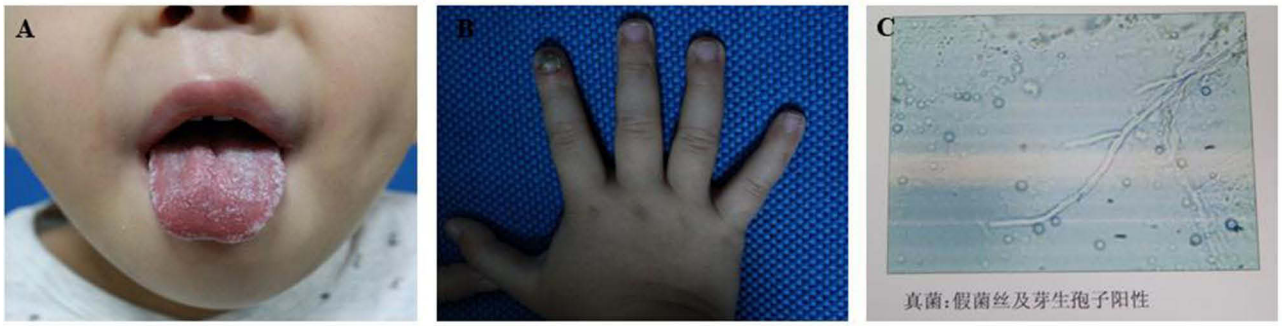

Figure 1 Patient No.1 (**A**) Image of oral mucosal of the patient No.1 (**B**) Image of right-hand fingers of the patient No.1 (**C**) Microscopic findings of oral mucosa from the patient No.1.

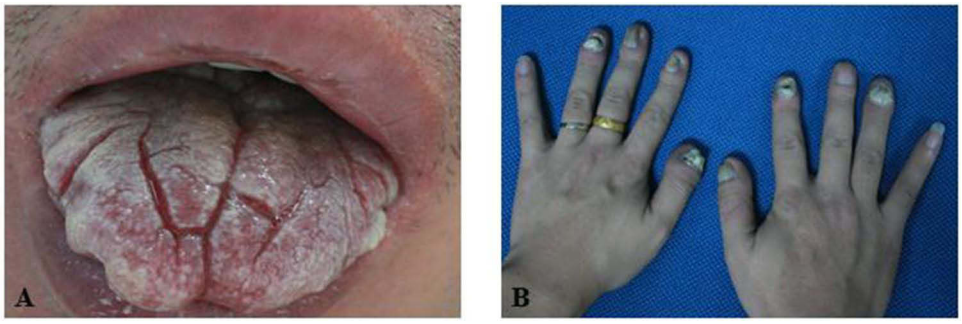

Figure 2 Patient No.2 (**A**) Image of oral mucosal of the father of the patient No.1 (**B**) Image of fingers of the father of the patient No.1.

blood mononuclear cells did not reveal any common exon mutations on *CARD9, STAT1, IL-17R, STAT3, IL-12R*, and *IL-6R*.

Patient No. 3

A 6-year-old child reported a history of thrush spanning five years and nail thickening over the past three years. Additionally, the patient had a history of hypothyroidism for two years and was of short stature. The child initially developed oral mucosal leukoplakia six months after birth, which improved with effective antifungal treatment. However, the child returned for follow-up due to the recurrence of oral mucosal leukoplakia. Physical examination revealed white spots and fissure lines on the oral mucosa, along with thickening of the tongue. Mild changes suggestive of onychomycosis were observed in the patient's nails. The nail grooves gradually deepened, there was discoloration around the nails, and the nails became brittle (Figure 3). Despite these symptoms, the child exhibited normal cognitive ability. Blood tests showed normal levels of white blood cells and immunoglobulins, including IgA, IgG, IgM, and IgE. However, serum hormone assay revealed lower concentration of FT4 (Free Thyroid Hormone 4) and at 22.39 pmol/L (normal range: 12.1–21 pmol/L), along with higher levels of TSH (Thyroid Stimulating Hormone) at 6.11pmol/L (normal range: 0.2–5 pmol/L). These data indicate reduced FT4 levels accompanied by increased TSH levels, an indicative of hypothyroidism. Direct microbiological examination of the nails and oral mucosa revealed the presence of hyphae. Samples from the oral mucosa and nails were inoculated onto SDA and blood agar plates at 37°C or 3 days, resulting in the growth of yeast colonies. The colony was identified as *C. parapsilosis* by morphology and molecular sequencing. The patient was diagnosed with CMC and hypothyroidism. The patient was not consanguineous and there were no similar cases within the family. The same panel of gene sequencing as patient No.1 did not reveal any exon mutations in this patient.

Patient No. 4

A 40-year-old male presented with thickened fingernail caps, recurrent generalized plate flaking for over 10 years, and a 20-year history of vitiligo. The patient had been experiencing recurrent oral mucosal leukoplakia since early childhood.

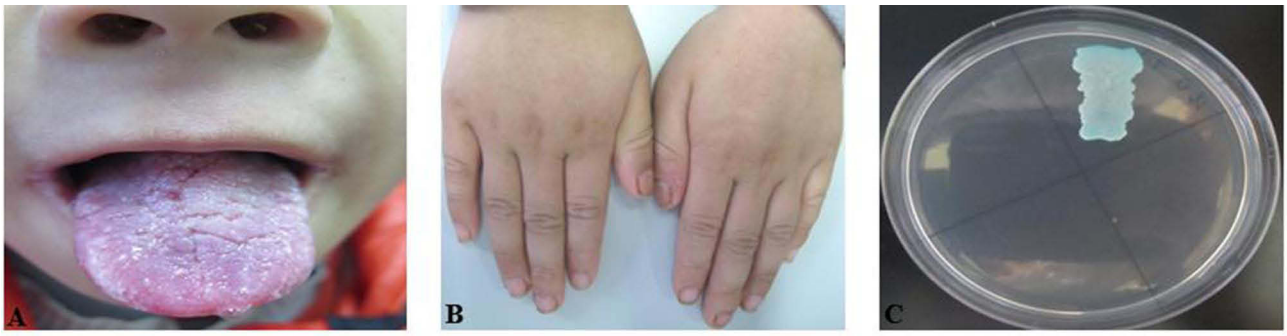

Figure 3 Patient No.3 (**A**) Image of oral mucosal of the child (**B**) Image of fingers of the child (**C**) Results of incubation on SDA at 37°C from the oral mucosal of the patient.

While symptoms could be improved with effective antifungal treatment, the recurrence of oral mucosal leukoplakia prompted the patient to seek medical attention. Upon physical examination, a white membrane covering almost the entire tongue was observed, accompanied by a deep crack in the middle. The nail plates appeared thickened, blackened, and brittle (Figure 4). The patient also manifested as flaky white patches on the face, as well as upper limb version friend-flaking symptoms (Figure 5). Additionally, scaly red patches with clear border appeared on the arms and back, accompanied by simultaneous pimples and blisters on the edges (Figure 6). Scales were sampled from the hands, oral cavity and back, superlatively. Light microscopy detection revealed the presence of a large number of fungal hyphae from

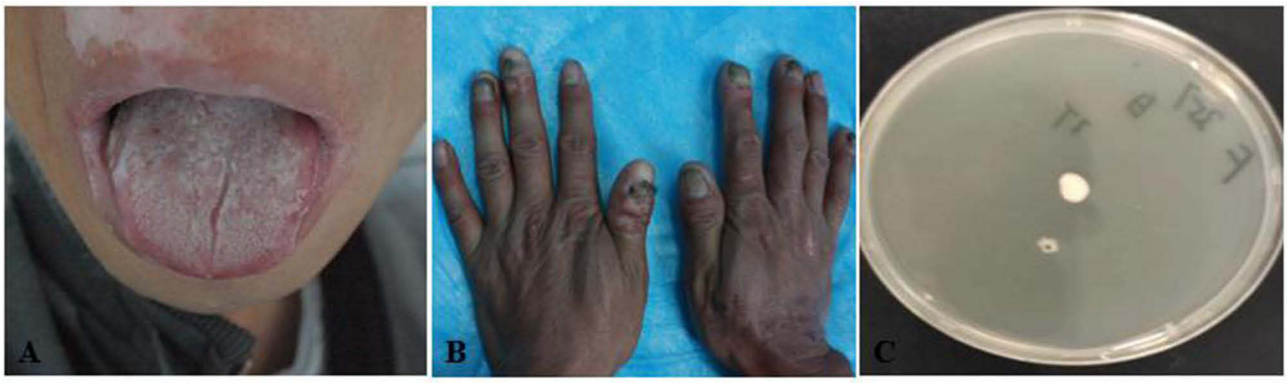

Figure 4 Patient No.4 (**A**) Image of oral mucosal of the patient (**B**) Image of fingers of the patient (**C**) Results of incubation on SDA at 37°C from the oral mucosal of the patient.

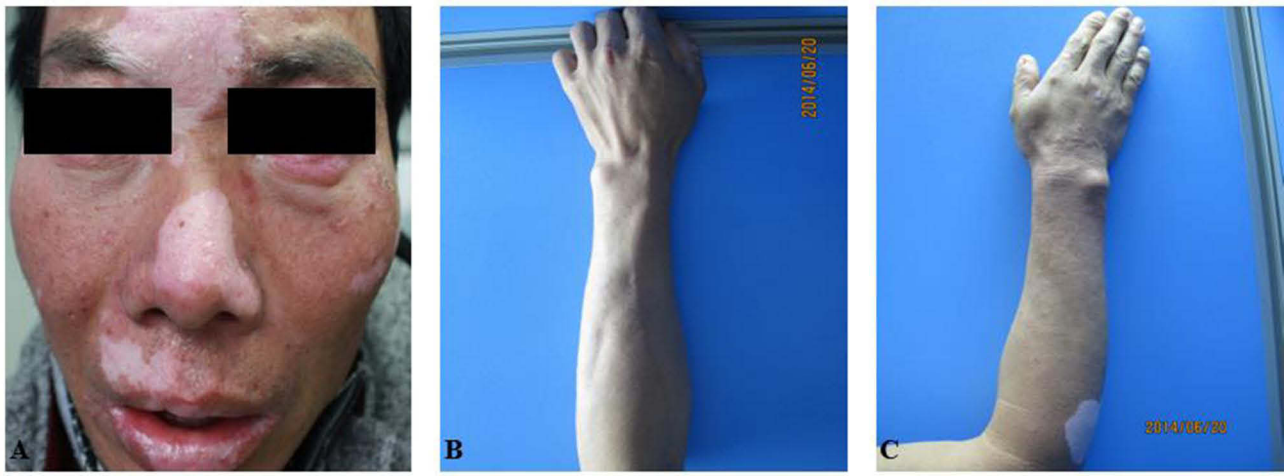

Figure 5 Patient No.4 (**A**) Image of white spot on the face of the patient (**B**) Image of right upper limb of the patient (**C**) Image of left upper limb of the patient.

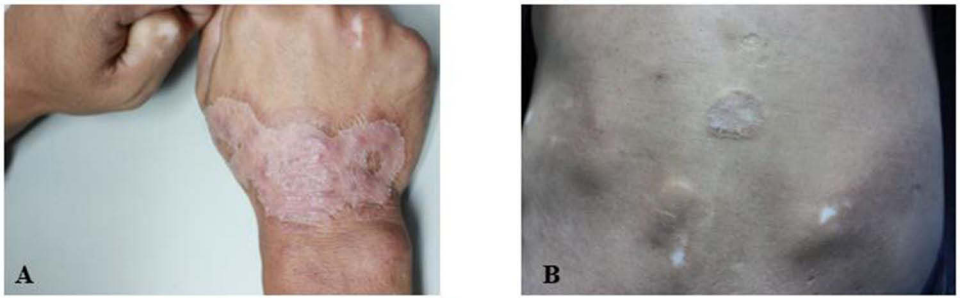

Figure 6 Patient No.4 (**A**) Image of *Trichophyton rubrum* infection on the right-hand (**B**) Image of *Trichophyton rubrum* infection on the back.

all the lesions. *Trichophyton rubrum* was isolated and identified from lesions on the upper limbs and back, and *C. albicans* isolated from the oral mucosa and nails by morphology and molecular sequencing. There is no known family history of similar disease or condition. Gene sequencing in the blood mononuclear cells did not reveal any exon mutations in the genes.

Discussion

Chronic mucocutaneous candidiasis (CMC) typically manifests during childhood, with onset commonly observed around one year of age. The condition is often characterized by infections of the oral mucosa and nails. CMC is often sporadic and may result from chromosomal gene mutations or secondary to other T-cell immunodeficiency diseases. Family history of CMC is relatively rare. Comorbidities are frequently observed in CMC patients, and prolonged exposure to *Candida* spp. in the mucosa can elevate the risk of developing cancer. Hence, early diagnostic screening and effective treatment are crucial for managing CMC patients.

Oral mucosal leukoplakia is an early symptom of CMC and is typically observed a few months after birth. Patients with CMC often exhibit a thickened tongue with visible lines, which become more prominent with age. We speculated that *Candida* spp. infection in the epithelium of the tongue stimulates its proliferation, resulting in inflammation and thickening of the tongue. While the grooved tongue, often painless, can be attributed to genetic factors and is commonly observed in conditions such as psoriasis and other infectious diseases, refractory tongue fissures have also been documented in cases of CMC, which could serve as a sign of early CMC. Nail infections caused by *Candida* spp. are common manifestations of CMC as well, particularly in patients aged 5–6 years. As the disease progresses, the infection of the oral mucosa and nails tends to deepen. Intraesophageal candidiasis is commonly associated with esophageal strictures and esophageal cancer.[5] In these cases, oral culture and fecal cultures could be used to effectively screen for esophageal *Candida* infections instead.

CMC is usually complicated by various autoimmune diseases including thyroid disorders, hematopoietic system disorders, and vitiligo (Table 1 and Figure 7). These diseases are often characterized by the production of abnormal immunoglobulin (specifically anti-melanocytes and haemophilic antibodies). It has been observed that some CMC patients have higher serum IgG levels when compared to health individuals without CMC condition.[6] Interestingly, research has demonstrated that elevated IgG levels in patients with CMC are associated with an increased likelihood of developing lung disease.[7] Therefore, screening for those autoantibodies can aid in the early diagnosis of these comorbidities.

Table 1 A Retrospective Study of CMC Patients Over the Last Five Years

Mutation Site	Gender	First Onset Age (Age)	Duration (Year)	Family History	Strain	Comorbidities	Reference	reporting Year
	male	3 months	<10Y (5Y)	√	*C. albicans*	none	P.1	
	male	1 year old	>10Y (29Y)	√	*C. albicans*	none	P.2	
	male		<10Y (5Y)		*C.parapsilosis*	hypothyroidism	P.3	
	male		<10Y (5Y)		*C. albicans*	Vitiligo, Disseminated *T. marneffei* infection	P.4	
	male	2 months	<10Y (4Y)		*C. albicans*	Impetigo infection	8	2023
STAT1	female	6 months	>10Y (18Y)		*Candida spp.*	Hypothyroidism, growth retardation, hair loss, pneumonia, interstitial lung disease	9	2017
STAT1	male	2.5 years old	<10Y		*Candida spp.*	None	9	2017
STAT1	female	2 years old	>10Y (18Y)		*Candida spp.*	None	9	2017
STAT1	male	4 years old	>10Y(25Y)		*Candida spp.*	Vitiligo	9	2017
STAT1	female	1 years old	<10Y		*Candida spp.*	None	9	2017
STAT1	male	4 years old	>10Y (20Y)		*Candida spp.*	None	9	2017
STAT1	male	1 year old	>10Y (20Y)		*Candida spp.*	None	9	2017
STAT1	male	after birth	<10Y (2Y)		*C. albicans*	Hemophagocytic lymphohistiocytosis	10	2023
STAT1	male	after birth	<10Y (5Y)		*Candida spp.*	Autoimmune diabetes; Autoimmune hepatitis	11	2022
STAT1	female	1.5 years old	<10Y		*Candida spp.*	Acute bronchial pneumonia; Cytomegalovirus infection	12	2022

(*Continued*)

Table 1 (Continued).

Mutation Site	Gender	First Onset Age (Age)	Duration (Year)	Family History	Strain	Comorbidities	Reference	reporting Year
STAT1	male	3 months	>10Y (20Y)		*C. albicans*	Disseminated *T. marneffei* infection	13	2021
STAT1	female	childhood	<10Y (2Y)		*C. albicans*	hypothyroidism	14	2023
IL17RC	male	1 year old	>10Y (12Y)		*C. albicans*	Refractory fissured tongue	15	2023
AIRE	male	6 months	<10Y (2Y)	√	*C. albicans*	Retinitis pigmentosa	16	2022
AIRE	male	after birth	>10Y		*Candida spp.*	Binocular cataract, Bypoparathyroidism, Addison's disease	17	2017
	female	childhood	<10Y (2Y)		*Candida spp.*	Woolly hair	18	2021
STAT1	female	childhood	>10Y		*C. albicans*	Hypothyroidism	2	2019
STAT1	male	5 years old	>10Y (61Y)		*C. albicans*	Tongue squamous cell carcinoma; non-insulin dependent diabetes mellitus	2	2019
STAT1	male	4 years old	>10Y (15Y)		*C. albicans*	Systemic sclerosis; Pulmonary fibrosis; Recurrent esophageal strictures	2	2019
STAT1	female	infancy	>10Y		*C. albicans*	Aplastic anemia; type 1 diabetes mellitus	19	2021
STAT1	female	early childhood	>10Y		*C. albicans*	Herpetic stomatitis; Hypothyroidism; Hyperparathyroidism	20	2022
STAT1	male	3–4 months	<10Y (9Y)		*C. albicans*	Pancytopenia	21	2022
STAT1	male	6 months	<10Y (5Y)		*C. albicans*	Tuberculosis	22	2021
STAT1	female	2 years old	<10Y (6Y)		*Candida spp.*	Recurrent tinea capitis infections; Bronchiectasis; Hypothyroidism	23	2020
STAT1	male	data missing			*Candida spp.*	Bronchiectasis; Diffuse myocarditis	24	2022
CARD9	female	5 years old	<10Y (2Y)		*Candida spp.*	Meningoencephalitis	25	2023
CARD9	female	1.5 years old	<10Y (3Y)		*C. albicans*	*Candida* meningitis	26	2019
IL-12R	female	after birth	<10Y (3Y)		*Candida spp.*	bacille Calmette-Guérin lymphadenitis	27	2015
IL17RA	male	8 months	<10Y (3Y)	√	*Candida spp.*	Staphylococcal Skin Infections	28	2023
IL17RA	female	6 months	>10Y (12Y)		*Candida spp.*	None	29	2017
IL17RA	female	6 months	>10Y (10Y)		*Candida spp.*	Asthma	29	2017
IL17RA	male	childhood	>10Y		*Candida spp.*	a hiatal hernia gastroesophageal reflux.	29	2017
IL17RA	female	1 year old	>10Y(30Y)	√	*Candida spp.*	hyperthyroidism	29	2017
IL-17RC	female	3 months	<10Y (2Y)		*Candida spp.*	None	30	2023
mannose receptor	female	1.5 years old	>10Y (28Y)		*Candida spp.*	Hepatomegaly; polyadenopathy;	31	2021
TRAF3IP2	male	1 years old	>10Y (17Y)		*Candida spp.*	Hypergammaglobulinemia; bronchiectasis	32	2021
TRAF3IP2	male	6 months	>10Y (12Y)		*Candida spp.*	Atopic dermatitis; recurrent parotitis	33	2019

Note: ——— clinical data of patients with CMC in China.

CMC condition has been associated with multiple gene mutations in *STAT1, IL-17RA*, and *AIRE*. Additionally, a small number of CMC patients with the mutation in *STAT1* or *TRAF3IP2* have been found to have esophagus or vaginal membrane involvement and many other diseases. For instance, *STAT1* mutations are found in autoimmune diseases and

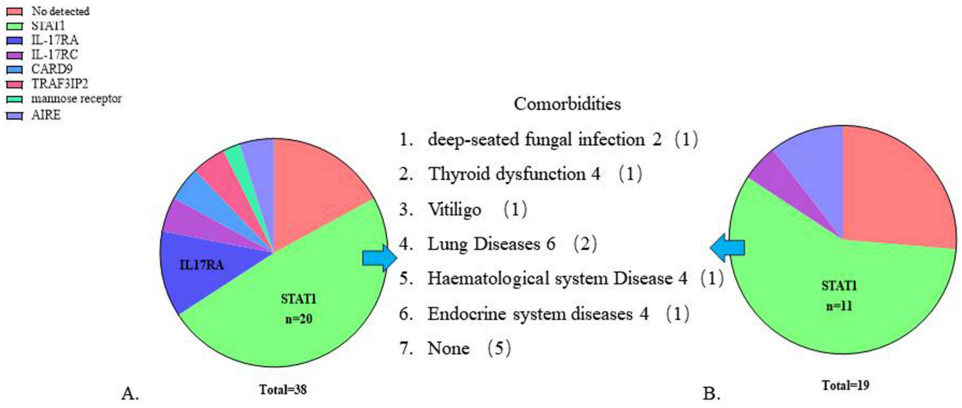

Figure 7 (**A**) Mutation site and common complications in CMC patients worldwide in the last 5 years from the database (**B**) Mutation site and common complications in CMC patients in China in the last 5 years.

deep-seated infections.[4] *STAT1* mutation in hypothyroidism and type 2 diabetes are complicated with aplastic anemia, systemic sclerosis, and bronchiectasis.[2,14] Mutations in *IL-17R* and the mannose receptor responsible for mucosal fungal clearance can result in mucosal candidiasis and bacterial skin infections.[28,34] Mutations in *TRAF3IP2*, an articulatory protein involved in signaling downstream of the IL-17 receptor, are associated with hypergammaglobulinemia and atopic dermatitis, which are related to the antibody levels in the body. In addition to susceptibility to *Candida spp., AIRE* mutations are involved in eye diseases.[35] Therefore, the effective screening of these commonly mutated genes can help predict the occurrence and complications of CMC. In the past, identification of new mutation sites in patients was challenging due to the lack of high-throughput sequencing technology. However, with advancements in sequencing technology, more mutation sites in patients with CMC have been identified in recent years. The information regarding clinical manifestations and gene mutations in reported patients with CMC is detailed in Table 1. We observed a gradual increase in cases favoring the functional acquisition of STAT1 due to gene mutations.[36]

There are significant challenges in treating CMC due to its genetic predisposition and T-cell dysfunction, leading to limited effective therapeutic options. Currently, clinical treatments mainly include the use of antifungal drugs such as amphotericin B, fluconazole, itraconazole, voriconazole, and topical nystatin. Relief from skin lesions is typically observed within two weeks of antifungal treatment. However, the prolonged use of antifungal agents may lead to resistance and reduced efficacy. Although *Candida* speciation is not commonly conducted in CMC patients, it can provide valuable insights into antifungal therapy. We encountered two cases of CMC caused by *C. parapsilosis*, that presented with the same symptoms as *C. albicans* infection. One case was associated with hypothyroidism, whereas the other had additional infections. An epidemiological study conducted in dermatology clinics revealed that *C. albicans* infections were more severe and required longer treatment than non-*C. albicans* infections (N-CA) infections.[37] However, a specific link between *Candida* species and CMC has not been reported. Immunoglobulins, such as IgG, can enhance the phagocytosis of microorganisms by binding to their surfaces, thereby aiding in the clearance of fungal infections.[38] Clinical trials investigating the use of intravenous and oral human polyvalent IgG in patients with CMC have been conducted. Human polyvalent IgG administered as a mouthwash has been reported as an adjuvant treatment for CMC, particularly for oral candidiasis.[39]

JAK inhibitors targeting the STAT pathway have shown promise for the treatment of infectious skin diseases.[40] Clinical trials have demonstrated a significant improvement in symptoms in patients with CMC with the use of JAK inhibitors for a short course, although side effects have been reported.[41] Therefore, JAK inhibitors or other gene-targeted drugs could be potential therapeutic options in the future treatment of CMC.[42] Single-cell sequencing of STAT-GOF patients with CMC revealed upregulation of tumor necrosis factor alpha-induced protein 3 (TNFAIP3).[43] TNFAIP3 has been reported be linked to suppressing the innate immune response and is involved in autoimmune diseases, suggesting it as a potential therapeutic target for CMC.

In addition to gene-targeted approaches, the use of drugs that maintain or promote T cell recovery represents another potential option for CMC treatment. For example, stimulation with granulocyte-colony stimulating factor (GM-CSF) or granulocyte monocyte-colony stimulating factor (G-CSF) may enhance Th17 cell differentiation and aid in recovery from fungal infection.[44] Clinical studies have shown that a combination of G-CSF and antifungal agents is highly effective in treating invasive fungal infections associated with CARD9-induced immunodeficiency.[45] Recently, biologics targeting GM-CSF, such as otilimab, gimsilumab, and lenzilumab, have undergone clinical trials worldwide for various skin conditions.[46] Additionally, hematopoietic stem cell transplantation may be considered as a treatment option.[47]

Ethics Approval and Informed Consent

This study was approved by the Institutional Research and Ethics Committee of Jining No. 1 People's Hospital to publish the case details. All patients or the parents of the patient gave consent to publish provided written informed consent for publication of this case report and any accompanying images. The study was carried out in accordance with the principles of the Declaration of Helsinki. The first author vouches for the completeness and accuracy of the data and for the adherence of the study to the protocol.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest regarding the publication of this paper.

References

1. Hon-Balla B, Erdős M. Chronic mucocutaneous candidiasis. *Orv Hetil*. 2022;163(5):171–180. doi:10.1556/650.2022.32409
2. Carey B, Lambourne J, Porter S, Hodgson T. Chronic mucocutaneous candidiasis due to gain-of-function mutation in STAT1. *Oral Dis*. 2019;25(3):684–692. doi:10.1111/odi.12881
3. Okada S, Puel A, Casanova JL, Kobayashi M. Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. *Clin Transl Immunology*. 2016;5(12):e114. doi:10.1038/cti.2016.71
4. Okada S, Asano T, Moriya K, et al. Human STAT1 gain-of-function heterozygous mutations: chronic mucocutaneous candidiasis and type I interferonopathy. *J Clin Immunol*. 2020;40(8):1065–1081. doi:10.1007/s10875-020-00847-x
5. Domingues-Ferreira M, Grumach AS, Duarte AJ, De moraes-vasconcelos D. Esophageal cancer associated with chronic mucocutaneous candidiasis. Could chronic candidiasis lead to esophageal cancer. *Med Mycol*. 2009;47(2):201–205. doi:10.1080/13693780802342545
6. Lehmann PF, Reiss E. Comparison by ELISA of serum anti-Candida albicans mannan IgG levels of a normal population and in diseased patients. *Mycopathologia*. 1980;70(2):89–93. doi:10.1007/BF00443073
7. Bentur L, Nisbet-Brown E, Levison H, Roifman CM. Lung disease associated with IgG subclass deficiency in chronic mucocutaneous candidiasis. *J Pediatr*. 1991;118(1):82–86. doi:10.1016/S0022-3476(05)81852-9
8. Wang Z, Zhang Y, Ma W. Chronic mucocutaneous candidiasis: a case report. *Clin Cosmet Invest Dermatol*. 2023;16:231–236. doi:10.2147/CCID.S396802
9. Wang X, Zhang R, Wu W, et al. New and recurrent STAT1 mutations in seven Chinese patients with chronic mucocutaneous candidiasis. *Int J Dermatol*. 2017;56(2):e30–e33. doi:10.1111/ijd.13427
10. Ruan P, Zhang Y, Chen H, Chen H, Dong Z. Heterozygous gain-of-function mutations in human STAT1: a case of hemophagocytic lymphohistiocytosis due to chronic mucocutaneous candidiasis in a 17-month-old male. *Pediatr Blood Cancer*. 2023;70(6):e30284. doi:10.1002/pbc.30284
11. Cao B, Liu M, Zhao Y, Gong C. Chronic oral mucocutaneous candidiasis, recurrent respiratory infection, hepatosplenomegaly, and autoimmune diabetes mellitus: a case report of a gain-of-function mutation of STAT1 in a Chinese boy. *Front Pediatr*. 2022;10:1001290. doi:10.3389/fped.2022.1001290
12. Liu L, Huang Y, Liao Y, Shu S. Autosomal dominant chronic mucocutaneous candidiasis with STAT1 mutation can be associated with chronic active hepatitis: a case report. *Front Pediatr*. 2022;10:990729. doi:10.3389/fped.2022.990729
13. Chen K, Tan J, Qian S, Wu S, Chen Q. Case report: disseminated talaromyces marneffei infection in a patient with chronic mucocutaneous candidiasis and a novel STAT1 gain-of-function mutation. *Front Immunol*. 2021;12:682350. doi:10.3389/fimmu.2021.682350
14. Hou F, Zhang T, Chen F, Jiang L. Novel STAT1 mutation in a paediatric case of chronic mucocutaneous candidiasis complicated by primary hypothyroidism: clinical presentation, genetic analysis and prognostic implications. *BMJ Case Rep*. 2023;16(12):e258133. doi:10.1136/bcr-2023-258133
15. Xie Y, Zhou P, Gao Y, Li R, Hua H, Wang X. Chronic mucocutaneous candidiasis presenting as refractory fissured tongue in a patient with IL-17RC mutation: the first reported case of Chinese ethnicity. *Emerg Microbes Infect*. 2023;12(2):2231567. doi:10.1080/22221751.2023.2231567
16. Ma Y, Wang X, Li R. AIRE gene mutation predisposing chronic mucocutaneous candidiasis and pigmented retinitis in two kids from a Chinese family. *Emerg Microbes Infect*. 2022;11(1):1705–1706. doi:10.1080/22221751.2022.2090860
17. Zhu W, Hu Z, Liao X, et al. A new mutation site in the AIRE gene causes autoimmune polyendocrine syndrome type 1. *Immunogenetics*. 2017;69(10):643–651. doi:10.1007/s00251-017-0995-5
18. Gaurav V, Grover C. Co-occurrence of chronic mucocutaneous candidiasis with woolly hair. *Skin Appendage Disord*. 2021;7(6):510–514. doi:10.1159/000516743
19. Bazan-Socha S, Gradzikiewicz A, Celińska-Lowenhoff M, Matyja-Bednarczyk A, Maciołek A, Bąbol-Pokora K. Chronic mucocutaneous candidiasis, pancytopenia, and systemic mycosis in a patient with STAT1 gene mutation ineffectively treated with ruxolitinib. *Cent Eur J Immunol*. 2022;47(1):92–94. doi:10.5114/ceji.2022.114884
20. Balasundaram A, George R, Abraham A, Michael JS. Chronic mucocutaneous candidiasis due to signal transducer and activator of transcription 1 (STAT 1) mutation in an Indian patient - A case report. *Indian Dermatol Online J*. 2022;13(1):90–93. doi:10.4103/idoj.IDOJ_898_20
21. Dabas A, Arora P, Kumar S, Kapoor S, Yadav S. STAT 1 mutation associated with chronic mucocutaneous candidiasis and pancytopenia. *Pediatr Allergy Immunol*. 2021;32(4):798–800. doi:10.1111/pai.13451
22. Baghad B, Benhsaien I, El Fatoiki FZ, et al. Chronic mucocutaneous candidiasis with STAT1 gain-of-function mutation associated with herpes virus and mycobacterial infections. *Ann Dermatol Venereol*. 2020;147(1):41–45. doi:10.1016/j.annder.2019.09.597

23. Alidrisi D, Maksood L, Alqahtani W, et al. A child with bronchiectasis, chronic mucocutaneous candidiasis, and hypothyroidism secondary to STAT1 gain-of-function mutation: a case report and review of the literature. *Clin Case Rep*. 2022;10(4):e05791. doi:10.1002/ccr3.5791
24. Staels F, Roosens W, Giovannozzi S, et al. Case report: myocarditis in congenital STAT1 gain-of function. *Front Immunol*. 2023;14:1095595. doi:10.3389/fimmu.2023.1095595
25. Martin S, Balligand E, Peeters J, et al. A 7-year-old child with headaches and prolonged fever associated with oral and nail lesions. *Open Forum Infect Dis*. 2019;6(11):ofz229. doi:10.1093/ofid/ofz229
26. Herbst M, Gazendam R, Reimnitz D, et al. Chronic Candida albicans meningitis in a 4-year-old girl with a homozygous mutation in the CARD9 gene (Q295X). *Pediatr Infect Dis J*. 2015;34(9):999–1002. doi:10.1097/INF.0000000000000736
27. Hatipoglu N, Güvenç BH, Deswarte C, et al. Inherited IL-12Rβ1 deficiency in a child with BCG adenitis and oral candidiasis: a case report. *Pediatrics*. 2017;140(5). doi:10.1542/peds.2016-1668
28. Yakıcı N, Oskay Halaçlı S, Tan Ç, et al. A novel interleukin 17 receptor a mutation in a child with chronic mucocutaneous candidiasis and staphylococcal skin infections. *Turk Arch Pediatr*. 2023;58(4):442–447. doi:10.5152/TurkArchPediatr.2023.22311
29. Kılıç M, Özcan MH, Taşkın E, Şen A. A family with interleukin-17 receptor A deficiency: a case report and review of the literature. *Turk J Pediatr*. 2023;65(1):135–143. doi:10.24953/turkjped.2022.40
30. Noma K, Tsumura M, Nguyen T, et al. Isolated chronic mucocutaneous candidiasis due to a novel duplication variant of IL17RC. *Res Sq*. 2023. doi:10.21203/rs.3.rs-3062583/v1
31. Vasconcelos DM, Bertolini DL, Ferreira MD. Chronic mucocutaneous candidiasis associated with paracoccidioidomycosis in a patient with mannose receptor deficiency: first case reported in the literature. *Rev Soc Bras Med Trop*. 2021;54:e0008–2021. doi:10.1590/0037-8682-0008-2021
32. Bhattad S, Dinakar C, Pinnamaraju H, Ganapathy A, Mannan A. Chronic mucocutaneous candidiasis in an adolescent boy due to a novel mutation in TRAF3IP2. *J Clin Immunol*. 2019;39(6):596–599. doi:10.1007/s10875-019-00664-x
33. Marujo F, Pelham SJ, Freixo J, et al. A novel TRAF3IP2 mutation causing chronic mucocutaneous candidiasis. *J Clin Immunol*. 2021;41(6):1376–1379. doi:10.1007/s10875-021-01026-2
34. Mirza VS, Zaino ML, Feldman SR. Innate error immunities of the Th17 immune pathway associated with chronic mucocutaneous candidiasis: a systematic review. *J Drugs Dermatol*. 2023;22(12):1197–1203. doi:10.36849/JDD.7579
35. Qian G, Yan X, Xuan J, Zheng D, He Z, Shen J. A novel AIRE mutation leads to autoimmune polyendocrine syndrome type-1. *Front Cell Dev Biol*. 2022;10:948350. doi:10.3389/fcell.2022.948350
36. Asano T, Noma K, Mizoguchi Y, Karakawa S, Okada S. Human STAT1 gain of function with chronic mucocutaneous candidiasis: a comprehensive review for strengthening the connection between bedside observations and laboratory research. *Immunol Rev*. 2023;322(1):81–97. doi:10.1111/imr.13300
37. Leeyaphan C, Bunyaratavej S, Foongladda S, et al. Epidemiology, clinical characteristics, sites of infection and treatment outcomes of mucocutaneous candidiasis caused by non-albicans species of Candida at a dermatologic clinic. *J Med Assoc Thai*. 2016;99(4):406–411.
38. Barros N, Alexander N, Viens A, et al. Cytokine augmentation reverses transplant recipient neutrophil dysfunction against the human fungal pathogen Candida albicans. *J Infect Dis*. 2021;224(5):894–902. doi:10.1093/infdis/jiab009
39. Pedraza-Sánchez S, Méndez-León JI, Gonzalez Y, et al. Oral administration of human polyvalent IgG by mouthwash as an adjunctive treatment of chronic oral candidiasis. *Front Immunol*. 2018;9:2956. doi:10.3389/fimmu.2018.02956
40. Luo Y, Alexander M, Gadina M, O'Shea JJ, Meylan F, Schwartz DM. JAK-STAT signaling in human disease: from genetic syndromes to clinical inhibition. *J Allergy Clin Immunol*. 2021;148(4):911–925. doi:10.1016/j.jaci.2021.08.004
41. Borgström EW, Edvinsson M, Pérez LP, et al. Three adult cases of stat1 gain-of-function with chronic mucocutaneous candidiasis treated with JAK inhibitors. *J Clin Immunol*. 2023;43(1):136–150. doi:10.1007/s10875-022-01351-0
42. Jing D, Liang G, Li X, Liu W. Progress in molecular diagnosis and treatment of chronic mucocutaneous candidiasis. *Front Immunol*. 2024;15:1343138. doi:10.3389/fimmu.2024.1343138
43. Lu X, Zhang K, Jiang W, et al. Single-cell RNA sequencing combined with whole exome sequencing reveals the landscape of the immune pathogenic response to chronic mucocutaneous candidiasis with STAT1 GOF mutation. *Front Immunol*. 2022;13:988766. doi:10.3389/fimmu.2022.988766
44. van Hamburg JP, Tas SW. Molecular mechanisms underpinning T helper 17 cell heterogeneity and functions in rheumatoid arthritis. *J Autoimmun*. 2018;87:69–81. doi:10.1016/j.jaut.2017.12.006
45. Du B, Shen N, Hu J, Tao Y, Mo X, Cao Q. Complete clinical remission of invasive Candida infection with CARD9 deficiency after G-CSF treatment. *Comp Immunol Microbiol Infect Dis*. 2020;70:101417. doi:10.1016/j.cimid.2020.101417
46. Kumar A, Taghi Khani A, Sanchez Ortiz A, Swaminathan S. GM-CSF: a double-edged sword in cancer immunotherapy. *Front Immunol*. 2022;13:901277. doi:10.3389/fimmu.2022.901277
47. Wang Q, Dufresne SF, Vinh DC, Aubin MJ. Chronic mucocutaneous candidiasis presenting as Candida endophthalmitis. *Can J Ophthalmol*. 2016;51(2):e55–8. doi:10.1016/j.jcjo.2015.11.004