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·综述·

慢性皮肤黏膜念珠菌病的研究进展

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【摘要】 慢性皮肤黏膜念珠菌病(chronic mucocutaneous candidiasis，CMC)是一组以皮肤、甲、口腔和生殖器黏膜反复或持续发生念珠菌感染超过6个月为特征的疾病。本文对CMC的病因及发病机制、临床表现、诊断、治疗等方面进行综述，以期为相关临床诊疗工作提供参考。目前研究认为，CMC是一种免疫缺陷病，发病机制复杂。CMC患者在防御念珠菌感染的非特异性免疫和(或)特异性免疫中存在各种缺陷，导致患者无法抵御念珠菌感染。根据病因，CMC可分为原发性CMC和继发性CMC，原发性CMC多与基因突变导致的辅助性T细胞17(T helper cell 17，Th17)及白细胞介素-17(interleukin-17，IL-17)的免疫缺陷有关，而继发性CMC常与人类免疫缺陷病毒感染、糖尿病、接受免疫抑制治疗等因素相关。原发性CMC常表现为念珠菌感染，且不同基因突变导致的CMC常有不同伴发症状；继发性CMC除浅表器官的念珠菌感染和原发疾病的表现外，还可伴有深部真菌感染。对CMC进行诊断除需结合病史、临床特点外，还依靠涂片镜检、真菌培养、免疫学检查及基因测序和分析等辅助检查的结果，诊断为原发性CMC需排除上述继发性因素。目前三唑类、棘白菌素类、多烯类等抗真菌药为CMC的主要治疗方法，JAK抑制剂等生物制剂的免疫疗法为CMC患者的临床治疗提供了更多的选择，基因治疗亦有潜在的临床应用价值。

【关键词】 慢性皮肤黏膜念珠菌病；　口腔念珠菌病；　念珠菌感染；　免疫缺陷；　基因突变；　辅助性T细胞17；　白细胞介素-17；　抗真菌药物；　免疫疗法
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Research progress on chronic mucocutaneous candidiasis

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【Abstract】 Chronic mucocutaneous candidiasis (CMC) is an infectious phenotype characterized by recurrent or persistent infections caused by *Candida* species that affect the skin, nails, oral, and genital mucosae for a duration exceeding six months. Current research suggests that CMC is an immunodeficiency disease with a complex pathogenesis. Patients with CMC have various defects in nonspecific and/or specific immunity against *Candida* infection, resulting in the inability of patients to defend themselves against *Candida* infection. CMC can be stratified into primary CMC and secondary CMC based on etiology. Primary CMC is often associated with genetic mutations leading to immunodeficiencies

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in T helper cell 17 and interleukin-17, whereas secondary CMC is frequently linked to factors such as human immunodeficiency virus infection, diabetes mellitus, and immunosuppressive therapy. Primary CMC typically manifests as Candida infections, with distinct genetic mutations often correlating to varied concomitant symptoms. Secondary CMC may present with not only superficial mucosal *Candida* infections and manifestations of the underlying primary disease but also with invasive fungal infections. Diagnosing CMC requires an integration of medical history and clinical presentation, supplemented by the outcomes of auxiliary diagnostic procedures, including microscopic examination of fungal smear, fungal culture, immunological testing, and genetic sequencing and analysis. Furthermore, confirming primary CMC requires exclusion of the aforementioned secondary factors. At present, antifungal drugs such as triazoles, echinocandins, and polyenes are the main treatment for CMC. Moreover, immunotherapy with biologics such as Janus kinase (JAK) inhibitors provides more options for the clinical treatment of patients with CMC. Gene therapy also has potential clinical application value. In this review, we discuss the etiologies, pathogenesis, clinical manifestations, diagnosis, and treatments of CMC, aiming to provide a reference for the clinical diagnosis and treatment of CMC.

【Key words】 chronic mucocutaneous candidiasis; oral candidiasis; *Candida* infection; immunodeficiency; gene mutation; T helper cell 17; interleukin-17; antifungal drugs; immunotherapy

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慢性皮肤黏膜念珠菌病(chronic mucocutaneous candidiasis,CMC)是一组以皮肤、甲、口腔和生殖器黏膜反复或持续发生念珠菌感染超过6个月为特征的疾病[1],可伴有其他感染和免疫性疾病。该病需结合多种辅助检查方法进行诊断,以及早干预和治疗。本文将从CMC的定义和分类、临床表现、病因及发病机制、辅助检查和诊断、治疗等方面探讨CMC的研究进展。

1　CMC的分类

根据病因可将CMC分为原发性CMC(primary CMC)和继发性CMC(secondary CMC)[2]。

原发性CMC发病与基因突变导致的辅助性T细胞17(T helper cell 17,Th17)及白介素-17(interleukin-17,IL-17)的免疫缺陷相关[3-6],主要由致病基因突变导致。其发病率为1/5 000,患者发病年龄较早,通常于婴幼儿时期发病。根据是否伴有除皮肤、甲、口腔和生殖器黏膜念珠菌感染以外的其他临床表现又可将原发性CMC分为综合征型CMC和孤立型CMC。综合征型CMC除念珠菌感染外通常还伴有其他感染和严重的免疫性疾病,孤立型CMC则以念珠菌感染作为主要或唯一的临床表现,通常无其他临床症状和体征,部分患者可伴有皮肤黏膜葡萄球菌感染[7]。

继发性CMC与人类免疫缺陷病毒(human immunodeficiency virus,HIV)感染、免疫抑制治疗、长期抗生素治疗、恶性肿瘤患者接受放疗或化疗、糖尿病等导致的机体免疫缺陷或抑制相关,发病年龄相比原发性CMC较晚[2,4]。

2　CMC的临床表现

CMC的临床表现多样,可伴发肿瘤[8-9]和/或自身免疫性疾病[4,10-13],但都有共同的特征,即念珠菌感染,包括皮肤、甲、口腔和生殖器黏膜等的反复或持续性的感染。

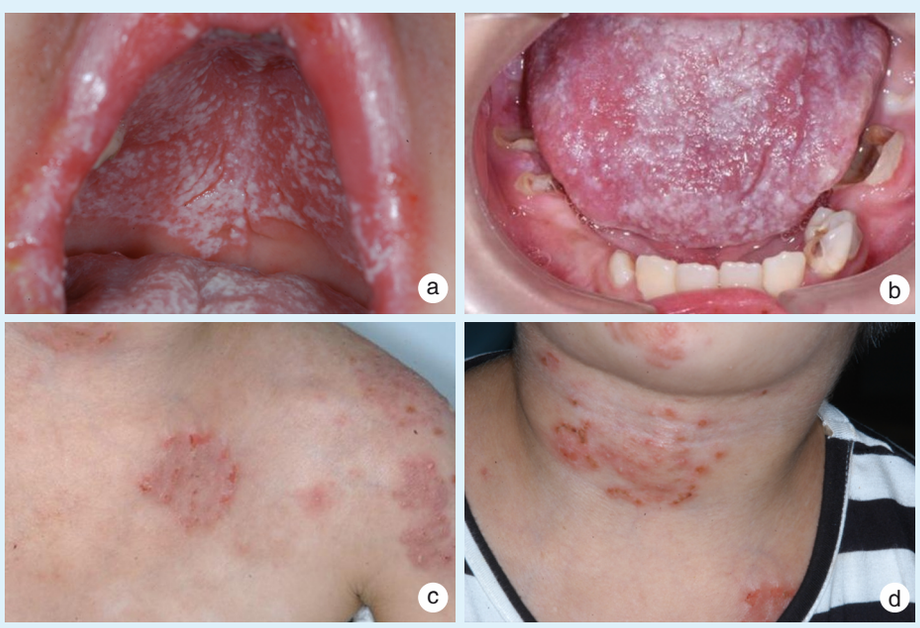
口腔黏膜念珠菌感染:55%~100%的CMC患者有口腔黏膜病变,常表现为念珠菌性口角炎和/或唇炎,即口角和口唇潮红糜烂、干燥皲裂、脱屑、结痂等,严重者进食酸、辣等刺激食物时疼痛;患者通常还表现为反复发作的急性假膜型念珠菌性口炎,即舌和颊部出现白色或灰色假膜(图1a&1b),假膜擦除后可见红色或出血创面,或表现为黏膜萎缩,充血发红,可出现白色角化斑块或结节状增生,后者可能与癌症发生相关。此外,慢性肉芽肿性病变也是CMC患者常见的口腔表现;患者还可伴发复发性阿弗他溃疡,口腔内出现反复发作的圆形或椭圆形的溃疡,有明显的灼痛感[7,14-20]。

念珠菌性甲真菌病:15%~72%的CMC患者有念珠菌性甲真菌病,表现为甲板过度角化增厚呈

灰白色或黄棕色改变，表面粗糙，质地脆弱，可伴有甲沟炎或甲周炎[14-17, 19]。

皮肤念珠菌感染：6%～57%的CMC患者表现为皮肤念珠菌感染，出现皮肤红斑、丘疹、脓疱、糜烂、肉芽肿、脱屑和鳞屑样损害（图1c＆1d），以及白色或灰褐色斑块。[7, 14, 16, 17, 19-22]。

食管、生殖器等黏膜念珠菌感染：5%～56%的CMC患者表现为食管念珠菌感染，患者并发胸骨后疼痛、吞咽困难及食管狭窄，常因口腔食管疼痛导致进食困难，造成营养不良、体重减轻[7, 14, 16, 23-24]；9%～18%的CMC患者表现为生殖器黏膜念珠菌感染，患者外生殖器黏膜出现红斑、丘疹、脱屑、痒痛和糜烂，阴道有白色分泌物等[7, 14, 16-17]。



a-b：oral mucosal lesionsin patients with chronic mucocutaneous candidiasis；recurrent acute pseudomembranous *Candida* stomatitis，characterized by white or gray pseudomembranous lesions on the tongue and cheeks；c-d：cutaneous lesions in patients with chronic mucocutaneous candidiasis，skin erythema，papules，pustules，erosions，granulomas，desquamation，and scale like lesions

Figure 1　Examples of oral mucosal and cutaneous lesions in patients with chronic mucocutaneous candidiasis

图1　慢性皮肤黏膜念珠菌病患者口腔黏膜及皮肤病损示例

3　CMC的病因及发病机制

3.1　原发性CMC

由基因突变或缺陷导致的Th17细胞及IL-17的免疫缺陷在原发性CMC的发病中至关重要[4, 6]。Th17细胞由$CD4^+$T细胞分化而来，$CD4^+$T细胞被不同抗原刺激后会分化出不同的细胞因子，包括Th1、Th2、Th17，Th17细胞选择性分泌IL-17，通过招募感染部位的中性粒细胞、巨噬细胞等，诱导抗微生物肽等发挥着免疫介导作用，与炎性疾病、自身免疫性疾病和肿瘤的发生相关[25-27]。IL-17家族包括IL-17A～F共6个成员，其中，IL-17A和IL-17F以同源二聚体（IL-17A/A和IL-17F/F）或异源二聚体（IL-17A/F）的形式，在宿主对抗皮肤和黏膜的念珠菌感染中发挥着不可替代的作用[28]。CMC除念珠菌感染外，可伴或不伴有其他感染和严重的免疫性疾病，不同基因突变导致的CMC的伴发症状不同，各类CMC的伴发症状详见表1。

3.1.1　综合征型CMC　综合征型CMC由基因突变或缺陷导致，主要包括常染色体显性遗传（autosomal dominant，AD）的信号转导与转录激活子1（signal transducer and activator of transcription 1，STAT1）基因功能获得性突变（gain of function，GOF）、信号转导与转录激活子3（signal transducer and activator of transcription 3，STAT3）基因、丝裂原活化蛋白激酶8（mitogen-activated protein kinase 8，MAPK8）基因突变和常染色隐性遗传（autosomal recessive，AR）的自身免疫调节因子（autoimmune regulator，AIRE）基因、维A酸相关孤儿受体C（retinoid acid-related orphan receptor C，RORC）基因、胞质分裂作用因子8（dedicator of cytokinesis 8，DOCK8）基因、

表1　原发性慢性皮肤黏膜念珠菌病的病因、免疫异常和临床表现

Table 1　Etiology, immunologic abnormalities and clinical manifestations of primary chronic mucocutaneous candidiasis

Type of CMC	Involved gene	Inheritance	Underlying immune mechanism	Characteristic	References
Syndromic CMC	*STAT1*	AD	Defective differentiation of Th17 cells	Multiple infections (bacteria, viruses, mycobacteria, and/or invasive fungi), autoimmune diseases, aneurysms, and tumors	[29, 30]
	STAT3	AD	Impaired differentiation of Th17 cells, decreased levels of IL-17	HIES, presenting as characteristic facial appearance, pneumatocele formation, fracture due to minor external force (pathological fracture), osteoporosis, scoliosis,	[31]
	DOCK8	AR	Impaired differentiation of Th17 cells	joint hyperextension, delayed loss	[32]
	ZNF341	AR	Impaired differentiation of Th17 cells	of deciduous tooth	[33, 34]
	AIRE	AR	Neutralizing autoantibodies specifically counteract Th17 cytokines, with decreased levels of IL-17F and IL-22	APECED, hypoparathyroidism and Addison′s disease, along with potential endocrine complications (such as hypothyroidism, hypogonadism, and type 1 diabetes mellitus) and non-endocrine systemic complications(such as autoimmune hepatitis, autoimmune gastritis, and asplenia)	[35-37]
	RORC	AR	Decreased levels of IFN-γ, IL-17A/F produced by T cells	MSMD, presenting as susceptible	[38, 39]
	IL12RB1	AR	Decreased levels of IFN-γ and IL-17 produced by T and NK cells	to weakly virulent mycobacteria	[40, 41]
	IL12B	AR	Decreased levels of IFN-γ and IL-17 produced by T and NK cells	and salmonellosis	[40-42]
	CARD9	AR	Impaired Th17 cell response, decreased IL-17 levels	Superficial fungal infections and invasive fungal infections	[43]
	MAPK8	AD	Impaired Th17 cell development, diminished cellular response toIL-17RA/IL-17RC, and impaired IL-17A/F immunity	Connective tissue disease	[44]
Isolated CMC	*IL-17RA*	AR	Suppression of IL-17RA or IL-17RC expression and absence of cellular responses to IL-17A and IL-17F homo- or heterodimers	Recurrent respiratory tract infections, recurrent staphylococcal skin infections	[45]
	IL-17RC	AR	Suppression of IL-17RA or IL-17RC expression and absence of cellular responses to IL-17A and IL-17F homo- or heterodimers	Usually without clinical signs and symptoms other than *Candida* infection of the skin, nails, oral and genital mucosa	[7]
	ACT1	AR	Impaired interaction of ACT1 and IL-17 receptors and impaired cellular response to IL-17A/IL-17F	Recurrent staphylococcal skin infections	[46, 47]
	IL-17F	AD	Decreased IL-17F and receptor binding function, decreased biological function of IL-17F homodimer and IL-17A/F heterodimer	Usually without clinical signs and symptoms other than *Candida* infection of the skin, nails, oral and genital mucosa	[28, 48]

CMC: chronic mucocutaneous candidiasis; AD: autosomal dominant; AR: autosomal recessive; HIES: hyper-immunoglobulinE syndrome; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; MSMD: Mendelian susceptibility to mycobacterial disease; IL-17RA: IL-17 receptor A; IL-17RC: IL-17 receptor C; STAT1: signal transducer and activator of transcription 1; STAT3: signal transducer and activator of transcription 3; MAPK8: mitogen-activated protein kinase; DOCK8: dedicator of cytokinesis 8; ZNF341: zinc finger transcription factor 341; AIRE: autoimmune regulator; RORC: retinoid acid-related orphan receptor C; CARD9: caspase recruitment domain-containing protein 9; IL12RB1: interleukin-12 receptor β1; IL12RB: interleukin-12 receptor β

锌指蛋白341（zinc finger transcription factor 341，ZNF341）基因和白细胞介素12受体β1（interleukin-12 receptor β1，IL12RB1）、L-12p40、胱天蛋白酶募集域蛋白9（caspase recruitment domain-containing protein 9，CARD9）基因等突变或缺陷。

3.1.1.1　AD *STAT1* GOF突变　*STAT1* GOF突变的确切分子机制仍不明确，目前主要涉及的两个假说为STAT1去磷酸障碍及STAT1蛋白水平升高[29]。STAT1去磷酸障碍表现为磷酸化STAT1在核内聚集，致使Th17细胞的分化产生缺陷，IL-17水平下降[30]。*STAT1* GOF突变患者中，绝大多数发展为CMC[49]；CMC患者中最常突变的基因是*STAT1*，近年来有越来越多的新的*STAT1*基因突变位点被发现[50-54]。

3.1.1.2　AD *STAT3*突变、AR *DOCK8*突变、AR *ZNF341*突变　STAT3是由细胞因子（如IL-6、IL-23）激活的重要信号转导和转录调节因子，STAT3磷酸化后形成二聚体，转移到细胞核内，促进RORγT的表达，进而调控Th17细胞的分化[55-56]。有报道*STAT3*突变（均为功能丧失性突变）患者中60.9%表现为CMC[57]，从患者中分离的初始$CD4^+$T细胞显示向Th17细胞的分化受损，患者体内IL-17的水平明显减少[31]。

DOCK8对T细胞的增殖和分化起着非常重要的作用，研究表明*DOCK8*突变患者的$CD4^+$T细胞向Th17的分化障碍，同时使STAT3的活化和核转位受损，进而影响与STAT3转录相关的细胞因子分化[32]。据报道*DOCK8*突变患者中41.9%发展为CMC[57]。*STAT3*突变和*DOCK8*突变均可致高IgE综合征（hyperimmunoglobulin E syndrome，HIES）。

转录因子ZNF341常染色体隐性遗传的纯合无义突变可导致患者产生类似于*STAT3*突变所致的HIES临床表现，患者表现为复发性皮肤和黏膜的念珠菌感染，其机制在于ZNF341是STAT3表达的正向调节因子，*ZNF341*突变导致STAT3水平不足，进而影响Th17细胞的分化[34]。

3.1.1.3　AR *AIRE*基因突变　*AIRE*基因突变导致自身免疫性多内分泌疾病-念珠菌病-外胚层营养不良（autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy，APECED，又称APS-I）这一常染色体隐性遗传病，CMC是其主要的表现之一，患者也常伴有其他的自身免疫性疾病[35]。伴发CMC的APECED的核心病因是患者体内产生了中和性自身抗体特异性对抗Th17细胞因子（IL-17A、IL-17F或IL-22），致使外周血单核细胞的IL-17F和IL-22分泌水平降低；也有新研究显示，干扰素γ（Interferon-γ，IFN-γ）升高可能是APECED患者伴发CMC的另一种机制[36]。

3.1.1.4　AR *RORC*基因突变　编码维生素A相关孤儿受体γ（retinoid-related orphan receptor gamma，RORγ）和维生素A相关孤儿受体γ-t（retinoid-related orphan receptor gamma t，RORγt）的*RORC*基因发生突变（功能丧失性突变）导致患者发生复杂的感染现象，报道的7例*RORC*突变患者全部发展为由分枝杆菌感染的疾病，其中6例伴发CMC[38]。*RORC*在宿主对抗念珠菌感染中起着重要作用，RORγT由Th17细胞表达，是Th17细胞分化的主要调节因子，*RORC*突变患者的T细胞产生IL-17A/F水平下降[38-39, 55]。

3.1.1.5　AR *IL12RB1*和*IL12B*突变　*IL12RB1*基因编码IL-12Rβ1，*IL12B*基因编码IL-12p40，IL-12与其受体IL-12Rβ1、IL-12Rβ2结合，诱导NK细胞和T细胞产生IFN-γ；IL-23二聚体由IL-12p40和p19形成，与受体IL-12Rβ1、IL-23R结合，诱导T细胞产生IL-17[41]。研究表明，IL-12Rβ1或IL-12p40缺陷使IL-12和IL-23的表达障碍、T细胞和NK细胞对IL-12和IL-23的细胞反应受损、产生IFN-γ和IL-17的能力下降，患者对念珠菌的易感性增加，导致CMC的发生[40-42]。

3.1.1.6　AR *CARD9*突变　*CARD9*基因突变可引起以常染色体隐性遗传的CMC[58]。CARD9介导的免疫在宿主对抗真菌感染的过程中十分重要，CARD9突变导致中性粒细胞向感染区域募集的功能受损，但是，只有部分CMC患者的Th17细胞反应受损、IL-17水平降低导致的IL-17免疫能力缺陷，CARD9缺陷患者中IL-17水平的降低、Th17细胞缺陷与CMC的发生之间的机制尚不完全清楚[43]。

3.1.1.7　AD *MAPK8*突变　*MAPK8*基因编码c-Jun氨基末端激酶1（c-Jun N-terminal kinase 1，JNK1），JNK1是JNK家族中成员之一，是MAPK信号通路的组成部分，对Th17细胞的分化和IL-17RA/ IL-17RC抵御念珠菌感染的保护性皮肤黏膜免疫至关重要[44]。据报道，1个法国家族的三代成员中分别发现因*MAPK8*功能丧失型突变致JNK1缺陷的患者，表现为CMC和结缔组织病，研究表明，JNK1缺陷通过损害转化生长因子-β（transforming growth factor-β，TGF-β）依赖的Th17细胞发育、减弱成纤

维细胞对IL-17RA/IL-17RC的应答，影响了IL-17A/F的生物学功能[44]。

3.1.2　孤立型CMC　孤立型CMC指以皮肤、甲、口腔和生殖器黏膜反复或持续的念珠菌感染作为患者主要或唯一的临床表现，通常无其他临床症状和体征，部分患者可伴发皮肤黏膜葡萄球菌感染。其病因包括AR *IL-17RA*、AR *IL-17RC*、AR *ACT1*及AD *IL-17F*突变等（见表1）。

3.1.2.1　AR *IL-17RA*和*IL-17RC*突变　IL-17RA和IL-17RC是IL-17受体家族的成员，IL-17A和IL-17F通过IL-17受体复合物（IL-17R，由IL-17RA和IL-17RC亚单位组成）介导炎性反应[59]。*IL-17RA*或*IL-17RC*基因突变抑制了IL-17RA或者IL-17RC的表达，阻止了成纤维细胞对IL-17A和IL-17F同源或异源二聚体的细胞反应，导致常染色体隐性遗传的CMC的发生[7, 45]。

3.1.2.2　AR *ACT1*突变　ACT1（又称TRAF3IP2）是IL-17受体下游信号转导途径中的接头蛋白，在正常的抗念珠菌感染的免疫防御中起关键作用[47]。据报道，*ACT1*突变影响了ACT1和IL-17受体的相互作用，损害了成纤维细胞对IL-17A/IL-17F的反应，影响了IL-17免疫，导致常染色体隐性遗传CMC的发生[46-47]。

3.1.2.3　AD *IL-17F*突变　*IL-17F*杂合错义突变会使IL-17F和受体结合功能下降，导致IL-17F同源二聚体及IL-17A/F异源二聚体的生物学功能下降，引起常染色体隐性遗传的CMC发生[28, 48]。

3.2　继发性CMC

HIV感染、免疫抑制治疗、长期抗生素治疗、恶性肿瘤患者接受放疗或化疗、糖尿病等导致机体免疫缺陷或抑制，易使念珠菌这一机会致病菌引起CMC，同时易使患者发生严重的深部真菌感染[2, 4]。

4　CMC的诊断及辅助检查

CMC的诊断主要依靠病史、临床特点以及相应的辅助检查结果[1, 60]。具体诊断流程及方法见图2。在临床诊疗过程中，可根据患者自身的病情、意愿、经济情况以及医生的经验，酌情选择检查的项目和调整检查的顺序。

5　CMC的治疗

5.1　抗真菌药物治疗

抗真菌药物已成为CMC的主要治疗方法，包括抗真菌药物的局部使用和全身治疗，目前临床常用的抗真菌药物包括三唑类、棘白菌素类、多烯类抗真菌药物。

5.1.1　口服抗真菌药物　三唑类抗真菌药抑制真菌细胞膜中的α-1，4-去甲基化酶，阻止麦角固醇的合成，致使真菌细胞膜破损，膜通透性增加，产生抗真菌作用[61]。氟康唑、伊曲康唑、泊沙康唑等三唑类药物是临床常用的CMC治疗用药[60, 62]，氟康唑高效安全，耐受好，副作用少，伊曲康唑在治疗皮肤和甲真菌感染上具有很好的疗效，泊沙康唑具有广谱的抗真菌活性[63]。

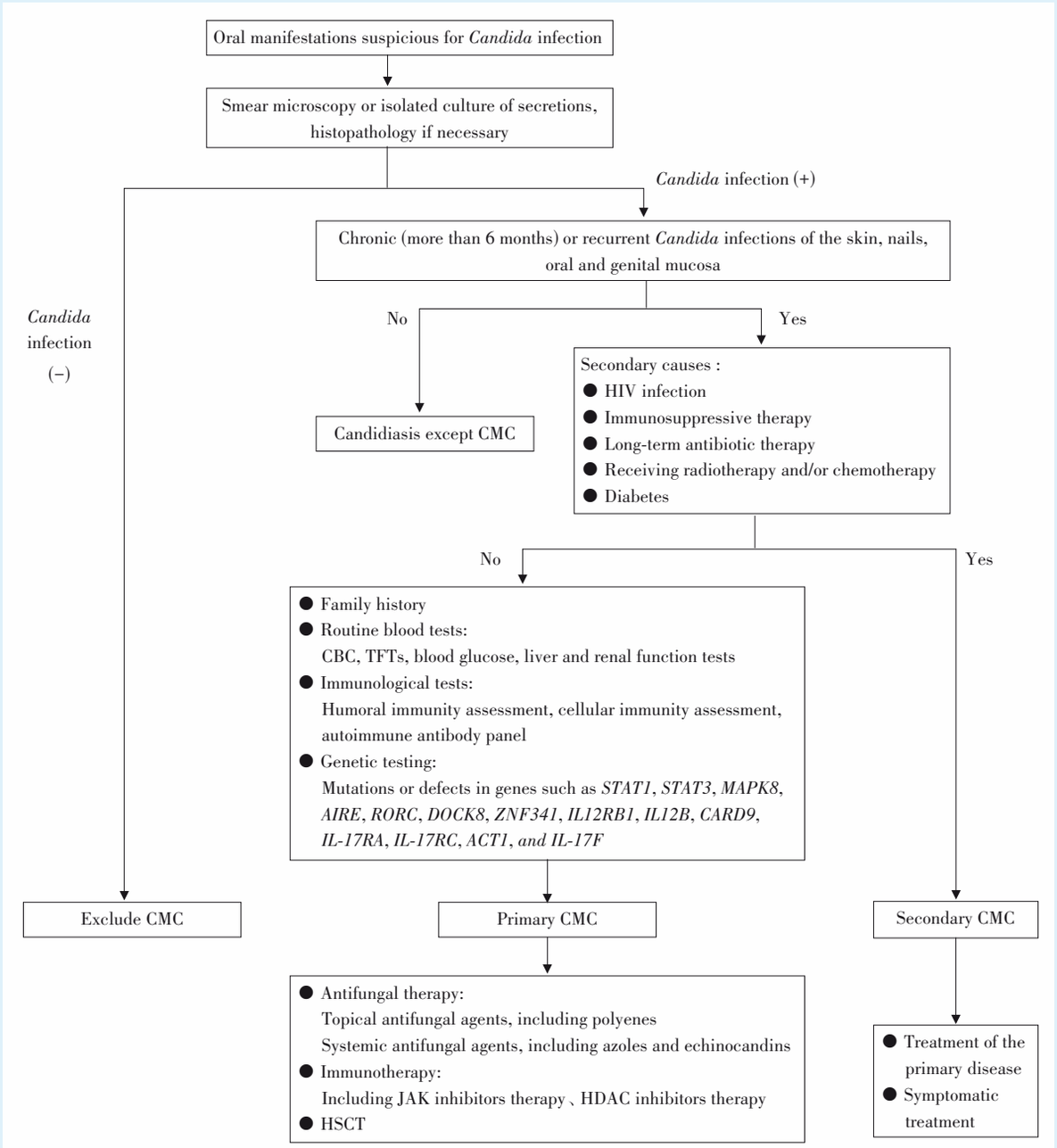
棘白菌素类抗真菌药非竞争性抑制真菌β-1，3-D-葡聚糖合成酶，造成细胞壁中β-葡聚糖含量减少，导致细胞壁结构的破坏，致使菌体裂解、死亡[64]。棘白菌素类[65]是对抗念珠菌的高效制剂，包括卡泊芬净、米卡芬净、阿尼芬净和雷扎芬净等。

多烯类抗真菌药物（包括制霉菌素和两性霉素B）与真菌细胞膜中的麦角固醇相结合，干扰代谢，增加细胞膜通透性，导致菌体死亡[66]。多烯类抗真菌药杀菌力强，抗真菌活性范围广，耐药性低[67-68]。

5.1.2　抗真菌药物的局部联合应用　两种多烯类抗真菌药，如含漱制霉菌素悬浊液，并结合两性霉素B含片的使用，可缓解口腔念珠菌感染；念珠菌性口角炎的治疗使用纳他霉素、盐酸阿莫罗芬乳膏、咪康唑凝胶、氯己定凝胶等可缓解[16, 24]。食管感染和皮肤感染同样可使用以上治疗方法。女性生殖系统感染可通过短期的阴道氟康唑治疗得到控制。增厚的指甲/趾甲可通过应用40%尿素膏加以去除，在治疗过程中，应辅以伊曲康唑等全身药物且所有的治疗应持续6周以上[16, 24]。

5.2　JAK抑制剂治疗

JAK家族包括JAK1、JAK2、JAK3和酪氨酸激酶2（tyrosine kinase 2，TYK2），JAK是一种与细胞因子受体相关的细胞内蛋白，在受体刺激时募集STATs并促进信号转导，可被各种JAK抑制剂抑制[69]。有报道使用JAK抑制剂缓解了*STAT1* GOF突变患者的CMC[70]。JAK1/2抑制剂鲁索替尼可改善大多数*STAT1* GOF突变病人的CMC和自身免疫性疾病的体征，提供了CMC患者进行免疫治疗的可行性，患者需进行长期治疗以维持疗效[70-71]。巴瑞替尼是一种新型的口服JAK1/2抑制剂，阻碍干扰素诱导的JAK-STAT1信号通路，可应用于CMC



CBC: complete blood count; TFTs: thyroid function tests; JAK: Janus kinase; HDAC: histone deacetylase; HSCT: hematopoietic stem cell transplantation; CMC: chronic mucocutaneous candidiasis; HIV: human immunodeficiency virus; STAT1: signal transducer and activator of transcription 1; STAT3: signal transducer and activator of transcription 3; MAPK8: mitogen-activated protein kinase; AIRE: autoimmune regulator; RORC: retinoid acid-related orphan receptor C; DOCK8: dedicator of cytokinesis 8; ZNF341: zinc finger transcription factor 341; IL12RB1: interleukin-12 receptor β1; IL12RB: interleukin-12 receptor β; CARD9: caspase recruitment domain-containing protein 9; IL-17RA: IL-17 receptor A; IL-17RC: IL-17 receptor C

Figure 2　Diagnostic and therapeutic procedures for chronic mucocutaneous candidiasis

图2　慢性皮肤黏膜念珠菌病诊断与治疗流程

患者治疗[10]。

5.3　粒细胞集落刺激因子(granulocyte colony-stimulating factor,G-CSF)和粒细胞巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor,GM-CSF)治疗

作为一种多效性细胞因子,G-CSF刺激造血祖细胞向中性粒细胞增殖和分化,促进粒细胞的存活和终末细胞功能[72],而GM-CSF则能够影响更多

类型的细胞，尤其是巨噬细胞和嗜酸性粒细胞[73]，在宿主对抗真菌感染中起到重要的作用。有报道[74]G-CSF治疗后CMC患者的临床症状完全缓解，亦有报道CMC患者在接受G-CSF治疗后没有得到临床缓解[75]，因此，仍需要更多的临床研究评估其疗法和适应证。

5.4　组蛋白去乙酰基酶（histone deacetylase，HDAC）抑制剂

HDAC抑制剂被认为是一种很有前景的CMC的治疗方法。HDAC抑制剂下调了磷酸化STAT1水平，同时保持了正常的磷酸化STAT3水平，体外试验中，HDAC抑制剂对组蛋白乙酰化的抑制作用使Th17细胞恢复到了接近正常水平，这提供了HDAC抑制剂可能在临床治疗*STAT1* GOF突变的CMC患者的证据[76]。

5.5　造血干细胞移植（hematopoietic stem cell transplantation，HSCT）

HSCT可作为CMC的根治手段[76]。Kiykim等[77]报道了*STAT1* GOF突变的CMC患者通过人类白细胞抗原（human leukocyte antigen，HLA）相合HSCT治疗后，患者的相关临床体征消失，提示其治疗潜力。也有文献报道了一例*STAT1* GOF突变的CMC患者合并纯红细胞再生障碍，在接受HSCT治疗后因严重并发症（胃肠道出血、肺部感染）导致治疗失败[78]。HSCT并非对所有病例都适用，也有因继发感染、排斥反应发生移植失败、死亡的风险[79-80]。研究表明，基因型-表型与移植结果无明显相关性，移植时年龄越小，预后越好，提示患者需要早期诊断、早期治疗。对具有严重临床表现的患者，尤其是在发生终末器官损害之前，应积极治疗病症、密切监测疾病进展、进行早期的供体筛查。

5.6　其他治疗方法

由于基因突变或缺陷可导致CMC，因此，基因治疗或可成为CMC的治疗手段。但目前对于真菌感染的基因治疗尚在实验阶段而尚未在临床治疗中应用。Gordon-Thomson等[81]报道通过逆转录病毒载体将人类的壳三糖酶基因整合到中国仓鼠卵巢细胞（CHO细胞）中，转基因CHO细胞能够持续分泌活性壳三糖酶，并在体内外模型中均展现出对抗真菌感染的潜力。对于原发性CMC，基因治疗有潜在的临床应用价值，但临床应用仍需要进一步的研究探索。

6　总结与展望

CMC的病因及发病机制复杂，且处在不断的探索中，临床表现除念珠菌感染之外，可伴有其他感染性和免疫性疾病，为临床上的诊断带来较大困难。因此，结合相关辅助检查成为CMC诊断的要点之一。抗真菌药物是目前临床常用的治疗方法，合理应用可以使CMC患者念珠菌感染得到缓解和控制，但患者常因伴发的其他感染性和免疫性疾病导致病情加重或恶化。以治疗免疫缺陷问题的免疫疗法为CMC患者提供了更多的治疗选择，但是，由于患者的疗效不一，未来需要更多的研究以明确CMC的免疫治疗方案，以期提高CMC患者的治愈率，减轻CMC患者的痛苦。

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