·综述·

非HIV马尔尼菲篮状菌病的研究进展

黄丽萍，陆艾丽，彭劼（南方医科大学南方医院感染内科，广州 510515）

【摘要】马尔尼菲篮状菌（TM）是一种机会性致病菌，主要发生于HIV感染者，而近年来关于非HIV患者的报道逐年增多，与机体的免疫功能低下有关。儿童免疫功能低下的主要因素为各种原发性免疫缺陷，成人免疫功能低下的主要因素则为抗γ干扰素抗体综合征、自身免疫性疾病、激素和/或免疫抑制剂使用、恶性肿瘤、糖尿病等。非HIV马尔尼菲篮状菌病患者的临床表现以播散型感染最为常见，可能合并其他机会性感染、继发噬血细胞综合征。HIV与非HIV马尔尼菲篮状菌病患者的临床表现及预后存在一定差异，且目前尚无关于非HIV马尔尼菲篮状菌病的标准治疗方案。本研究对非HIV马尔尼菲篮状菌病的流行病学、免疫功能低下因素、临床表现、诊断、治疗和预后进行综述。

【关键词】马尔尼菲篮状菌病；免疫功能低下；临床表现；治疗
DOI：10.19871/j.cnki.xfcrbzz.2022.02.018

Progress on Talaromycosis in non-HIV-infected patients

Huang Liping, Lu Aili, Peng Jie *(Department of Infectious Diseases, Southern Medical University Nanfang Hospital, Guangzhou 510515, China)*

【Abstract】 *Talaromyces marneffei* is an opportunistic pathogen, which mainly occurs in human immunodeficiency virus (HIV)-infected patients. Whereas, non-HIV Talaromycosis patients increased in recent years which was related to the compromised immune conditions of hosts. The most common underlying diseases in children were various primary immunodeficiency diseases. The most common underlying diseases in adults were anti-interferon-gamma autoantibody (AIGA) syndrome, autoimmune diseases, glucocorticoid and/or immunosuppressive therapy, malignancy, diabetes and so on. Most non-HIV Talaromycosis patients occurred disseminated infection, and might coinfected with other opportunity pathogens and had secondary hemophagocytic lymphohistiocytosis. The clinical manifestations and prognosis of non-HIV Talaromycosis patients were different from that of HIV-infected patients. Herein, we reviewed the epidemiology, immunodeficiency, clinical manifestations, diagnosis, treatment and prognosis of non-HIV Talaromycosis.

【Key words】Talaromycosis; Immunodeficiency; Clinical manifestations; Treatment

马尔尼菲篮状菌（*Talaromyces marneffei*，TM）感染主要发生于HIV感染者，而近年来非HIV马尔尼菲篮状菌病的报道逐年增多。本研究对非HIV马尔尼菲篮状菌病的研究进展进行综述。

1 流行病学

TM是一种双相真菌，25℃时呈菌丝相生长，37℃时则为酵母相，显微镜下呈中间有分隔的圆形到椭圆形的酵母细胞。竹鼠在1956年被发现为TM的自然动物宿主，竹鼠生活环境的周围土壤、粪便以及竹根等都能分离出TM[1,2]。2010年泰国一项研究发现13%狗鼻拭子TM核酸测序呈阳性，但培养阴性，考虑狗可能是TM潜在的动物宿主[3]。马尔尼菲篮状菌病可能主要通过呼吸道吸入环境中的真菌孢子，导致肺部感染，继而播散至全身各个脏器[4]；皮肤、消化道也是病原体的潜在入侵途径[5-7]。

首例自然感染TM的病例报道于1973年，为霍奇金淋巴瘤患者，该患者HIV感染情况不详[8]。自1988年首例HIV合并TM感染患者被报道后[9]，1988至1990年，马尔尼菲篮状菌病随着HIV感染的流行而增多，随后因高效抗反转录病毒治疗（highly active antiretroviral therapy，HAART）及减少HIV传播的相关措施的实施，HIV合并马尔尼菲篮状菌病的发病数减少，但非HIV马尔尼菲篮状菌病逐渐增多，考虑与原发性免疫缺陷、器官移植、自身免疫性疾病、生物制剂应用等密切相关[10]。马尔尼菲篮状菌病主要流行于印度、东南亚部分国家以及中国南部。在非流行

基金项目：国家自然科学基金（81971949）
通信作者：彭劼，Email：pjie138@163.com

引用格式：黄丽萍，陆艾丽，彭劼.非HIV马尔尼菲篮状菌病的研究进展[J/CD].新发传染病电子杂志，2022,7（2）：89-94. Huang Liping, Lu Aili, Peng Jie. Progress on Talaromycosis in non-HIV-infected patients[J/CD].Electronic Journal of Emerging Infectious Diseases,2022,7(2):89-94.

地区如欧美及大洋洲等也有散发报道，这类患者常合并器官移植等影响免疫功能的因素，且发病前有疫区旅行史[11,12]。此外，相对旱季而言，马尔尼菲篮状菌病在雨季发病更加常见[13]。

2 免疫功能低下的因素

2.1 儿童　儿童发病年龄较小，多数在5岁以下，存在各种原发性免疫缺陷，如CD40配体缺陷、*STAT1*基因突变、低丙种球蛋白血症、高IgE综合征和白血病等[14,15]。发病前常出现鹅口疮、反复肺部感染等表现，往往存在体液免疫或细胞免疫功能异常，但也有部分儿童既往身体健康[16,17]，因此有必要深入探讨这类儿童的免疫状况。Lee等[18]制定出一套适合儿童患者的免疫筛查流程图，建议从免疫球蛋白、淋巴细胞计数亚群分析起始，根据检测结果决定后续CD40L或STAT3特定基因测序、STAT1磷酸化检测、全外显子测序等以明确儿童原发性免疫缺陷类型。

2.2 成人

2.2.1 抗γ干扰素抗体　抗γ干扰素抗体（anti-interferon-gamma autoantibody，AIGA）综合征是一种晚发型免疫缺陷性疾病[19]。AIGA好发于免疫正常人群[20]，研究表明AIGA与患者出现多重机会性感染[21-23]、感染播散[24]、病情活动[25]及不良预后密切相关，但研究人群主要为非结核分枝杆菌（nontuberculous mycobacteria，NTM）感染患者。在马尔尼菲篮状菌病相关研究中，20.41%非HIV马尔尼菲篮状菌病成年患者存在AIGA[14]；94.8%无基础疾病的免疫正常患者存在AIGA[26]，提示AIGA已成为非HIV患者罹患马尔尼菲篮状菌病的最常见易感因素。相较AIGA阴性患者，AIGA阳性的马尔尼菲篮状菌病患者较少合并呼吸系统基础疾病，更容易出现其他机会性感染、骨骼受累等[27]。50%以上的AIGA患者存在反应性皮炎如Sweet综合征、小叶性脂膜炎等[28]；Chi等[29]建议由NTM、TM等机会性致病菌引起的感染性或反应性皮肤病患者，如果无免疫功能低下，应完善AIGA检测。

AIGA相关报道主要发生于东南亚地区，存在一定的遗传倾向，与HLA-DRB1、HLA-DQB1等位基因密切相关[26,29-31]。IFN-γ可激活巨噬细胞分化，是固有免疫中重要的促炎因子，通过与吞噬细胞上的IFN-γ受体结合，促进吞噬细胞分泌IL-12，IL-12作用于NK细胞及T细胞，促进后者分泌IFN-γ，形成IL-12/IFN-γ循环，AIGA可阻断该通路，抑制人体免疫[21]。AIGA可抑制M1型巨噬细胞分泌细胞因子，并抑制巨噬细胞吞噬及降解病原体的能力[32]。AIGA阳性患者Th1细胞因子生成增加，而Th2、Th17细胞因子生成较对照组相仿，提示患者可能存在其他细胞免疫功能改变，共同导致免疫缺陷[33]。

相较AIGA阴性患者，非HIV马尔尼菲篮状菌病合并AIGA阳性患者经标准抗真菌治疗后预后不佳[27]。Guo等[26]研究提示AIGA阳性的非HIV马尔尼菲篮状菌病患者病死率较高（30.2%），44.2%的患者存在感染复发或合并其他机会性感染，仅有18.6%的患者经抗真菌治疗后痊愈。AIGA阳性的非HIV马尔尼菲篮状菌病患者，经积极抗真菌治疗后病情仍进展或复发，可尝试使用CD20单抗（利妥昔单抗）、CD38单抗（达雷妥尤单抗）、糖皮质激素、环磷酰胺等药物治疗[34]。由于免疫调节药物可抑制宿主免疫功能，增加感染风险，如何平衡免疫调节药物的风险及获益，以及药物的选择、剂量、干预时机及疗程等有待商榷。

2.2.2 其他免疫功能低下因素　非HIV马尔尼菲篮状菌病患者合并其他常见的免疫功能低下因素依次为自身免疫性疾病、激素和/或免疫抑制剂使用、恶性肿瘤、糖尿病、器官移植等[14]。Lao等[35]回顾性研究发现结缔组织病合并侵袭性真菌病（invasive mycoses，IM）的发生率为0.5%（32/6911），TM感染仅占IM的6.25%（2/32），但死亡率高达100%。大部分系统性红斑狼疮（systemic lupus erythematosus，SLE）患者在感染TM前，曾接受免疫抑制剂药物治疗，且在疾病初期常被误诊为SLE病情活动；抗真菌治疗有助于改善患者预后，而未接受抗真菌治疗的患者病死率可达100%[7]。患者合并的恶性肿瘤主要为血液系统疾病如白血病、淋巴瘤、多发性骨髓瘤；其次为肺癌、结肠癌、口腔癌、鼻咽癌、甲状腺癌等[14]。患者合并的最常见器官移植类型为肾脏移植，其他有肺移植、肝移植、骨髓造血移植等[10]。然而，仍然有部分非HIV患者，其潜在的免疫功能低下因素尚不明确，有待进一步研究。

3 临床表现

3.1 主要临床表现　马尔尼菲篮状菌病分为局限型和播散型感染，以播散型感染多见。局限型感染主要发生在病原菌入侵部位，最常见于肺部、皮肤，此外，消化道（从口咽到结肠）也可能出现局灶受累[6,36]。播散型感染，以富含单核-巨噬细胞的组织器官如肝脏、脾脏、淋巴结等最易受到侵犯[14]。

大多数非HIV马尔尼菲篮状菌病患者会出现发热、乏力、体重下降等非特异性症状。其他症状则根据感染部位不同而表现各异。①患者常出现呼吸系统受累，可累及肺部、气管、支气管和胸膜，表现为

咳嗽、咳痰、呼吸困难、胸痛、咯血等症状[10,37]。若气管受侵犯，可能造成气道塌陷、气管狭窄，需要外科干预行气管成形术[38]。肺部影像学改变包括磨玻璃影、炎性渗出、实变、结节、空洞、囊样变等，可伴有纵隔或肺门淋巴结肿大、胸腔积液，少数情况下可伴有邻近骨质破坏[10,39]。部分患者存在肺癌基础疾病，因此，在诊断TM感染时需警惕出现遗漏肺癌的诊断[40]。支气管镜检查可见息肉、黏膜下肿物、支气管管壁不规则、支气管狭窄等[41,42]。②患者常出现皮肤或皮下组织病变，主要表现为皮下脓肿、结节、丘疹、溃疡和红斑[10,37]。若患者突然出现痛性红斑或结节，组织病理提示大量中性粒细胞浸润，但病原学培养呈阴性，需考虑Sweet综合征等反应性皮肤病[29,43]。③患者常出现淋巴结、肝脏和脾脏肿大，有时会被误认为淋巴瘤[10,44]。④约20%患者合并骨关节受累[10,45]，表现为骨痛、关节痛、关节紊乱、周围软组织损害。X线片或CT检查可见多处虫蚀样溶骨性破坏、骨折、周围软组织肿胀等；全身骨扫描、PET-CT提示多处骨骼摄取增加，椎骨、颅骨、股骨和肋骨最常受累[46]。⑤少数患者可出现消化道受累，表现为腹泻、腹痛、血便、厌食、呕吐等不适，肠镜检查可见溃疡、糜烂、水肿、出血、鹅卵石样改变，腹部CT可见肠壁水肿增厚、部分肠梗阻、肠系膜淋巴结肿大等，需与炎症性肠病、肠结核等相鉴别。消化道受累可独立出现，也可伴随全身广泛播散[5,6,47]。⑥中枢神经系统侵犯较罕见，主要发生于HIV感染者（尤其是$CD4^+$T淋巴细胞计数＜100/μl的患者），而在非HIV感染者中仅有数例报道。患者表现为头痛、头晕、意识改变、癫痫、面瘫、肌力下降、视物模糊、复视、听力下降等。头颅MRI检查可见颅内异常信号、脑室扩张、脑膜强化等改变。该疾病进展迅速，预后差、病死率高，需要进行早期诊断、早期抗真菌治疗[48-50]。⑦其他表现：患者血白细胞增高或降低，中性粒细胞、淋巴细胞降低，贫血，血小板增多或降低，真菌菌血症等[10]。

3.2 多重机会性感染 因为非HIV马尔尼菲篮状菌病患者多数存在免疫低下，所以可能合并其他机会性感染，例如NTM、隐球菌、念珠菌、巨细胞病毒、带状疱疹等，导致病情反复[16,51-53]。NTM与TM双重感染患者，NTM或TM感染在疾病早期容易被漏诊，这可能与两者的临床表现相似有关，最终导致疾病预后不佳。高滴度AIGA水平是NTM与TM双重感染的独立危险因素[23]。

3.3 继发噬血细胞综合征 马尔尼菲篮状菌病可继发噬血细胞综合征，主要发生于学龄前儿童，多合并基础疾病或反复感染史，表现为发热、体重下降、咳嗽、肝脾大、淋巴结肿大等。实验室检查提示贫血、血小板减少、肝功能异常、铁蛋白升高、乳酸脱氢酶升高、NK细胞减少等。一旦继发噬血细胞综合征，病死率较高，需及时抗真菌治疗及支持治疗[16,17]。

3.4 HIV与非HIV马尔尼菲篮状菌病 HIV与非HIV马尔尼菲篮状菌病患者的临床表现相似，均以全身播散性感染、单核-巨噬系统受累最常见[54]，但两者间仍存在诸多差异（表1）。此外，虽然HIV与非HIV马尔尼菲篮状菌病患者均容易合并其他机会性感染，但非HIV马尔尼菲篮状菌病患者相对更常见[55]，且非HIV马尔尼菲篮状菌病患者对抗真菌的应答反应更差、死亡率更高[55,56]。

表1 HIV与非HIV马尔尼菲篮状菌病的临床表现比较

临床表现	HIV患者	非HIV患者	文献
年龄	相对年轻	相对年长	[55,57,58]
合并基础疾病	少	大多数	[56,58,59]
常见皮肤表现类型	丘疹，溃疡	皮下脓肿，结节	[37]
骨关节受累	少	相对较多	[55]
起病至确诊时间	短	长	[60]
曾被误诊为结核感染	少	较多	[10,58]
$CD4^+$T淋巴细胞计数	＜200/μl	多数正常	[55-57,60,61]
血培养阳性率	较高	相对较低	[55,58]

4 诊断

马尔尼菲篮状菌病诊断金标准：①临床组织标本或体液培养出TM；②细胞学检查；③组织病理检查发现巨噬细胞内或细胞外存在TM。组织培养阳性的标本主要来源于骨髓、血液、淋巴结、肺组织和皮肤等[14]，培养阳性需要4～5d，有时需长达14d[62]。

其他实验室检测技术也有助于诊断：①宏基因组二代测序技术（metagenomic next-generation sequencing，mNGS），所需时长最短为24h，有助于早期而精准地诊断病原菌[48]，尤其有助于非HIV马尔尼菲篮状菌病的诊断[63]。由于TM在环境中广泛分布，当mNGS测出的序列数较少时，易被误认为背景菌，此时需结合患者临床表现、追踪组织培养结果或诊断性抗真菌治疗等以明确诊断[64]。②血清Mp1P抗原检测，Mp1P分布于TM细胞壁，并可作为毒力因子被大量分泌。Mp1P抗原检测具有较高的灵敏度（80%～86.3%）及特异度（93.17%～98.1%），且诊断时长仅需6h，与隐球菌、曲霉菌、念珠菌和组织胞浆菌等无交叉反应，可作为HIV合并TM感染的早期筛查手段[65-67]。

5 治疗

TM的体外药物敏感试验结果显示两性霉素B、伏立康唑、伊曲康唑和泊沙康唑的最小抑菌浓度

（minimum inhibitory concentrations，MIC）较低，而氟康唑、阿尼芬净、米卡芬净、卡泊芬净、氟胞嘧啶MIC值较高[68,69]。目前治疗主要包括诱导期、巩固期和维持期。①诱导期：首选两性霉素B脂质体（3～5mg/kg，1次/d）或两性霉素B脱氧胆酸盐（0.7mg/kg，1次/d）静脉输注2周，次选伏立康唑治疗，不推荐伊曲康唑用于诱导治疗。②巩固期：伊曲康唑或伏立康唑200mg，2次/d，口服10周。③维持期（二级预防）：伊曲康唑200mg，1次/d，口服，直至$CD4^+$T淋巴细胞计数＞100/μl且维持≥6个月（同时接受HAART）[62]。因两性霉素B存在肾功能损害、低钾血症、输注反应等不良反应，且需经中心静脉给药，而伏立康唑不良反应相对较少，且伏立康唑用于非HIV马尔尼菲篮状菌病初始治疗的疗效更可靠[70]，部分患者无法耐受两性霉素B，可选用伏立康唑用于初始治疗。此外，泊沙康唑可能具有较好的抗真菌疗效，尤其是对于合并严重肝肾功能不全患者[71]。

非HIV马尔尼菲篮状菌病的治疗疗程尚无统一标准。Kawila等[55]研究发现非HIV患者的中位治疗疗程为180d，疗程长于HIV马尔尼菲篮状菌病患者。Ouyang等[70]研究发现伏立康唑疗程超过16周具有满意的疗效和远期预后。此外，尽管非HIV患者具有较高的$CD4^+$T淋巴细胞计数，但多数患者仍存在免疫功能低下，目前已有报道少数患者接受伊曲康唑二级预防治疗[37,72]，但非HIV马尔尼菲篮状菌病患者是否需要二级预防以及二级预防疗程等问题仍需进一步研究。

6 预后

非HIV马尔尼菲篮状菌病死亡率为27.7%，较合并HIV患者高（20.7%），考虑可能与延误诊断有关，其中有13.4%非HIV马尔尼菲篮状菌病患者初期被误诊为结核而接受经验性抗结核治疗[10]。合并免疫功能低下的非HIV马尔尼菲篮状菌病患者在院期间死亡率高达40.8%，复发率26.0%，其中儿童死亡率高于成人，而成人复发率高于儿童[14]。

非HIV马尔尼菲篮状菌病逐年增多，与患者免疫功能低下相关。患者的临床表现以播散型感染、单核-吞噬细胞系统受累最常见，整体预后不佳。临床医师应提高对非HIV马尔尼菲篮状菌病的认识，尤其是面对合并各种基础疾病的免疫功能低下患者，应避免漏诊或误诊，目前除应用传统诊断技术外，mNGS、Mp1P等检测技术有助于诊断，早诊断、早治疗有助于改善患者预后。此外，若遇到免疫正常的马尔尼菲篮状菌病患者，应深入了解患者免疫功能低下因素，如存在原发性免疫缺陷、AIGA、自身免疫性疾病等。

参考文献

[1] LI XQ, YANG YB, ZHANG X, et al. Isolation of Penicillium marneffei from soil and wild rodents in Guangdong, SE China[J]. Mycopathologia, 2011,172(6):447-551.
[2] HUANG XW, HE GH, LU S, et al. Role of Rhizomys pruinosus as a natural animal host of Penicillium marneffei in Guangdong, China[J]. Microb Biotechnol,2015,8(4):659-664.
[3] CHAIWUN B, VANITTANAKOM N, JIVIRIYAWAT Y, et al. Investigation of dogs as a reservoir of Penicillium marneffei in northern Thailand[J]. Int J Infect Dis, 2011, 15(4):e236-e239.
[4] LI YH, LUO HL, FAN JT, et al. Genomic analysis provides insights into the transmission and pathogenicity of Talaromyces marneffei[J]. Fungal Genet Biol, 2019, 130:54-61.
[5] ZHAO YK, LIU JY, LIU JH, et al. Recurrent Talaromyces marneffei Infection Presenting with Intestinal Obstruction in a Patient with Systemic Lupus Erythematosus[J]. Mycopathologia, 2020, 185(4):717-726.
[6] LU YS, SHI Q, YU J. Drug-related talaromycosis: A case report[J]. Int J Immunopathol Pharmacol, 2020,34:1-6.
[7] WEI JS, QIU Y, ZENG W, et al. Talaromyces marneffei Infection in Systemic Lupus Erythematosus Patients: Report of Two Cases and Review of the Literature[J]. Infect Drug Resist, 2020, 13:3811-3816.
[8] DISALVO AF, FICKLING AM, AJELLO L. Infection caused by Penicillium marneffei: description of first natural infection in man[J]. Am J Clin Pathol,1973,60(2):259-263.
[9] PETO TE, BULL R, MILLARD PR, et al. Systemic mycosis due to Penicillium marneffei in a patient with antibody to human immunodeficiency virus[J]. J Infect, 1988, 16(3):285-290.
[10] CHAN JF, LAU SK, YUEN KY, et al. Talaromyces (Penicillium) marneffei infection in non-HIV-infected patients[J]. Emerg Microbes Infect,2016,5(3):e19-e27.
[11] VERGIDIS P, RAO A, MOORE CB, et al. Talaromycosis in a renal transplant recipient returning from South China[J]. Transpl Infect Dis, 2021, 23(1):e13447-e13451.
[12] STATHAKIS A, LIM KP, BOAN P, et al. Penicillium marneffei infection in a lung transplant recipient[J]. Transpl Infect Dis, 2015, 17(3):429-434.
[13] CHARIYALERTSAK S, SIRISANTHANA T, SUPPARATPINYO K, et al. Seasonal variation of disseminated Penicillium marneffei infections in northern Thailand: a clue to the reservoir?[J]. J Infect Dis, 1996, 173(6):1490-1493.
[14] QIU Y, FENG X, ZENG W, et al. Immunodeficiency Disease Spectrum in HIV-Negative Individuals with Talaromycosis[J]. J Clin Immunol, 2021, 41(1):221-223.
[15] LEE PP, CHAN KW, LEE TL, et al. Penicilliosis in children without HIV infection--are they immunodeficient?[J]. Clin Infect Dis, 2012, 54(2):e8-e19.
[16] PAN ML, QIU Y, ZENG W, et al. Talaromycosis-Associated Secondary Hemophagocytic Lymphohistiocytosis in Nine Human Immunodeficiency Virus-Negative Patients: A Multicenter Retrospective Study[J]. Infect Drug Resist, 2019, 12:3807-3816.
[17] GUO J, LI BK, LI TM, et al. Characteristics and Prognosis

of Talaromyces marneffei Infection in Non-HIV-Infected Children in Southern China[J]. Mycopathologia, 2019, 184(6):735-745.

[18] LEE PP, LAO-ARAYA M, YANG J, et al. Application of Flow Cytometry in the Diagnostics Pipeline of Primary Immunodeficiencies Underlying Disseminated Talaromyces marneffei Infection in HIV-Negative Children[J]. Front Immunol, 2019, 10:2189-2202.

[19] HÖFLICH C, SABAT R, ROSSEAU S, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with Mycobacterium cheloneae and Burkholderia cocovenenans[J]. Blood, 2004, 103(2):673-675.

[20] AOKI A, SAKAGAMI T, YOSHIZAWA K, et al. Clinical Significance of Interferon-γ Neutralizing Autoantibodies Against Disseminated Nontuberculous Mycobacterial Disease[J]. Clin Infect Dis, 2018, 66(8):1239-1245.

[21] SHIH HP, DING JY, YEH CF, et al. Anti-interferon-γ autoantibody-associated immunodeficiency[J]. Curr Opin Immunol, 2021, 72:206-214.

[22] BROWNE SK, BURBELO PD, CHETCHOTISAKD P, et al. Adult-onset immunodeficiency in Thailand and Taiwan[J]. N Engl J Med, 2012, 367(8):725-734.

[23] QIU Y, HUANG J, LI Y, et al. Talaromyces marneffei and nontuberculous mycobacteria co-infection in HIV-negative patients[J]. Sci Rep, 2021, 11(1):16177-16186.

[24] SHIMA K, SAKAGAMI T, TANABE Y, et al. Novel assay to detect increased level of neutralizing anti-interferon gamma autoantibodies in non-tuberculous mycobacterial patients[J]. J Infect Chemother, 2014, 20(1):52-56.

[25] YOSHIZAWA K, AOKI A, SHIMA K, et al. Serum Anti-interferon-γ Autoantibody Titer as a Potential Biomarker of Disseminated Non-tuberculous Mycobacterial Infection[J]. J Clin Immunol, 2020, 40(2):399-405.

[26] GUO J, NING XQ, DING JY, et al. Anti-IFN-γ autoantibodies underlie disseminated Talaromyces marneffei infections[J]. J Exp Med, 2020, 217(12): e20190502.

[27] CHEN ZM, LI ZT, LI SQ, et al. Clinical findings of Talaromyces marneffei infection among patients with anti-interferon-γ immunodeficiency: a prospective cohort study[J]. BMC Infect Dis, 2021, 21(1):587.

[28] ANGKASEKWINAI N, SUPUTTAMONGKOL Y, PHOOMPOUNG P, et al. Clinical outcome and laboratory markers for predicting disease activity in patients with disseminated opportunistic infections associated with anti-interferon-γ autoantibodies[J]. PLoS One, 2019, 14(4):e0215581.

[29] CHI CY, CHU CC, LIU JP, et al. Anti-IFN-γ autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1*16:02 and HLA-DQB1*05:02 and the reactivation of latent varicella-zoster virus infection[J]. Blood, 2013, 121(8):1357-1366.

[30] PITHUKPAKORN M, ROOTHUMNONG E, ANGKASEKWINAI N, et al. HLA-DRB1 and HLA-DQB1 Are Associated with Adult-Onset Immunodeficiency with Acquired Anti-Interferon-Gamma Autoantibodies[J]. PLoS One, 2015, 10(5):e0128481.

[31] Ku CL, Lin CH, Chang SW, et al. Anti-IFN-γ autoantibodies are strongly associated with HLA-DR*15:02/16:02 and HLA-DQ*05:01/05:02 across Southeast Asia[J]. J Allergy Clin Immunol, 2016, 137(3):945-948.e8.

[32] KRISNAWATI DI, LIU YC, LEE YJ, et al. Blockade Effects of Anti-Interferon- (IFN-) γ Autoantibodies on IFN-γ-Regulated Antimicrobial Immunity[J]. J Immunol Res, 2019, 2019:1629258.

[33] CHRUEWKAMLOW N, MAHASONGKRAM K, PATA S, et al. Immune Alterations in Patients with Anti-Interferon-γ Autoantibodies[J]. PLoS One, 2016, 11(1):e0145983.

[34] CHAWANSUNTATI K, RATTANATHAMMETHEE K, WIPASA J. Minireview: Insights into anti-interferon-γ autoantibodies[J]. Exp Biol Med, 2021, 246(7):790-795.

[35] LAO MX, ZHAN ZP, SU F, et al. Invasive mycoses in patients with connective tissue disease from Southern China: clinical features and associated factors[J]. Arthritis Res Ther, 2019, 21(1):71-80.

[36] WONGKAMHLA T, CHONGTRAKOOL P, JITMUANG A. A case report of Talaromyces marneffei Oro-pharyngo-laryngitis: a rare manifestation of Talaromycosis[J]. BMC Infect Dis, 2019, 19(1):1034-1039.

[37] HE LY, MEI X, LU S, et al. Talaromyces marneffei infection in non-HIV-infected patients in mainland China[J]. Mycoses, 2021, 64(10):1170-1176.

[38] QIU Y, LU DC, ZHANG JQ, et al. Treatment of Disseminated Talaromyces marneffei with Tracheal Infection: Two Case Reports[J]. Mycopathologia, 2015, 180(3-4):245-249.

[39] QIU Y, PAN MQ, ZHANG JQ, et al. Two Unusual Cases of Human Immunodeficiency Virus-Negative Patients with Talaromyces marneffei Infection[J]. Am J Trop Med Hyg, 2016, 95(2):426-430.

[40] 杨蓬, 刘萍, 李秋文, 等. 肺癌合并马尔尼菲蓝状菌病1例并文献复习[J/CD].新发传染病电子杂志, 2019, 4(03):169-172.

[41] CHENG D, DING XH. Rare misdiagnosed case of penicilliosis marneffei in an immunocompetent patient[J]. J Int Med Rs, 2020, 48(10):300060520959484.

[42] YU XM, MIAO KJ, ZHOU CS, et al. T. marneffei infection complications in an HIV-negative patient with pre-existing pulmonary sarcoidosis: a rare case report[J]. BMC Infect Dis, 2018, 18(1):390-394.

[43] SU SS, ZHANG SN, YE JR, et al. Disseminated Talaromyces marneffei And Mycobacterium avium Infection Accompanied Sweet's Syndrome In A Patient With Anti-Interferon-γ Autoantibodies: A Case Report[J]. Infect Drug Resist, 2019, 12:3189-3195.

[44] CHEN DH, CHANG CD, CHEN M, et al. Unusual disseminated Talaromyces marneffei infection mimicking lymphoma in a non-immunosuppressed patient in East China: a case report and review of the literature[J]. BMC Infect Dis, 2020, 20(1):800-807.

[45] WEI HY, LIANG WJ, LI B, et al. Clinical characteristics and risk factors of Talaromyces marneffei infection in human immunodeficiency virus-negative patients: A retrospective observational study[J]. World J Emerg Med, 2021, 12(4):281-286.

[46] QIU Y, ZHANG JQ, LIU GN, et al. Retrospective analysis of 14 cases of disseminated Penicillium marneffei infection

with osteolytic lesions[J]. BMC Infect Dis, 2015, 15:47-53.
[47] PAN ML, HUANG J, QIU Y, et al. Assessment of Talaromyces Marneffei Infection of the Intestine in Three Patients and a Systematic Review of Case Reports[J]. Open Forum Infect Dis, 2020, 7(6):ofaa128.
[48] WANG DM, MA HL, TAN MQ, et al. Next-generation sequencing confirmed the diagnosis of isolated central nervous system infection caused by Talaromyces marneffei in an immunocompetent patient[J]. Chin Med J, 2020, 133(3):374-376.
[49] LE T, HUU CHI N, KIM CUC NT, et al. AIDS-associated Penicillium marneffei infection of the central nervous system[J]. Clin Infect Dis, 2010, 51(12):1458-1462.
[50] LI YY, DONG RJ, SHRESTHA S, et al. AIDS-associated Talaromyces marneffei central nervous system infection in patients of southwestern China[J]. AIDS Res Ther, 2020, 17(1):26-34.
[51] JIN WH, LIU JH, CHEN K, et al. Coinfection by Talaromyces marneffei and Mycobacterium abscessus in a human immunodeficiency virus-negative patient with anti-interferon-γ autoantibody: a case report[J]. J Int Med Res, 2021, 49(1):300060520976471.
[52] HE SS, LV DQ, XU YZ, et al. Concurrent infection with Talaromyces marneffei and Cryptococcus neoformans in a patient without HIV infection[J]. Exp Ther Med, 2020, 19(1):160-164.
[53] CHAN JF, CHAN TS, GILL H, et al. Disseminated Infections with Talaromyces marneffei in Non-AIDS Patients Given Monoclonal Antibodies against CD20 and Kinase Inhibitors[J]. Emerg Infect Dis, 2015, 21(7):1101-1106.
[54] 郑祎，王辉.艾滋病合并马尔尼菲篮状菌感染的诊治临床研究进展[J/CD].新发传染病电子杂志，2021, 6（2）：151-154.
[55] KAWILA R, CHAIWARITH R, SUPPARATPINYO K. Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infection in Northern Thailand: a retrospective study[J]. BMC Infect Dis, 2013, 13:464-468.
[56] SHEN Q, SHENG L, ZHANG J, et al. Analysis of clinical characteristics and prognosis of talaromycosis (with or without human immunodeficiency virus) from a non-endemic area: a retrospective study[J]. Infection, 2021, 5:1-10.
[57] 曹静，谢浩俊，成卫英，等. HIV阴性与HIV阳性的马尔尼菲蓝状菌病患者临床特点分析[J].中国皮肤性病学杂志，2018, 32(10):1158-1162.
[58] 张建全,杨美玲,钟小宁,等.人免疫缺陷病毒抗体阴性与阳性者播散性马尔尼菲青霉菌病的临床及实验室特征[J].中华结核和呼吸杂志，2008，21(10):740-746.
[59] WONG SS, WONG KH, HUI WT, et al. Differences in clinical and laboratory diagnostic characteristics of penicilliosis marneffei in human immunodeficiency virus (HIV)- and non-HIV-infected patients[J]. J Clin Microbiol, 2001, 39(12):4535-4540.
[60] LI HR, CAI SX, CHEN YS, et al. Comparison of Talaromyces marneffei Infection in Human Immunodeficiency Virus-positive and Human Immunodeficiency Virus-negative Patients from Fujian, China[J]. Chin Med J (Engl), 2016, 129(9):1059-1065.
[61] QIN YY, HUANG XJ, CHEN H, et al. Burden of Talaromyces marneffei infection in people living with HIV/AIDS in Asia during ART era: a systematic review and meta-analysis[J]. BMC Infect Dis, 2020, 20(1):551-564.
[62] MASUR H, BROOKS JT, BENSON CA, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America[J]. Clin Infect Dis, 2014, 58(9):1308-1311.
[63] TSANG CC, TENG JLL, LAU SKP, et al. Rapid Genomic Diagnosis of Fungal Infections in the Age of Next-Generation Sequencing[J]. J Fungi, 2021, 7(8):636-650.
[64] CHEN QH, QIU Y, ZENG W, et al. Metagenomic next-generation sequencing for the early diagnosis of talaromycosis in HIV-uninfected patients: five cases report[J]. BMC Infect Dis, 2021, 21(1):865-872.
[65] THU NTM, CHAN JFW, LY VT, et al. Superiority of a Novel Mp1p Antigen Detection Enzyme Immunoassay Compared to Standard BACTEC Blood Culture in the Diagnosis of Talaromycosis[J]. Clin Infect Dis, 2021, 73(2):330-336.
[66] 韩静，蒋忠胜，王刚，等. 广西人类免疫缺陷病毒感染者/艾滋病患者合并马尔尼菲篮状菌感染的特征及Mp1p抗原快速筛检的研究[J].微生物与感染，2021, 16(1):19-25.
[67] 李凌华，肖赛银，何艳，等. 血清Mp1p抗原检测对艾滋病合并马尔尼菲蓝状菌病的诊断价值[J].中华传染病杂志，2017, 35(3):157-160.
[68] LEI HL, LI LH, CHEN WS, et al. Susceptibility profile of echinocandins, azoles and amphotericin B against yeast phase of Talaromyces marneffei isolated from HIV-infected patients in Guangdong, China[J]. Eur J Clin Microbiol Infect Dis, 2018, 37(6):1099-1102.
[69] BOON-LONG J, MEKHA N, POONWAN N, et al. In vitro antifungal activity of the new triazole D0870 against Penicillium marneffei compared with that of amphotericin B, fluconazole, itraconazole, miconazole and flucytosine[J]. Mycoses, 1996, 39(11-12):453-456.
[70] OUYANG Y, CAI S, LIANG H, et al. Administration of Voriconazole in Disseminated Talaromyces (Penicillium) Marneffei Infection: A Retrospective Study[J]. Mycopathologia, 2017, 182(5-6):569-575.
[71] LANG Q, CHUGHTAI A, KONG WF, et al. Case Report: Successful Treatment of Pulmonary Talaromyces marneffei Infection with Posaconazole in a Renal Transplant Recipient[J]. Am J Trop Med Hyg, 2020, 104(2):744－747.
[72] ZHANG J, HUANG XY, ZHANG X, et al. Coinfection of disseminated Talaromyces marneffei and Mycobacteria kansasii in a patient with papillary thyroid cancer: A case report[J]. Medicine, 2017, 96(52):e9072-e9076.

【收稿日期】 2021-11-03