

曲霉菌 *Aspergillus salwaensis* 致脊柱感染 1 例

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摘要: 报道 1 例 *Aspergillus salwaensis* 致脊柱感染及实验室检测。采集 2020 年 6 月 17 日承德医学院附属医院收治的 1 例脊柱感染患者的炎性肉芽、坏死组织标本进行镜检、培养,对分离得到的菌株进行基质辅助激光解吸电离飞行时间质谱(matrix-assisted laser desorption ionization time-of-flight mass spectrometry, MALDI-TOF-MS)鉴定、分子鉴定及体外抗真菌药敏试验。患者女,62 岁,临床表现以无明显诱因反复胸背部疼痛为主,初步诊断脊柱感染,左氧氟沙星治疗 7 d 效果不佳,行胸椎后路病灶清除术治疗,组织标本镜下可见真菌菌丝,分离到的菌株无典型结构,经 MALDI-TOF-MS 多次鉴定均无结果,氟康唑治疗 7 d 后病情好转,胸背部疼痛较术前减轻,予出院,门诊随访。后通过内转录间隔区(internal transcribed spacer, ITS)序列分析确定该菌为 *Aspergillus salwaensis*,立即与临床医生沟通,联系患者将抗真菌药物更换为伏立康唑,术后 1 年随访患者自觉恢复良好,术区无疼痛,脊柱活动正常。对于无明显诱因的腰背部疼痛且常规抗生素治疗效果不佳的患者应考虑到脊柱真菌感染的可能。直接涂片报告镜检结果对临床抗真菌药物的选择有重要意义。对于此类罕见的丝状真菌,菌落形态和镜下形态均不太典型、质谱鉴定不出结果时,采用 ITS 序列分析等分子生物学方法有助于尽早鉴定出真菌种类,提高鉴定速度。

关键词: 曲霉菌; *Aspergillus salwaensis*; 脊柱感染; 丝状真菌; 基质辅助激光解吸电离飞行时间质谱

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A case of *Aspergillus salwaensis*-induced spinal infection

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Abstract: To report a case of *Aspergillus salwaensis*-induced spinal infection and its laboratory detection. The inflammatory granulation and necrotic tissue samples of a patient with spinal infection were collected from the Affiliated Hospital of Chengde Medical College on June 17, 2020 for direct smear microscopy and culture, and the isolated strain was identified by microscopy by smear staining, matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF-MS), molecular identification and in vitro antifungal susceptibility test. The patient was 62 years old female and presented with recurrent chest and back pain with no obvious cause. The initial diagnosis was spinal infection, after 7 days of treatment with levofloxacin, the effect was not good. Surgery was then performed remove the lesion via posterior thoracic debridement, and fungal hypha was observed under microscope in tissue specimens. The isolated strains had no typical structure, MALDI-TOF-MS was used for identification for many times, but there was no identification result. After 7 days of fluconazole treatment, the patient's condition improved, and her chest and back pain were alleviated compared to before surgery. The patient was discharged and followed up in the outpatient department, the fungus was later identified as *Aspergillus salwaensis* by sequence analysis of the internal transcribed spacer (ITS) gene sequencing, and the patient's antifungal medication was changed to voriconazole after with the attending physician. The patient consciously recovered well with no pain in the operative area and normal spinal activity at 1 year follow-up. The possibility of spinal fungal infection should be considered in patients with back pain without a clear cause and poor response to routine antibiotic treatment. Direct smear report of microscopic results are very important for guiding clinical antibiotic selection for rare filament fungi with atypical colony and microscopic morphology and unsuccessful MALDI-TOF-MS identification, molecular biological methods such as ITS sequence analysis can be helpful for early identification of the fungal species, improving identification speed.

Keywords: *Aspergillus*; *Aspergillus salwaensis*; spinal infection; filamentous fungi; matrix-assisted laser desorption ionization-time of flight mass spectrometry

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曲霉菌(*Aspergillus*)是一种相对罕见的条件性致病菌,其感染通常见于免疫缺陷、骨髓和器官移植、癌症、造血系统疾病、艾滋病的患者,随着抗生素的广泛使用、化疗或免疫抑制治疗的不断应用,曲霉菌感染的患病率和致死率均明显上升^[1]。曲霉菌感染最常见于肺部,其次是皮肤、鼻窦等,少见于脊柱感染^[2-5]。本文报道1例由*Aspergillus salwaensis*引起的脊柱感染,由该菌引起的感染极为罕见,本文对*Aspergillus salwaensis*进行实验室检测,为脊柱真菌感染鉴定提供临床参考。

1 资料与方法

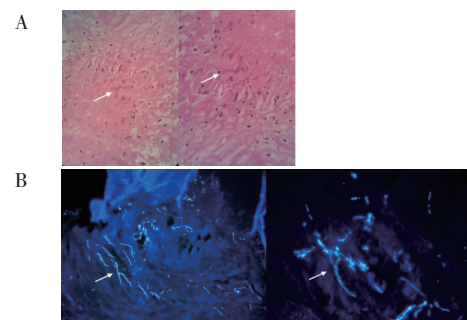
1.1 临床资料 患者女,62岁,主诉“反复胸背部疼痛4个月,加重1个月余”于2020年6月17日来承德医学院附属医院就诊。患者自诉4个月前无明显诱因出现胸背部疼痛,无发热、低热盗汗、咳嗽等症状,未予重视。1个月前,胸背部疼痛症状加重,昼夜疼痛无明显差异,与劳累关系不大。胸腰椎生理曲度尚存在,略有后凸畸形,胸椎椎体棘突间及椎旁压痛、叩击痛阳性,不向双下肢放射,其余体格检查未见异常。既往高血压病史,最高可达190/100 mmHg,未规律服用降压药,否认其他系统疾病。MR示胸椎(T10~11)间隙明显变窄,椎体边缘不光整,信号欠均匀。初步诊断:(1)脊柱感染,(2)高血压3级(高危)。予乳酸左氧氟沙星氯化钠注射液0.5 g qd 7 d抗感染治疗,效果不佳,患者仍诉背部疼痛向肋间放射。辅助检查:血常规、尿常规、降钙素原、C-反应蛋白、肝肾功能基本正常,红细胞沉降率41 mm/h(参考范围0~20 mm/h),布鲁氏菌抗体检测、结核杆菌 γ 干扰素释放试验均为阴性。为明确诊断,患者在全麻下行胸椎后路病灶清除,取髂骨植骨融合,椎弓根钉棒内固定术。术中刮除椎间隙内组织,可见炎性肉芽、坏死组织、终板,留取组织送标本送病理及微生物学检查。2020年6月30日坏死组织荧光染色可见真菌菌丝,微生物培养回报标本有真菌生长,考虑真菌感染。给予患者口服抗真菌药物(氟康唑胶囊150 mg qd)。7 d后患者病情好转,胸背部疼痛较术前减轻,予出院(2020-07-07),门诊随访。

1.2 方法 标本涂片镜检和真菌培养:将组织标本分别接种于血琼脂平板、中国蓝琼脂平板及沙保罗琼脂平板(温州康泰)各1块,置于35℃恒温培养箱中孵育,同时制备涂片进行HE染色和荧光染色镜检。真菌药敏试验:采用抗生素浓度梯度法(E-test法)对该菌进行体外抗真菌药物敏感性试验。将分离到的菌株在沙保罗平板上35℃培养5 d至孢子成熟,挑取菌落用生理盐水制备0.5麦氏浊度的菌悬液,用无菌拭子将菌悬液均匀涂布于RPMI-1640琼脂平板上(温州康泰),置于生物安全柜待表面干燥后,将两性霉素B、伊曲康

唑和伏立康唑E-test抗真菌药敏试条(温州康泰)贴于平板上,35℃孵育,72 h后菌落生长良好,读取药敏结果。基质辅助激光解吸电离飞行时间质谱(matrix-assisted laser desorption ionization time-of-flight mass spectrometry, MALDI-TOF-MS)鉴定:采用标准甲酸-乙腈提取法对受试菌株进行分析前处理。在生物安全柜内用无菌拭子刮取菌落表面约1~2 cm直径的孢子和菌丝至无菌去离子水中,加入900 μ L无水乙醇,涡旋震荡仪震荡混匀,室温条件下13 000 r/min半径6 cm离心3 min,弃上清;添加40 μ L 70%甲酸溶液,并用涡旋震荡仪震荡使菌体沉淀完全重悬;后加入40 μ L乙腈溶液,用涡旋震荡仪混匀。13 000 r/min半径6 cm离心3 min,取1 μ L离心后的上清液于靶板上,干燥后加1 μ L VITEK MS-CHCA基质溶液;晾干后将靶板放入梅里埃VITEK MS质谱仪进行微生物鉴定。分子鉴定:提取纯化后菌落的DNA,以通用引物ITS1: 5'-TCCGTAGGTGAACCTGCGG-3'和ITS4: 5'-TCCTCCGCTTATTGATATGC-3'扩增,将测序结果与BLAST(Basic Local Alignment Search Tool)数据库比对(北京睿博兴科生物技术有限公司)。

2 结果

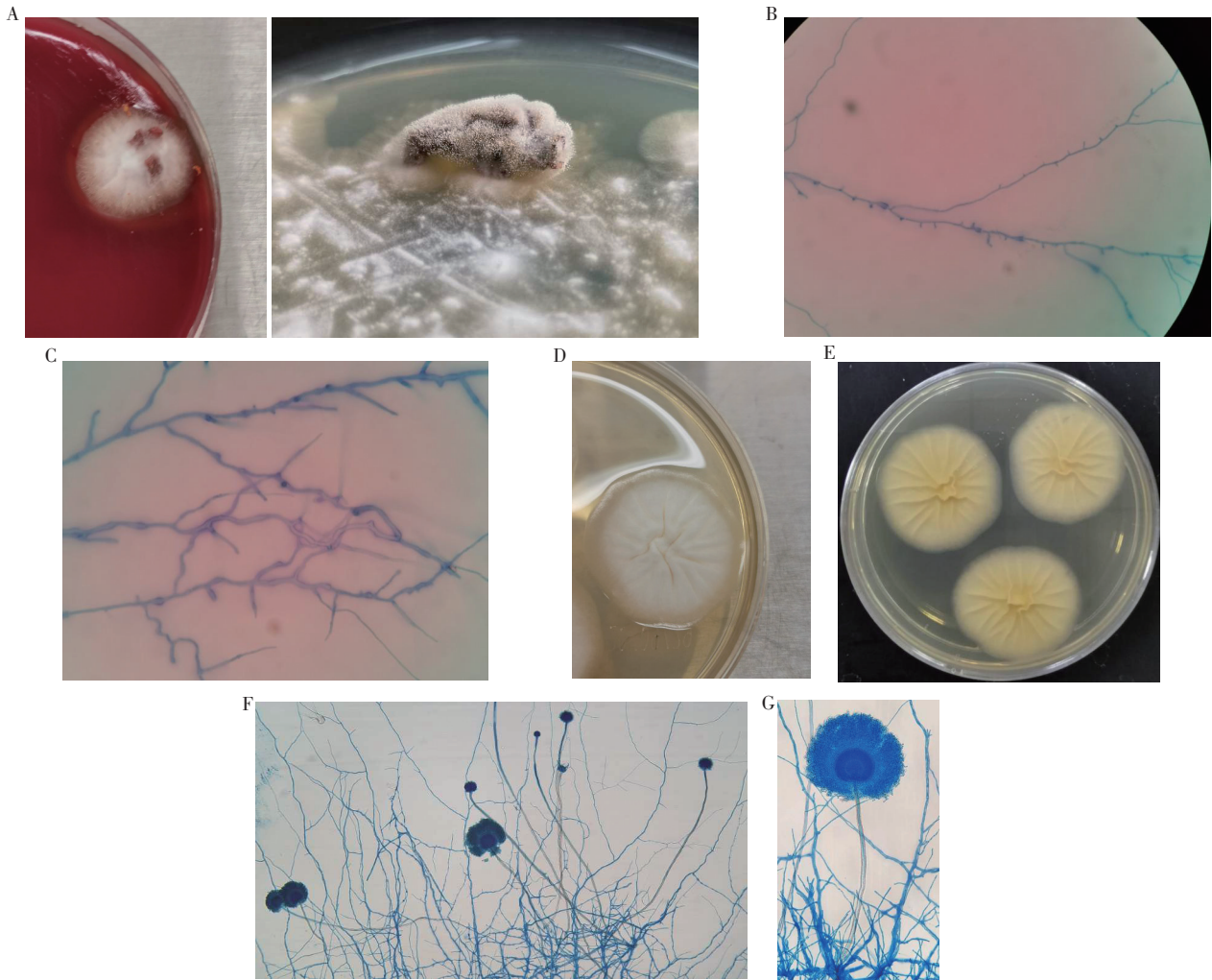
2.1 标本涂片镜检和真菌培养 组织标本HE染色和荧光染色镜检可见有隔真菌菌丝(图1)。标本接种72 h后组织标本上生长出白色绒毛状菌落(图2A),转至SDA平板分别置于35℃及28℃环境培养72 h,菌落生长缓慢,28℃条件下生长较快于35℃。取纯培养物进行乳酸棉酚蓝染色,镜下可见菌丝较细,未见曲霉头,部分菌丝上可见棒状小分生孢子(图2B),无其它典型结构。将培养物继续培养7 d,菌落正面呈白色絮状,有放射状褶皱,中心处有细小颗粒,无渗出物,背面为淡黄色(图2C),镜下可见典型曲霉菌属分生孢子头,顶囊为球形,分生孢子球状、双轮,呈放射状布满顶囊,分生孢子梗壁粗糙(图2D)。



注:A.白色箭头处可见真菌菌丝(HE染色,×100)B.白色箭头处可见真菌菌丝(荧光染色,×100) Note: A. Fungal hyphae are seen at the white arrow (HE staining, ×100); B. Fungal hyphae are seen at the white arrow (fluorescent staining, ×100);

图1 组织标本染色镜检

Fig. 1 Microscopic examination of tissue specimen by staining



注:A.组织标本培养72 h可见绒毛状菌落;B、C. 培养物培养72 h镜下形态,B.菌丝较细,未见曲霉头(乳酸酚棉兰染色,×40),C.可见棒状小分生孢子(乳酸酚棉兰染色,×100);D、E. SDA上培养7 d后菌落形态(D.菌落正面形态,E.菌落背面形态);F、G. SDA上培养7 d后镜下形态,F.为菌丝及分生孢子头(乳酸酚棉兰染色,×40),G.可见典型曲霉菌属分生孢子头(乳酸酚棉兰染色,×100)。

Note: A. The villous colonies were observed in the tissue samples after 72 h culture; B, C. The culture was cultured for 72 h under the microscope, B. Hypha is fine, no aspergillus head (laetophcnol cotton lalue, ×40), C. The clav-shaped microconidia (laetophcnol cotton lalue, ×100); D, E. Colony after 7 d of culture on SDA (D. Front, E. Back); F, G. 6 Microscopically after 7 d of culture on SDA, F. Hypha and conidia head (laetophcnol cotton lalue, ×40), G. Typical conidial head of *Aspergillus* (laetophcnol cotton lalue, ×100).

图2 组织标本培养物菌落特点及镜下形态

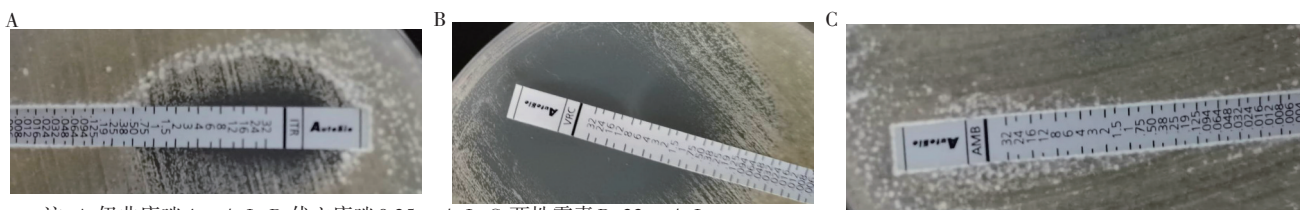
Fig. 2 Colony characteristics and microscopic morphology of tissue specimen culture

2.2 MALDI-TOF MS 用梅里埃 VITEK MS 质谱仪进行鉴定,重复多次检测均无鉴定结果。

2.3 分子鉴定 经北京睿博兴科生物技术有限公司靶向 DNA 测序鉴定(2020-07-14),结果与 BLAST 数据库比对,显示该序列与 *Aspergillus salwaensis* 菌株序

列相似度为 99.62%,鉴定为 *Aspergillus salwaensis*。

2.4 真菌药敏实验 72 h 后读取 E-test 法 MIC (minimal inhibitory concentration) 值结果,伊曲康唑、伏立康唑和两性霉素 B 的 MIC 值分别是 4 μg/mL、0.25 μg/mL、>32 μg/mL,见图 3。



注:A.伊曲康唑 4 μg/mL;B.伏立康唑 0.25 μg/mL;C.两性霉素 B>32 μg/mL。

Note: A. Itraconazole 4 μg/mL; B. Voriconazole 0.25 μg/mL; C. Amphotericin B >32 μg/mL.

图3 抗真菌药物敏感性试验结果(E-test法,72 h)

Fig. 3 In vitro antifungal drug sensitivity test results (E-test method, 72 h)

3 讨论

脊柱真菌感染的患者临床表现往往缺乏特异性,可以表现为发热、盗汗、全身不适等症状,但无明显诱因的腰背部疼痛是患者就诊的主要原因^[6-8]。本例中患者无发热,4个月前无明显诱因出现胸背部疼痛,白细胞计数及炎症因子均在正常范围内,MR显示胸椎椎间隙明显变窄,椎体边缘不光整,临床考虑脊柱感染。脊柱真菌因其症状、体征及实验室检查与其他类型的脊柱感染差别不明显,影像学表现也缺乏特征性改变,CT和MR有助于明确脊柱真菌感染的感染范围,与化脓性脊柱炎相比,脊柱真菌感染通常侵及椎体前部,一般不累及椎间盘,这些改变与结核性脊柱炎等类似,并不是真菌性脊柱炎的特异性表现^[6,9-10]。真菌性脊柱感染诊断的关键则是病灶的微生物学检查和组织病理学检查。

Aspergillus salwaensis 为曲霉菌属,2013年首次分离自卡塔尔 Salwa 海滩^[11],目前少见人类感染病例的相关报道。曲霉菌是仅次于念珠菌的第二大致病菌,也是脊柱真菌感染中常见的病原体^[12-13]。DEVIN 等^[14]总结了美国1948年1月—2010年9月共157例脊柱真菌感染的病例特征,曲霉菌所导致的脊柱真菌感染可占38.2%。近年来,曲霉菌性脊柱炎患病率已超过念珠菌性脊柱炎^[15]。脊柱真菌感染的治疗目前没有标准的操作规程,主要是药物和手术治疗,手术时彻底清创是很有效的治疗方法。有文献报道,曲霉菌导致的真菌脊柱感染的患者中,手术治疗的患者生存率高于药物治疗^[2]。由于在鉴定结果出来之前,患者已经出院,本例患者术后选择口服氟康唑全身抗真菌治疗。而以往研究显示氟康唑对曲霉菌属无活性^[16],因此并不推荐采用,因本例患者胸椎后路病灶清除术中切除了感染的椎间隙内组织、坏死软组织和终板,患者术后固定物固定良好,脊柱稳定性恢复,胸背部疼痛麻木不适症状较前减轻。在鉴定结果(2020-07-14)出具后,由于患者已出院(2020-07-07),微生物室工作人员迅速与临床医生沟通,联系患者将抗真菌药物更换为口服伏立康唑片,首次400 mg,其后改为200 mg bid,治疗6个月并定期复查。患者因在外地居住,未遵医嘱来本院门诊复查,术后1年电话随访患者自觉恢复良好,术区无疼痛,脊柱活动正常。

实验室鉴定对真菌特别是丝状真菌的鉴定存在一定困难。目前大多微生物实验室仍采用传统方法鉴定丝状真菌,如根据菌落形态和镜检特征等。此类方法对无典型特征的菌株鉴定困难、耗时长,容易误诊。在本病例里分离得到的 *Aspergillus salwaensis* 生长缓慢,标本接种72 h后才在组织标本上生长出白色

绒毛状菌落,转种SDA培养皿72 h后,菌落和镜下形态并不典型,不能确定菌种,继续培养至第7天才从镜下看到曲霉菌属分生孢子头,明确为曲霉菌属。

MALDI-TOF MS作为近年发展起来的新型软电离质谱技术,通过检测每种微生物中独特的肽/蛋白质指纹图谱,与数据库中特征性的质量峰进行比对,可在几分钟内实现对被测微生物的鉴定。MALDI-TOF-MS已被多项研究报道用于细菌和念珠菌的鉴定,简单、准确、快速、经济^[17-19],也有研究表明MALDI-TOF-MS对常见真菌鉴定临床准确率较高,其对丝状真菌的鉴定率可达92.70%^[20]。尽管MALDI-TOF技术在临床真菌鉴定方面得到了长足发展,但仍存在不足:检测前标本的预处理及蛋白的提取尚未建立标准化程序;不同的培养基、培养温度及培养时间,真菌蛋白表达差异可能会影响鉴定结果。此外,临床上一些病原真菌的参考数据库尚不够完善,少数临床真菌因缺乏特异性峰值或峰数目不足,导致其产生的谱值过低而不能鉴定^[21]。本例中,由于 *Aspergillus salwaensis* 不在数据库中,梅里埃VITEK MS质谱仪未能将其鉴定。因此MALDI-TOF-MS需要对数据库不断开发和更新,以便将可鉴定范围覆盖到更多真菌物种中,提升对真菌的鉴定能力。分子技术可以在物种水平上准确鉴定出许多种丝状真菌,如ITS序列分析在微生物菌种鉴定领域应用越来越广,可将丝状真菌菌株鉴定到组甚至是种^[22]。但分子技术往往检测成本高,周期长,且需要专业的知识,基层开展常规检测存在一定困难。

综上所述,脊柱真菌感染的临床表现和影像学检查缺乏特异性,往往呈现慢性炎症的改变,对于无明显诱因的腰背部疼痛且常规抗生素治疗效果不佳的患者应考虑到脊柱真菌感染的可能。直接涂片镜检报告临床镜检结果对医生最初抗菌药物的选择有很重要的意义。此外,对于在此类罕见的丝状真菌,菌落形态和镜下形态均不太典型、质谱鉴定不出结果,采用ITS序列分析等分子生物学方法有助于尽早鉴定出真菌种类,提高鉴定速度。

伦理审查与知情同意 本研究获得承德医学院附属医院伦理委员会批准(批准号:CYFYLL2020245),患者基本信息的采集和各项检测均获得受检者或其家属的知情同意

利益冲突声明 所有作者声明不存在利益冲突

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