

以胸痛为首发症状的惠普尔养障体肺部感染1例及文献回顾

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摘要

惠普尔养障体(*Tropheryma whipplei*, TW)是一种革兰氏阳性放线菌, 广泛存在于土壤、污水和外部环境中, 同时以无症状病原体存在于人群中, 属于条件致病菌。惠普尔病(Whipple disease, WD)是由TW感染引起的罕见的复杂性多系统损害性疾病, 其主要影响消化系统、关节、神经系统及心血管系统。TW引起的肺部感染临床少见, 其发病机制尚不明确, 诊疗思路亦尚未统一。国内外关于TW肺炎的相关研究非常少, 随着宏基因组下一代测序(Metagenomic next generation sequencing, mNGS)的普及, TW引发的肺部感染病例发现率较前有所增加。TW引发的WD具有临床症状不典型、病情进展迅速、死亡率高等特点, 因此早期识别并规范化诊疗对于改善TW感染患者预后具有重要意义。本研究回顾性分析1例以间断胸痛为首发表现的TW肺部感染患者的临床资料, 旨在为临床医师提供一定诊疗思路, 现报道如下。

关键词

惠普尔养障体, 肺部感染, 宏基因组下一代测序, 多西环素

Tropheryma whipplei Pulmonary Infection with Chest Pain as the First Symptom: A Case Report and Literature Review

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Abstract

Tropheryma whippelii (TW) is a Gram-positive actinomycete that is widely present in soil, sewage and external environment, and also exists in humans as an asymptomatic pathogen. Whipple disease (WD) is a rare complex multi-system damaging disease caused by TW infection, which mainly affects the digestive system, joints, nervous system and cardiovascular system. Pulmonary infection caused by TW is rare in clinic, its pathogenesis is not clear, and the diagnosis and treatment ideas have not been unified. There are very few relevant studies on TW pneumonia at home and abroad. With the popularization of metagenomic next generation sequencing (mNGS), the detection rate of pulmonary infection caused by TW has increased. WD caused by TW is characterized by atypical clinical symptoms, rapid disease progression, and high mortality. Therefore, early identification and standardized diagnosis and treatment are of great significance for improving the prognosis of TW infected patients. This study retrospectively analyzed the clinical data of a case of TW pulmonary infection with intermittent chest pain as the first manifestation, aiming to provide certain diagnosis and treatment ideas for clinicians. The report is as follows.

Keywords

Tropheryma whippelii, Lung Infection, Metagenomic Next Generation Sequencing, Doxycycline

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1. 引言

惠普尔养障体是一种革兰氏阳性放线菌，其感染可引起一种罕见的复杂性多系统损害性疾病——惠普尔病，其主要影响消化系统、关节、神经系统及心血管系统等，呼吸系统影响较少见，仅为 10%~11% [1] [2]。全世界每年发病率约为 1/1,000,000，平均发病年龄为 55 岁，该疾病在男性中较常见，男女比例为 4:1 [3] [4] [5]。本研究描述了一例 21 岁男性惠普尔养障体肺部感染患者，诊疗流程如下。

2. 临床资料

患者，男，21 岁，以“间断胸痛 2 月，再发 1 天”之主诉于 2023 年 6 月 30 日就诊于我院。2 月前无明显诱因出现胸痛，位于心前区，呈针刺样，持续数秒至数分钟不等，休息后可缓解，无其余不适，未予重视及规律诊治。1 天前上述症状再发，疼痛部位及性质同前，程度加重，持续时间约 5 分钟，无其余不适。门诊以“胸痛原因待查”收住我院心血管内科。既往体健。

入院查体：体温 36.5℃，脉搏 70 次/min，呼吸 20 次/min，血压 110/70 mmHg。心肺腹查体未见阳性体征。

诊疗经过：患者于 2023 年 6 月 30 日以“胸痛原因待查”入住心血管内科，入院当天完善胸部 CT (图 1)示右肺上叶胸膜下及左肺下叶前内基底段近斜裂处簇状、团片状高密度影，多考虑炎性病变，左肺下叶前内支气管部分腔内密度增高、堵塞。考虑肺部感染引起胸痛。7 月 2 日转科至我院呼吸与危重症医学科，予以莫西沙星(0.4 g，每日一次，静脉滴注)。7 月 6 日 mNGS 检测结果回报：惠普尔养障体，停用莫西沙星，改用头孢曲松(2 g，每日一次，静脉滴注)，7 月 9 日出院。

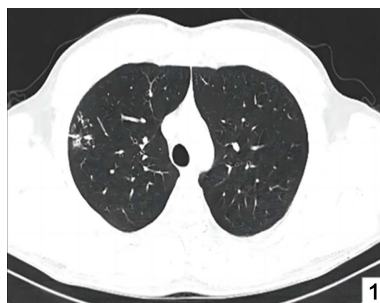


Figure 1. On June 30th (First chest CT)
图 1. 6月30日(首次胸部CT)

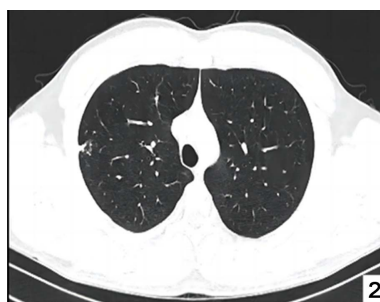


Figure 2. On July 31st, take medication for 30 days (Doxycycline 100 mg, once every 12 hours)
图 2. 7月31日, 服药30天(多西环素100 mg, 每12时1次)

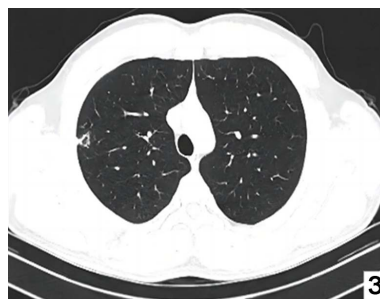


Figure 3. On August 29th, the medication was discontinued for 28 days
图 3. 8月29日, 停药28天

随访及转归: 患者于2023年7月9日出院, 出院后口服多西环素(100 mg, 每12小时1次), 期间患者未诉不适。7月31日复查胸部CT(图2), 患者肺部渗出较6月30日明显吸收, 嘱患者停药, 1月后复查。8月29日复查胸部CT(图3), 肺部渗出较7月31日无明显扩大, 暂不予以抗生素治疗, 待其自然吸收, 嘱患者定期随访。

3. 讨论

惠普尔养障体(*Tropheryma whipplei*, TW)是一种革兰阳性条件致病菌, 其常见于污水、污土及其他外部环境中, 易感于免疫缺陷患者及污物接触史患者, 主要传播途径为粪-口传播、口-口传播[6], 可引起一种罕见的慢性复发性、累及多系统的疾病——惠普尔病(Whipple disease, WD)。本研究中患者既往无

免疫抑制剂服用史,完善 T 细胞亚群检测未见异常,可基本排除免疫功能障碍。入院追问患者病史,自诉 4 月前餐厅打工史,有剩饭及废物接触史。这可能为患者感染原因,但其否认口腔污物接触史。

TW 急性感染常表现为胃肠炎、肺炎和菌血症。胃肠炎最常见的临床表现为腹泻及腹部周期性绞痛[7]。菌血症方面的研究较少,目前认为其引发的急性感染属于自限性疾病,突出症状为发热[8]。肺炎患者主要表现为发热、咳嗽、咳痰、呼吸困难等非特异性表现[9]。胃肠道症状为惠普尔养障体最常见的首发症状,本研究中患者未诉消化道症状,临床表现仅为间断胸痛,结合影像学表现,多考虑病灶侵犯胸膜引起,其余无不适,查体未见阳性体征。经典 WD 引起肺部感染较常见,但作为肺部急性感染的病原体,尤其是没有肠道症状的前提下直接引起肺部急性感染,其病原学需进一步明确[10]。可惜的是,该研究者中患者未进一步完善相关检查明确其是否有肠道病菌定植。

WD 在早期阶段因其罕见性及广泛的非特异性表现而容易漏诊,常见的诊断方法是组织病理学和聚合酶链式反应(Polymerase chain reaction, PCR),而 TW 的培养条件较为困难,不常规使用[11]。大多数经典 WD 患者十二指肠黏膜中定植大量细菌,可通过十二指肠活检标本中找到 TW 确诊,由于 TW 在十二指肠内分布不均,建议多处采取样本,此外,还可从胃窦、空肠和(或)回肠中采取样本[12]。TW 的组织学检测主要采用 PAS (Periodic acid-schiff stain)染色进行[13],但其不是一种特异性方法,由其他细菌(如马红球菌、鸟分枝杆菌、棒状杆菌、蜡样芽孢杆菌、组织包浆菌或真菌)引起的感染 PAS 染色也可呈阳性[14]。然而,在慢性局部感染中,PAS 染色十二指肠样本可能是阴性[15] [16] [17]。PCR 是目前诊断 WD 的主流技术,它被认为有更高的敏感性和特异性,但可能出现假阳性[13]。近年来随着基因测序技术的迅速发展,宏基因组下一代测序(Metagenomic next generation sequencing, mNGS)在诊断少见病原体感染方面具有显著优势[18]。本研究中患者症状轻微,非特异性较强,临床常见相关病原学筛查均无阳性病原体,患者均无消化道症状,完善十二指肠活检更是不现实的。本研究患者正是通过支气管肺泡灌洗液 mNGS 检测出唯一可疑病原体——惠普尔养障体。

TW 感染的治疗主要是早期抗生素治疗,目前认为有效的药物有青霉素、链霉素、四环素、头孢曲松、美罗培南、多西环素、羟氯喹等[4],其结论无较大规模的研究,均来自于小样本,且治疗后易复发。目前一项 40 例 WD 患者的随机对照试验[19]显示,在头孢曲松或美罗培南治疗 14 天后给予复方新诺明 12 月维持治疗,38 例患者均康复(2 例患者死于非 WD);且 7 名中枢神经系统感染的患者,治疗成功后 36 个月脑脊液 PCR 为阴性,药物可穿透血脑屏障可能是此疗法被推荐的原因。目前,另一种头孢曲松后复方新诺明替代疗法为羟氯喹联合多西环素,此疗法为针对 TW 唯一体外杀菌治疗[20]。经典 WD 采用多西环素(200 mg/天)和羟氯喹(600 mg/天),持续 12 个月;局限性 TW 感染,多西环素(200 mg/天)和羟氯喹(600 mg/天)治疗 12 至 18 个月,终生随访[20] [21],然而目前只有少数研究对其进行了前瞻性试验[19] [22],因此其体内应用该治疗的证据并不充足。然而,本研究中患者注射头孢曲松钠 7 天后口服多西环素 30 天,复查胸部 CT 炎性渗出较前明显吸收,且临床症状明显改善,停用抗生素 1 月后复查胸部 CT 未见进展,且渗出面积较前仍有减少。这是否意味着,对于症状轻微且炎症渗出病灶较小的患者,抗生素使用时长可减少?但此仍需要不断地临床研究。

目前 TW 感染的患者一般建议每 6 个月行 1 次十二指肠标本活检,若结果呈阳性,则需继续治疗。然而该诊疗方案由于以下原因逐渐过时。其一,活检样本获取价格昂贵且易出现并发症;其二,治疗成功后巨噬细胞可在固有层中保留数年,因此,PAS 染色阳性不能被视为细菌存活;其三,由于生物膜会影响细菌载量检测,当其细菌载量较低时,PCR 会出现假阴性[23]。目前出现的 mNGS 检测,对于 TW 的敏感性 & 特异性均较高,但其价格高昂。因此,对于 TW 引发感染的随访方式需进一步探索。

本研究中,患者既往体健,无免疫功能缺陷及免疫抑制剂服用史,且症状轻、实验室检查未见阳性指标,属于 TW 非易感人群,极易漏诊。因此,对于罕见病原体感染的患者,mNGS 检测也可能是一个

更好的选择。治疗方面，对于肺部病灶较小的 TW 感染患者，可在头孢曲松后单用多西环素治疗，抗生素使用可个体化处理。

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