

以足底感染为首发表现的血行播散性结核 1 例报道

金文婷¹ 张尧¹ 黄英男¹ 陈翔² 林佳冰² 胡必杰^{1,2} 潘珏^{1△}

(¹复旦大学附属中山医院感染病科, ²医院感染管理科 上海 200032)

【摘要】 报道 1 例以左足底局部感染起病的血行播散性结核病例的临床、影像及诊治过程。血行播散性结核发病率低,仅占结核病的 1%~2%,临床表现多样且非特异性,诊断非常困难。本例通过宏基因组二代测序技术,在外周血检测到结核分枝杆菌复合群,为早期诊断结核病提供了非常重要的病原依据。后续骨髓活检、淋巴结活检病理提示肉芽肿、痰、左足脓液、淋巴结组织均培养到结核分枝杆菌,最终明确诊断为血行播散性结核。

【关键词】 血行播散性结核; 粟粒性结核; 宏基因组二代测序

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Haematogenic disseminated tuberculosis with initial manifestation of foot infection: a case report

JIN Wen-ting¹, ZHANG Yao¹, HUANG Ying-nan¹, CHEN Xiang², LIN Jia-bing², HU Bi-jie^{1,2}, PAN Jue^{1△}

(¹Department of Infectious Diseases, ²Department of Hospital Infection Management, Zhongshan Hospital, Fudan University, Shanghai 200032, China)

【Abstract】 We reported the clinical feature, diagnosis and treatment of a case of haematogenic disseminated tuberculosis initially presenting with foot infection. Hematogenous disseminated tuberculosis has a low incidence, accounting for only 1%–2% of tuberculosis. Its clinical manifestations are non-specific and varied, making it difficult to diagnosis. In this case, the *Mycobacterium tuberculosis complex* was detected in the peripheral blood by the metagenomic next-generation sequencing, which provided a very important pathogenic basis for the early diagnosis of tuberculosis. Subsequently, bone marrow biopsy and lymph node biopsy pathology showed granuloma. Culture results of sputum, left foot pus and lymph node were all *Mycobacterium tuberculosis* positive. Finally, hematological disseminated tuberculosis was confirmed.

【Key words】 haematogenic disseminated tuberculosis; military tuberculosis; next-generation sequencing

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血行播散性结核是由结核分枝杆菌血行播散所致,可由进展性原发感染所致,或者通过潜伏病灶再激活、播散引起^[1],也称为粟粒性结核^[2],发病率占结核病的 1%~2%^[1],更常见于免疫抑制人群,如 HIV 感染等。最常累及肺部,可见于全身各脏器,临床表现多样且非特异性,取决于主要受累部

位^[3]。目前血行播散性结核仍然是一种疑难杂症,即使富有经验的临床医师仍不易诊断,尽管有有效治疗方法,死亡率仍非常高。

病例资料 男性,67 岁,因“左足底红肿 3 月余,发热伴咳嗽气急 1 月余”收入复旦大学附属中山医院。否认基础疾病,有铁粉工作史 2 年。

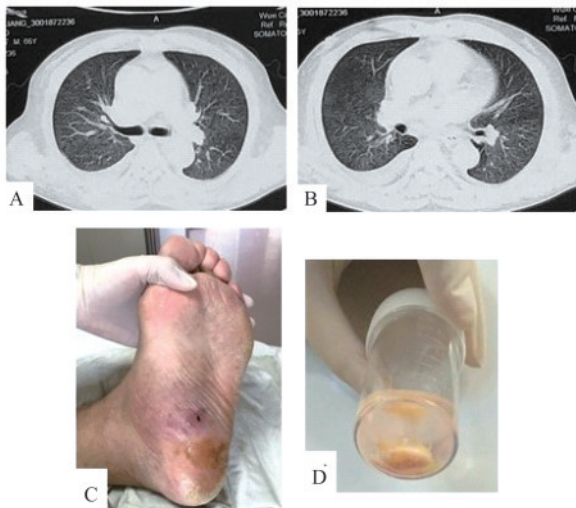
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[△]Corresponding author E-mail: pan.jue@zs-hospital.sh.cn

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现病史 3个月前开始出现左侧足底疼痛,局部逐渐形成肿块,皮肤红、皮温高,有压痛,当地医院查WBC正常,CRP 34.2 mg/L,ESR 49 mm/H,考虑感染,予以头孢唑林抗感染后无好转。外院局麻下切开引流,内见乳白色渗液及血性积液,多次分泌物普通细菌培养阴性,病灶有所好转。1个月前开始干咳,2天后出现发热伴畏寒、全身乏力、纳差,左足底疼痛加重,红肿范围较前增大,3天前出现胸闷气促,外院多次检查血常规:WBC不升高,CRP、ESR升高,自身抗体、肿瘤标志物、血培养:两次阴性,胸部CT示双肺弥漫性病变(图1A、1B),多种抗感染治疗无好转,拟“发热待查”收入我院感染科。

入院后查体及检查结果 查体:体温38.9℃,气促,呼吸25次/分,全身未及皮疹,左侧腹股沟区可及1.5 cm左右肿大淋巴结。双肺呼吸音清,未及干湿啰音;心律齐,心率115次/分,各瓣膜区未及杂音;左足底内侧可见3 cm×4 cm红肿病灶,皮温略高,有压痛(图1C)。辅助检查血常规:WBC $3.36 \times 10^9/L$, NE 72%, Hb 107 g/L, Plt $200 \times 10^9/L$, ESR 8 mm/H, hs-CRP 82.9 mg/L, PCT 0.82 ng/mL, Scr 148 $\mu\text{mol/L}$, CEA 5.9 ng/mL; HIV 抗体阴性;细胞免疫:淋巴细胞 525 cells/ μL , CD4T 淋巴细胞 152 cells/ μL , CD8 T 淋巴细胞 103 cells/ μL , CD4/CD8 1.5;血培养(双侧5瓶)2次均阴性;心超:未见瓣膜赘生物。



A and B: CT images of the chest in different sections (diffuse lesions in bilateral lungs, right pleural effusion). C: Left plantar lesion; D: Left inguinal lymph node.

图1 血行播散性结核患者的临床图像

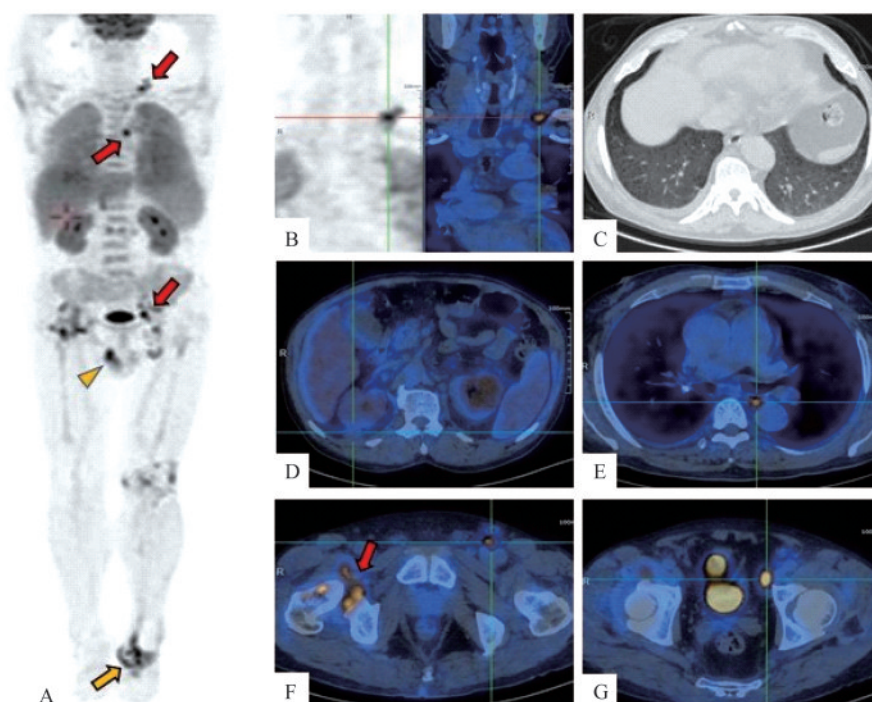
Fig 1 Clinical images of the patient with haematogenous disseminated tuberculosis

住院后诊治经过 入院后第3天(D3), T-SPOT A/B 53/58;痰涂片找细菌、真菌、抗酸杆菌均阴性,细菌、真菌培养阴性;PET/CT:(1)两肺弥漫性炎症、全身多处(左侧颈部和锁骨区、胸内、腹膜后、盆腔及左侧腹股沟)淋巴结炎以及右侧附睾、右侧髋关节、左侧膝关节、左侧足底软组织炎性病变可能,肝脾肿大伴糖代谢弥漫性增高;(2)右侧胸腔少量积液,心包积液(图2)。D4血宏基因二代测序(metagenomic next-generation sequencing, mNGS)检出结核分枝杆菌复合群序列4 reads。考虑全身多部位结核感染可能,其他病原体感染不能除外,予以异烟肼、利福平、莫西沙星、利奈唑胺四联抗结核同时覆盖阳性菌及非典型病原体。

D5左侧足底脓肿穿刺,脓液涂片找细菌、真菌、抗酸杆菌均阴性,细菌、真菌培养阴性。痰mNGS检出结核分枝杆菌复合群序列1 read。D8行骨髓穿刺+活检;D9左侧腹股沟淋巴结活检(图1D),活检组织涂片抗酸杆菌阴性;D10骨髓病理:骨髓组织中局灶可见可疑肉芽肿结节,肉芽肿结节内见到组织细胞、多核巨细胞、上皮样细胞,抗酸染色阴性(图3A)。诊断:肉芽肿性病变,考虑结核感染累及骨髓,建议排除结节病。D11足部脓液mNGS检出结核分枝杆菌复合群序列数3 561 reads。D20淋巴结病理:肉芽肿性病变,未见明显凝固性坏死,肉芽肿结节大小不等,灶区融合,抗酸染色阳性,结核PCR弱阳性,考虑淋巴结结核(图3B、3C)。考虑血行播散性结核后调整方案为异烟肼、利福平、乙胺丁醇、莫西沙星抗结核治疗。

查体颈强直可疑阳性,中枢结核感染不排除,行腰椎穿刺术,脑脊液压力200 mmH₂O,脑脊液检查:蛋白0.47 g/L,葡萄糖2.6 mmol/L,氯119 mmol/L,红细胞1个/mm³,白细胞1个/mm³;脑脊液找细菌、真菌、抗酸杆菌、脱落细胞阴性,细菌、真菌培养阴性。头颅MRI:脑干、颅内弥漫性散在结节病灶,脑膜、脑实质内均见,T1WI呈低信号,T2WI稍高信号,DWI未见明显高信号,增强后明显强化(图4)。D22痰结核培养阳性;D32左足底分泌物结核培养阳性;D47左侧腹股沟淋巴结组织结核培养阳性。

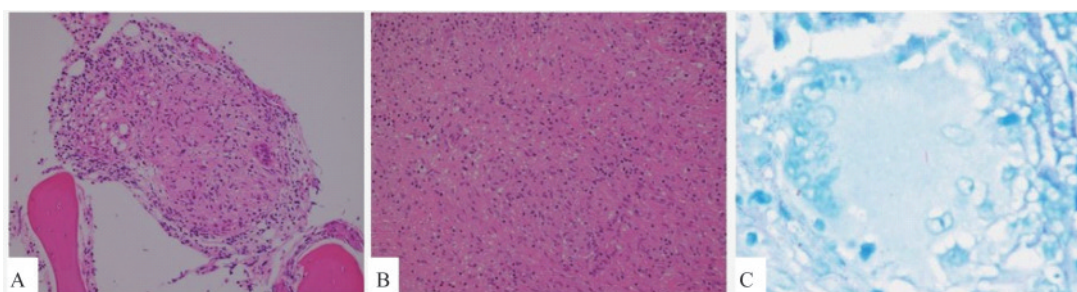
最终诊断及治疗后随访 患者血行播散性结核诊断明确(肺、淋巴结、骨髓、左足、脑、肝脾、附睾、骨关节累及可能),住院1月余,出院继续抗结核治疗(异烟肼、利福平、乙胺丁醇、吡嗪酰胺)。患者



PET/CT showed diffuse inflammation in two lungs, various lymphadenitis (left cervical and clavicular, intrathoracic, retroperitoneal, pelvic, and left inguinal area) and soft tissue inflammatory lesions in the right epididymis, right hip joint, left knee joint and left plantar; hepatosplenomegaly with diffuse increased glucose metabolism; slight pleural effusion; pericardial effusion. A: Systemic metabolic map (lymph node: red arrow; left foot lesion: yellow arrow; right epididymis: yellow triangle); B: Left cervical lymph node with SUV of 8.2; C: Uniformly increased diffuse density in both lungs with SUV_{max} of 6.8; D: Slightly enlarged spleen and elevated glucose metabolism in liver and spleen parenchyma with SUV_{max} of 4.5; E: Enlarged mediastinal lymph node; F: Abnormally elevated glucose metabolism around the right hip joint with SUV of 9.7; G: Enlarged left pelvic lymph node enlargement with SUV of 12.4.

图2 血行播散性结核患者的PET/CT影像

Fig 2 PET/CT images of the patient with haematogenic disseminated tuberculosis



A: Bone marrow biopsy pathology (100 \times): Two granulomatous nodules were observed in bone marrow tissue; B: Pathology of left inguinal lymph node (200 \times): Unequal granulomatous nodules were seen in lymph node tissue, with focal area fusion; C: Acid fast staining of left inguinal lymph node section (1 000 \times): Acid fast positive bacilli were seen. HE staining.

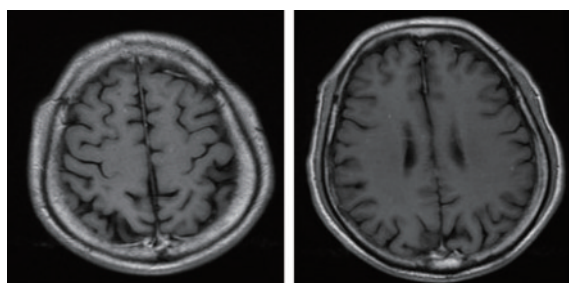
图3 血行播散性结核患者骨髓及淋巴结病理

Fig 3 Pathology of bone marrow and lymph node of the patient with haematogenic disseminated tuberculosis

在当地医院规律随访,一线四联抗结核共14个月,无发热,左足底病灶已愈合,浅表不可及肿大淋巴结,肺内病灶较前吸收。

讨论 血行播散性结核常见于婴幼儿和儿童,近几十年随着HIV感染者和免疫抑制剂的使用者

增多,发现成人中也并不少见。但因临床表现多样且非特异性,影像学表现不典型,常造成诊断延误。该患者无明确基础疾病史,以左侧足底感染为首表现,起病初期仅考虑普通细菌感染,抗细菌联合切开引流治疗,感染未控制,2个月 after 出现呼吸道症



T1WI enhancement demonstrates diffuse nodules in the brain.

图4 血行播散性结核患者头颅增强MRI图像

Fig 4 Cranial enhanced MRI images of the patient with haematogenous disseminated tuberculosis

状及全身播散性病灶。

mNGS是一种新兴的非培养技术,其检测方法不依赖于临床怀疑的靶病原,而是对同一样本中所有的微生物进行核酸测序^[4]。mNGS与传统培养方法相比具有显著的优势,近年逐渐应用于临床标本直接检测协助临床诊断^[5-9]。mNGS较传统培养敏感性高,特别是对病毒、结核分枝杆菌、真菌及厌氧菌^[10]。有研究显示mNGS诊断结核病的敏感性高于传统检测方法,且不劣于Xpert-MTB RIF^[11]。本例是我科第1例外周血mNGS检测到结核分枝杆菌者,因该病原体为胞内菌,破壁相对困难且并非实验室常见背景菌,虽检出序列数为4 reads仍考虑有意义。因本单位非结核病定点医院当时未行Xpert-MTB RIF检测,结合患者发热、多部位病灶(多发淋巴结,肝脾肿大,肺内病灶形态)、T-SPOT阳性,临床考虑血行播散性结核可能。目前mNGS仍不能作为确诊依据,且未见相关外周血mNGS检出结核分枝杆菌复合群的报道。本例若无mNGS作为辅助诊断依据,后续骨髓病理提示肉芽肿性病变、淋巴结病理确诊结核性淋巴结,从一元论考虑,临床仍需考虑血行播散性结核可能。

随着高分辨CT的临床应用,大部分肺部粟粒性病灶可被诊断,该患者因有铁粉接触史而造成一定混淆。通过PET/CT、mNGS、常规微生物及病理,最终确诊为血行播散性结核。综上所述,血行播散性结核发病率低、症状不典型,临床需提高认识和警惕。mNGS对早期快速锁定病原体、及早抗结核治疗起到至关重要的作用。

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订。黄英男,陈翔,林佳冰 基因测序结果解读。胡必杰 论文指导。潘珏 论文指导和修订。

利益冲突声明 所有作者均声明不存在利益冲突。

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