

以不明原因发热为主要表现的感染性心内膜炎的诊治：个案报道及文献复习

刘伶伟

青岛大学附属医院风湿免疫科，山东 青岛

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摘要

目的：提高对感染性心内膜炎(infective endocarditis, IE)认识程度。方法：对1例不明原因发热为首要症状的IE患者临床特点及诊疗经过进行分析讨论。结果：51岁男性患者，反复发热4月，颈部淋巴结肿痛半月，抗核抗体及类风湿因子阳性，多次复查心脏超声后示主动脉瓣赘生物形成。结论：IE临床表现缺乏特异性，早期诊断有利于病情控制。

关键词

感染性心内膜炎，发热，诊断

Diagnosis and Treatment of Infectious Endocarditis with Unexplained Fever as the Main Manifestation: A Case Report and Literature Review

Lingwei Liu

Department of Rheumatology and Immunology, The Affiliated Hospital of Qingdao University, Qingdao Shandong

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Abstract

Objective: To improve the recognition of infective endocarditis (IE). Method: Analyzed and discussed the clinical characteristics, diagnosis and treatment of a patient with infectious endocardi-

tis (IE) whose primary symptom was unexplained fever. Results: It was observed that a 51-year-old male who experienced recurrent fever for four months, swollen and painful cervical lymph nodes for two weeks, and tested positive for antinuclear antibody and rheumatoid factor. Repeated echocardiography revealed the formation of aortic valve vegetation. Conclusion: IE is an important consideration in the search for the cause of unexplained fever, and early diagnosis is beneficial for disease control.

Keywords

Infective Endocarditis, Fever, Diagnosis

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1. 引言

不明原因发热(fever of unknown origin, FUO)一直以来都是临床诊疗工作中的一大难题,是多种不同疾病过程中的共同临床表现[1]。感染性心内膜炎(infective endocarditis, IE)是一种罕见的、危及生命的疾病,心内膜结构因细菌、真菌等微生物的感染而引发局部炎症,进而产生持续性的菌血症,起病隐匿,临床表现多样,无特异性,早期诊断困难,疾病进展可出现严重并发症,包括心力衰竭、脓肿形成、房室传导异常、人工瓣膜功能障碍以及栓塞[2]。现对我院收治的 1 例不明原因发热的 IE 患者进行分析,讨论其临床表现、辅助检查、诊断、治疗和预后,以提高诊断意识,避免误诊漏诊。

2. 病例简介

患者男性,51 岁,主诉“反复发热 5 月余,颈部淋巴结肿痛半月”,于 2021 年 9 月 24 日入住青岛大学附属医院风湿免疫科。

2.1. 现病史

2021 年 4 月,患者无明显诱因和病因出现发热,体温最高 39.1℃,好发于午后,偶伴畏寒、寒战,伴咳嗽、咳少量黄白色粘痰,伴双手掌肿痛,口干、眼干,明显脱发,偶有夜间盗汗,2 月内体重下降 10 kg。外院查 CRP: 24.66 mg/L。心脏超声:室间隔增厚、主动脉瓣中度反流、三尖瓣少量反流、左室顺应性下降。胸部 CT 未见异常,左氧氟沙星抗感染后症状无好转。为进一步诊治 2021 年 6 月于我科住院治疗,查血常规:白细胞(white blood cell, WBC) $11.00 \times 10^9/L$,中性粒细胞(neutrophil, Neut) $7.60 \times 10^9/L$,单核细胞(monocyte, MO) $0.99 \times 10^9/L$; C 反应蛋白(C-reactive protein, CRP): 68.81 mg/L;降钙素原(procalcitonin, PCT): 0.09 ng/mL;红细胞沉降率(erythrocyte sedimentation rate, ESR): 16.00 mm/1h;肝功:谷氨酰基转移酶(glutamyl transpeptidase, GGT) 60.20 U/L,肌酸激酶(creatine kinase, CK): 35.5 U/L;癌胚抗原: 3.92 ng/mL;类风湿因子(rheumatoid factor, RF): 59.40 IU/mL;EB 病毒 DNA 定量: $8.60E+004$ IU/mL(参考值: $\leq 5.0E+003$ IU/mL);EB 病毒抗体分析:衣壳抗原 IgG 86.53 AU/mL,核抗原 IgG 30.55 AU/mL;抗核抗体及其滴度:阳性,滴度 1:1000,核型均质型;补体、抗双链 DNA、ENA 抗体谱、抗中性粒细胞胞浆抗体(antineutrophil cytoplasmic antibody, ANCA)、抗环瓜氨酸肽抗体、布鲁氏菌胶乳凝集试验、结核感染 T 细胞检测、免疫球蛋白、HLA-B27/B7 检测未见异常。心脏超声:左室射血分数 62%,左房扩大,主动脉瓣反流(轻-中度),二尖瓣反流(轻微),三尖瓣反流(轻微),左室舒张功能减低,升主动脉扩

张；右手 MR 平扫：双手指深、指浅屈肌腱鞘炎可能；唇腺活检：粘膜下纤维增生伴胶原化，内见少许涎腺组织，伴极少量浆细胞浸润，局灶伴导管扩张。消化系统超声、泌尿系统超声、眼科相关检查未见明显异常；诊断为“EB 病毒感染，未分化结缔组织病可能性大”，给予甲泼尼龙 12 mg Qd 抗炎、硫酸羟氯喹 0.2 g Bid 免疫抑制，更昔洛韦 0.25 g Q12h 抗病毒，左氧氟沙星 0.5 g Qd 抗感染治疗后未再发热，好转出院。患者出院后规律口服甲泼尼龙、硫酸羟氯喹，半月前甲泼尼龙减量至 8 mg Qd 时再次出现反复发热，体温最高 39.1℃，伴左侧颈部淋巴结肿痛，外院静滴“头孢哌酮舒巴坦”后颈部肿痛明显缓解，仍发热，热峰降至 38℃。

2.2. 既往史、个人史、家族史

高血压病史 3 年，血压最高 150/100 mmHg，平素服用“硝苯地平控释片 30 mg Qd”降压，血压维持在 120/80 mmHg 左右。吸烟 20 余年，20 支/天。家族史无特殊。

2.3. 入院查体

体温：36.3℃，脉搏：85 次/分，呼吸：16 次/分，血压：127/80 mmHg，神志清，精神良好。咽后壁充血，双肺呼吸音清，未闻及明显干湿性啰音。心律齐，各瓣膜听诊区未闻及病理性杂音。腹软，无压痛及反跳痛。双下肢无水肿。

2.4. 实验室检查

血常规：WBC $15.44 \times 10^9/L$ ，Neut 81.40%，Neu $12.57 \times 10^9/L$ 。

PCT：0.13 ng/mL；CRP：29.85 mg/L；ESR：12.30 mm/h；铁蛋白 403.20 ng/mL。

尿液分析、粪便常规分析及隐血试验未见异常。

血生化：肝功：总蛋白 60.00 g/L，AST 56.80 U/L，ALT 221.80 U/L，ALB 34.10 g/L，GGT 180.70 U/L；肾功、肌酸激酶均正常。

免疫相关检验：ANA 及滴度测定：弱阳性，滴度 1:100，核型胞浆颗粒型；RF：21.60 IU/mL；CD4 绝对计数：424.00 cells/ μ L；白细胞介素、肿瘤坏死因子、免疫球蛋白未见异常。

内分泌相关检验：空腹血糖(fasting blood glucose, FBG) 6.58 mmol/L；甲功五项正常。

感染相关检验：EB 病毒衣壳抗原 IgG 83.34 AU/mL；EB 病毒核抗原 IgG 56.35 AU/mL；巨细胞病毒 IgG > 500.00 IU/mL；血培养未见细菌、厌氧菌生长，抗链球菌溶血素 O 测定、真菌 G 试验及 GM 试验、布鲁氏菌胶乳凝集试验结果均为阴性。

2.5. 影像学检查

胸部 CT：未见明显异常。体表肿物超声：右侧颈部淋巴结肿大，考虑反应增生性。心脏超声：左室射血分数 58%，考虑感染性心内膜炎，主动脉瓣叶回声增强、增粗、毛糙，无冠瓣可见大小约 1.20 cm × 0.60 cm 强回声附着，随心动周期摆动，主动脉瓣赘生物形成可疑，主动脉瓣反流(中度)，心房扩大，左室扩大，肺动脉高压(轻度)，左室舒张功能减低。

2.6. 诊疗经过

患者主动脉瓣赘生物经心脏超声明确，伴反复发热，最终诊断：感染性心内膜炎。住院期间给予甲泼尼龙 18 mg Qd 抗炎、硫酸羟氯喹 0.2 g Bid 免疫抑制、头孢他啶 2.0 g Q12h 抗感染，伐昔洛韦 0.3 g Bid 抗病毒治疗。患者于 2021-10-11 转入心血管外科行主动脉瓣置换术、主动脉瓣赘生物清除术。病理：主动脉瓣膜组织呈慢性化脓性炎伴肉芽组织增生并粘液变，可见炎性纤维素性渗出及坏死。术后门诊规律

随访,病情稳定,未再发热。

3. 讨论

IE (infective endocarditis)是指侵及特定心脏组织的感染,是一种潜在致命性的疾病,可累及心内膜、自体心脏瓣膜、人工心脏瓣膜或各种植入的心脏装置,350年前首次被发现,超过2/3的患者为男性,平均发病年龄超过65岁,在75~79岁的男性中,发病率最高为19.4/10万人,也可见于年轻患者[3][4]。欧洲人群中IE年发病率约为3~10/10万人,较为罕见[5]。伴随对于疾病认知的深入和诊疗技术的提高,以及侵入性手术、心脏植入装置的广泛开展应用,发病率逐年增加[6]。Chen等人报道在过去十年中IE相关的发病率和死亡人数增长迅速,尽管在影像学诊断、预防措施、手术以及抗生素干预治疗方面有显著改善,IE的死亡率仍然高达15%~30%[7][8]。中国关于IE的研究相对较少,我国的一项研究表明IE的发病率在0.33~0.72/1000人之间,院内死亡率为10.6%,年死亡率为11.3%[9]。疾病持续进展可出现心力衰竭、严重感染、血管栓塞等危及生命的并发症,总体预后差[10]。

IE的临床表现多样,病程复杂多变,且缺乏特异性,发热是常见的就诊原因,可伴有畏寒、寒战、纳差、体重减轻等症状,查体可闻及心脏杂音,给早期诊断带来了挑战[11][12]。心脏受累可表现为瓣膜赘生物、脓肿、心肌心包炎等,赘生物脱落随血液流动可累及全身各个器官,导致真菌性动脉瘤、脑栓塞、脾梗死[13][14]。皮肤及眼部表现包括瘀点、Osler结节、Janeway损害和Roth斑[15][16]。瓣膜退行性变、人工瓣膜、留置导管、植入心脏装置、静脉注射毒品、糖尿病、人类免疫缺陷病毒感染等是现有报道中发现的疾病危险因素,先天性心脏病也会增加罹患IE的风险[15][17][18][19]。风湿性心脏病仍然是发展中国家IE最常见的诱发因素,占比31%[20]。近年来研究发现,金黄色葡萄球菌取代草绿色链球菌成为导致IE的首要致病微生物,约有31%的病例由金黄色葡萄球菌引起,草绿色链球菌占比较前下降,肠球菌属也是常见的IE致病微生物[11][17][19][21]。血培养阴性的IE诊断存在一定的困难,需要重点关注,有大约10%的IE病例血培养阴性,最常见的原因是明确诊断前接受了抗生素治疗,或是由于获取标本不理想,致病菌为真菌或苛氧菌也可见阴性结果[15]。血清学检测如分子检测和聚合酶链反应(Polymerase chain reaction, PCR),有助于发现常规细菌培养中不生长以及生长环境要求苛刻的微生物,如立克次体及巴尔通体[22][23]。

IE的诊断通常需要结合临床、微生物学和超声心动图综合诊断。一旦怀疑为IE,需立即进行诊断评估。血培养是诊断IE至关重要的实验室检查,明确致病微生物,为抗生素的选择提供依据。超声心动图作为诊断IE的影像学检查基石,指南建议所有疑似心内膜炎的患者均应接受经胸超声心动图(transsthoracic echocardiography, TTE)检查[24]。经食管超声心动图(transoesophageal echocardiography, TEE)为侵入性检查,在诊断IE以及表征病变和识别局部并发症方面具有重要作用[25]。对于疑似自体瓣膜心内膜炎,TTE的敏感性为50%~90%,特异性为90%。对于疑似人工瓣膜心内膜炎,TTE的敏感性不及TEE(40%~70% vs. 85%~90%)[26]。另外,心脏CT、心脏MRI、PET-CT等影像学检查方法对IE的诊断有一定的辅助作用[27][28][29]。IE的诊断基于Duke标准,涵盖临床表现、病原学、病理学、影像学等方面,需要满足2个主要标准,或1个主要标准和3个次要标准,或5个次要标准即可诊断为明确的IE[25]。2023年由国际心血管感染性疾病学会修订的Duke标准细化了各项准则,将IE分为三大类:明确的心内膜炎,可能的心内膜炎,排除的心内膜炎,增加外科手术中IE检查的主要标准,PCR或其他基于核酸的检测、IgM和IgG抗体检测鉴定致病微生物等[30]。

有研究表明心内科、心血管外科、感染性疾病科、病理科、超声科、影像科等多学科协作管理IE可有效缩短手术时间(16.4天 vs. 10.3天)、降低长期死亡率(34% vs. 16%)[31][32]。所有的患者均应根据经血培养或血清学检查发现的病原体选择合适的抗生素及早进行抗感染治疗,此外瓣膜组织培养对于术后

抗菌治疗具有指导意义[23] [24] [33]。抗生素的应用有助于降低严重脓毒症、多器官功能障碍综合征、卒中和猝死发生的风险[34]。约 40%~50% 的 IE 患者应当进行手术干预, 手术治疗的具体指征包括: 心力衰竭; 持续抗感染治疗后仍存在菌血症和瓣周并发症; 赘生物 > 10 mm, 尤其是存在二尖瓣前叶受累和栓塞时[17] [35]。欧洲心脏病学会指南将手术时机定义为紧急手术(24 小时内)、紧急手术(几天内)或择期手术(抗生素治疗 1~2 周后) [25]。有研究表明, 早期的手术干预有助于降低院内死亡率[36]。

细菌、真菌或病毒感染、恶性肿瘤、自身炎症疾病或自身免疫疾病以及其他原因可导致 FOU, 其中自身炎症和自身免疫性疾病约占 5%~32% [37] [38] [39], 恶性肿瘤占比 2%~25% [37] [40] [41]。本例中患者病情迁延, 反复发热, 且伴有口干、眼干、脱发、关节痛等表现, 期间行 ANA 检测示阳性, 滴度 1:1000, 核型均质型, 类风湿因子阳性, 发热时不同时段留取血培养 2 次均为阴性, 完善指关节超声、手 MRI、眼科相关检测、唇腺活检未见明显异常, 首次心脏超声示瓣膜反流, 自身免疫疾病仍不能排除, 予以激素抗炎、免疫抑制治疗后仍反复发热, 炎症指标高于正常范围, 进一步排查感染可能, 再次行心脏超声检查发现主动脉瓣赘生物形成, 满足 2 条主要标准(心脏超声见赘生物形成、手术获取的瓣膜组织示感染性病变)和 2 条次要标准(发热、类风湿因子阳性), 最终临床诊断为 IE。

通过分析该病例提示我们: 因 IE 发病率低、受累器官不同、临床表现各异, 对于 FOU 的患者, 将 IE 纳入系统性疾病鉴别范围内是必要的, 详细询问病史及进行体格检查, 积极完善血培养及心脏超声检查, 综合病史、临床表现、实验室及影像学检查结果诊断, 及早识别 IE, 避免延误诊治, 改善患者预后。

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