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发热伴血小板减少综合征的诊断与鉴别诊断

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摘　要

发热伴血小板减少综合征(severe fever with thrombocytopenia syndrome, SFTS)是一种人畜共患性疾病，在多个国家内流行，中国属于疫情严重的国家之一。近年来，发热伴血小板减少综合征临床症状和体征不显著的临床病例越来越多，易造成漏诊或误诊。患者未得到正确救治而导致病情加重，增加治疗难度及影响患者预后。为提高临床医生对于该病的认识水平和诊治水平，本文就近年来国内外对发热伴血小板减少综合征在诊断与鉴别诊断方面的研究进展作综述。

关键词

发热伴血小板减少综合征，诊断，鉴别诊断

Diagnosis and Differential Diagnosis of Severe Fever with Thrombocytopenia Syndrome

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Abstract

Severe Fever with thrombocytopenia syndrome is a zoonotic disease, which is prevalent in many countries, and China is one of the countries with serious epidemic situation. In recent years, there are more and more clinical cases of severe fever with thrombocytopenia syndrome whose clinical symptoms and signs are not obvious, which is easy to cause missed diagnosis or misdiagnosis. The patient is not treated correctly, which leads to the aggravation of the disease, increasing the difficulty of treatment and affecting the prognosis of the patient. In order to improve clinicians' un-

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derstanding, diagnosis and treatment of the disease, this paper reviews the research progress in diagnosis and differential diagnosis of severe fever with thrombocytopenia syndrome at home and abroad in recent years.

Keywords

Severe Fever with Thrombocytopenia Syndrome, Diagnosis, Differential Diagnosis

1. 引言

发热伴血小板减少综合征(severe fever with thrombocytopenia syndrome, SFTS)是一种新发人畜共患性疾病，其致病病毒发热伴血小板减少综合征病毒(SFTS 病毒)于 2013 年在中国最先命名[1]。其主要经蜱叮咬传播[2]，可出现人传人[3]。在日本[4]、韩国[5]及美国[6]也有病例报道，但中国的疫情较严重。临床表现主要为发热(多在 38℃以上，病情较重者可达 40℃以上)、血小板减少(多为(30~60) × 10^9/L)、胃肠道症状(恶心呕吐、厌食、腹痛腹泻等症状)和白细胞减少(多为(1.0~3.0) × 10^9/L) [1] [7]。致死率约为 10% [8]。症状体征不显著时，临床表现不易与其它疾病鉴别，影响患者健康及生命安全。本文对 SFTS 在诊断与鉴别诊断方面的研究进展作综述，以提高临床诊断率。

2. SFTS

2.1. 流行病学史

人群普遍易感。夏秋季，在丘陵、林区、山地等地工作、生活或旅游史等或发病前 2 周内有被蜱叮咬史的人应警惕 SFTS 感染[3] [7]。

2.2. 临床表现

SFTS 典型的感染过程可分为四个不同的时期：潜伏期、发热期、极期和恢复期。蜱虫叮咬后的潜伏期受多种因素影响，包括病毒剂量和感染途径[9]，一般为 1~2 周[7]。发热期的特征是发热(病情重者可达 40℃以上，热程可至 10 天以上)，伴乏力、全身酸痛、头痛、头晕、胸闷、恶心、呕吐和腹痛、腹泻等胃肠道症状，查体可有淋巴结增大、肺部湿啰音、腹部压痛[7]。极期亦可有发热期的表现，病情严重者可出现神经系统障碍(如烦躁、意识障碍、痉挛、癫痫持续状态)、皮肤瘀斑(skin ecchymosis)、出血(bleed) (如消化道、肺等)、呼吸窘迫(respiratory distress)，甚至因休克(shock)、弥散性血管内凝血(disseminated intravascular coagulation, DIC)等多脏器功能衰竭而死亡[7]。恢复期患者症状逐渐改善[7]。病程大约为 2 周，大部分患者预后良好，有基础疾病史、神经精神症状、出血倾向或低钠血症及老年患者预后较差[7]。

Li 等人[10]对 2096 例 SFTS 临床特征研究发现症状发生率较高的有：发热(100%)、乏力(96.8%)、肌痛(82.3%)；咳嗽(51.1%)；厌食(77.6%)、恶心(71.8%)；淋巴结肿大(54.0%)，而其它症状如头痛、头晕等非特异症状、呼吸困难等呼吸系统症状、腹泻等消化道症状、出血症状及神经系统症状出现者占比例不高。

2.3. 实验室检查

2.3.1. 常规实验室检查

1) 血常规：可见白细胞计数及血小板计数下降[7]。

2) 生化检查：不同程度天冬氨酸氨基转移酶(AST)、谷丙转氨酶(ALT)、肌酸激酶(CK)、乳酸脱氢酶(LDH)、胆红素升高[11]，低钠血症、低钙血症[11]。

3) 肾功能：肌酐、尿素增高[7]。

4) 凝血常规：凝血功能障碍，活化部分凝血活酶时间(APPT)和凝血酶原时间(PT)延长、D-二聚体(D-D)和纤维蛋白原降解产物(FDP)水平升高[3] [12]。

5) 炎症指标或细胞因子或趋化因子：C-反应蛋白(CRP)升高，白细胞介素 6 (IL-6)、IL-10、IFN 诱导蛋白 10 (IP-10)、单核细胞趋化蛋白 1 (MCP-1)和干扰素-γ (IFN-γ)水平升高，但 IL-8、转化生长因子 β1 (TGF-β1)和调节正常 T 细胞表达和分泌的活化因子(RANTES)降低[13]。

6) 贫血三项：铁蛋白水平升高[14]。

7) 尿常规：蛋白尿、血尿[7]。

2.3.2. 病原学及血清学检查

病毒分离应于生物安全二级及以上实验室进行[7]。可用电子显微镜和分子或血清学方法(血清中和试验、间接免疫荧光试验和 ELISA)、逆转录酶(RT) PCR、实时 RT-PCR、等温扩增技术等方法确认 SFTS 病毒。近期，SFTSV 感染是通过检测 IgM 抗体或 IgG 抗体血清转换，或恢复期滴度较急性期抗体滴度至少增加 4 倍来诊断的[9]。元基因组下一代测序(mNGS)等新诊断方法方法亦有案例报道[15]。

2.4. SFTS 诊断

我国目前根据流行病学史、临床表现和实验室检查结果进行诊断，根据不同结果诊断为疑似病例和确诊病例诊断[7]。

3. 鉴别诊断

3.1. 肾综合征出血热

肾综合征出血热(hemorrhagic fever with renal syndrome, HFRS)是由汉坦病毒属导致的一种感染性疾病，以褐家鼠和黑线姬鼠等鼠类为主要宿主动物和传染源[16]。HFRS 典型病例病程可分为六个时期：潜伏期、发热期、低血压休克期、少尿期、多尿期和恢复期。“三痛”(头痛、腰痛、眼眶痛)和“三红”(颜面、颈部、胸部充血) [17]为 HFRS 症状。其发热、头痛等症状与 SFTS 症状相似，我国出现过 HFRS 病例误诊为 SFTS [18]。HFRS 诊断亦是根据流行病学史、临床表现和实验室检查结果[17]。

3.2. 恙虫病

恙虫病，是由恙虫病东方体(属于立克次体科)引起，由恙螨叮咬传播给人的一种自然疫源性传染病。临床表现特点为发热、皮疹、头痛、淋巴结肿大、叮咬部位焦痂或溃疡形成以及胃肠道症状[19]。Park 等人[20]研究发现白细胞减少、血小板减少和低 C 反应蛋白是 SFTS 的危险因素，并用这 3 个变量生成预测评分，用于鉴别 SFTS 与焦痂或皮疹阴性的恙虫病。Heo 等人[21]用神经症状、腹泻、白细胞减少和正常 CRP 值这四个因素生成 SFTS 预测评分系统来区分地方性人畜共患病。

3.3. 人粒细胞无形体病

人粒细胞无形体病(human granulocytic anaplasmosis, HGA)是经蜱传播的人兽共患自然疫源性疾病，

其病原体为嗜吞噬细胞无形体，临床表现主要为发热、头痛、肌痛/关节痛、胃肠道症状和全血细胞减少[22] [23] [24]。可通过血清学检测、PCR 检测细菌 DNA 或细胞培养等实验室检查助于诊断[25]。

3.4. 钩端螺旋体病

钩端螺旋体病是由致病性螺旋体引起的一种人畜共患疾病，临床表现主要为发热、畏寒、头痛、眼结膜充血、腓肠肌疼痛等表现[26]。除行血常规等一般检查外，还应行血清学检查(如酶联免疫吸附试验(ELISA)或显微镜凝集试验(MAT))和病原学检查[27]。

3.5. 登革热

登革热是由登革病毒引起的一种急性传染病，主要传播媒介是伊蚊，临床表现为乏力、发热、头痛、关节痛、肌痛、皮疹、淋巴结肿大等症状[28]。通过血清学检查和病原学检查以便诊断[29]。

3.6. 上呼吸道感染/流行性感冒

上呼吸道感染/流行性感冒属于急性呼吸道传染病，临床表现可表现为高热、乏力、头痛以及胃肠道症状，通过病原学和血清学确诊[30]。

3.7. 流行性脑脊髓膜炎

流行性脑脊髓膜炎是由脑膜炎奈瑟菌引起的一种急性传染病，临床表现按照病情可分为普通型、爆发型、轻型、慢性型四型，特征性临床表现为突发高热、剧烈头痛、频繁呕吐、脑膜刺激征等表现，通过脑脊液检查及细菌性检查来确诊[31]。

3.8. 伤寒/副伤寒

伤寒作为一种急性肠道传染病，是由伤寒杆菌引起，主要通过粪口途径传播，典型临床表现可分为初期(乏力、发热、头痛、胃肠道症状)、极期(可出现表情淡漠、相对缓脉、玫瑰疹等特征性临床表现)、缓解期、恢复期四期[32] [33] [34]。副伤寒是由副伤寒甲、乙、丙杆菌引起，临床表现与伤寒具有极大相似性。均通过细菌性检查和血清学检查便于诊断[32] [35]。

3.9. 败血症

败血症是由病原菌(包括细菌、真菌、厌氧菌)侵入血液系统并在其中生长繁殖而产生大量毒素并诱发全身炎症反应综合征的急性全身性感染[36]。临床表现根据致病病原菌不同而表现出异同点，如肺炎链球菌败血症可具有发热、肝脾肿大、神经系统等症状[37]。可通过病原学确诊。

3.10. 血栓性血小板减少性紫癜

血栓性血小板减少性紫癜(thrombotic thrombocytopenic purpura, TTP)，特征性表现主要为发热、微血管病性溶血、血小板减少性紫癜、神经系统异常及肾脏损害[38]。TTP 的诊断是根据特征性临床表现、ADAMTS13 活性、抗 ADAMTS13 自身抗体为诊断依据[38]。

4. 总结

综上所述，本文章汇总了不易和 SFTS 鉴别的相关疾病，包括 HFRS、恙虫病、人粒细胞无形体病、钩端螺旋体病、登革热等疾病，SFTS 的早期诊断具有挑战性。应进一步探索研究这些疾病，争取尽早确诊疾病，改善患者预后。

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