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腺病毒与川崎病临床鉴别研究进展

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摘　要

川崎病(Kawasaki Disease, KD)是一种以全身血管炎性、发热出疹性疾病，主要影响5岁以下儿童，病因尚未完全明确。近年来，许多研究表明，感染因素是导致KD的发病的重要因素。其中，腺病毒(Adenovirus, AdV)作为一种常见的病原体，因其感染后临床症状与KD高度重叠，临床误诊风险显著增加。本文通过综述AdV感染与KD的流行病学关联、临床特征、实验室检查及潜在病理机制差别，旨在为临床医生提供鉴别诊断的关键线索，减少误诊率，优化治疗策略。

关键词

川崎病，腺病毒，感染，临床鉴别，儿童

Advancements in Clinical Differentiation between Adenovirus and Kawasaki Disease

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Abstract

Kawasaki disease (KD) is a systemic vasculitis and febrile exanthematous condition predominantly affecting children under the age of five. The etiology of KD remains incompletely elucidated. Recent studies have increasingly highlighted the significance of infectious agents as potential etiological factors in KD. Notably, adenovirus (AdV), a prevalent pathogen, poses a considerable risk of clinical misdiagnosis due to the substantial overlap in clinical manifestations between AdV infection and

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KD. This article provides a comprehensive review of the epidemiological associations, clinical characteristics, laboratory diagnostics, and potential pathophysiological distinctions between AdV infection and KD. The objective is to furnish clinicians with critical insights for differential diagnosis, thereby reducing the incidence of misdiagnosis and enhancing treatment strategies.

Keywords

Kawasaki Disease, Adenovirus, Infection, Clinical Differentiation, Children

1. 引言

KD 是一种以全身血管炎为主要特征的急性发热性疾病，好发于 5 岁以下儿童，病因未明[1]。自 1967 年首次报道以来，KD 发病率持续上升，已成为儿童获得性心脏病的首要病因，严重的心脏并发症表现为冠状动脉瘤的形成，是心肌梗塞或猝死的病因[2] [3]。此外，KD 还可能出现心肌炎、心包炎以及心脏功能不全等心脏并发症[4]，这可能导致长期的健康问题甚至死亡。尽管美国心脏病协会提出了基于发热时长及典型临床表现的诊断标准(如四肢末端改变、皮疹等) [5]，但其早期诊断仍面临挑战。AdV 感染与 KD 的临床表现高度重叠(如高热、结膜炎、皮疹)，导致临床误诊率高达 20%~30%，且误诊患儿冠状动脉病变风险增加 1.5 倍[4] [5]。然而，既往研究多局限于症状学对比，机制研究严重不足：既往研究指出，80%的相关文献聚焦临床特征，仅 15%探讨免疫或分子机制差异[4] [6] [7]。值得注意的是，AdV 与 KD 的病理机制存在本质区别：前者以病毒直接侵袭宿主细胞为主，后者则涉及感染后免疫失调引发的自身免疫性血管炎。尽管分子模拟假说(如 AdV 衣壳蛋白与血管内皮抗原的交叉反应)被提出[5] [8]，但其具体机制及临床意义尚未阐明。本综述通过整合流行病学、临床及分子机制证据，旨在为临床医生提供鉴别诊断的关键线索，减少误诊率，优化治疗策略。

2. 流行病学证据

AdV 是一种常见的病原体，在全球范围内普遍存在，是儿童呼吸道感染的主要病因之一。其感染的流行病学特征因地区和时间而异。例如，在中国广州地区，AdV 感染的年发生率在 3.92%到 13.58%之间，并且每四到五年会出现一个流行高峰[9]。在中国杭州地区，2019 年夏季暴发后，2020~2024 年间季节性特征趋于弱化[10]。AdV 具有多种不同的血清型，每种血清型在基因结构和抗原特性上均存在差异，在致病力、感染途径、潜伏期以及临床表现等方面表现出显著的多样性[9] [11] [12]。AdV 感染的临床负担在特定人群中尤为突出。回顾性研究证实 2018~2023 年间儿科 AdV 感染中严重病例多为年幼患儿，常伴有呼吸困难、活动减少、支气管肺炎及遗传疾病等[13]，更值得关注的是，在免疫功能低下的儿童中，AdV 感染的风险更高，且病情可能更为严重[14] [15]。

近年多项研究揭示了 AdV 感染与 KD 的流行病学关联。一项队列研究显示，AdV 感染患儿 KD 发病率较未感染组升高 5.29 倍，其中 3~5 岁儿童、女性、低城市化地区及过敏体质人群风险增幅尤为显著[16]。季节性相关性进一步佐证该关联性：KD 与 AdV 感染在冬春季呈同步流行趋势[17]-[20]。此外，不同地区的发病率差异进一步强调了 AdV 与 KD 之间的关系。在 2019 年新型冠状病毒大流行期间，为控制疫情传播，各地实施了多项缓解措施，随后观察到 KD 的发病率有所降低，这一观察结果为传染性病

原体假说提供了支持[21] [22]。马忠正等研究发现，KD 合并呼吸道感染患儿中 AdV 检出率显著高于单纯病毒感染组[23]。Ashwini Sankannaavr 等[24]研究显示急性 AdV 感染可诱发 KD 的发生。与此同时，不能否认 KD 与 AdV 共存的可能性，Turnier 等人[25]在基于 PCR 研究与分析后发现 KD 患儿样本中存在 4.7%的 AdV，揭示了 AdV 在样本中的分布及其潜在影响。同时，一项前瞻性研究报道，KD 患儿呼吸道病毒细胞 PCR 阳性率高达 50.4%，其中 AdV 占比 8.0% [26]。

3. 腺病毒与川崎病临床特征

发热：高热是 KD 及 AdV 感染的共有表现。KD 患儿发热通常为持续性，高于 39.0℃，持续时间较长，至少 5 天，未经治疗可达 1 周至 3 周[27]，抗生素治疗无效。AdV 感染的发热持续时间较短，平均持续时间为 4.9 天[28]，但具体时间因感染类型和严重程度而异。

黏膜改变：球结膜充血是 KD 眼部表现的典型特征，几乎在所有病例中都会出现，表现为非化脓性、弥漫性的球结膜充血，通常在发热后不久开始出现[29]。部分 KD 患者可能出现葡萄膜炎、视网膜病变甚至视神经盘水肿等严重眼部并发症[30] [31]。随后出现口腔黏膜改变，包括唇红肿、干燥甚至皲裂，有时伴有唇部剥脱，舌乳头突起、颜色鲜红，出现“草莓舌”[32]。由 AdV 感染引起的结膜炎通常表现为结膜充血，并可能伴有眼部分泌物增多、眼睑水肿和异物感等症状，发生率相对较低，这种状况通常为单侧性，但在少数情况下，可能会发展为双侧性，但通常不会导致严重的视力损害[33]-[35]。同时有研究表明，AdV 感染的眼部表现通常不伴随明显的炎症性改变，这与其他类型的结膜炎有所不同[36]。AdV 感染虽然也可能导致口腔黏膜的改变，但通常表现为更为轻微的咽炎或扁桃体炎，且伴随其他上呼吸道感染症状[37] [38]。

皮肤症状：KD 的皮疹通常在发热后 5 天内出现，表现类型多样，最常见的是麻疹样斑丘疹，但也可能有红斑性狼疮样红斑、荨麻疹或细小脓疱疹等[27]，常见于躯干、头面部和四肢[39]。有研究报告指出，KD 患者可能会出现类似银屑病的皮疹，这种皮疹通常在 KD 发病后数天至数月出现，并可能自限性消退[40]。KD 除典型的红斑和皮疹，还可能包括早期脱屑性会阴红斑，这种表现虽然在儿科报告中较少被关注，但在诊断中具有重要价值[41]。皮疹的严重程度和持续时间可能与疾病的严重程度有关。值得注意的是，另一个独特的皮肤特征是卡介苗接种部位的红斑和硬结[42]，研究显示接种部位的“靶心”皮肤图案与系统性受累的严重程度有关[43]。此外，在 KD 的急性期，患者可能会出现手和脚的红肿和硬性水肿，并可能伴有疼痛。在亚急性期，发热后 2~3 周，手指和脚趾可能会出现脱屑[44]，是 KD 的典型症状之一，常常被用作诊断的一个重要依据。研究表明，AdV 感染所致的皮疹是非特异性的，可能局限于身体的某一部位，例如腹部或臀部，并且在衣物摩擦下可能加重。这种皮疹通常被称为“儿童偏侧性皮疹”，其特征是皮疹最初出现在身体的一侧，然后可能扩展到对侧，但程度较轻[45]，且较少见，通常不伴随典型的 KD 特征性皮疹。

淋巴结肿大：颈部淋巴结肿大是 KD 的常见症状之一，通常与发热同时或在发热之前出现，常为单侧颈前淋巴结无痛性肿大，偶尔会有压痛，直径通常较大，且在 1 岁以下的婴儿中，颈部淋巴结肿大的发生率较低，而在 1 至 5 岁的儿童中则较为常见[46] [47]，通常伴随典型的皮疹、口腔黏膜变化和手足变化等全身性表现。与 KD 不同，AdV 感染引起的淋巴结肿大通常是全身性的，而非局限于颈部或单侧性，且伴随呼吸道症状和局部炎症反应。

4. 腺病毒与川崎病实验室检查特征

在实验室检查方面，KD 患者的白细胞计数通常轻至中度升高，范围在 10~20 × 10^9/L 之间，并且以中性粒细胞为主，急性期尤为明显[48] [49]。在儿童 AdV 感染中，白细胞计数通常正常或轻度升高，范围在 8~15 × 10^9/L 之间，但在某些重症病例中，如 AdV 肺炎或脓毒症，白细胞计数可能显著升高，超过

20×10^9/L，伴有淋巴细胞减少[50] [51]。KD 患儿 C 反应蛋白(C-reactive protein, CRP)水平通常会显著升高，达到 50~100 mg/L，与炎症反应和血管炎的活动密切相关，但通常低于重症 AdV 感染的水平[52]。AdV 在重症患者中，CRP 水平常常超过 100 mg/L，甚至在某些情况下超过 200 mg/L [53]。研究表明，KD 患者的红细胞沉降率(Erythrocyte Sedimentation Rate, ESR)通常超过 40 mm/h，甚至可以达到 100 mm/h 以上[54] [55]。儿童 AdV 感染 ESR 在中度感染时通常在 20~60 mm/h 之间，而在重症感染时可超过 80 mm/h，这种变化与 CRP 的变化趋势相似，随着炎症的控制，ESR 和 CRP 的水平会逐渐下降[56]。降钙素原(Procalcitonin, PCT)水平在 AdV 感染中显著升高，而在 KD 中升高不明显[53] [57]。此外，KD 患者的血清中可能出现特定的生物标志物，如新型免疫调节因子 PK2 (Prokineticin 2)，这在 AdV 感染中并不常见[58]。但在 AdV 感染的患儿中伴随着较高的病毒载量和特定的病毒种类[38]。此外，KD 患者的血清铁蛋白水平显著高于其他急性发热性疾病患者，这一生物标志物可以帮助区分 KD 与 AdV 感染[59]。研究人员开发了一种基于基因表达谱的诊断方法，通过分析血液中的基因转录本丰度，可以有效地区分 KD 与 AdV 感染[60]。在 KD 的急性期，血小板计数可能正常或减少，而在亚急性期则显著升高，通常达到 400-1000×10^9/L，而儿童在轻度 AdV 感染的情况下，血小板计数可能轻微减少，而在重症感染中，血小板计数可能显著降低，甚至低于 100×10^9/L [61] [62]。在 KD 患者中，N-末端脑钠肽前体(N-terminal Pro-Brain Natriuretic Peptide, NT-proBNP)水平显著升高，而在儿童 AdV 感染患者中通常正常或仅轻微升高。研究表明，KD 患者中冠状动脉扩张的发生率显著高于其他发热相关的急性疾病患者[63]。

5. 病理机制

AdV 感染与 KD 的病理机制均涉及病毒感染与宿主免疫反应的相互作用，但二者在触发炎症的分子通路、免疫应答特征及靶器官损伤模式上存在显著差异。深入解析其机制异同点，可为临床鉴别提供分子层面的理论依据。

5.1. 触发机制：病原体直接损伤与免疫异常激活

AdV 感染以病毒直接侵袭宿主细胞为核心机制。AdV 通过纤维蛋白与宿主细胞表面受体结合，进入呼吸道上皮细胞或肠道细胞后启动复制，导致细胞溶解性坏死并释放促炎因子，引发局部炎症反应[64]。重症 AdV 感染还可通过病毒血症播散至肝脏、心脏等器官，引起多系统损伤[50]。相比之下，KD 的发病更倾向于“感染后免疫失调假说”：特定病原体(如 AdV)可能作为分子模拟的触发因素，通过交叉反应性抗原激活遗传易感个体的异常免疫应答。研究表明，KD 患者的 HLA-B*15:21 (Human Leukocyte Antigen B*15:21)等位基因频率显著升高，提示遗传背景在免疫识别异常中起关键作用[65]。此外，AdV 衣壳蛋白与 KD 患者血管内皮抗原的分子模拟现象，可能驱动自身抗体产生，进而攻击血管内皮细胞[37]。

5.2. 免疫应答特征：Th1/细胞毒性反应 vs. Th17/自身免疫优势

AdV 感染以 Th1 型免疫反应和细胞毒性 T 细胞激活为主。AdV 特异性 CD8+ T 细胞通过分泌干扰素-γ和颗粒酶 B 直接清除感染细胞，但过度反应可能导致组织损伤(如重症肺炎) [17]。KD 则表现为辅助性 T 细胞 17 (T helper 17 cell, Th17)通路和浆细胞异常活化。患者外周血中白细胞介素-17 (Interleukin-17, IL-17)、白细胞介素-23 (Interleukin-23, IL-23)水平显著升高，促进中性粒细胞浸润及血管壁炎症；同时，B 细胞分化为浆细胞后产生大量抗内皮细胞抗体，通过补体激活途径加重血管损伤[66]。值得注意的是，AdV 感染虽可短暂激活 Th17 通路，但缺乏 KD 中持续的自身抗体生成，这一差异可能解释二者血管炎严重程度的不同[67]。

5.3. 关键分子通路：细胞因子风暴与特异性生物标志物

二者均存在细胞因子风暴，但组分和动力学不同。AdV 感染早期即出现 IL-6、IL-8 和 PCT 的急剧升

高，出现细菌样炎症反应；而 KD 以 IL-1β、IL-6 和肿瘤坏死因子-α (Tumor Necrosis Factor-alpha, TNF-α)持续高表达为特征，且伴随特异性标志物如 PK2 和微小 RNA-200c (microRNA-200c, miR-200c)的异常上调[58] [68]。此外，KD 患者细胞因子信号抑制因子 3 (Suppressor of Cytokine Signaling 3, SOCS3)表达受抑，导致 Janus 激酶－信号转导与转录激活子(Janus Kinase-Signal Transducer and Activator of Transcription, JAK-STAT)信号通路过度激活，加剧血管炎症；而 AdV 感染中 SOCS3 通过负反馈抑制干扰素信号，限制免疫病理损伤[69]。这些分子差异为鉴别诊断提供了潜在靶点：如血清 PK2 和 PCT 的联合检测可有效区分二者[53] [58]。

5.4. 血管损伤机制：直接侵袭与免疫复合物沉积

AdV 可直接感染血管内皮细胞，引发局部坏死性血管炎，病理可见内皮细胞核内包涵体及中性粒细胞浸润[64]。KD 的血管损伤则主要由免疫复合物介导：抗内皮抗体与抗原结合后沉积于血管壁，激活补体系统并招募巨噬细胞，导致冠状动脉平滑肌细胞凋亡和基质金属蛋白酶过度表达，最终引发动脉瘤形成[63] [70]。这一机制差异解释了为何 KD 更易累及中型动脉(如冠状动脉)，而 AdV 感染以微血管病变为主。

AdV 感染与 KD 的病理机制在触发因素、免疫应答类型及终末器官损伤模式上存在本质区别。未来研究需进一步探索交叉反应性抗原的分子特征及遗传－环境互作机制，以开发特异性诊断标志物和靶向治疗策略。

6. 结语

本综述系统剖析腺病毒感染与川崎病的临床特征、实验室检查、病理机制差异，明确二者在触发因素、免疫应答及血管损伤模式上的本质区别。因此，面对发热患儿需鉴别川崎病与腺病毒感染时，诊疗应遵循多维度评估原则，结合病史及体征进行初步筛查，继而通过实验室动态监测炎症标志物、血小板及 NT-proBNP，并行心脏超声与病原学检测。全程强调心脏超声随访与指标动态监测以实现精准鉴别与干预。以提供更加精准、高效的诊疗服务，切实保障儿童的健康与生命安全。

利益冲突

所有作者均声明不存在利益冲突

致　谢

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