

doi: 10.13241/j.cnki.pmb.2014.31.018

人腺病毒 55 型感染肺部病变与外周血淋巴细胞关系研究 *

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摘要 目的: 探讨人腺病毒 55 型感染肺部病变与外周血淋巴细胞改变的关系及致病意义。**方法:** 以 50 例经胸部 CT 证实为腺病毒肺炎的患者为研究对象(肺炎组), 调查其外周血细胞及 T 淋巴细胞亚群变化情况, 并与同期腺病毒 55 型感染未出现肺部病变的患者 30 例(非肺炎组)对照; 亚组分析 50 例肺炎组中多肺叶病变与单肺叶病变患者之间 T 淋巴细胞变化的差异。**结果:** 与非肺炎组患者相比, 肺炎组患者急性期外周血淋巴细胞比例明显降低、单核细胞比例明显升高($P < 0.01$); 肺炎组 CD3⁺T 淋巴细胞比例、CD3⁺CD4⁺T 淋巴细胞比例及 CD4/CD8 比值较非肺炎组均有明显降低($P < 0.01$)。亚组分析显示, 肺炎组患者肺部病变范围不同, T 淋巴细胞亚群的变化亦有差异, 多肺叶病变组患者 CD3⁺CD8⁺T 淋巴细胞比例较单肺叶病变组明显升高、CD4/CD8 比值较单肺叶病变组明显降低($P < 0.05$)。**结论:** HAdV-55 感染引起肺炎病变时, 宿主存在明显的细胞免疫功能受损, 且与肺部病变程度有一定正相关。

关键词: 腺病毒感染; 肺炎; 淋巴细胞; 腺病毒 55 型

中图分类号: R373; R563 **文献标识码:** A **文章编号:** 1673-6273(2014)31-6073-03

The Relationship of Lung Lesions and Peripheral Blood Lymphocytes in Patients Infected with Human Adenovirus Type 55*

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ABSTRACT Objective: To explore the relationship between and pathogenic significance of lung lesions and peripheral blood lymphocytes in patients infected with human adenovirus type 55 (HAdV-55). **Methods:** The changes of peripheral blood cells and T lymphocyte subsets were investigated in 50 patients with adenovirus pneumonia confirmed by chest CT scan (Group pneumonia), compared with 30 patients without lung lesions in the same period of adenovirus type 55 infection (Group non-pneumonia). The differences between the changes of T lymphocytes in pneumonia cases of multiple lung lesions and single lobe lesions were analyzed. **Results:** Compared with that of non-pneumonia patients, the decreased peripheral blood lymphocyte proportion and increased monocyte proportion were found in acute period patients with pneumonia infected with HAdV-55 ($P < 0.01$). The CD3⁺T lymphocyte proportion, CD3⁺CD4⁺T lymphocyte proportion and CD4/CD8 ratio in patients with pneumonia were significantly lower than that in non-pneumonia cases ($P < 0.01$). Subgroup analysis showed that, the changes of T lymphocyte subsets were different between cases with multiple pulmonary lobes lesions and that with single lobe lesions. The CD3⁺CD8⁺T lymphocytes proportions in patients with multiple lobes lesions were significantly higher and CD4/CD8 ratio lower than that of patients with single lobe lesions respectively ($P < 0.05$). **Conclusions:** Our data shows that the host cell immune function has been impaired, which is positively related to the degree of pulmonary lesions in patients infected with HAdV-55.

Key words: Adenovirus; Pneumonia; Lymphocytes; Adenovirus type 55

Chinese Library Classification(CLC): R373; R563 **Document code:** A

Article ID: 1673-6273(2014)31-6073-03

前言

腺病毒(adenovirus, ADV)是引起人类急性呼吸道感染的

常见重要病原体之一, 尤其是重症肺炎的主要病原体, 儿童和青少年多见, 某些型别常引起暴发流行, 近几年有增加趋势, 可发展成致命的重症肺炎, 病死率高^[1-3], 但目前尚无特异性治疗

* 基金项目: 军队系统十二五重点课题“重要传染病防控关键技术与装备研究-军队重要呼吸道及虫媒传染病临床特征、重症预警及优化治疗研究”(BWS11J048)

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(收稿日期: 2014-04-11 接受日期: 2014-05-05)

方法。本文对一组青少年 ADV 感染病例进行研究,调查肺部病变与机体细胞免疫之间可能存在的关系,探讨 ADV 感染的发病及重症化机制,为有效治疗提供依据。

1 资料和方法

1.1 研究对象

2012 年 1 月~3 月某地突发一批发热伴呼吸道感染症状患者,经解放军疾病预防控制中心和三〇二医院分别采用免疫荧光法、聚合酶联反应法(PCR)和/或血清特异性 IgM 抗体联合双向检测,确诊为人腺病毒 55 型感染。选择其中 50 例经胸部 CT 证实为腺病毒肺炎患者为研究对象(简称肺炎组),调查其外周血细胞及 T 淋巴细胞亚群变化情况,并与同期 55 型腺病毒感染但 CT 检查未出现肺部影像学病变的患者 30 例进行对照(简称非肺炎组)。

1.2 肺部 CT 检查

采用美国通用 Bright Speed 16 排 SVS#CT99 型号 CT 机,在急性期患者吸气末屏气后由肺尖至膈肌逐层扫描,扫描参数是 120kV,100~500mAs,螺距 1.375:1。

1.3 外周血淋巴细胞检测

患者入院后即采外周血常规送检全血细胞分析、血液生化、血细菌培养;同时留取 EDTA 抗凝血 3 mL,用流式细胞术

检测外周血淋巴细胞各亚群的比例。血样经过 BD FACSCalibur 流式细胞仪检测后,通过软件分析获得各淋巴细胞亚群比例及 CD4/CD8 比值。MultiTest 试剂盒由美国 BD 公司提供,按说明书操作。

1.4 统计学处理

所有数据用 Epi Data V3.1 软件录入并建立数据库,结果以(均值±标准差)表示,在 STATA 7.0 for Windows 医学专业统计软件平台完成相关统计学处理,组间比较采用 t 检验,计算 Fisher 精确概率,P 值 <0.05 认为有统计学意义。

2 结果

2.1 人口学特征

两组患者均为青年男性,年龄 17-26 岁,其中肺炎组平均年龄(20.06±2.21)岁,非肺炎组平均年龄(19.57±1.67)岁,两组差异无统计学意义(P<0.05)。

2.2 肺炎组与非肺炎组患者急性期外周血白细胞及各分类细胞比较

数据显示两组白细胞总数和中性粒细胞比例均相似,差异无统计学意义(P>0.05),但肺炎组淋巴细胞比例较非肺炎组明显降低、单核细胞比例较非肺炎组显著升高,二者差异均有统计学意义(P<0.01)(表 1)。

表 1 两组患者急性期外周血白细胞及分类比较($\bar{x} \pm s$)

Table 1 Comparison of the peripheral white blood cells between two groups patients with acute infection($\bar{x} \pm s$)

组别 Groups	例数 Cases (n)	白细胞数 Lymphocyte	中性粒细胞比例 Neutrophil(%)	淋巴细胞比例 Lymphocyte(%)	单核细胞比例 Monocyte(%)
肺炎组 Pneumonia	50	5.26±1.51	0.57±0.18	0.30±0.12	0.12±0.03
非肺炎组 Non pneumonia	30	5.89±1.27	0.51±0.12	0.39±0.05	0.08±0.02
P value		0.0448	0.0943	0.0001	0.0000

2.3 肺炎组与非肺炎组患者急性期外周血 T 淋巴细胞亚群的变化。

结果显示肺炎组 CD3⁺T 淋巴细胞比例、CD3⁺CD4⁺T 淋巴

细胞比例及 CD4/CD8 比值较非肺炎组均有降低,差异有统计学意义(P<0.01)。肺炎组 CD3⁺CD8⁺T 淋巴细胞比例随略有降低,但差异无统计学意义(P>0.05)(表 2)。

表 2 两组患者急性期 T 淋巴细胞亚群比较($\bar{x} \pm s$)

Table 2 Comparison of the T lymphocyte subsets between two groups patients with acute infection($\bar{x} \pm s$)

组别 Groups	例数 Cases	CD3 ⁺ (%)	CD3 ⁺ CD4 ⁺ (%)	CD3 ⁺ CD8 ⁺ (%)	CD4/CD8
肺炎组 Pneumonia	50	61.36±10.28	32.96±6.33	28.57±9.91	1.26±0.34
非肺炎组 Non pneumonia	30	68.65±7.12	40.12±5.76	30.16±4.59	1.81±0.26
P value		0.001	0.000	0.4115	0.000

2.4 不同肺部病变患者急性期外周血 T 淋巴细胞亚群比较

50 例经肺部 CT 扫描显示有肺部炎症病变的患者按炎症累计肺叶数量再分组,其中多肺叶病变者 19 例、单肺叶病变者 31 例。比较多肺叶病变组与单肺叶病变组患者急性期外周血 T

淋巴细胞亚群,结果显示两组 CD3⁺T 淋巴细胞比例、CD3⁺CD4⁺T 淋巴细胞比例的差异均无统计学意义(P>0.05),但多肺叶病变组 CD3⁺CD8⁺T 淋巴细胞比例及 CD4/CD8 比值均高于单肺叶病变组,且差异有统计学意义(P<0.05)(表 3)。

表 3 不同肺部病变患者急性期 T 淋巴细胞亚群比较($\bar{x} \pm s$)

Table 3 Comparison of the T lymphocyte subsets between patients with different lung lesions($\bar{x} \pm s$)

组别 Groups	例数 (Case)	CD3 ⁺ (%)	CD3 ⁺ CD4 ⁺ (%)	CD3 ⁺ CD8 ⁺ (%)	CD4/CD8(%)
多肺叶病变组 Multiple lobar lesions	19	63.51±7.23	32.58±6.82	29.37±7.35	1.31±0.46
单肺叶病变组 Single lobar lesions	31	62.57±9.68	33.16±6.23	25.07±5.83	1.58±0.21
P value		0.717	0.759	0.026	0.007

3 讨论

人腺病毒(Human adenovirus, HAdv)是从人腺样组织培养物中分离出的双链 DNA 病毒,型别众多,截至 2009 年先后有 A-G 七个亚群,54 个不同血清型的 HAdv 被确认。不同血清型 HAdv 可引起不同类型的临床疾病,比如 B1、C、E 群腺病毒主要引起呼吸道疾病,B2 群主要引起泌尿系统感染。由于腺病毒基因不断重组与变异,新型别不断出现^[4-6]。2010 年 Walsh MP^[7]等通过全基因序列计算机比对分析技术发现了一个新的腺病毒血清型,该型病毒以 B14 型腺病毒为基本骨架,插入部分 B11 型腺病毒的六邻体结构,且不与 11 型和 14 型血清起反应,因此命名为人腺病毒 55 型(HAdv-55),仍属于 B 群。HAdv-55 流行时间短,人群普遍对其缺乏免疫力,因此容易暴发流行。

现有资料显示,HAdv-55 型主要在军营、学校等青少年聚集场所暴发流行^[8-10],以发热、咳嗽、咳痰、咽痛、咽部充血、扁桃体和颈部淋巴结肿大等上呼吸道感染症状为临床特点;肺部 CT 扫描显示,该型病毒感染可致半数以上的患者发生影像学可见的肺部炎症,显示为单肺叶或多肺叶的渗出性病变或片状团簇状影^[11,12],甚至发展为重症肺炎而死亡^[13,14]。目前,对于 HAdv-55 致病机制知之甚少,因此尚无特效治疗措施^[15]。有研究显示,病毒本身诱发的、T 淋巴细胞主导的机体细胞免疫紊乱可能参与了腺病毒重症肺炎的发生^[16-19],本课题组在研究甲型 H1N1 流感病毒所致重症肺炎的发病机制时也有相似发现^[20]。

本研究发现,与 HAdv-55 感染未出现肺炎病例相比,肺炎组患者急性期外周血淋巴细胞比例明显降低、单核细胞比例明显升高($P < 0.01$),说明 HAdv 感染引起的肺炎组患者发生了更为明显的免疫细胞改变。进一步分析外周血 T 淋巴细胞亚群显示,肺炎组 CD3⁺T 淋巴细胞比例、CD3⁺CD4⁺T 淋巴细胞比例及 CD4/CD8 比值较非肺炎组均有明显降低($P < 0.01$),提示 HAdv-55 可能损害了宿主的细胞免疫功能,使之明显下降,进而打破了整个机体免疫应答网络系统的平衡,导致不同程度的全身炎症反应综合征(systemic inflammatory response syndrome, SIRS),若 SIRS 进一步加重,则引起受累器官的炎症病变。亚组分析发现,肺炎组患者肺部病变范围不同,T 淋巴细胞亚群的变化亦有差异,本研究肺炎组患者按肺部 CT 扫描病变程度细分为多肺叶病变组 19 例、单肺叶病变组 31 例,对比发现多肺叶病变组与单肺叶病变组患者急性期外周血 CD3⁺、CD3⁺CD4⁺T 淋巴细胞比例差别很小,无统计学意义;但差异均有统计学意义,此结果或提示 HAdv-55 致多肺叶病变者细胞免疫功能紊乱更加严重,CD3⁺CD8⁺T 淋巴细胞可能参与了宿主早期的抗感染机制,具有一定靶抗原杀伤作用。

总之,HAdv-55 感染引起肺炎病变时,宿主存在明显的细胞免疫功能受损,主要表现为 CD3⁺、CD3⁺CD4⁺T 淋巴细胞下降和 CD4/CD8 比例失衡,且与肺部病变程度有一定正相关;多肺叶病变组 CD3⁺CD8⁺T 淋巴细胞比例较单肺叶病变组明显升高、CD4/CD8 比值较单肺叶病变组明显降低。进一步研究 HAdv-55 感染期间更多参与的免疫细胞数量与功能的变化将有利于深入了解腺病毒肺炎的发生机制,对重症病例的早期预警、个体化炎症控制及免疫干预具有重要意义。

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190

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(上接第 6075 页)

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