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肺癌患者外周血 T 淋巴细胞分型与抗核抗体之间的关系研究 *

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摘要 目的:研究肺癌患者外周血 T 淋巴细胞分型与抗核抗体之间的关系。**方法:**选择 2019 年 1 月到 2021 年 6 月在我院接受治疗的肺癌患者 81 例作为研究组,并选择同期健康志愿者 81 例作为对照组,检测并比较两组患者外周血 CD4⁺、CD8⁺ 和 CD4⁺/CD8⁺ 淋巴细胞比例,以及抗核抗体血清滴度。比较不同抗核抗体、年龄、性别、TNM 分期、肿瘤分化程度以及病理类型肺癌患者外周血 CD4⁺、CD8⁺ 和 CD4⁺/CD8⁺ 淋巴细胞比例。**结果:**(1)肺癌患者外周血 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞比例显著低于对照组,而 CD8⁺ 淋巴细胞比例显著高于对照组 ($P<0.05$);(2)III+IV 肺癌患者外周血 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞比例均显著低于 I+II 肺癌患者,而 CD8⁺ 淋巴细胞比例均显著高于 I+II 肺癌患者 ($P<0.05$);(3)小细胞肺癌患者外周血 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞比例均显著低于非小细胞肺癌患者,而 CD8⁺ 淋巴细胞比例均显著高于非小细胞肺癌患者 ($P<0.05$);(4)肺癌患者抗核抗体血清滴度显著高于对照组 ($P<0.05$);(5)抗核抗体阳性患者 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞亚群比例均显著低于抗核抗体阴性患者,而 CD8⁺ 淋巴细胞亚群比例显著高于抗核抗体阴性患者 ($P<0.05$)。**结论:**肺癌患者外周血 T 淋巴细胞亚群表达异常,并且其表达水平可能与抗核抗体滴度有关。

关键词:肺癌;T 淋巴细胞;抗核抗体

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Relationship between the Typing of T Lymphocytes in Peripheral Blood of Patients with Lung Cancer and Antinuclear Antibodies

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ABSTRACT Objective: To study the application effect of Da Vinci robot under general anesthesia in elderly abdominal surgery.

Methods: The 81 patients with lung cancer who were treated in our hospital from January 2019 to June 2021 were selected as the research group, and 81 healthy volunteers who underwent physical examinations in our hospital during the same period were selected as the control group to detect and compare the peripheral blood CD4⁺, The ratio of CD8⁺ and CD4⁺/CD8⁺ lymphocytes, and the serum titer of antinuclear antibodies. Compare the ratio of CD4⁺, CD8⁺ and CD4⁺/CD8⁺ lymphocytes in peripheral blood of patients with different antinuclear antibodies, age, gender, TNM stage, tumor differentiation, and pathological types of lung cancer patients. **Results:** (1) The ratio of CD4⁺ and CD4⁺/CD8⁺ lymphocytes in peripheral blood of lung cancer patients was significantly lower than that of the control group, while the ratio of CD8⁺ lymphocytes was higher than that of the control group ($P<0.05$); (2) III+IV lung cancer patients the ratio of CD4⁺ and CD4⁺/CD8⁺ lymphocytes in peripheral blood was lower than that of patients with I+II lung cancer, and the ratio of CD8⁺ lymphocytes was higher than that of patients with I+II lung cancer ($P<0.05$); (3) Small The proportion of CD4⁺ and CD4⁺/CD8⁺ lymphocytes in peripheral blood of patients with cell lung cancer was lower than that of patients with non-small lung cancer, and the proportion of CD8⁺ lymphocytes was higher than that of patients with non-small lung cancer ($P<0.05$); (4) The serum titer of antinuclear antibodies in patients with lung cancer was higher than that in the control group ($P<0.05$); (5) The proportions of CD4⁺ and CD4⁺/CD8⁺ lymphocyte subsets in patients with positive antinuclear antibodies were lower than those in patients with negative antinuclear antibodies, and the proportion of CD8⁺ lymphocyte subsets was higher than that of antinuclear antibody-negative patients ($P<0.05$). **Conclusion:** The expression of T lymphocyte subsets in peripheral blood of lung cancer patients is abnormal, and the expression level may be related to antinuclear antibody titer.

Key words: Lung cancer; T lymphocytes; Antinuclear antibodies

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前言

肺癌是一种恶性肿瘤,主要发病于肺部支气管黏膜或腺体,是全球范围内最常见的恶性肿瘤之一,其死亡率也居于恶性肿瘤最高。肺癌患者的主要临床症状咳嗽、痰中带血或咯血、喘鸣以及胸痛等症状,虽然此病无传染性,但存在一定的家族聚集性^[1,2]。据2020年全球最新癌症负担数据显示^[3],2020年中国新发癌症中,男性肺癌新发病例539181例,占男性癌症新发病例比例为31.4%;女性肺癌新发病例276382例,占女性癌症新发病例比例为22.2%,表明我国是名副其实的“肺癌大国”。当前主要治疗方法包括手术治疗、放疗或化疗,不同肺癌患者临床治疗方案的选择不仅患者临床分期和肿瘤的分化程度有关,而且与患者自身免疫功能、营养状态以及心理状况密切相关^[4,6]。外周血淋巴细胞(Peripheral blood lymphocyte)主要位于血液循环,该淋巴细胞由T细胞和B细胞组成,其中T细胞占70%~80%和B细胞占20%~30%组成^[7,8]。在机体免疫细胞中,T淋巴细胞是数目最多、最重要的功能细胞,其细胞亚群主要包括CD4⁺和CD8⁺T淋巴细胞,这些T淋巴细胞亚群在人体内的比例直接影响免疫功能^[9,10]。抗核抗体(Antinuclear antibody, ANA),是一组对细胞核内的DNA、RNA、蛋白或这些物质的分子复合物产生的自身抗体,与患者自身免疫疾病或免疫功能有关^[11-13]。然而,目前关于肺癌患者外周血T淋巴细胞亚群与抗核抗体之间关系的研究较少。本研究通过检测81例肺癌患者外周血T淋巴细胞亚群比例和抗核抗体水平,探讨肺癌患者外周血T淋巴细胞亚群与抗核抗体之间的关系。

1 资料与方法

1.1 一般资料

选择2019年1月到2021年6月在我院接受治疗的肺癌患者81例作为研究组,并选择同期81例健康志愿者作为对照组,该志愿者在我院进行体检。

纳入标准:(1)确诊为肺癌患者;(2)年龄18-75周岁;(3)临床资料完整;(4)临床分期和分化程度明确;(5)血液采集前未进行治疗。

排除标准:(1)合并其他恶性肿瘤;(2)合并免疫系统疾病、糖尿病或其他影响免疫系统的疾病;(3)合并非肿瘤引起的免疫缺陷病;(4)慢性病毒感染患者;(5)既往化疗、放疗、免疫治疗或靶向药物治疗史。

1.2 研究方法

两组研究对象均于清晨采集外周血,采用流式细胞仪(BD公司,FACSVerse™)检测外周血CD4⁺、CD8⁺和CD4⁺/CD8⁺T淋巴细胞亚群分型,同时选用将血清稀释不同倍数以检测抗核抗体滴度。比较不同性别、年龄、临床分期、分化程度以及病理类型肺癌患者外周血CD4⁺、CD8⁺和CD4⁺/CD8⁺T淋巴细胞亚群比例。同时,以血清稀释30倍是否可检出抗核抗体为基准,将肺癌患者分为抗核抗体阳性组和抗核抗体阴性组,比较两组肺癌患者外周血CD4⁺、CD8⁺和CD4⁺/CD8⁺T淋巴细胞亚群比例。

1.3 观察指标

1.3.1 外周血T淋巴细胞分型 所有研究对象采集清晨空腹外周血,离心以收集血细胞,加入红细胞裂解液以裂解红细胞,余下细胞加入CD3-PE抗体、CD4-TITC抗体和CD8-APC抗体避光孵育半小时,通过流式细胞仪分析T淋巴细胞亚型。

1.3.2 抗核抗体滴度 所有研究对象采集清晨空腹外周血,离心以收集血清,分别将血清稀释10-100倍,通过间接荧光法测定ANA血清滴度。

1.4 统计学方法

应用SPSS 22.0 统计学分析软件记录和分析本研究数据,独立样本t检验或卡方检验比较两组数据间差异, $P<0.05$ 表示差异显著具有统计学意义。

2 结果

2.1 两组外周血T淋巴细胞亚群比较

比较两组研究对象外周血CD4⁺、CD8⁺和CD4⁺/CD8⁺淋巴细胞比例,结果显示:研究组患者CD4⁺和CD4⁺/CD8⁺淋巴细胞亚群比例均显著低于对照组研究对象,而CD8⁺淋巴细胞亚群比例显著高于对照组研究对象($P<0.05$)。具体如表1所示。

表1 两组外周血T淋巴细胞亚群比较(% $\bar{x}\pm s$)

Table 1 Comparison of T lymphocyte subsets in peripheral blood between the two groups(% $\bar{x}\pm s$)

Groups	n	CD4 ⁺	CD8 ⁺	CD4 ⁺ /CD8 ⁺
Control group	81	43.82±4.55	31.69±3.62	1.38±0.19
Research group	81	31.72±4.05 [#]	38.31±3.52 [#]	0.83±0.11 [#]

Note: Compared with control group, [#] $P<0.05$.

2.2 肺癌患者外周血T淋巴细胞亚群与临床病理特征

比较81例肺癌外周血CD4⁺、CD8⁺和CD4⁺/CD8⁺淋巴细胞比例与患者年龄、TNM分期、性别、分化程度以及病理类型关系,结果显示:III+IV肺癌患者外周血CD4⁺和CD4⁺/CD8⁺淋巴细胞比例均显著低于I+II肺癌患者,而III+IV肺癌患者外周血CD8⁺淋巴细胞比例均显著高于I+II肺癌患者($P<0.05$);

小细胞肺癌患者外周血CD4⁺和CD4⁺/CD8⁺淋巴细胞比例均显著低于非小细胞肺癌患者,而小细胞肺癌患者外周血CD8⁺淋巴细胞比例均显著高于非小细胞肺癌患者($P<0.05$);而外周血淋巴细胞亚型在不同性别、年龄以及分化程度的肺癌患者中比较无显著差异($P>0.05$)。具体如表2所示。

表 2 肺癌患者外周血 T 淋巴细胞亚群与临床病理特征的相关性(%, $\bar{x} \pm s$)

Table 2 Correlation between peripheral blood T lymphocyte subsets and clinicopathological characteristics in patients with lung cancer (%, $\bar{x} \pm s$)

Indexs		n	CD4 ⁺	CD8 ⁺	CD4 ⁺ /CD8 ⁺
Gender	Male	51	31.65±4.65	38.60±3.67	0.82±0.15
	Female	30	31.84±4.06	37.82±3.26	0.84±0.15
Age	<60 years	42	31.70±4.82	38.62±3.29	0.82±0.18
	≥ 60 years	39	31.59±4.12	37.97±3.65	0.83±0.13
TNM stage	I+II	46	33.02±4.59	35.26±3.98	0.94±0.20
	III+IV	35	30.11±4.03*	42.31±3.23*	0.71±0.11*
Differentiation stage	High	46	31.62±4.23	38.60±3.65	0.82±0.16
	Low + moderate	35	31.85±4.62	37.93±3.88	0.84±0.21
Pathological types	Non-small cell	65	32.23±4.12	37.02±3.65	0.87±0.14
	Small cell	16	29.65±3.49*	43.55±4.02*	0.68±0.09*

Note: Compared with the pathological characteristics of the same index, * $P<0.05$.

2.3 两组血清抗核抗体水平比较

本比较 81 例对照组健康志愿者和 81 例肺癌患者血清抗核抗体滴度,结果显示肺癌患者抗核抗体血清滴度显著低于对照组健康志愿者($P<0.05$)。以血清稀释 30 倍是否可以检测出

抗核抗体为基准,比较两组研究对象抗核抗体检出情况,结果显示对照组研究对象抗核抗体检测阳性率为 98.47%,显著高于研究组 20.99%的抗核抗体阳性率($P<0.05$)。具体如表 3 所示。

表 3 两组血清抗核抗体水平比较

Table 3 Comparison of serum antinuclear antibody levels between the two groups

Groups	n	ANA (titer)	ANA positive (n (%))
Control group	81	1:50±7.32	76 (98.47)
Research group	81	1:30±5.39 [#]	17 (20.99) [#]

Note: Compared with control group, [#] $P<0.05$.

2.4 肺癌患者血清抗核抗体与外周血 T 淋巴细胞亚群

以血清稀释 30 倍是否可检测抗核抗体为基准将 81 例肺癌患者分为抗核抗体阳性患者($n=17$)和抗核抗体阴性患者($n=64$),比较两组肺癌患者外周血 CD4⁺、CD8⁺ 和 CD4⁺/CD8⁺

淋巴细胞比例,结果显示抗核抗体阳性患者 CD4⁺和 CD4⁺/CD8⁺ 淋巴细胞亚群比例均显著低于抗核抗体阴性患者,而 CD8⁺ 淋巴细胞亚群比例显著高于抗核抗体阴性患者($P<0.05$)。具体如表 4 所示。

表 4 肺癌患者血清抗核抗体与外周血 T 淋巴细胞亚群的相关性研究

Table 4 Correlation between peripheral blood T lymphocyte subsets and serum antinuclear antibodies in patients with lung cancer

Groups	n	CD4 ⁺	CD8 ⁺	CD4 ⁺ /CD8 ⁺
ANA positive	17	30.15±4.65 [#]	41.26±3.02 [#]	0.73±0.08 [#]
ANA negative	64	32.14±4.08	37.53±3.82	0.86±0.11

Note: Compared with ANA negative, [#] $P<0.05$.

3 讨论

在中国肺癌 2020 年新发病患者数为 82 万,是发病率最高的恶性肿瘤,并且过去 40 年,中国肺癌死亡率增加 4 倍,取代胃癌成为癌症死亡的主要原因,占中国所有癌症死亡的 27.3%^[14,15]。更为重要的是,由于肺器官的代偿性极好,所以肺癌早期的症状表现不明显,极易被忽视,当确诊时,发现大部分肺癌患者已处于中晚期,这不仅加大肺癌患者的治疗难度,且导致肺癌患者预后较差^[16,17]。此外,目前研究发现,环境污染、抽烟、职业接触、电离辐射以及自身免疫状态都与肺癌的发生发展有关,并且研究指出肺癌患者体内免疫功能抑制或紊乱导致

肿瘤细胞逃脱免疫细胞的"监测"而"逃逸",不仅会引起肿瘤细胞的恶性增殖,而且增加肿瘤细胞转移的风险^[18-20]。因此,监测肺癌患者免疫功能对选择合适的治疗方案和预测预后意义重大。

T 淋巴细胞亚群作为检测机体细胞免疫功能的重要指标,其对于诊断疾病、分析发病机制、疗效观察以及预后的检测均具有重要价值^[21,22]。本文通过比较 81 例肺癌患者和 81 例健康志愿者外周血 CD4⁺、CD8⁺ 和 CD4⁺/CD8⁺ T 淋巴细胞比例发现,肺癌患者 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞亚群比例均显著低于健康志愿者,而 CD8⁺ 淋巴细胞亚群比例较健康志愿者高,表明与健康人群相比,肺癌患者的细胞免疫功能低下。这一结果与

牛越等人^[22]以及 Karpathiou G 等人^[23]的研究结果一致,即肺癌患者外周血淋巴细胞亚群比例均显著低于健康人群,而 CD8⁺淋巴细胞亚群高于健康人群。进一步分析可知:在人体中,CD4⁺T 淋巴细胞是一种具有免疫功能的细胞,属淋巴细胞分类中的 T 辅助细胞,是很重要的直接反应机体免疫力的指标,其在健康人群外周血中含量越高,表明机体免疫功能越高^[24]。CD8⁺T 淋巴细胞作为淋巴细胞的又一亚型,其可分泌各种细胞因子进而参与机体的免疫作用,可杀伤某些病毒、肿瘤细胞等抗原物质。该细胞和自然杀伤细胞一起构成机体重要防线,用于机体抗病毒以及抗肿瘤免疫,所以在恶性肿瘤患者体内多表达升高^[25]。而 CD4⁺/CD8⁺ 在人体内相对稳定,只有当机体免疫功能出现紊乱时才会发生变化,在临床上被用于评估患者免疫功能^[26]。

此外,为了进一步探究肺癌患者外周血淋巴细胞亚群与临床病理特征之间的相关性,本研究在不同肺癌患者中比较外周血淋巴细胞亚群比例后发现 CD4⁺ 和 CD4⁺/CD8⁺T 淋巴细胞亚群比例随肺癌患者临床分期升高而降低,而 CD8⁺T 淋巴细胞正相反;小细胞肺癌患者外周血 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞比例均显著低于非小肺癌患者,而 CD8⁺ 淋巴细胞比例均显著高于非小肺癌患者表明肺癌分期越高患者免疫功能越低,且小细胞肺癌患者免疫功能更低。这一结果与 Lee PH^[26]和李爱杰^[27]等人研究结果一致,即 CD4⁺ 和 CD4⁺/CD8⁺T 淋巴细胞亚群比例随肺癌恶性程度增高而降低,而 CD8⁺T 淋巴细胞亚群比例随肺癌恶性程度增高而增高。进一步分析可知:大多数癌细胞均在身体器官免疫力低下时所发生。此外,肺癌患者咳嗽、咯血以及胸闷胸痛等不适症状会直接影响患者饮食和身体营养状况,这将不利于患者免疫功能。

重要的是,本文研究还发现肺癌患者抗核抗体滴度显著低于健康志愿者,并且抗核抗体阳性患者 CD4⁺ 和 CD4⁺/CD8⁺ 淋巴细胞亚群比例均显著低于抗核抗体阴性患者,而 CD8⁺ 淋巴细胞亚群比例显著高于抗核抗体阴性患者,表明肺癌患者血清抗核抗体水平可能与患者自身免疫功能有关。这一结果与麦涛等人^[28]以及 Morimoto K 等人^[29]的研究一致,即肺癌患者血清抗核抗体水平升高,并且与肺癌患者疾病进展有关。进一步分析可知:在肿瘤的发展进程中,由坏死或凋亡的肿瘤细胞所释放的异常物质引起特异性抗体的产生,而抗核抗体则由恶性肿瘤细胞细胞核裂解物诱导产生,所以其水平随肺癌恶性程度升高而升高^[30]。

综上所述,本文结果表明:(1)肺癌患者外周血 CD4⁺、CD8⁺ 和 CD4⁺/CD8⁺T 淋巴细胞表达异常;(2)肺癌患者外周血 T 淋巴细胞亚群比例可能与抗核抗体水平有关。

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