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高凝状态对非小细胞肺癌患者深静脉血栓形成的影响*

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摘要 目的:探讨高凝状态对非小细胞肺癌患者深静脉血栓形成的影响,为临床治疗提供依据。**方法:**选择2010年5月至2013年6月在我院接受治疗的非小细胞肺癌患者195例,记录患者姓名、年龄、性别、病理类型、手术、临床分期、放化疗、伴随疾病、身体状况评分(eastern cooperative oncology group, ECOG 评分)及是否发生血栓等指标。调查入选患者的高凝状态指标,包括血小板(platelet, PLT)、纤维蛋白原(fibrinogen, Fib)、血浆凝血酶原时间(plasma prothrombin time, PT)、凝血酶时间(thrombin time, TT)、活化部分凝血活酶时间(activated coagulation time of whole blood, APTT)和D-二聚体(D-dimer)。**结果:**195例非小细胞肺癌患者中,PLT高于正常上限的有42例(21.5%),FIB升高的有78例(40%),TT延长的有12例(6.2%),PT缩短的有45例(23.1%),D-D升高的有60例(30.8%),APTT缩短的有15例(7.7%)。两项指标异常的有62例(31.8%),FIB和D-D升高的有32例(16.4%);三项指标异常的有27例(13.8%),PLT、FIB及D-D升高的有15例(7.7%);四项指标异常的有5例(2.6%),PLT、FIB及D-D升高,而PT缩短的有5例(2.6%)。所有患者各凝血指标中位值PLT为 $219 \times 10^9/L$, FIB为3.6 g/L, TT为13.4 s, PT为10.8 s, D-D为0.341 mg/L, APTT为29.7 s。**结论:**高凝状态对非小细胞肺癌患者深静脉血栓形成具有重要的促进作用,应受到临床的重视。

关键词:高凝状态;非小细胞肺癌;静脉血栓形成;临床意义

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Effect of the Hypercoagulability on the Formation of Deep Vein Thrombosis in Patients with Non-small Cell Lung Cancer*

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ABSTRACT Objective: To investigate the high coagulation state on the formation of deep vein thrombosis for patients with non-small cell lung cancer so as to provide a basis for clinical treatment. **Methods:** 195 patients with non-small cell lung cancer who were treated in our hospital from May 2010 to June 2013 were selected. Then the clinical data of patients such as the name, the age, the gender, the pathological type, surgery, radiation and chemotherapy, the clinical stages, with disease and health score (ECOG) and the indexes of blood clots were recorded. The high coagulation state indicators, including the PLT, the fibrinogen (Fib), the plasma prothrombin time, the thrombin time (TT), the activated partial thrombin time (APTT) and the D dimer (D-D) of patients were detected and analyzed. **Results:** Among the 195 patients with non-small cell lung cancer, 42 cases (21.5%) with the PLT that higher than the normal, 78 patients (40%) with the FIB elevated, TT extended in 12 cases (6.2%), PT a shortened in 45 cases (23.1%), D-D rising in 60 cases (30.8%), APTT shortening in 15 cases (7.7%). Two indicators of abnormal in 62 patients (31.8%), FIB and D-D rise in 32 cases (16.4%); There are three indicators of abnormal 27 cases (13.8%), PLT, FIB and D-D rising in 15 cases (7.7%). There were four indicators of abnormal in 5 cases (2.6%), PLT, FIB and D-D higher, and PT lower in 5 cases (2.6%). The median blood coagulation indexes were: PLT $219 \times 10^9/L$, FIB 3.6 g/L, TT 13.4 s, PT 10.8 s, D-D 0.341 mg/L, APTT 29.7 s. **Conclusions:** High coagulation state plays an important role in the promotion of deep vein thrombosis for patients with the non-small-cell lung cancer that should be brought to the attention in the clinical.

Key words: Hypercoagulability; Non-small-cell lung cancer; Deep vein thrombosis; Clinical significance

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前言

高凝状态(hyper-coagulable state, HCS)是指多种因素引起的血管内皮损伤,止血、凝血、纤溶及抗凝系统功能失调的一种病理过程,而血液凝固性增高则容易导致血栓形成等血液系统

发生改变^[1,2]。非小细胞肺癌(Non small cell lung cancer, NSCLC)属于肺癌的一种,它包括鳞癌、腺癌、大细胞癌,发病率和死亡率居癌症的首位。研究表明,非小细胞肺癌患者深静脉血栓(deep venous thrombosis, DVT)的发生率为13.6%^[3-5]。近年来,高凝状态对恶性肿瘤患者并发症发生的影响越来越受到重

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视^[9]。本文拟对非小细胞肺癌高凝状态实验室特征进行研究,分析 195 例非小细胞肺癌患者高凝状态的临床资料,期望能够为非小细胞肺癌合并静脉血栓的早期诊治及预防提供依据。

1 资料与方法

1.1 患者资料

选择 2010 年 5 月至 2013 年 6 月在我院接受治疗的非小细胞肺癌患者 195 例,均获得影像学、病理学及细胞学诊断为腺癌、鳞癌及大细胞癌的患者。其中男性患者 132 例,女性患者 63 例;年龄 32-75 岁,平均年龄为(59.8±3.7)岁。

1.2 数据收集

记录患者姓名、年龄、性别、病理类型、手术、临床分期、放化疗、伴随疾病、身体状况评分(eastern cooperative oncology group, ECOG 评分)及是否发生血栓等指标,调查入选患者的高凝状态指标,包括血小板(platelet, PLT)、纤维蛋白原(fibrinogen, Fib)、血浆凝血酶原时间(plasma prothrombin time, PT)、凝血酶时间(thrombin time, TT)、活化部分凝血活酶时间(activated coagulation time of whole blood, APTT)和 D-二聚体(D-dimer)。

1.3 统计学方法

采用 SPSS17.0 统计软件进行分析,各指标采用单样本 t 检验,计量资料采用均数±标准差($\bar{x} \pm s$)。

2 结果

非小细胞肺癌(non-small cell lung cancer, NSCLC) 195 例患者中,PLT 高于正常上限 42 例(21.5%),FIB 升高 78 例(40%),TT 延长 12 例(6.2%),PT 缩短 45 例(23.1%),D-D 升高 60 例(30.8%),APTT 缩短 15 例(7.7%)。两项指标异常 62 例(31.8%),FIB 和 D-D 升高 32 例(16.4%);三项指标异常 27 例(13.8%),PLT、FIB 及 D-D 升高 15 例(7.7%);四项指标异常 5 例(2.6%),PLT、FIB 及 D-D 升高,而 PT 缩短 5 例。

对 195 例患者各凝血指标进行单样本 t 检验,PLT 为 $235.76 \times 10^9/L$ (95%CI 221.03~250.49 $\times 10^9/L$),FIB 为 3.77 g/L (95%CI 3.56~3.99 g/L),TT 为 13.55 s (95%CI 13.22~13.87 s),PT 为 12.29 s (95%CI 10.85~13.73 s),DD 为 0.624 mg/L (95%CI 0.452~0.797 mg/L),APTT 为 30.19 s (95%CI 29.48~30.9 s)。195 例患者各凝血指标中位值 PLT 为 $219 \times 10^9/L$,FIB 为 3.6 g/L,TT 为 13.4 s,PT 为 10.8 s,D-D 为 0.341 mg/L,APTT 为 29.7 s。

3 讨论

恶性肿瘤与凝血功能之间存在一定的关系,可能会导致出血及血栓性并发症的发生。研究显示,恶性肿瘤患者发生 VTE 的可能机制为以下三方面:①血液成分异常;②管壁损伤;③血管内皮损伤。异常的静脉血管壁导致血浆凝血蛋白质和纤维蛋白原在血管内过度聚积,并与瘤细胞或良性基质细胞及前凝血物质一起形成血栓^[7-10]。本研究共观察 195 例 NSCLC 患者的临床资料,发现 170 例患者(87%)出现不同程度的凝血指标异常,9 例患者存在静脉血栓形成。

纤维蛋白原(Fibrinogen, FIB)是由肝脏产生的人体内重要的凝血因子,被激活后可转变为纤维蛋白多聚体,具有极强的交织网络功能,可使血细胞形成血块,也可与血小板膜表面糖蛋白结合而介导血小板聚集反应^[11,12]。据研究显示,恶性肿瘤、深静脉血栓形成、糖尿病及其引起的酮症酸中毒、急性心肌梗死、冠状动脉粥样硬化性心脏病等容易引起 FIB 升高,而重症肝炎、肝硬化、原发性纤维蛋白溶解症等易引起其降低^[13]。本研究中,78 例患者 FIB 升高,说明肿瘤细胞进入血液后与血管内皮细胞及血小板相互作用,释放生物活性物质,促使血小板激活,血小板分泌的富组氨酸糖蛋白(HRG)与 FIB 结合可阻止 FIB 的降解,最终导致 FIB 升高。D-二聚体(D-dimer)是纤维蛋白单体活化因子交联后,再经纤溶酶水解作用下所产生的一种特异降解产物,升高反映机体凝血和纤溶系统的双重激活,是血管中纤维蛋白形成的敏感指标,间接反映了血管内皮受损,可作为体内高凝状态和纤溶亢进的分子标志物之一^[14]。本研究中,非小细胞肺癌患者 D-二聚体数值升高,提示血栓患者体内存在高凝状态及纤溶亢进。凝血酶原时间(Prothrombin Time, PT)能够反映外源性凝血系统发生异常,PT 缩短见于高凝状态,PT 延长见于先天性凝血因子缺乏、获得性凝血因子缺乏应用肝素、血液循环中存在凝血酶原、因子 V 及纤维蛋白原等物质的抗体等^[15,16]。活化部分凝血活酶时间(Activated Partial Thromboplastin Time, APTT)则是内源凝血系统较为常用检测标志物,APTT 增高主要为纤维蛋白原缺乏症、血浆中凝血因子缺乏等,而 APTT 降低则表明体内高凝^[17,18]。凝血酶时间(Thrombin time, TT)延长提示抗凝系统处于激活状态^[19]。本研究成果显示,非小细胞肺癌患者 FIB 升高,TT 和 D-D 升高,PT 和 APTT 缩短,几项指标中,PT、APTT 和 FIB 是反应凝血系统的指标,D-D 是反应纤溶系统的指标,PT 和 APTT 缩短,TT、FIB 和 D-D 升高均提示高凝状态。结果说明,非小细胞肺癌患者的凝血纤溶系统发生异常。既往研究表明,APTT,PT 和 TT 在恶性肿瘤的阳性率亦可达 10%,PT、TT、APTT 时间缩短见于血液高凝状态,这与本研究结果基本一致^[20]。

综上所述,高凝状态对非小细胞肺癌患者深静脉血栓的形成具有促进作用,应受到临床的重视。但有关非小细胞肺癌患者血浆 PT、APTT、TT 值的变化报告尚不统一,这可能与病例的选择、样本数量等因素有关,我们将在后续研究中需扩大样本继续探讨非小细胞肺癌高凝状态的实验室特征及其防治。

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