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Research on the Relationship among VEGF, Tissue Factor, D-Dimer and Lung Cancer*

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ABSTRACT Objective: To investigate the relationship among boold levels of vascular endothelial growth factor (VEGF), tissue factor (TF), D-Dimer and thromboembolic events in patients with lung cancer. **Methods:** From March to September 2013, 83 cases of the first diagnosis lung cancer patients of the affiliated hospital of Qingdao University were collected as lung cancer group, 11 lung cancer patients accompanied with venous thromboembolism (VTE) as lung cancer with VTE group and 80 normal healthy as controls. VEGF, TF and D-Dimer levels in serum were detected by enzyme-linked immunosorbent assay (ELISA). The correlation among VEGF, TF, D-Dimer and lung cancer was analyzed. **Results:** VEGF, TF and D-Dimer levels in serum of lung cancer group and lung cancer with VTE group were significantly higher than that in normal control group ($P < 0.05$). VEGF, TF and D-Dimer levels of lung cancer with VTE group were observably higher than that in lung cancer group ($P < 0.05$) . The expression of VEGF and TF and D-Dimer was positively correlation in lung cancer with VTE patients. **Conclusions:** VEGF, TF and D-Dimer are important marks of lung cancer patients accompanied with thromboembolism events. The risk of venous thrombosis of lung cancer patients can be evaluated by measuring the levels of VEGF, TF and D-Dimer, in order to applicate anticoagulant therapy pertinently.

Key words: Lung cancer; VEGF; TF; D-Dimer; VTE

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Introduction

Lung cancer is one of the malignant tumor, with the way of people's life and environment changing, many countries have reported that the incidence and mortality of lung cancer increased significantly in recent 50 years, it threatens to human's health and life greatly. The risk of venous thrombosis in lung cancer patients is increased 20-fold compared to the general population[1]. It is the second cause of lung cancer patient's death. Research proved that the root cause of thrombosis is lung cancer patients accompanied with hypercoagulability, meanwhile, hypercoagulability is correlative with invasion and metastasis[2]. It attaches great importance to prevent and treat hypercoagulability. This study was to investigate the relationship between VEGF, TF, D-Dimer and prognosis, thromboembolic events.

1 Materials and Methods

1.1 General Information

From March to September 2013, 83 cases of the first diagnosis lung cancer patients of the affiliated hospital of Qingdao University were collected as lung cancer group (all diagnosed by cell or tissue pathology, excluding serious heart, liver, kidney and thrombotic diseases, etc). 45 male patients, 38 female patients, with median age of 64.3 (range, 29-89) years. 11 lung cancer patients accompanied with venous thromboembolism as lung cancer with VTE group (all diagnosed by CT, pulmonary angiography or color Doppler ultrasonography). 7 male patients, 4 female patients, with median age of 58 (rang, 33-78) years. 80 normal healthy as controls (didn't use any anticoagulant drugs in the past three months). 42 male patients, 38 female patients, with median age of 56.3 (rang, 20-76) years.

1.2 Specimens Collected

Fasting blood of all subjects were collected and put in a centrifuge (3000r/min) 15 minutes. Serum was collected and stored in -80℃ refrigerator to be tested.

1.3 Measurement Method

VEGF, TF and D-Dimer levels in serum were detected by enzyme-linked immunosorbent assay (ELISA). Elisa Kit was provided by ALTRU Biomedical Inc.

1.4 Statistical Analysis

SPSS17.0 software was used to statistical analyze the data. Statistical comparisons were done by using one-way analysis of variance. Significant differences between groups were resolved using the LSD-t test. Data were denoted as mean± SD. Correlation analysis was performed with Sperman correlation analysis between VEGF and TF and D-Dimer. Values of $P < 0.05$ were considered to be statistically significant.

2 Results

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VEGF, TF and D-Dimer levels in serum of lung cancer group and lung cancer with VTE group were significantly higher than that in normal control group. VEGF, TF and D-Dimer levels of lung cancer with VTE group were observably higher than that in lung cancer group. The expression of VEGF and TF and D-Dimer is positively correlation in lung cancer with VTE patients (r= 0.54, 0.27, P< 0.05) (Table 1).

Table 1 The levels of VEGF, TF and D-Dimer in serum were compared between groups($\bar{x}\pm s$)

Groups	number(n)	VEGF(pg/mL)	TF(pg/mL)	D-Dimer(μg/L)
Lung cancer	83	(273.46± 102.08) *	(1253.76± 239.95) *	(476.32± 328.17) *
Lung cancer with VTE△	11	(483.75± 116.53) *△	(1479.32± 281.04) *△	(1343.74± 481.29) *
Controls	80	(182.21± 63.75)	(597.62± 195.13)	(271.46± 152.13)

Note: *Denotes difference at an obviously significant level (P<0.05), compared with the controls.

△ Denotes difference at an obviously significant level (P<0.05), compared with the lung cancer.

3 Discussion

Thromboembolic disease is one of the main reason shortening lifecycle of cancer patients. The pathogenesis of thrombotic disorders in patients with cancer includes hypercoagul ability, venous stasis, and vessel wall damage [3]. One hundred years ago, Annand Trousseau observed that malignant tumor patients were often accompanied with vein thrombosis, and proposed the relationship between lung cancer and thrombus[4]. It has been demonstrated that lung cancer patients with VTE have a 2-4-fold decreased survival during the first year[5,6]. The immediate cause of death in 10 percent lung cancer patients is pulmonary embolism. adenocarcinoma is the most, accounting for 70 percent. 70 percent of these cases are attributable to a presumptive deep vein thrombosis caused by the hypercoagulable state of malignancy [7]. Therefore, it is very important to early detect and prevent that lung cancer patients accompany with vein thrombosis.

Vascular endothelial growth factor (VEGF) is a multifunctional glycosylation secretory polypeptide factor, molecular weight is 34 ~42kD, the sequence is highly conserved, its glycoprotein monomer connecting by disulfide bone becomes dimer, it will have biological activity. VEGF is the most powerful and specific angiogenesis regulation factor, among various cell factors participating in tumor angiogenesis. VEGF promotes the establishment of newborn vascular net and neovascularization by stimulating proliferation of endothelial cells. The expression of it is closely related with the proliferation of the newborn blood vessels and density of the micrangium in tissues. Furthermore, VEGF regulate vascular permeability by changing the integrity of some vascular bed endothelial structure. As a result of blood vessels wall more vulnerable causes thrombosis, in addition, the abnormally rise of vascular permeability elevating blood viscosity is another important factors. Studies proved that VEGF had both antithrombotic and thrombotic effect[8]. Cacciola discovered that there existed a positive correlation between the VEGF level in serum of polycythemia vera patients and the incidence of thrombosis[9]. Prior to chemotherapy a 100 μg/mL increase in serum VEGF was associated with a 40% increased risk of VTE, while a 10 μg/ml increase in plasma VEGF was associated with a 20% increased risk of VTE [10]. Most patients with proven symptomatic VTE can be safely anticoagulated, including those receiving anti-VEGF therapy, such as bevacizumab [11]. This study confirmed that the expression of VEGF increased obviously in lung cancer group and lung cancer with VTE group, and VEGF was positive correlation with TF and D-Dimer.

Tissue factor (TF) is a strong promoter causing the blood-coagulation in vitro and vivo and plays an important role in a series of pathophysiology process such as hemostasis, tissue repair, thrombosis. TF has a shorter cytoplasmic domain, which mediates several downstream signaling effects, including activation and upregulation of VEGF[12]. TF promotes tumor angioge-nesis by up-regulating the expression of VEGF and inhibiting the production of angiogenin. The mechanism of TF promotes the expression of VEGF mainly by singal transduction of cytoplasmic tail and intracellular singal transduction of TF-FⅦa complex and thrombin activating protease-activated receptors of cell surface [13]. Associations have been proved between TF expression and microvessel density in lung cancer[14], throughout all gastrointestinal cancers[15-18], prostate cancer [19], and gliomas [20]. The relationship between TF and VEGF expression are described in breast cancer [14,21] and prostate cancer[22]. D-Dimer is end products after cross-linked fibrin of thrombin and factor XⅢ impacting being degraded by plasmin. It is the minimum fragment of fibrin degradation products. Elevated levels of it marks dual activation of blood coagulation and fibrinolysis system, which is sensitive and specific indicators of secondary fibrinolytic hyperfunction. This study showed that VEGF and D-Dimer levels were positively correlated in lung cancer group and lung cancer with VTE group.

In conclusion, it was demonstrated that VEGF not only involved in the proliferation of newborn blood vessels but also was important marker of lung cancer patients with venous thrombosis. The risk of venous thrombosis in lung cancer patients can be speculated by measuring VEGF, TF and D-Dimer levels in serum and anticoagulants can be used preventively.

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VEGF、组织因子及 D- 二聚体与肺癌关系的研究 *

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摘要 目的:探讨肺癌患者血浆 VEGF、组织因子及 D- 二聚体水平与并发静脉血栓的关系及其相关性。**方法:**收集 2013 年 3 月至 2013 年 9 月,青岛大学附属医院收治的初诊肺癌患者 83 例为肺癌组,肺癌并静脉栓塞组 11 例,健康体检组 80 例,应用酶联免疫吸附(ELISA)法测定 VEGF、TF、D- 二聚体的水平并进行比较分析。**结果:**肺癌组和肺癌并静脉栓塞组血浆 VEGF、TF 及 D- 二聚体水平均高于健康对照组, 肺癌并静脉栓塞组血浆 VEGF、TF 及 D- 二聚体水平高于肺癌组,VEGF 与 TF 及 D- 二聚体的表达呈正相关。**结论:**VEGF、TF 及 D- 二聚体是肺癌患者并发静脉血栓的重要标志物,可通过测定其在肺癌患者血浆中的水平来推测并发静脉血栓的危险性,以针对性应用抗凝治疗。

关键词:肺癌;VEGF;TF;D- 二聚体;静脉血栓

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