RESEARCH ARTICLE

Analysis of Relationships Between Prethrombotic States and Cervical Cancer

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Abstract

Objective: To analyze the relationship between a prethrombotic state and the occurrence of thrombosis, as well as survival time for patients with cervical cancer. Methods: Patients with first diagnosis of cervical cancer were subgrouped according to FIGO staging, and two D-dimer levels were assessed. According to the results, patients are divided into an observation group (abnormal) and control group (normal). Results: For 106 patients with cervical cancer, 38 with abnormal D-dimer, the abnormal rate is 35.9%, of which stage I accounted for 6.5%, stageII 38.5%, stage III 50%, and stage IV 61.1% (p=0.013); The level of D-dimers in stageI wass 0.87±0.68ug/ml, while in stage II it was 1.50±1.35ug/ml, stage III 2.60±1.86ug/ml and stage IV 18.6±53.4ug/ml (P=0.031); after follow-up of patients for 2-30 months, the mortality of observation group is 21.1%, while for control group it was 2.94% (p <0.01). In the observation group, survival time was 15.1±5.8 months, while for control group it was 21.0±5.4 months, the difference between two groups being highly significant (p=0.000). Conclusion: There is a direct correlation between prethrombotic state and the grade malignancy of cervical cancer. The level is positively correlated with clinical stage, and is inversely related to survival time, so that a prethrombotic state could be used to predict the prognosis for patients with cervical cancer.

Keywords: Prethrombotic state - cervical cancer - prospective studies - prognostic prediction

Introduction

Prothrombotic state, also known as hyper-coagulable state, refers to a pathological process of hemostasis, coagulation and fibrinolysis disorders caused by multiple factors (Linkins et al., 2013). Studies have confirmed that pro-thrombotic state is closely related to the tumor. The mergence of malignant tumor and pro-thrombotic state is the root cause of thrombus formation and hyper-coagulable state is related to the invasion and transference of malignant tumor (Khosa et al., 2010).

D-dimer, a specific degradation products of fibrin monomer which have experienced the cross-linking to activating factor and the hydrolysis of plasmin, is the molecular marker of coagulation and fibrinolysis activation. Its level increase specifically reflects the dual activation of blood coagulation and fibrinolysis system and it could be used as a specific marker of fibrin formation in blood vessels as well as a hyper-coagulable and fibrinolytic sign (Zhang et al., 2012). There have been little report and literature about the relationship between pro-thrombotic state and cervical cancer. How to prevent and deal with hyper-coagulable state also has not gotten much clinical attention. Adopting the prospective clinical

study method, this paper studies the relationship between pro-thrombotic state andervical cancer clinical staging as well as the survival time by detecting D- dimer of patients with cervical cancer.

Materials and Methods

General Information

From January 2012 to June 2014, 106 patients had been diagnosed as cervical cancer in gynecology and oncology department. This research follows ethical standards established by IRB. It has obtained the approval of this commission and the consent of patients and have signed informed consent with them.Case inclusion criteria: being diagnosed as invasive cervical cancer through transcervical biopsy pathology and having clinical staging for cervical cancer according to FIGO staging criteria. Among 106 cervical cancer cases who are aged from 36 to 82 years old and with a median age of 50.9 years, 98 cases are squamous carcinoma of cervix patients and 8 cases are adenocarcinoma patients. They are divided into two groups according to D-dimer value: abnormal D-dimer value group, a total of 38 cases, and normal group, a total of 68 cases. Tumor staging: the observation group:

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2 cases in first stage, 15 cases in second stage, 11 cases in third stage, 10 cases in fourth stage; the control group: 29 cases in first stage, 24 cases in second stage, 7 cases in third stage and 8 cases in fourth stage. In observation group, 24 cases mainly have had surgical treatment and 14 cases mainly have had radio-chemical treatment, while in control group, 31 cases mainly have had surgical treatment and 37 cases mainly have had radio-chemical treatment. Both groups have excluded their combination with other malignant cancer, diabetes, cirrhosis and other diseases and they had not received radiotherapy and chemotherapy before diagnosis. Besides, the differences of two groups in terms of age and treatment was not significant ($P>0.05$), so they are comparable.

Methods

We phlebotomize 3ml in early morning and place it anticoagulant tube which contains 1/10 volume of anticoagulant (0.109mol / L sodium citrate). Then we gently mix them by inversion and centrifuge 3000/min in 10 min and then collect the supernatant (plasma) so as to put it in -20°C refrigerator. All tests have plasma separation were within 2h after blood collection and they are completed within 4h. We have used Sysmex CA7000 automatic coagulation analyzer and related reagents to detect D-dimer levels.

Statistical Treatment

We have adopted SPSS 19 statistical software, with $\bar{x}\pm s$ as mean value, analysis of variance as the method of group comparison, $P<0.05$ difference as statistically significance and Kaplan-Meier method to have survival analysis.

Results

The incidence of pro-thrombotic state

Among the 106 cases of cervical cancer, D-dimer value of 38 cases are abnormal and their abnormal rate is 35.9%, among which the first stage patients occupy 6.5% (2/31), the second stage 38.5% (14/39), the third stage 50.0% (9 / 18), the fourth stage 61.1% (11/18), so the comparative difference between each of the groups was significant ($x^2 = 3.792, P = 0.013$).

D- dimer levels and tumor stage

In this group of cases, the D-dimer level of the first stage of 31 cases is $0.87\pm0.68\mu$g/ml; 39 cases of the second stage is $1.50\pm1.35\mu$g/ml; 18 cases in the third stage is $2.60\pm1.86\mu$g/ml ; 18 cases in the fourth stage is $18.58\pm53.37\mu$g/ml, so the comparative difference between each of the groups was significant (F=3.072, $P= 0.031$).

D- dimer and survival time

The deadline of follow-up study of all patients is June 2014 and the time of follow-up study is 2-30 months. The overall survival time of observation group is 15.1 ± 5.8months, that is, and that of the control group is 21.0 ± 5.4months. So the comparative difference between each of the groups was significant (F = 28.257, $P = 0.000$). During follow-up, 8 cases dead in the observation group,
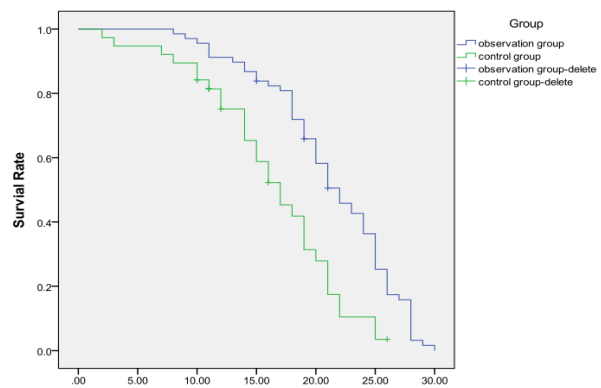

Figure 1. Overall Survival (Months)

with the mortality rate as 21.05% and 2 cases dead in the control group, with the mortality rate as 2.94%, so the comparative difference between each of the groups was significant ($x^2 = 11.60, P <0.01$) (Figure 1).

Discussion

Prothrombotic state, also known as hyper-coagulable state, is a pathological state caused by increased blood coagulation due to hemostatic function hyperthyroidism or decreased anti-thrombotic function (Zhao et al., 2013). Aramnd Trousseau first reported cases of cancer patients with migratory phlebitis in 1865 and in 1872 this scholar reported that "even without the presence of inflammation, spontaneous coagulation is likely to happen in malignant tumor cases which is called Trousseau's syndrome (Cao et al., 2013). Since then, prothrombotic state began to receive clinical attention.

Studies have shown (Uppal et al., 2012; Lauw et al., 2013; Abu Saadeh et al., 2013), tumor cells can destroy the balance of blood coagulation-anticoagulation-fibrinolytic system by a variety of mechanisms, so that the body is in a prothrombotic state. Tumor growth can destroy the vascular wall or compress blood vessels and cause vascular endothelial cell damage and release pro-coagulant and finally cause the pro-thrombotic state. Tumor cells can also adhere to vascular endothelium and release tissue factors (TF) having procoagulant activity, cancer pro-coagulant (CP), plasminogen activator inhibitor-1 (PAI-1), human fibrinogen-like protein2 (hfgl2) and induce inflammation as well as release cytokines, directly or indirectly causing damage to the vessel wall, thereby activating the blood coagulation system and finally causing coagulation disorders. In addition, surgery, chemotherapy, hormonal therapy, catheter therapy and some medications can also cause the hypercoagulable state.

Cervical cancer is the most common gynecologic malignancies and reports of its incidence of prothrombotic state vary (Cui et al., 2015). Liu (Liu, 2013) studied 76 cases of cervical cancer. They found that the incidence of prothrombotic state is 48.6% and the D-dimer level of metastas is higher than that of those without distant metastasis. Besides, the positive rate and D-dimer levels increase as the increase of malignant degree and staging. Hu (Hu et al., 2013) studied 166 cases of squamous carcinoma of cervix and found that blood D-dimer levels of non-metastasis group is higher than that of metastasis

group (1.0642 ± 0.899mg/L vs 0.6164 ± 0.355mg/L). The difference is significant, indicating that the abnormalization of blood D-dimer level is related to tumor size and vascular infiltration. Luo (Luo et al., 2014) have a retrospective analysis of clinical data of patients with cervical carcinoma surgery. they found that D-dimer level of cervical cancer is higher when compared with benign cervical lesions and that D-dimer levels were significantly decreased after surgery. Besides, they also found that D-dimer level increase is the independent risk factor of venous thromboembolism's formation of early invasive cervical cancer three days after the surgery and that the formation of venous thromboembolism is a major reason causing the death of surgical patients. This set of data show that the incidence of prothrombotic state is 35.9%. In subgroup analysis, the incidence rate of tumor stage one to four were 6.5%, 38.5%, 50.0% and 61.1%, showing that the incidence rate of prothrombotic state increases along with the increase of disease stage, which is in line with literature reports (Cui et al., 2015; Fidan et al.2013), indicating the close relationship of prothrombotic state and cervical cancer and that the more later the prothrombotic state, the higher the incidence rate of cervical cancer. However, due to small samples number, this result still needs further clinical validation.

The incidence of prothrombotic state of cervical cancer, on the one hand, is associated with thrombotic events, leading to life quality decrease or even death of patients. In a recent related study including 235, 149 cases of malignant tumor patients, the incidence rate of the combination of tumor with thrombus is up to four percent to twenty percent and the autopsy rate is about fifty percent. Besides, A high incidence of thromboembolism has been observed in the first few months after the diagnosis of malignant tumor, especially three months after it, with OR as 53.5 (95% CI 8.6~334.3) (Cao et al., 2013). Caine et al (2002) thought that 20% of venous thromboembolism occurs in tumor patients, 15% of all cancer patients will have symptomatic venous thromboembolism and venous thromboembolism would be discovered in 50% of them in autopsy. Venous thromboembolism is often fatal. Up to 30% of patients die from thrombotic diseases within 30 days. The mortality rate per year of cancer patients combined with thrombus is three times of that of non-cancer patients. Therefore, thromboembolic events has become the second largest cause of death in cancer patients (Lyman et al., 2007).

On the other hand, the incidence of cervical cancer prothrombotic state is also closely related to tumor transference. Prothrombotic state is not only pathological reflection induced by tumor but also is likely to become an important causing factor of tumor and an independent risk factor for cancer prognosis. According to the clinical study of Hu (Hu et al., 2010) on the blood hyper-coagulable state of 180 cases of cancer patients, D-dimer levels were not significantly associated with tumor stage and the D-dimer in early tumor group, locally advanced group and distant metastasis gradually increased, suggesting that D-dimer content in plasma is related to tumor staging. This study shows that, compared with first and second stage, D-dimer level in third and three stage of cervical cancer

significantly increases, the differences are statistically significant and the comparative difference between each of the groups was significant, indicating that the more later the tumor stage is, the higher the D-dimer levels, and then the higher D-dimer levels, On the contrary, it also shows that along with the development of tumor, the incidence of prothrombotic state would increase and its expression extent is associated with tumor malignant degree and progression of disease (Zhao et al., 2014). Why it happens? On one hand, prothrombotic state has participated in the invasion and metastasis of tumor cells, so it shows the invasiveness of tumor cell. In the development period of malignant tumor, due to the constant infiltration, transference and destruction of tumor cells, pro-coagulant continues to enter into the blood, directly or indirectly activating coagulation process. By adhering with micro-thrombus, malignant tumor cells are colonized in vascular endothelium so as to evade the immune attacks and extravasate into surrounding tissues, thereby promoting the invasion and metastasis of tumor cells. On the other hand, prothrombotic state is closely related to disease progression, tumor staging, tumor angiogenesis, metastasis, cell adhesion, spreading movement and cell proliferation and differentiation (Farge et al., 2010). They have promoted tumor growth in varying degrees and their complementary relationship is more common in patients with advanced cancer. In clinical practice (Yu et al., 2013), we also found that the positive rate of plasma D- dimer of patients whose disease have been completely or partially relieved is significantly lower than that of those who do not have any relief or progression. Thus, the plasma D- dimer level in patients with malignant tumors plays a supporting role in cancer clinical staging and prognosis judgment.

This study found that the mortality rate of prothrombotic state group is 21.05%, while that of the control group is 2.94%. Besides, the survival time are respectively 15.1±5.8 and 21.0±5.4 months, which is statistically significant, indicating that prothrombotic state has great impact on patients' survival. Zhang (Zhang et al., 2014) compared the plasma D-dimer detection value of 72 cases of malignant tumors between 0 to 4 weeks before their death and 4 to 8 weeks before their death and they found that D-dimer detection value of former was significantly higher than the detection level of 4 to 8 weeks (P=0.002), indicating that D-dimer concentration level increases as the disease deteriorates. Besides, disease progression is related to the activation of coagulation and fibrinolysis system and patients in terminal stage are in hyper-coagulable state. So plasma D-dimer level increase is related to poor prognosis of terminal stage cancer patients. Therefore, prothrombotic state can not only indirectly predict the hap-penning of malignant biological behavior such as tumor invasion and metastasis. Its deterioration extent can also remind patients of its progresses and the prognosis is poor. Therefore, we believe that prothrombotic state can predict the recurrent risk of cervical cancer and that clinic should give much attention to the prothrombotic state of cervical cancer patients and even consider adjuvant therapy to prevent recurrence, if necessary (Colombo et al., 2012). On the other hand, we should discover prothrombotic state in time

in clinical work and give targeted anticoagulant therapy, which can not only reduce thrombotic events, improve the life quality of patients and prolong lifetime, but also has a practical significance in the transference of tumor and the improvement of clinical anti-tumor effects.

In summary, this study suggests that the combination of cervical cancer and pro-thrombotic state is associated with clinical staging. Cervical cancer might induce organism to show hyper-coagulable state in its incubation period or malignant tumor and thrombosis may share some common mechanisms. If this assumption is correct, then anticoagulant drugs can interfere not only with the malignant transformation of cells but also the development of tumors (Bobek et al., 2012). Therefore, pro-thrombotic state can be used as an important index of clinical staging and prognosis prediction. Besides, discovering prothrombotic state and giving anti-coagulation therapy timely and improving blood hyper-coagulable state may have positive clinical significance in reducing thrombotic events, improving the life quality of patients, prolonging lifetime and preventing tumor invasion as well as transference. This could also be another important aspect in anti-tumor treatment.

Acknowledgements

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