RESEARCH COMMUNICATION

Vascular Events in Lung Cancer

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Abstract

Background and aims: In lung cancer, many factors have prognostic significance, including thrombocytosis, which is frequently observed. Associations between vascular events, which are the outcomes of paraneoplastic symptoms, and mortality and morbidity has been evaluated in many studies. The aim of the present study was to evaluate the relationship between thrombocytosis and vascular events. Materials and Methods: In total, 281 patients, who were histopathologically diagnosed with lung cancer between March 2007 and August 2009, were evaluated retrospectively. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (ver. 11.5 for Windows). Analysis of the distribution of constant variance for normality was assessed using the Shapiro-Wilk test. Nominal variables were evaluated using Pearson's chi-squared or Fisher's exact chi-squared tests. Significant correlations between continuous variables were investigated using Spearman's correlation test. Results: Of the 281 patients, 234 (83.3%) were males and 47 (16.7%) were females, with a median age of 60.6 (31–83 years). Histopathologically, 40 (14.2%) were diagnosed with small-cell lung cancer and 241 (85.8%) with non-small cell lung cancer. In total, 17 (6.04%) vascular events were identified: 11 (64.7%) deep vein thromboses, three (17.6%) pulmonary thromboembolisms, one (5.9%) cerebral arterial thrombosis, and one (5.9%) vena cava superior thrombosis. Thrombocytosis was not determined during thrombosis, but during subsequent visits. Conclusions: Thrombocytosis is frequently observed in patients with lung cancer. Further prospective studies are required to evaluate the need for prophylactic anticoagulants in these patients. The association between vascular events and survival, the next step of the present study, will be evaluated prospectively.

Keywords: Lung cancer - thrombocytosis - vascular event

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Introduction

Cancer increases the risk of thromboembolic events. Among the risk factors for thromboembolism are prolonged immobilization, particularly during hospital stays, surgery, and chemotherapy, with or without adjuvant hormone therapy (Prandoni, 2006). Thrombocytosis, which is frequently observed in patients with malignancies, can result in thrombosis and its prognostic significance has been indicated in patients with lung cancer (Pedersen and Milman, 1996). In the present study, we retrospectively evaluated thrombocytosis and vascular events in patients with lung cancer.

Materials and Methods

This retrospective clinical study included 281 consecutive patients with lung cancer, treated at the Atatürk Chest Diseases and Chest Surgery Education and Research Hospital between March 2007 and August 2009. The medical records of the patients were reviewed retrospectively. In total, 234 men and 47 women (average age, 60.6 years; range, 31–83), were included. Each patient was staged according to the tumour, node, metastasis (TNM) system of classification (Detterbeck et al., 2009). The histologic type according to the World Health Organization (WHO) classification was non-small cell lung cancer (NSCLC) in 240 and small-cell lung cancer (SCLC) in 41 patients. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 30, 1 in 175, 2 in 70, 3 in 4, and 4 in 2 patients.

Thrombocytosis was defined as a platelet count > 375×10^3. Platelet counts were determined using automated complete blood cell counters from ethylenediamine tetra-acetic acid (EDTA)-anticoagulated blood samples. In our laboratory, the normal range (95% confidence limit) for platelet counts is $155–375\times10^3$ μL. Deep vein thrombosis was diagnosed by venous doppler ultrasound and pulmonary embolism by computed tomography (CT) angiography. Cerebral artery thromboembolism was diagnosed by cerebral magnetic resonance (MR) scanning. Superior vena cava thrombosis and thoracic aorta thrombosis were diagnosed by spiral CT.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (ver. 11.5 for Windows). Analysis of the distribution of constant

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Table 1. Characteristics of Patients

Number of patients	281
Age	60.59 (31-83 years)
Male	234 (83.3%)
Female	47(16.7%)
Non-small cell lung cancer	240 (85.4%)
Small cell lung cancer	41(14.6%)
Platelet count > $375x10^3$	105(37.4%)
Platelet count < $375x10^3$	176(62.6%)
TNM stage	
IA	5 (1,8%)
IB	21 (7,5%)
IIA	4 (1,4%)
IIB	15 (5,3%)
IIIA	69 (24,6%)
IIIB	40 (14,2%)
IV	127 (45.2%)

Table 2. Characteristics of Vascular Events

Total	17
Deep venous thrombosis	11(%64.70)
Pulmonary thromboembolism	3(%17.64)
Cerebral artery thromboembolism	1 (%5.88)
Superior vena cava thrombosis	1 (%5.88)
Thoracal aorta thrombosis	1 (%5.88)
Platelet count > $375x10^3$	5(%29.4)
Platelet count < $375x10^3$	12(%70.6)
TNM Stage	
IA	1 (5,9%)
IIB	2 (11,8%)
IIIA	1 (5,9%)
IIIB	1 (5,9%)
IV	12 (70,5%)
Histological type	
Squamous cell carcinoma	2 (11,76%)
Adenocarcinoma	6 (35,29%)
Small cell carcinoma	2 (11,76%)
Unclassified	7 (41,17%)

variance for normality was assessed using the Shapiro-Wilk test. Descriptive statistics for continuous variables are shown as the mean±standard deviation or median (minimum–maximum), and, for nominal variables, the number of cases and percentages (%) are cited. The mean difference between groups was evaluated with Student's t-test when the number of independent groups was two and with one-way analysis of variance when the number of independent groups was more than two. Nominal variables were evaluated using Pearson's chi-squared or Fisher's exact chi-squared tests. Significant correlations between continuous variables were investigated using Spearman's correlation test. A p-value < 0.05 was deemed to indicate statistical significance.

Results

In the clinical records, 105 (37.4%) of 281 lung cancer patients manifested thrombocytosis at the first evaluation at our hospital; the characteristics of these patients are shown in Table 1. The platelet counts in NSCLC patients did not differ significantly from those in SCLC patients. Thrombocytosis was significantly associated with gender (p = 0.041); female patients manifested thrombocytosis more frequently than male patients. Additionally, thrombocytosis was more common in patients with advanced disease; the frequency of thrombocytosis was 12.5% in patients with TNM stages I and II and increased to 87.5% in patients with TNM stages III and IV. However, thrombocytosis did not correlate with clinical stage, histological type, or age.

In total, 17 (6.0%) vascular events were recorded and their characteristics are shown in Table 2. The most frequent vascular event was deep vein thrombosis (64.7%). Additionally, 82% of patients with vascular events were in advanced disease, with 29% presenting with thrombocytosis. No significant correlation was observed between vascular events and thrombocytosis, histological type, or TNM stage. Vascular events were significantly related to ECOG PS (p = 0.021): patients with vascular events had poorer PS.

Discussion

In the present study, we examined the relationship between thrombocytosis and clinicopathologic factors. At the initial evaluation at our hospital, 37% of patients had thrombocytosis, which was similar to that reported in previous studies (16–46%; Costantini et al., 1990; Gislason and Nõu, 1985; Engan and Hannisdal, 1990; Aoe et al., 2004). Thrombocytosis is usually recognized as a complication occurring at the late or terminal stages of disease, particularly in lung cancer. In our study, thrombocytosis was more common in patients with advanced disease; the frequency was 12.5% in patients with TNM stage I and II and 87.5% in patients with stage III and IV. However, thrombocytosis did not correlate with clinical stage (Pedersen and Milman, 1996; Aoe et al., 2004), histological type, or age (Tomita et al., 2008; Pedersen and Milman, 2003) as in previous studies. When we evaluated the relationship between thrombocytosis and gender, female patients manifested thrombocytosis more frequently than male patients. This may be because anemia was more common in the female patients.

Circulating platelets are known for their roles in vascular haemostasis, thrombosis, atherosclerosis, and inflammation (Jurasz et al., 2004). Although the mechanism underlying the development of thrombocytosis in lung cancer patients remains unclear, tumour-associated elevation of bone marrow-stimulating cytokines, such as interleukin (IL)-6, IL-1 (Suzuki et al., 1993; Tefferi et al, 1994; Alexandrakis et al., 2002), and macrophage colony-stimulating factor (M-CSF; Lidor et al., 1993), may be a possible mechanism (Tomita et al., 2008) because these cytokines could lead to thrombocytosis.

Haemostatic abnormalities are frequently observed in patients with malignancies. Additionally, the pathophysiological mechanisms inducing hypercoagulability in cancer patients are complex. Within the vasculature, circulating cancer cells interact with endothelial cells, leukocytes, and platelets. The activation of coagulation can be initiated by many factors: direct generation of thrombin by cancer cell procoagulants, thrombin generation by cancer cell-stimulated host cells, damage to normal tissue from tumour masses, infection, tissue necrosis, introduction of mucin into the

circulation, surgical trauma, chemotherapy toxicity, and the effects of venous access devices. Additionally, cellular mechanisms involving endothelial cells, monocytes/macrophages, and platelets play a vital role in cancer-induced abnormalities of haemostasis (Jurasz et al., 2004). In our study, the incidence of vascular events was 17 (6%) and no significant correlation was observed between vascular events and thrombocytosis, histological type, or TNM stage. Only 29% of patients with vascular events had thrombocytosis at the initial evaluation at our hospital; however, all patients had thrombocytosis during follow-up. Pederson and Milman reported that the frequency of thromboembolic episodes was 7% and did not correlate with the presence of thrombocytosis (Engan and Hannisdal, 1990). In our study, 82% of patients with vascular events were in advanced disease. Vascular events were significantly related to ECOG PS ($p = 0.021$); patients with vascular events had poorer PS.

In conclusion, thrombocytosis is frequently observed in patients with lung cancer. Cancer cells have been shown to aggregate platelets and this ability correlates with their metastatic potential. Antiplatelet drugs affect both haemostasis and cancer-induced thrombosis (Jurasz et al., 2004). Further prospective studies are required to evaluate the need for primary thromboprophylaxis in these patients. The association between coagulation parameters and survival, the next step of the present study, will be evaluated prospectively.

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