Original Article

The predictive role of thrombocytosis in identifying patients with advanced lung carcinoma in an urban medical center

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ABSTRACT

Study Objectives: Lung carcinoma is leading cause of death from cancer, thus an important subject for review. Lung carcinoma is associated with various prognostic factors including both clinical and objective findings; therefore, a review of thrombocytosis regarding predicting stage at initial diagnosis was prompted. **Materials and Methods:** A retrospective chart review of 180 patients diagnosed with lung carcinoma at Saint Michael's Medical Center between 2009 and 2013 and comparison with platelet level at time of diagnosis. The pathological diagnosis of lung cancer was made by either trans-bronchial or CT guided biopsy. **Design:** A retrospective chart review of 180 patients diagnosed with lung carcinoma at Saint Michael's Medical Center between 2009 and 2013 and comparison with platelet level at time of diagnosis. **Results:** No statistical significance was determined between advanced (including advanced staging of small cell lung cancer [SCLC] and Stage IIIb-IV of non-SCLC [NSCLC]) lung cancer staging and elevated platelet level ($P = 0.078$ and confidence interval [CI] of −89.103–4.774). However, on a subgroup analysis of cases including only NSCLC showed a statistically significant difference between limited and advanced stages ($P = 0.0.18$ and CI of −95.756–9.104). **Conclusions:** Thrombocytosis is associated with various neoplasms, included lung cancer as indicated in this retrospective study. In fact, thrombocytosis has been implicated with advanced staging of both SCLC and NSCLC, therefore indicating poor outcomes and mortality.

Key words: Advanced lung cancer, predictor, thrombocytosis

INTRODUCTION

According to the recent World Health Organization reports, lung cancer is the most common type of malignancy and the leading cause of death from cancer, approximately 19.4% of cancer deaths per annum.[1] Therefore, factors such as prognosis and mortality play a crucial role with lung cancer diagnosis, including hematologic manifestations. It began in the 1860s with French internist Dr. Armand Trousseau's correlation of malignancy and platelets leading to the diagnosis of migratory venous thrombophlebitis.[2] Over the past century, many studies have implicated the significance of thrombocytosis in various types of malignancy, with a reported incidence of 10%–57%.[3] Currently, the most important prognostic factor for both small cell lung cancer (SCLC) and non-SCLC (NSCLC) is tumor stage, with advanced stage disease being associated with worse outcomes.[4-7] In our study, we will evaluate the implication of thrombocytosis as a poor prognostic indicator with a specific patient population.

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MATERIALS AND METHODS

The study is a retrospective cohort study including an electronic medical records review of patients diagnosed with lung cancer at Saint Michael's Medical Center, Pulmonary Department, between 2009 and 2013. The Institutional Review Board of Saint Michael's Medical Center granted approval before data collection.

The study included a review of 180 patients, above the age of 18 and diagnosed by either transbronchial or computed tomography-guided biopsy, resulting in a pathological diagnosis of lung cancer. As per pathology reports and immunohistological staining, the histology subtype of lung cancer was recorded. At the time of diagnosis, platelet count and hemoglobin were noted. Excluded from the study were patients with known disorders that may cause abnormal platelet counts, which included a history of splenectomy, myeloproliferative disorder, severe liver cirrhosis, acute inflammatory disease, or prior treatment with neoadjuvant chemotherapy or radiotherapy. Study also included demographic data for participants such as age at the time of diagnosis, gender, ethnicity, comorbidities, and smoking history.

Using the updated tumor node metastasis (TNM) staging system, each lung cancer case was staged at initial evaluation and diagnosis. Further review of tumor registry records included mortality of participants; however, date of death was not documented in aforementioned records.

Upon the final review of 180 patients, several cases were excluded due to missing data, such as platelet count at time of diagnosis. Therefore, the total number of cases with complete data for statistical analysis was 106. The patients who met inclusion criteria were categorized into two subgroups: SCLC and NSCLC. The stages of lung cancer and the platelet level were compared using *t*-test. Subgroup analysis was conducted using ANOVA test. The statistical analyses were conducted using SPSS software (IBM analytics, San Antonio, Texas, USA).

RESULTS

A total of 106 case studies were included in the study, with a mean age of 65.72 years, with the minimum of 45 years and maximum of 96. In regard to ethnicity, 32.1% was African American, 21.7% was Hispanic, 17% was Caucasian, and 0.9% was Asian. Regarding gender, there were 62 male patients comprising 58.5% of the total, with 43 female patients comprising 40.6%. Due to the high correlation of tobacco use, confirmed data included 84 cases with smoking history and 14 patients with no smoking history. There was no statistically significant difference between the groups with regard to age, gender, and history of smoking [Table 1].

We categorized the types of lung cancer into NSCLC and SCLC. There were 94 cases of NSCLC, comprising 84.9%; 12 cases of SCLC, comprising 11.3%.

There were 106 with pathology reports indicating stage of lung cancer, which included limited staging (included Stage I, Stage II, and Stage IIIa) and advanced staging (included Stage IIIb and Stage IV). The number of limited stage cases was 39, comprising 36.8%, with number of advanced stage cases was 67, comprising 63.2%. The mean platelet count was 286.29, with the minimum count of 47 and maximum count of 837.

Categorizing the data in regard to limited and advanced state, the mean platelet count for the group with limited staging lung cancer was 259.64, with standard deviation of 107.697.

The mean platelet count for the group with advanced staging of lung cancer was 301.81, with standard deviation of 122.821. Although the mean platelet count was higher at the time of diagnosis of all lung cancers in advanced stage when compared to the limited stage, there was no statistical difference achieved with $P = 0.078$ and confidence interval (CI) of −89.103–4.774 [Table 2 and Figure 1].

On a subgroup analysis including only the NSCLC, the mean platelet count in limited stage and advanced stage was 255.32 and 307.75 with a statistically significant $P = 0.0.18$ and CI of −95.756–9.104 [Table 3 and Figure 2].

Table 1: Patient variable characteristics of age, gender and smoking status

Variable	Limited	Advanced	*P*
Age	65.76	65.70	0.977
Gender, male/female	21/18	41/25	0.526
Smoking, no/yes	3/31	11/53	0.158

Table 2: Platelet values categorized as limited and advanced lung cancer

Lung cancer stage at diagnosis	*n*	Mean	SD	SEM
Platelet count				
Limited	39	259.64	107.697	17.245
Advanced	67	301.81	122.821	15.005

SD: Standard deviation, SEM: Standard error of mean

Table 3: Platelet values categorized as limited and advanced lung cancer in nonsmall cell lung cancer cases

Lung cancer stage at diagnosis	*n*	Mean	SD	SEM
Platelet count				
Limited	37	255.32	84.359	13.868
Advanced	57	307.75	127.130	16.839

SD: Standard deviation, SEM: Standard error of mean

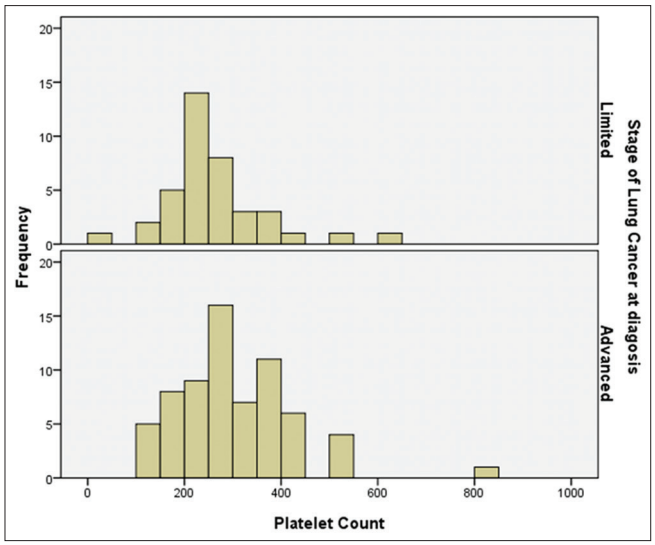

Figure 1: Histogram of the platelet count and the lung cancer stages in all the lung cancers

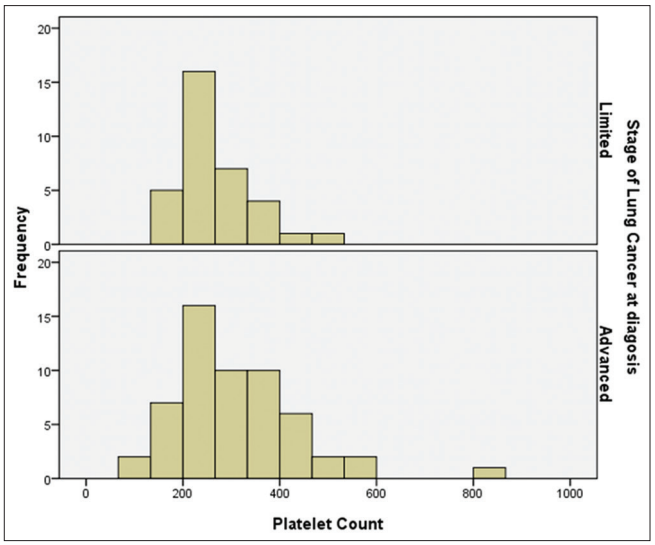

Figure 2: Histogram demonstrating platelet count in all stages of non small cell lung cancer.

DISCUSSION

The role of platelets in hematologic physiology is predominantly known as hemostasis. Cytokines, interleukins (ILs), and thrombopoietin stimulate platelet production in bone marrow as megakaryocytes. Platelets continue to circulate in the vascular space or spleen until stimulated by coagulation factors such as collagen and thrombin. During hemostasis, platelets contribute with endothelial adhesion, aggregation, and activation through release of dense and alpha granules. The coagulation cascade is initiated; platelets are recruited ultimately forming fibrin.[8]

Given the importance of platelets, thrombocytosis serves as a pathological clue to diagnosis. The evaluation of thrombocytosis involves identifying initial classification regarding etiology. Physiologic thrombocytosis is most commonly seen in postsplenectomy or postthrombocytopenia, with the body's response to overcompensate. Primary thrombocytosis involves pathology within the bone marrow, such as essential thrombocythemia, hereditary thrombocytosis, or a myeloproliferative disorder. Secondary thrombocytosis is the most commonly encountered etiology in the inpatient clinical setting. Secondary or reactive thrombocytosis is identified with a precipitating factor such as neoplasms, inflammation, infection, iron deficiency anemia, or hemolytic anemia.[9] Our study examined the correlation between neoplasm and reactive thrombocytosis.

In relation to neoplasms, there are many prognostic factors associated with lung carcinoma. Primarily, histological and pathological staging is broadly considered the most important prognostic marker. Lung cancer is classified as either SCLC (seen in 15% of cases) or NSCLC (seen in 85%). NSCLC can be further divided as adenocarcinoma, squamous cell, large cell, or bronchioloalveolar carcinoma; NSCLC is staged through TNM with Stage IIIb and IV associated with poor prognosis due to unresectable lesions or metastatic spread, respectively. SCLC is staged as either limited or extensive disease, both with a median survival of 1 year. Other prognostic factors include vascular invasion of tumor, size, inoperable lesions and presence of pulmonary symptoms not limited to superior vena cava syndrome, hemoptysis, and acute respiratory failure.[10]

In our study, we reviewed the significance of thrombocytosis in association with prognosis. Thrombocytosis is prevalent in a wide range of malignancies and has been estimated to occur in about 10%–57% of all patients. Our study involved a review of 106 patients, which included a statistical significance of thrombocytosis in NSCLC and advanced staging. Unfortunately, the true physiologic mechanism remains unclear. It has been suggested that the tumor cells induce thrombocytosis by secreting various cytokines and growth factors, such as IL-1 beta, IL-6,[11] and macrophage colony-stimulating factor.[12] Therefore, the tumor cells are responsible for causing thrombocytosis, and an increased tumor burden will result in increased tumor signaling and predisposition to thrombocytosis. However, platelets also seem to influence the growth of the malignant tumor, and several studies have indicated the use of antiplatelet agents to prevent metastasis.[13-15] Platelets may be involved in promoting hypercoagulability by providing a procoagulant surface, shielding tumors from immune system surveillance, or amplifying their growth.[14,15] Platelet-derived microparticles may promote tumor chemotaxis, adhesion, and proliferation. Various

hematopoietic proteins may be influencing such processes as angiogenesis, metastasis, and proteolysis. The precise mechanisms are only starting to be elucidated, but the list of potentially involved factors includes those secreted by the tumor, by platelets, by bone marrow endothelial cells, and by megakaryocytes. The important question that needs to be answered is whether thrombocytosis is a by-product of tumor growth, stimulated by its growth factors, or whether it represents a process that independently promotes tumor spread, thus worsened prognosis.

CONCLUSION

Thrombocytosis is observed in many types of malignancies and many studies have indicated that an elevated platelet count may portend a poor a prognosis. Even though the degree of thrombocytosis in this study is not significantly high, it does suggest that patients with advanced disease will have a poor prognosis as evidenced by the statistical significance of thrombocytosis in NSCLC and advanced stage lung cancer

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Conflicts of interest
There are no conflicts of interest.

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