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Review Article

THROMBOCYTOSIS IN SOLID TUMORS

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ABSTRACT

Thrombocytosis has been suggested to be a poor prognostic indicator in malignancies. Platelet granules contain a variety of growth factors which are secreted immediately after platelet activation which have been implicated in tumor progression and in the development of metastasis. This independent prognostic factor may provide a simple approach to improved risk stratification of patients in future clinical trials.

Key Words: *Platelets, Thrombocytosis, Interleukin-6.*

INTRODUCTION

The association of thrombocytosis with malignancies has been known for more than 100 years. [1] Studies have shown that thrombocytosis is associated with a poor prognosis in various gyanecological and non-gyanecological malignancies.[2-8] Recently, thrombocytosis was reported in patients with lung cancer,[2,3] colon[3] and renal cell carcinomas,[4] and gynecological malignancies such as cervical cancer,[5,6] ovarian cancer[7] and vulvar cancer.[8] We conducted MEDLINE and PUBMED search of the literature on the prognostic impact of thrombocytosis in gyanecological cancer, solid malignancy, renal cell carcinoma, thrombocytosis in carcinoma breast, thrombocytosis , platelet count. References of all publication were also searched.

We tried to analyse the impact of thrombocytosis on the prognosis of solid malignancies.

Thrombocytosis is defined as an elevated platelet counts above 4.5×10^9/l. Difficulties in interpreting abnormalities of the platelet count in malignancy arise because several conditions may influence the platelet levels. Malignancy is often accompanied by disseminated intravascular coagulation and bone marrow involvement, which tend to lower peripheral platelet counts. Treatment with chemotherapy and radiation therapy also decreases platelet count.

Platelets or thrombocytes are small, irregularly-shaped anuclear cell fragments which are derived from fragmentation of precursor megakaryocytes.[9] Megakaryocyte and platelet production is regulated by Thrombopoetin, a hormone usually produced by the liver and kidneys.[10, 11] Old platelets are destroyed by phagocytosis in the spleen and by Kupffer cells in the liver. A reserve of platelets is stored in the spleen and is released when needed by sympathetically-induced splenic contraction.

INTERACTION OF TUMOR CELLS AND PLATELET

The steps involved in metastasis of tumor are entry of tumor cells in the bloodstream, , an intravascular phase followed by extravasation of tumor cells from the capillaries resulting in metastasis at the distant site.

Platelets participate in tumor progression by contributing to the metastatic cascade, protecting tumor cells from immune surveillance, regulating tumor cell invasion, and angiogenesis.

thrombin is being generated either by direct contact with platelets or indirectly by stimulating tissue factor-mediated activation of the coagulation system 5 In a study by Egan et al, that ovarian cancer induced platelet activation is mediated by adenosine 59-diphosphate released from tumor cells and can be blocked by adenosine 59-diphosphate receptor (P2Y12 and P2Y1) antagonists.6 Certain studies have also shown that tumor cells could lead to secretion of dense granules containing adenine nucleotides via the platelet Fcg receptor IIa.7 Platelet activation by tumors throughout all phases of the metastatic cascade leads to the release of platelet-derived factors stored in their granules that then mediates the inflammatory, proliferative, and proangiogenic activities of platelets to promote tumor growth, tissue invasion, and metastasis.8,9

The platelets secrete thrombospondin-1 which facilitates the adhesion of tumor cells to the endothelium, promotes extravasation in the metastatic cascade.[18] The thrombospondin levels have found to be elevated in women with gynecologic malignancies. Once the tumor cells have exited circulation, factors derived from activated platelets are able to induce neoangiogenesis thereby enabling growth at the metastatic site.[20] In addition, platelets secrete a lysophosphaditic acid a bioactive lipid with growth factor like signaling properties as a driving mechanism in bone metastasis by breast and ovarian cancer cells.Interleukin-6 has been associated with ovarian cancer related thrombocytosis. Studies have demonstrated a strong association between ascitic fluid Interleukin-6 levels and circulating platelet counts.[21,22]

Platelets participate in tumor progression by contributing to the metastatic cascade, protecting tumor cells from immune surveillance, regulating tumor cell invasion, and angiogenesis. Platelets contain one of the largest stores of angiogenic and mitogenic factors and the tumor vasculature is leaky, which allows platelets to come in contact with the tumor and deposit multiple angiogenic factors including vascular endothelial growth factor (VEGF) and thrombin to tumor cells, which in turn contributes to tumor progression.[18]

The pathophysiological mechanism of reactive thrombocytosis may be tumor-associated elevations of circulating platelets mediated by a direct promotion of megakaryocytopoiesis by tumor-derived humoral factors. Interleukin-6 (IL-6) and macrophage colony-stimulating factor (M-CSF) may be responsible for the development of cancer-related thrombocytosis. IL-6 is a potent stimulator of megakaryocytopoiesis and tumor cells have been shown to release IL-6 both *in vitro* and *in vivo*. These observations strongly suggest a role for IL-6 in tumor-associated thrombocytosis.[16,17]

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The average lifespan of a platelet is normally just 5 to 9 days. Platelets play a fundamental role in hemostasis and are a natural source of growth factors. They circulate in the blood of mammals and are involved in hemostasis, leading to the formation of blood clot. Platelets release a multitude of growth factors including Platelet-derived growth factor (PDGF), a potent chemotactic agent, and TGF beta, which stimulates the deposition of extracellular matrix. [12,13] Both of these growth factors have been shown to play a significant role in the repair and regeneration of connective tissues. Other healing-associated growth factors produced by platelets include basic fibroblast growth factor, insulin-like growth factor-1, platelet-derived epidermal growth factor and vascular endothelial growth factor.[14, 15]

Haemostatic abnormalities are frequently observed in patients with malignancy. Most patients with cancer have evidence of subclinical activation of blood coagulation. Clinically, cancer patients with advanced disease are characterized by a variety of thrombo-embolic disorders. The pathophysiological mechanism of reactive thrombocytosis may be tumor-associated elevations of circulating platelets mediated by a direct promotion of megakaryocytopoiesis by tumor-derived humoral factors. Interleukin-6 (IL-6) and macrophage colony-stimulating factor (M-CSF) may be responsible for the development of cancer-related thrombocytosis. IL-6 is a potent stimulator of megakaryocytopoiesis and tumor cells have been shown to release IL-6 both *in vitro* and *in vivo*. These observations strongly suggest a role for IL-6 in tumor-associated thrombocytosis.[16,17]

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Levin and Conley were the first who reported that approximately 40% of patients with inoperable malignancies had platelet counts higher than 400 x 10^9/l.[19] A brief review of literature demonstrating thrombocytosis as an important prognostic factor for survival has been presented below.

Gynecological Tumors

The platelets secrete thrombospondin-1 which facilitates the adhesion of tumor cells to the endothelium, promotes extravasation in the metastatic cascade.[18] The thrombospondin levels have found to be elevated in women with gynecologic malignancies. Once the tumor cells have exited circulation, factors derived from activated platelets are able to induce neoangiogenesis thereby enabling growth at the metastatic site.[20] In addition, platelets secrete a lysophosphaditic acid a bioactive lipid with growth factor like signaling properties as a driving mechanism in bone metastasis by breast and ovarian cancer cells.Interleukin-6 has been associated with ovarian cancer related thrombocytosis. Studies have demonstrated a strong association between ascitic fluid Interleukin-6 levels and circulating platelet counts.[21,22]

Julian *et al*. retrospectively reviewed sixty-five patients with invasive ovarian epithelial cancer and analyzed for the association preoperative thrombocytosis with other clinical and histopathological prognostic factors. Twenty of 65 (37.5%) patients had thrombocytosis at primary diagnosis. Patients with preoperative thrombocytosis were found to have lower hemoglobin (P < 0.0002), more advanced stage disease (P < 0.05) and higher grade tumors (P < 0.02). Patients with thrombocytosis had greater likelihood of suboptimal cytoreduction. Preoperative thrombocytosis is a frequent finding in ovarian carcinomas and their association with advanced stage disease and higher grade denotes that platelets play a role in the tumor growth and progression.[23]

Zeimet *et al*. investigated 130 women with epithelial ovarian tumors, 48 of whom (37%) had early stage (stage I and II) disease. Thrombocytosis was found to be associated with advanced stage disease, higher serum levels of CA 125, greater volumes of ascites, and greater chance of suboptimal cytoreduction (defined as residual tumor >2 cm in their report). However, survival did not differ for subjects with thrombocytosis.[24]

Menczer *et al*. carried out a similar retrospective study in a cohort of 70 patients with invasive epithelial ovarian carcinoma and claimed that thrombocytosis was a poor prognostic factor in these patients. They reported a higher incidence of thrombocytosis in women with advanced stage disease, and significantly shorter periods of survival.[25].

Li *et al.* found the incidence of thrombocytosis to be 22.4% in a cohort of 183 women diagnosed with epithelial ovarian tumors. Thrombocytosis was found to be significantly correlated with advanced stage and higher grade epithelial ovarian tumors, lymph node metastases, greater volume of ascites, and less optimal tumor cytoreduction (defined as residual tumor <1 cm in their report). Subjects with thrombocytosis had significantly shorter disease-free and overall survival. Consequently, thrombocytosis was defined as the sole independent negative prognostic factor for overall survival in women diagnosed with advanced stage epithelial ovarian tumors.[26]

Gungor *et al.* investigated 292 women with epithelial ovarian tumors undergoing primary surgical exploration, of whom 124 (42.5%) had thrombocytosis. Patients with thrombocytosis were found to have statistically higher levels of preoperative CA-125 levels, more advanced stage disease, higher grade tumors, and shorter periods of survival. Thrombocytosis is a significant negative prognostic factor for survival in patients with epithelial ovarian tumors.[27]

Preoperative thrombocytosis is an independent prognostic factor in stage III and IV endometrial cancer was studied by Scholz *et al*. They reported that five year disease-free survival was influenced significantly by FIGO stage (stage III vs. stage IV), thrombocytosis and cervical involvement. Overall five-year survival was significantly influenced by stage, cervical involvement and thrombocytosis.[28]

Gorelick *et al.* evaluated the role of preoperative thrombocytosis and its association with survival in a predominantly African American and Caribbean American urban population. Fourteen (18.2%) of 77 patients exhibited thrombocytosis. The median overall

survival in patients without thrombocytosis was 24.0 ± 4.5 months (n = 21) and in patients with thrombocytosis was 7.0 ±3.8 months (n = 8, P = 0.015). Data indicated that preoperative thrombocytosis among high-risk inner-city patients with stages III to IV endometrial cancer is an independent prognostic indicator.[29]

Thrombocytosis has been suggested to be a poor prognostic indicator in patients with cervical cancer. In a retrospective study by Hernandez *et al*. cumulative survival rate for the 93 patients with normal platelet counts was 65%, whereas it was 25% for the 20 with thrombocytosis.[30] Thrombocytosis continued to correlate strongly with poor survival even when adjusted for histologic type, patient age, and disease stage. Thrombocytosis is an independent indicator of poor prognosis in patients with cervical cancer.

Lopez *et al.* reviewed pretreatment platelet counts of 643 women treated for cervical cancer between 1983 and 1992 and correlated to each patient's age, stage of disease, histologic type, node status (when available), and outcome. The 5-year survival rate for patients with thrombocytosis was 57.1%, which was significantly worse than the 76.5% for those with normal platelet counts (P < 0.01). When adjusted for stage of disease, however, thrombocytosis failed to have a significant effect on patient survival. There was also no relation between thrombocytosis and the incidence of positive lymph nodes. Thrombocytosis was not found to be an independent prognostic factor in patients with carcinoma of the cervix in this series of 643 patients.[31]

Ofer *et al.* reviewed pretreatment platelet counts of 201 women treated for vulvar cancer and correlated to the patient's age, stage of disease, node status, histologic type, and outcome. Thrombocytosis was presented in 14.92% of patients with vulvar malignancies and in 15.46% of patients with squamous cell carcinoma of the vulva. No correlation was found between thrombocytosis and tumor size, incidence of lymph node metastases, or stage of the disease. The 5-year survival rate for patients with thrombocytosis was 89.29%, which was not significantly different from the 76.47% 5-year survival of patients with normal platelet counts (*P*= 0.586). When adjusted for age, histological differentiation, number of tumors, staging, incidence of nodal metastases, platelet count, hemoglobin, and white blood count, only the staging, number of tumors, and histological differentiation were associated with an unfavorable prognosis (*P*= 0.0001,*P*= 0.003,*P*= 0.03, respectively). Thrombocytosis was not found to be a prognostic factor in patients with carcinoma of the vulva in this series of 201 patients.[32]

Breast Cancer
Susanne *et al* studied the impact of pretreatment thrombocytosis on survival in primary breast cancer. They performed a retrospective, multivariate analysis of 4,300 patients with early-stage breast cancer. All subjects participated in one of five prospective, randomized, multicenter trials conducted by the Austrian Breast and Colorectal Cancer Study Group. Pretreatment thrombocytosis was observed in 161 patients (3.7%). Estimated median OS, breast cancer-related survival and DFS for patients with versus those without thrombocytosis was 71.0 versus 99.5, 72.0 versus 100.9, and 80.4 versus 88.4 months, respectively (p = 0.0054, p = 0.0095, p = 0.0199). A multiple Cox regression model including tumor and nodal status, grading, age, hormone receptor status and pretreatment thrombocytosis identified pretreatment thrombocytosis as an independent predictive factor for OS (p = 0.0064) and breast cancer-related survival (p = 0.0162). Thus elevated platelet counts at time of diagnosis were associated with poor prognosis in breast cancer.[33]

Lung Cancer

High circulating levels of platelets are found in patients with metastatic disease and have been related to extensive disease in patients with lung cancer. Elevated levels of platelet counts have been found to be a significant prognostic factor in carcinoma of the lung. However, the association between thrombocytosis and survival has been questioned in multivariate analyses.

Pedersen *et al.* studied prognostic significance of thrombocytosis in patients with primary lung cancer.[34] The prevalence of thrombocytosis and the prognostic information provided by platelet counts were analyzed in a large cohort of patients with primary lung cancer. At the time of diagnosis, pretreatment platelet counts were retrospectively recorded in 1,115 consecutive patients with histologically proven primary lung cancer. The prevalence of thrombocytosis in patients with lung cancer was compared with that in a series of 550 consecutive out-patients with benign lung disorders. In a multivariate survival analysis, thrombocytosis continued to correlate strongly with poor survival even when adjusted for histological type, sex, age, and TNM stage. In surgically resected patients, the frequency of preoperative and postoperative thrombocytosis differed significantly (23.0 vs. 8.9%). Survival rate was significantly reduced in patients with preoperative thrombocytosis. Thrombocytosis was not associated with an increased incidence of thromboembolism. Thus, thrombocytosis is an independent prognostic factor of survival in patients with primary lung cancer.

Gastric Cancer

Thrombocytosis was first reported in patients of gastric cancer by Levin and Clooney.[19] Poor prognosis associated with thrombocytosis in patients with gastric cancer was studied by Ikeda M *et al.* Thrombocytosis was found in 42 out of 369 patients. Platelet count was negatively correlated with hemoglobin. Mean platelet count was significantly increased in patients with noncurative operations. There was a positive correlation between the depth of tumor invasion and platelet count. One- and 3-year survival expectancies in patients with or without thrombocytosis were 52.4% and 23.4% and 85.7% and 72.9%, respectively. Thrombocytosis was identified as an independent prognostic factor after lymph node metastasis and depth of tumor invasion.[35]

Esophageal Cancer

Shimada *et al.* studied the clinic pathologic significance and prognostic value of platelet counts in patients with esophageal cancer. Platelet counts were measured before surgery in 374 patients diagnosed between 1987 and 1999 with primary esophageal squamous cell carcinoma. The multivariate prognostic value of platelet counts, tumor size, and TNM factors were determined using Cox's proportional hazards model. Platelet counts were significantly increased in patients with large tumors ($p < 0.001$), deep tumors, nodal involvement, and distant metastasis in univariate analysis. Adjusting for tumor size and TNM factors, multivariate analysis indicated that thrombocytosis as defined in this study was an independent prognostic factor.[36]

Brain Tumors

Preoperative platelet counts and other clinical and hematological parameters were reviewed from the records of 153 patients diagnosed between 1999 and 2004 with histologically confirmed glioblastoma by Borkmann *et al.* in order to evaluate the prognostic significance of preoperative thrombocytosis in these patients. Univariate log-rank tests showed that the median survival time of 29 patients with preoperative thrombocytosis (19%) was significantly shorter (4 months) compared to 124 patients with normal platelet counts (11 months). In a subset of patients (only operated patients with radiation therapy with or without additional chemotherapy), survival was likewise significantly shorter when preoperative thrombocytosis was diagnosed to patients with normal platelet count (6 months versus 13 months). In multivariate analysis, age, platelet count, preoperative prothrombin time, and degree of tumor resection were prognostic factors of survival.

Renal cell carcinoma

During the last decades numerous prognostic factors have been studied for predicting survival of renal cell carcinoma (RCC). The standard therapy for metastatic RCC has been immunotherapy with response rates of only 10-15%. Thombocytosis as a negative predictor of survival had been first documented in metastatic RCC by Symbas *et al.*[38] Gogus *et al.* performed a retrospective review on 151 patients who underwent radical nephrectomy for localized RCC. Advanced T stage and lymph nodal involvement correlated with thrombocytosis. Patients with thrombocytosis had a cause specific mean survival of 45.2 months compared with 76.6 months for those with normal platelet counts.[39]

A retrospective analysis of 700 previously untreated patients entering on institution review board-approved phase 1, 2, or 3 clinical trials in the United States and Europe was conducted between 1982 and 2002 by Suppiah *et al.* Thrombocytosis was present at study entry in 25% of patients. On univariate analysis, patients with elevated platelet counts had significantly shorter survival than patients with normal platelet counts; median survivals of 8.4 and 14.6 months, respectively. However, platelet count was associated with several clinical and biochemical factors, including gender, age, performance status, time from diagnosis to study entry, prior radiotherapy or nephrectomy, presence of liver metastasis, number of metastatic sites, amount of hemoglobin, white blood cell count, amount of lactate dehydrogenase, and amount of serum alkaline phosphatase. After adjusting for multiple factors, thrombocytosis continued to impact negatively on survival.[40]

DISCUSSION

Reactive or secondary thrombocytosis associated with malignancies has been established since the early 1870s, with an incidence of 10-57%.[19] Possible mechanisms include an overproduction of cytokines/growth factors stimulating megakaryocytes and their precursors. Serum IL-6 is increased in most patients with reactive thrombocytosis, and elevation of this cytokine has been detected in a significant number of patients with cancer. Bone marrow endothelial cells, kidney, and spleen are capable of Thrombopoetin (TPO) production. TPO is produced and released into the circulation at a constant rate by the liver.[10] Normal physiology of platelet production involves the clearance of TPO by high affinity TPO receptors on platelets and formation of a steady TPO concentration, thereby providing a basal stimulation of bone marrow megakaryocytes and normal rate of platelet production. However, in secondary thrombocytosis that can occur with malignancies, there can be up-regulation of TPO production by the liver, causing enhanced thrombopoiesis. Plasma TPO levels have also been shown to correlate with IL-6.[16]

Questions remain unanswered as to why thrombocytosis is associated with decreased survival in cancer patients. Several theories have been proposed on how platelets themselves have a significant role in tumor growth. Perhaps IL-6 and other cytokines, along with inflammation as a general phenomenon have an effect on the immune system and, thereby, result in worse survival.

Platelets have capabilities to enhance sequestration, adherence, and penetration of malignant cells through the endothelial wall.[18] They may also prevent the immune system from clearing tumor cells from the circulatory system. Thrombospondin, a platelet-secreted protein, is increased in patients with cancer, specifically in patients with metastasis, and may promote the adherence of tumor cells to the endothelial barrier, thus enhancing their escape from immune surveillance.

Tumor growth is dependent on formation of new blood vessels from preexisting capillaries (i.e., angiogenesis).[40] Tumor angiogenesis is dependent not only on endothelial cells and cancer cells but also on platelet-endothelium interactions. Platelets adhere to the tumor-related endothelium and release high concentrations of VEGF, which is a potent stimulator of angiogenesis.

Platelet granules contain a variety of factors such as VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), IL-6, thrombin, and fibrinogen.[14] These modulators are secreted immediately after platelet activation, and many have been implicated in various steps of tumor progression and in the development of metastasis. As one of the most significant proangiogenic cytokines, bFGF contributes to migration, proliferation, and differentiation of endothelial cells, and regulation of the expression of proangiogenic molecules. PDGF induces angiogenesis by means of stimulation of VEGF expression in tumor endothelial cells and by recruiting pericytes to new blood vessels. TGF-β has an active role in platelet aggregation and regulation of megakaryocyte activity.[13] This cytokine also regulates the activity of the VEGF system and enhances endothelial cell survival.[41]

In conclusion, the prevalence of thrombocytosis associated with various cancers portrays a worse survival, independent of other clinical or biochemical factors. With further studies, this single independent prognostic factor may provide a simple approach to improved risk stratification of patients in future clinical trial protocols.

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