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REVIEW

Thrombocytosis as a prognostic marker in gastrointestinal cancers

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Abstract

Thrombocytosis is an adverse prognostic factor in many types of cancer. These include breast cancer, ovarian and other gynecologic cancers, renal cell carcinoma and lung cancers. In gastrointestinal cancers of various locations and histologic types, thrombocytosis has been reported in general to be associated with adverse clinical outcomes. Platelet count measurement is well standardized and available in every clinical laboratory, making its use as a prognostic marker practical. This paper will discuss the data on the prognostic value of thrombocytosis in gastrointestinal cancers as well as pathogenic aspects of the association that strengthen the case for its use in clinical prognostication.

Key words: Thrombocytosis; Platelets; Cancer; Gastrointestinal; Prognosis

Core tip: Thrombocytosis arises as a prognostic factor in various cancers, although it is not clear whether there is a pathogenic contribution or thrombocytosis merely reflects a pro-carcinogenic inflammatory milieu. This paper discusses the utility of thrombocytosis as a prognostic factor in gastrointestinal cancers.

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INTRODUCTION

Platelets play an important role in hemostasis and vascular integrity. They have a unique mechanism of derivation as fragments from the cytoplasm of bone marrow megakaryocytes in a process called thrombopoiesis[1]. The cytokine thrombopoietin stimulates platelet production through ligation of its cognate surface receptor c-Mpl. Other signals also contribute to thrombopoiesis including SDF1 (stem cell derived factor 1, also called CXCL12) ligating receptor CXCR4, integrins and PF4 (platelet factor 4). Support is lent to megakaryocytes by the bone marrow microenvironment in the form of both soluble factors and of direct cell-cell interactions with specialized resident stromal cells[2]. Platelets are derived from proplatelets which represent long protrusions of the mature magakaryocyte cytoplasm[3]. Abnormalities in platelet number, either increase (thrombocytosis) or decrease (thrombocytopenia) accompany diverse pathologic conditions and may aid in their diagnosis[4]. An elevated platelet count has various causes and is either primary due to essential thrombocytosis or other myeloproliferative disorders or secondary to malignancy, infection, chronic inflammation, trauma or surgery, iron deficiency and splenectomy. The common denominator of most of these secondary conditions is inflammation[5]. Inflammatory cytokines stimulate the process of platelet production by megakaryocytes in the bone marrow. Cancer is a pathology that is often associated with thrombocytosis. This relates to the cytokine milieu of several malignancies that stimulates thrombopoiesis. Possibly due to this fact of association with a particular cytokines setting, thrombocytosis has been found to be an adverse prognostic

factor in many common malignancies. Thrombocytosis appears to be a universal marker of adverse outcomes in cancer. Its association with worse oncologic outcomes has been reported in early and advanced breast cancer[6,7], ovarian cancer[8,9], genitourinary cancers[10,11] and several other types[12,13].

PATHOGENESIS OF THROMBOCYTOSIS IN CANCER

A recent publication has shed some light to the pathogenesis of thrombocytosis in cancer[8] and confirmed previous reports on the role of cytokines and in particular of IL-6[14]. In ovarian cancer patients, thrombocytosis was significantly correlated with plasma levels of IL-6[8]. In mouse models bearing human ovarian cancer, human IL-6 stimulates hepatocytes through the IL-6 receptor to trigger thrombopoietin production. Thus a proposed model stipulates that ovarian cancer tumor cells produce IL-6 which then stimulates hepatic thrombopoietin production. Thrombopoietin increases thrombopoiesis through stimulation of megakaryocyte progenitors in the bone marrow[8]. In other cancers IL-6 may also play a similar role in favoring thrombocytosis and increased serum levels or tumor positivity by immuno-histochemistry have been detected in a variety of types, such as renal, prostate and breast carcinomas[15-17]. In malignant mesothelioma levels of serum IL-6 correlate with thrombocytosis[18]. IL-6 is produced locally in the tumor environment because pleural effusion levels were much higher than in serum. Interestingly in that case IL-6 may not be derived directly by mesothelioma tumor cells but by attracted immune cells because it was found that patients with tuberculous effusions had even higher levels of IL-6[18]. Specifically in gastrointestinal carcinomas, IL-6 is reported to be higher in patients with gastric and colorectal carcinoma compared to controls[19,20]. Except for the indirect effect through platelets, IL-6 has a role directly in gut carcinogenesis and possibly to chemotherapy response[21,22]. Nevertheless, IL-6 levels do not always correlate with thrombocytosis and other factors produced in bowel inflammatory microenvironment must play a role in its induction[23]. Tumor infiltrating lymphocytes and macrophages are present in various degrees in cancer sites and their role in both promoting and suppressing the tumor development is described[24]. Conditions in tumor micro-environment, such as hypoxia, affect the function of infiltrating immune cells and shape the panel of cytokines produced by them, which in their turn influence tumor cells[25]. In view of this discussion, platelet effects must be considered as constituting only part of the inflammatory process in cancer micro-environment and results of platelets influences should be interpreted with this larger perspective in mind.

The mechanistic basis of platelets contribution to carcinogenesis is a subject of investigation[26]. Circulating tumor cells may use platelets as a protective shield from the attack of the immune system and as facilitators for attachment to endothelial cells at metastatic sites. Platelets have also roles in carcinogenesis directly related to their normal function in promotion of vascular integrity[27]. Newly formed tumor vasculature lack the normal architecture and robustness of local resident vasculature and platelets have been shown to be indispensable for preventing hemorrhage in tumor beds[28]. Both alpha and dense granules of platelets carry bioactive molecules and growth factors. These include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), transforming growth factor β (TGFβ), interleukin 1β (IL-1β), IL-8, CXC motif containing ligand 12 (CXCL12), sphingosine 1-phosphate (S1P) and lysophosphatidic acid[29,30]. Each of these molecules may actively facilitate metastatic progression. An example is platelet-derived TGFβ which promotes an EMT (epithelial to mesenchymal transition) program in cancer cells through transcription factors Smad and NF-κB signaling[31]. EMT constitutes a program endowing epithelial cells with a mesenchymal phenotype that promotes mobility and metastasis while protecting them from anoikis (Apoptosis due to lack of adhesion)[32]. Platelet-derived TGFβ may also contribute to tumor immune evasion[33]. There exist quantitative differences in platelet cargo of bioactive factors and platelets from patients with cancer have a higher VEGF level than platelets from individuals without cancer[34]. As a result platelet counts may more accurately account for VEGF concentrations in the tumor and metastases sites environment where they are activated. Interestingly IL-6 signaling through the STAT3 (signal transducer and activator of transcription 3) is able to induce VEGF receptor VEGFR2 in colorectal cancer cells[35] and thus to complete a pro-carcinogenic loop in cancer cells that includes IL-6, platelets and VEGF.

THROMBOCYTOSIS IN ESOPHAGEAL CANCER

In 293 patients with esophageal squamous cell carcinoma, thrombocytosis, defined as platelets more than 293 × 10^9/L, which was the mean plus one standard deviation of a healthy control group, was present in 21% of patients and was not correlated with patients age and gender[36]. In contrast, it was a significant independent prognostic factor for overall survival[36]. This association was statistically significant for patients with stage Ⅲ and Ⅳ but not for stage Ⅰ and Ⅱ disease. In multivariate analysis, thrombocytosis, together with higher T stage, tumor size and nodal involvement, predicted for worse survival.

In another study which included mainly patients with squamous carcinomas but also a minority (7%) with esophageal adenocarcinomas, thrombocytosis, defined this time as platelets more than 400 × 10^9/L, was present in 4% of patients and it was not associated with age, gender, location along the esophagus, degree of differentiation, lymphovascular or perineural invasion or node

involvement[37]. It was observed more often in patients with adenocarcinoma and correlated with tumor size. Although this report did not study thrombocytosis as it pertains to prognosis, either overall or progression free survival, it did confirm the finding of the previous study regarding its lack of association with other possible prognostic factors.

THROMBOCYTOSIS IN GASTRIC CANCER

In a very large series of 1593 gastric adenocarcinoma patients, 6.4% had thrombocytosis (defined as platelets more than 400 × 10^9/L in this study)[38]. All patients had undergone gastrectomy with negative margins and extensive D2 lymph node dissection. Thrombocytosis was associated with higher T stage, node positivity and a worse survival. Despite that, in multivariate analysis, the prognostic value of thrombocytosis for long term survival was lost while T stage and node positivity remained statistically significant predictors of long term survival in these patients. Thrombocytosis was a strong predictor of overall recurrence and specifically of hematogenous metastasis but not of locoregional recurrence or peritoneal seeding[38]. These predictive values were retained even in multivariate analysis in this instance.

In another series of 369 gastric cancer patients, thrombocytosis was present in 11.4% and was associated with worse 1 year and 3 year survival[39]. The 1 year survival of patients with thrombocytosis was 72.9% while of those without thrombocytosis was 85.7%. The 3 year survival of patients with thrombocytosis was 23.4% while of those without thrombocytosis was 52.4%. Thrombocytosis was positively correlated with depth of tumor invasion and lymph node involvement[39].

In a smaller series of 98 patients operated for gastric carcinoma, pre-operative thrombocytosis was present in 21% and was associated with a statistically significant worse overall survival[40]. The 5 year survival of patients with thrombocytosis was 9.5% and of patients without thrombocytosis was 31.2% in this series. Interestingly the pro-angiogenic enzyme thymidine phosphorylase/platelet-derived endothelial cell growth factor expression was associated with thrombocytosis and both were independent predictors of survival in multivariate analysis[40]. Finally, a study of 181 gastric cancer patients investigated platelet number and serum VEGF level as prognostic factors and failed to correlate either with overall or progression-free survival. In contrast the ratio of VEGF to platelet number was significantly associated with progression-free survival in multivariate analysis[41]. This may relate to the pathophysiologic importance of activated platelet derived VEGF in promoting the neoplastic process.

THROMBOCYTOSIS IN PANCREATIC CANCER

Pre-operative thrombocytosis was investigated as a prognostic factor in 109 patients with pancreatic adenocarcinoma that were surgically resected[42]. It was found to be significantly associated with reduced overall survival. Significance was confirmed in a multivariate regression analysis. Disease-free survival was also worse with thrombocytosis in a series of patients with operable pancreatic cancer[43]. Mean progression-free survival was 4.9 and 46.5 mo for the thrombocytosis and normal platelet groups respectively. In this study prognosis was even better in the sub-group that retained a normal platelet count after the surgery.

In contrast to the above studies, a study that included pancreatic, duodenal and bile duct ampullary carcinomas found lower platelet counts to influence adversely overall and disease-free survival[44]. Lower pre-operative platelets counts were significantly associated with positive surgical margins, a fact that may at least partially explain the adverse prognostic association. Another explanation for this reverse association compared with the previously discussed studies is that this study used a lower cut-off to define high platelet counts at 300 × 10^9/L. The same cut-off of 300 × 10^9/L was used in another more extensive series of 205 patients exclusively with pancreatic adenocarcinoma that had negative results for an association of platelet counts with survival[45]. In both of these studies, results might have been blurred by inclusion of a significant number of patients with higher normal spectrum platelet number in the group of increased platelet counts.

THROMBOCYTOSIS IN HEPATOCELLULAR CARCINOMA

Platelets have a complex relationship with hepatic malignancies. On one hand, due to its association with cirrhosis hepatocellular carcinoma is often presenting with thromcytopenia which is also an adverse prognostic factor[46]. On the other hand, thrombopoietin, an important cytokine for thrombopoiesis, is produced by the liver and may lead to thrombocytosis if neoplastic cells mimic their normal counterparts and produce the cytokine[47] or alternatively if cancer cells stimulate normal liver to produce it[48]. An association of extreme thrombocytosis with both hepatocellular carcinoma and the childhood liver tumor, hepatoblastoma has been noted in the pediatric population[49]. Hepatoblastoma patients had significantly elevated levels of thrombopoietin compared to controls but only slightly elevated levels of IL-6 suggesting that thrombopoietin is down-stream to IL-6 in the pathway triggering thrombopoiesis[50]. Hepatocellular carcinoma patients with thrombocytosis have bigger tumors and a better liver function than patients with normal platelets[51]. A large study of 1154 patients disclosed a 2.7% incidence of thrombocytosis in hepatocellular carcinoma[52]. In addition, platelet count and thrombopoietin level correlated with effectiveness of treatment, decreasing after excision of the tumor and re-increasing upon recurrence. Thrombocytosis was significantly associated with younger age of the patients, higher tumor burden, development of portal

vein thrombosis by tumor involvement and a shorter mean survival time of less than 5 mo as opposed to over 12 mo in patients without thrombocytosis.

THROMBOCYTOSIS IN COLORECTAL CANCER

Thrombocytosis (more than 400×10^9/L) was evaluated as a prognostic factor in an extensive series of 1513 patients with localized colorectal cancer that had undergone surgery[53]. Patients with thrombocytosis had a significant worse overall survival than patients with normal platelets. Overall recurrence rate and distant metastatic recurrence but not loco-regional recurrence was worse in patients with thrombocytosis. These negative effects of thrombocytosis in overall survival and distant metastatic recurrence persisted over a 5 years period from surgery[53].

A retrospective series of 150 patients that underwent surgery for colorectal carcinoma disclosed that patients with pre-operative thrombocytosis had a 5-year survival of 13.3% while patients with normal count pre-operatively had a 5-year survival of 56.3%[54]. Thrombocytosis, together with lymph node positivity, increasing stage and presence of perineural invasion was statistically associated with worse survival. An association of thrombocytosis with survival or cancer specific survival in colorectal cancer was confirmed in two other larger series of 453 and 636 patients from Japan[55,56] and a smaller series of 180 patients from Europe[57]. The authors of one of these studies examined also thrombocytosis specifically in rectal cancer patients receiving chemo-radiotherapy[58]. They reported that patients with thrombocytosis before combined treatment had a lower rate of radiographic and pathologic response to treatment and a higher risk of local recurrence. In another study focusing in rectal cancer, patients with pre-operative thrombocytosis (more than 350×10^9/L) had a significantly worse survival than patients with lower counts[59].

Patients with node negative colorectal cancer represent a particular challenge for the medical oncologist because, although they have a risk for recurrence, they derive no clear benefit from chemotherapy as a whole group. Clinicopathologic characteristics such as T3 invasion, less complete lymph node dissection, high grade and clinical presentation with obstruction or perforation are used to assist in defining the need for adjuvant chemotherapy[60]. In node negative patients additional prognostic markers to guide therapeutic decisions would be particularly valuable. Thrombocytosis could be such a marker and it was found in an investigation of 198 patients with node negative disease to be associated with significantly worse survival than counterparts with normal pre-operative platelet counts[61]. In these node negative patients, thrombocytosis (platelet count more than 400×10^9/L) was independently associated in multivariate analysis, together with tumor depth (T stage), grade and lymphatic invasion, with both disease-free and overall survival.

In contrast to all the above investigations, a single study of 630 patients did not find a correlation of thrombocytosis with survival[62]. This study used a more stringent definition of thrombocytosis of platelet counts of more than 450×10^9/L and included patients of all stages. Inclusion of metastatic patients might have made the effect of platelet counts on outcome more difficult to discern. Despite this, the *P* value in the Cox multivariate model was just outside significance at 0.06[62].

CONCLUSION

Thrombocytosis occurs in a significant minority of patients with cancer and reflects the increase of thrombopoiesis-inducing cytokines in the tumor milieu. Thus it carries an adverse prognostic value both because of this reflection but also because platelets actively promote carcinogenesis and metastasis protecting tumor cells in their metastatic transit and providing bioactive molecules released upon activation in the tumor and metastatic sites. In the gastrointestinal tract, inflammation and infection play a significant role in carcinogenesis with several well-known associations such as inflammatory bowel disease and colorectal cancer, *Helicobacter pylori* infection and gastric cancer and viral hepatitis infection and hepatocellular carcinoma. In addition even in inflammation-independent cancers, cancer-associated molecular lesions may induce platelet-inducing cytokines. For example one of the most common colorectal cancer lesions, Smad4 mutations, lead to dysfunctional TGFβ signaling, resulting in its turn to increased IL-6 signaling[63]. Given these data, a combined treatment blocking IL-6 with the IL-6 monoclonal antibody inhibitor siltuximab or the IL-6R inhibitor tocilizumab together with an anti-platelet function inhibitor such as aspirin with or without inhibition of additional pathways activated by platelet granules cargo factors such as the CXCL12/CXCR4 or the VEGF/VEGFR axis could be a viable option for development in gastrointestinal cancer patients with thrombocytosis to improve their prognosis. Given its significance as a prognostic factor in gastrointestinal cancers and the ease and standardization of its measurement in the clinic, thrombocytosis should be considered as a factor in the stratification process of randomized trials in these cancers, as both a measure of the tumor inflammatory status but also an active propagator of the neoplastic process. Another emerging concept is that of thrombocytosis as a predictor of response to targeted treatments, for example of anti-VEGF therapies. A study in metastatic renal cell carcinoma has shown that patients with thrombocytosis had a higher risk to present a primary refractoriness to anti-VEGF treatments (OR = 1.7, $P = 0.0068$) than patients with normal platelets[64]. It remains to be seen if thrombocytosis could be a predictive factor for anti-VEGF therapies in gastrointestinal cancers and in particular colorectal cancer and hepatocellular carcinoma where the anti-VEGF monoclonal antibody bevacizumab and the small molecule inhibitor sorafenib are clinically used[65,66].

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