Abstract. Recent studies have addressed the prevalence and prognostic impact of thrombocytosis in various gynecologic and non-gynecologic malignancies. Thrombocytosis appears to be of prognostic value in certain patients with gynecologic malignancies. In this survey we review the published data and attempt to analyze the prognostic implications of thrombocytosis in patients with gynecologic malignancies.

The association between thrombocytosis and malignancies was first described over 100 years ago (1). Recent studies have addressed the prevalence and prognostic impact of thrombocytosis in various gynecologic and non-gynecologic malignancies (2-8). There are indications that a high platelet count is associated with a poor prognosis in carcinomas of the colon and lung and in malignant mesothelioma (2,3,6). Also thrombocytosis appears to be of prognostic value in patients with gynecologic malignancies. We conducted a MEDLINE search of the literature on the prognostic implications of thrombocytosis in gynecologic malignancies using the search terms "ovarian carcinoma", "endometrial carcinoma", "cervical carcinoma", "vulvar carcinoma", "prognosis", "platelet count" and "thrombocytosis" from 1966 onward. We also handsearched the reference sections of all obtained publications. In this survey we review the published data and attempt to analyze the prognostic implications of thrombocytosis in patients with gynecologic malignancies. Interactions between platelets and cancer and cancer metastasis have also been summarized, especially with regard to gynecologic malignancies.

Regulation of platelet synthesis

The body produces about 2 x 10^11 platelets per day. Platelet production is preceded by megakaryocytopenopsis and is regulated by a number of circulating humoral factors, including thrombopoietin. Primitive proliferating progenitor cells are committed to immature megakaryocytes and are finally differentiated to postmitotic megakaryocytes, losing their proliferative capacity in the process. Bone marrow stroma cells produce soluble cytokines allowing self renewal and differentiation of thrombopoiesis. To date 19 cytokine growth factors have been identified that regulate thrombopoiesis from early stem cells to postmitotic megakaryocytes (interleukins 1-13, G, M, GM-CSF, leukemia inhibitory factor, SCF and erythropoietin). Whereas these cytokines are not specific for stimulating thrombopoiesis, thrombopoietin is a specific stimulator of platelet production increasing megakaryocytes and maturation status. It is this system that regulates megakaryocyte development and the daily output of platelets.

Platelets and cancer

High levels of thrombopoietin have been found in patients with reactive thrombocytosis and with solid tumors (9). Patients with reactive thrombocytosis and with solid tumors had higher levels of thrombopoietin than patients with non-neoplastic conditions associated with reactive thrombocytosis or essential thrombocytosis (9). Tumor-related humoral factors with thrombopoietin-like activity (10, 11) and overcompensated megakaryocytopenosis due to tumor-induced disseminated intravascular coagulopathy (11-13) have been proposed in the etiology of reactive thrombocytosis in patients with malignant disease.

Interleukin-6 (IL-6), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin and tumor necrosis factor have been postulated to play a role in the development of thrombopoiesis and thrombocytosis (14-...
19). IL-6 is a potent stimulator of megakaryocytopoiesis and responsible for maturation of megakaryocytes (20, 21). Various epithelial ovarian cancer cell lines have been found to produce IL-6 (22-24). Elevated levels of IL-6 have been found in ascitic fluid and serum of patients with ovarian cancer (14, 25). High levels of IL-6 in ascitic fluid were significantly correlated with the circulating platelet count, suggesting a role for IL-6 in the development of tumor-associated thrombocytosis (14). Similarly, high levels of IL-6 in fluids from malignant ovarian cysts have been significantly correlated with increased platelet counts and low hemoglobin levels (25). Also, administration of recombinant human IL-6 increases the platelet count and decreases hemoglobin levels (26-28). Some cervical cancer cell lines have been found to secrete IL-6 and utilize it as an autocrine (29, 30) or paracrine (31) growth factor, or both (31). High levels of IL-6 have been found in sera (32, 33) and cervico-vaginal secretions (34) of patients with advanced cervical cancer. However, studies of IL-6 levels in patients with endometrial cancer are conflicting. Chopra et al. (35) found normal IL-6 levels in 59 women with stage I-IV disease whereas Scambia et al. (36) found elevated levels in 37% of their patients.

Chopra et al. found elevated levels of GmCSF in patients with advanced stage endometrial carcinoma, but GmCSF levels were not correlated with the platelet count (35). Although erythropoietin has been postulated to play a role in the development of thrombocytosis in animal studies, recombinant erythropoietin has not been found to have a significant effect on the platelet count in humans (37, 38).

**Platelets and metastasis**

There is evidence suggesting that platelets play a role in the development of tumor metastasis. Tumor cell-platelet interactions may influence the process of metastasis at different levels (39). Tumor cell-platelet aggregates have been shown to form during initial arrest of tumor cells in the capillary vascular bed and to play an important role in hematogenous tumor spread (40). Also, tumor cells can directly activate platelets (41). Platelets may protect tumor cells by coating the tumor cells and blocking their antigenic determinants from the host’s humoral and cellular defense mechanisms (42, 43). Anti-platelet agents and anticoagulants have potent inhibitory effects on tumor cell-platelet interactions and can prevent metastases in experimental settings in various malignancies (39, 43-46).

Thrombospondin-1 is an adhesive glycoprotein, richly secreted by platelets and an extracellular matrix component of many cell types including tumor cells and vascular endothelial cells (40, 41). Thrombospondin-1 supports the adhesion of tumor cells to endothelium and may promote metastasis by increasing the secretion of plasminogen activator inhibitor-1 and urokinase-type plasminogen activator levels (40, 41). This facilitates urokinase-type plasminogen activator-mediated cell invasion and metastatic spread of cancer cells. Nathan et al. (47) found significantly elevated plasma thrombospondin levels in patients with gynecologic malignancies. However, the thrombospondin level correlated with the stage of the disease but not with the platelet count (47). This suggests that elevated levels of thrombospondin can be ascribed to sources other than platelets (i.e., tumor cells) and high levels of thrombospondin are encountered in cancer patients, even when the platelet count is normal.

**Ovarian cancer and thrombocytosis**

Elevated platelet count (> 300,000/µL) and thrombocytosis (platelet count > 400,000/µL) are significantly more frequent in patients with ovarian cancer than in those with benign ovarian tumors (14, 47-51). Chalas et al. (48) and Hakverdi et al. (49) reported that the combined use of thrombocytosis and serum CA 125 values results in a high positive predictive value and specificity for detecting patients with ovarian cancer in patients presenting with a pelvic mass.

The reported prevalence of thrombocytosis in patients with ovarian cancer ranges from 22.4% (52-54) to 62.5% (14). These differences are probably due to the different proportions of patients with early stage disease in the different studies. Zeimet et al. (7) and Li et al. (53) found significantly higher rates of thrombocytosis (platelet count > 400,000/µL) in patients with stage III and IV than in those with stage I and II disease. Although not statistically significant, others also found thrombocytosis to be more common in ovarian cancer patients with stage III and IV disease than in those with early disease (49, 50, 52). In a series of 70 patients with invasive ovarian cancer, Menczer et al. (52) correlated the presence of thrombocytosis with established prognostic factors and with survival. Thrombocytosis was not correlated with age, grade, residual disease or advanced stage but patients with thrombocytosis did have a significantly worse prognosis than those without.

In contrast, in an analysis of 130 patients with ovarian cancer, Zeimat et al. (7) reported a statistically significant association of thrombocytosis with advanced stage, residual tumor mass > 2 cm after surgery, high CA 125 levels, high volume of ascites and low hemoglobin levels. Patients with thrombocytosis had a worse prognosis than those without (45% vs. 58%, respectively), but the difference was not statistically significant. In the stepwise logistic regression analysis, thrombocytosis was significantly associated with the presence of ascites and low hemoglobin concentrations. On the other hand, these data are also interesting because pretreatment tumor anemia (hemoglobin level < 12 g/dL)
has been found to be an independent prognostic factor in ovarian cancer (55). Like thrombocytosis, low serum hemoglobin concentrations (<12 g/dL) were significantly associated with higher residual tumor mass (55). However, platelet counts were not included in this study (55).

In line with the results of Zeimat et al. (7), Li et al. (53) recently reported significant association between pretreatment thrombocytosis and known poor prognostic factors of ovarian carcinoma (advanced stage, presence of residual tumor mass after surgery, high volume of ascites) in a series of 183 patients who had 22.4% thrombocytosis. Although Zeimat et al. could not determine significant differences in survival in stage I-IV disease with or without thrombocytosis, Li et al. separately analyzed stage III and IV disease and found that disease-free and overall survival rates were significantly affected by the presence of thrombocytosis in advanced stage disease. The main difference between both studies was the proportion of stage III and IV disease included in the study groups (63% (82/130) vs. 79.7% (146/183)).

Also, in an analysis of subcohort with stage III disease, patients with suboptimal tumor resection had a significantly higher mean preoperative platelet count (551,000/µL vs. 323,000/µL) and the presence of thrombocytosis (83.3% vs. 13.8%) than those without residual disease after surgery (53). In a multivariate analysis, the presence of thrombocytosis was a significant independent negative prognostic factor for overall survival in stage III and IV disease (53). On the other hand, there was no correlation between the presence of thrombocytosis and hemoglobin levels (53).

Using neural network analysis, Kappen et al. (56) identified thrombocytosis and low hemoglobin levels as additional predictive factors in ovarian cancer. Lund et al. (54) found a significant linear association between primary residual tumor size, stage, and platelet counts and that a high platelet count was associated with presence of residual tumor at second-look laparotomy. Additionally, in a recent retrospective study, a platelet count > 300,000/µL at the time of the recurrence was found to be a poor prognostic factor for overall survival in 31 women with recurrent ovarian cancer prior to second-line chemotherapy, whereas tumor anemia (serum hemoglobin level < 12g/dL) was of no prognostic value with respect to overall survival (57). In this study, a platelet count > 300,000/µL and tumor anemia were present in 55% and 42% of patients, respectively.

### Cervical cancer and thrombocytosis

A number of studies have evaluated the prognostic significance of thrombocytosis in patients with cervical cancer. In two series with patients with disease of all stages, the rate of thrombocytosis (platelet count > 400,000/µL) was 17% (4, 58). As in ovarian cancer, the rate of thrombocytosis was higher in patients with stage III and IV disease than in those with stage I and II disease (4, 58). Initially, Hernandez et al. (4) reported that thrombocytosis was an independent indicator of poor prognosis in 113 stage I-IV cervical cancer patients treated with radiotherapy. Surgical pathologic variables were not available in this study. Rodriguez et al. (5) found that an elevated platelet count (> 300,000/µL) was an independent prognostic factor for poor survival of 219 surgically treated patients with stage IB cervical carcinoma. The authors noted a significant association between elevated platelet count and large lesion size (greater than 4 cm) and low preoperative hematocrit levels, whereas age, race, pelvic node metastases, histology and tumor grade showed no statistical correlation with thrombocytosis. In contrast, a Gynecologic Oncology Group study (59) showed that thrombocytosis was not an independent prognostic factor for survival in 623 patients with surgically treated stage IB squamous cell carcinoma of the cervix but did find it to be a marker of tumor burden. Fifty-nine of these patients (9.5%) had thrombocytosis. However, patients with gross extrauterine disease, bulky pelvic nodal metastasis or periaortic nodal metastasis were excluded from the study. There was no association between thrombocytosis and age, hematocrit or pelvic node metastasis but thrombocytosis was significantly correlated with tumor size. This study shows that thrombocytosis is not associated with an increased risk of pelvic node metastasis and that it does not alter the course of disease in patients with early cervical cancer with favorable prognostic factors. Lopes et al. (58) evaluated the prognostic significance of thrombocytosis (platelet count > 400,000/µL) in 643 patients with cervical cancer of all stages and reported significantly poorer survival of patients with thrombocytosis, but thrombocytosis was not an independent prognostic factor when adjusted for stage. The authors (58) found the greatest differences in 5-year survival rates of patients with thrombocytosis in stage III and IV (19.5% vs. 35.2%, respectively) but small numbers of patients with stage III (n=54) and IV (n=11) disease precluded meaningful statistical analysis. As in other studies, thrombocytosis was not associated with increased risk for pelvic lymph node metastasis.

We have analyzed the prognostic implications of thrombocytosis (platelet count > 400,000/µL) in 128 patients with advanced (stage III and IV) cervical cancer (60). Thrombocytosis was present in 33 out of 128 (26%) patients. There was a significant association between thrombocytosis and low hemoglobin levels. Only 5 out of 16 patients (31%) with distant metastasis at the time of diagnosis (FIGO stage IVB) had thrombocytosis. During follow-up, distant progression or recurrence was not more frequent in stage III patients with thrombocytosis than in those with a normal platelet count. Interestingly, in stage III patients locoregional progression or recurrence was more frequent in patients with thrombocytosis (63% vs. 43%) but the differences did not reach statistical significance. In our series, patients with
thrombocytosis had a poorer prognosis overall than those with a normal platelet count. Thrombocytosis was significantly associated with a worse prognosis in stage III disease but not in stage IV disease. In the multivariate analysis, age and hemoglobin were significantly associated with prognosis, while thrombocytosis was not.

In a further Gynecologic Oncology Group study, thrombocytosis (platelet count > 400,000/µL) was present in 86 out of 296 patients (29.6%) and found to be associated with a poorer survival in patients with stage IIB – IVA cervical carcinoma, if the pelvic nodes were negative (61). In this study, thrombocytosis was related to tumor size (61). The authors observed significantly more frequent pelvic recurrences in patients with thrombocytosis than those without. Although not statistically significant, patients with thrombocytosis tended to have a lower hematocrit level than the patients without thrombocytosis (61).

The prognostic significance of pretreatment hemoglobin levels in cervical cancer treated with radiotherapy (with or without chemotherapy) has been described in numerous reports (62-65). Grogan et al. (65) reported that correction of anemia improves outcome and survival of patients receiving radiotherapy. The findings of the studies summarized above suggest that pretreatment thrombocytosis is more frequent in advanced cervical carcinoma and seems to be a marker of increased tumor burden or biologically aggressive tumor cell clones. Thrombocytosis is associated with a low hemoglobin level, which is an established adverse prognostic factor for cervical cancer patients treated with radiotherapy.

**Endometrial cancer and thrombocytosis**

We found thrombocytosis (platelet count > 400,000/µL) in 14% of 135 consecutive patients with endometrial carcinoma treated primarily with surgery (66). This is considerably higher than the 1.5% reported by Menczer et al. (67) in a series of 66 surgically treated patients. Menczer et al. (67) found a significant correlation between elevated platelet count (>300,000/µL) and unfavorable grade (G2 and G3) but not clinical stage. Patients with an elevated platelet count showed an excess of deep myometrial invasion and poorer survival but the differences were not statistically significant (67). In our study (66), thrombocytosis was significantly more frequent with advanced disease (stage II-IV), unfavorable grade (grade 2 and 3), deep myometrial invasion and lymph-vascular space invasion. The recurrence rate was significantly higher and 5-year survival was significantly worse in patients with thrombocytosis than in those without. In a multivariate analysis, thrombocytosis, age, grade and stage were significantly associated with poor prognosis. A flaw of our study was that only a limited number of patients underwent complete staging with lymphadenectomy. Furthermore, due to the small number of patients with stage II-IV disease, the patients were grouped into two main groups (stage I vs. stage II-IV) for the statistical analyses. Therefore, separately stage III and IV patients treated with surgery were evaluated for a longer period in a recent study with regard to thrombocytosis and its implications (68). This study also revealed that thrombocytosis is significantly associated with poor prognosis in advanced stage endometrial cancer whereas there was no statistical correlation between thrombocytosis and stage or pathology findings, such as histologic type, grade, myometrial invasion, cervical involvement, lymph-node status, or adnexal spread (68).

The association between thrombocytosis and low hemoglobin levels is well documented in cervical cancer. We also found in patients with endometrial cancer with thrombocytosis significantly more frequent hemoglobin levels < 12 g/dL than in those without thrombocytosis (69). Both low hemoglobin levels (<12 g/dL) and thrombocytosis were significantly correlated with 5-year survival rate in the univariate analyses. However, in the multivariate analyses, hemoglobin lost its prognostic power, whereas thrombocytosis continued to be a prognostic factor (69).

These results suggest that thrombocytosis is more frequent in advanced stage endometrial carcinoma and is associated with low hemoglobin levels as in cervical cancer. Thrombocytosis appears to be a prognostic factor in endometrial carcinoma. However, the prognostic significance of thrombocytosis has been evaluated mainly in our population and there are some overlaps of patients in the study groups. Therefore, the results of studies should be replicated in other series. It may be of clinical relevance, especially in advanced disease, since platelets are thought to facilitate the formation of blood-borne metastases, the risk of which increases with tumor size (40).

**Vulvar cancer and thrombocytosis**

Lavie et al. (70) reported that thrombocytosis (platelet count > 400,000/µL) had no effect on 5-year survival rate in 201 patients with primarily surgical treatment. Thirty out of 201 (14.9%) patients had thrombocytosis. There was no association between the presence of thrombocytosis and age, histologic type, presenting sign or stage (70). No correlation between platelet count and tumor size was found. Patients with normal platelet count had significantly high hemoglobin levels but hemoglobin levels had no influence on 5-year survival rate. In this study, 165 patients underwent groin node dissection. Thrombocytosis also had no effect on the incidence of positive groin nodes.

Hefler et al. (71) reported that the presence of pretreatment tumor anemia (hemoglobin < 12 g/dL) and elevated platelet count (> 300,000/µL) were significantly associated with a poor overall survival in the univariate but not in the multivariate analysis in 62 patients with vulvar carcinoma. Of the 62 patients, 17 (27.4%) had a platelet...
count > 300,000/µL and 19 (30.6%) had pretreatment tumor anemia (71). It appears that thrombocytosis is not an independent predictor of outcome in patients with vulvar carcinoma and does not increase the risk of groin lymph node metastases.

Summary

Pretreatment platelet counts have some prognostic value in patients with gynecologic malignancies. Suboptimal tumor resection and the presence of residual tumor mass after surgery, which are known to be closely related with aggressiveness of the tumor and established prognostic factors for ovarian carcinoma, are frequent in patients with ovarian carcinoma with thrombocytosis. Further, in cervical carcinoma, the larger the tumor burden the higher the rate of thrombocytosis in the studied patient population. Thrombocytosis is more frequent in advanced disease in patients with ovarian cancer, endometrial cancer and cervical cancer. Therefore, it may be a marker of tumor burden or biologically more aggressive disease.

However, the precise mechanisms underlying the cancer-associated thrombocytosis are not clearly understood. Whether thrombopoietin levels, an important regulator of megakaryocytopoiesis and thrombopoiesis, are elevated in patients' gynecologic malignancies with or without thrombocytosis, or whether thrombocytosis is an end result of the host reaction to advanced cancer, is unclear. Although it has been suggested that thrombocytosis might worsen prognosis by facilitating the occurrence of hematogenous metastasis (40), it has also been stressed (61) that platelets may not influence the metastatic process but could play a role in stimulating the tumor growth of established metastasis by the release of platelet-derived substances and growth factors such as platelet-derived growth factor, that is a potent mitogen for many cell types including ovarian surface epithelium (72).

Administration of some cytotoxic drugs results in a lowering of the platelet count. Whether decreasing the platelet count by cytotoxic drugs, or the inhibition of platelet activation by cyclooxygenase-2 inhibitors or nonsteroidal anti-inflammatory drugs preventing the tumor cell-induced platelet activation has a place in the treatment of malignant disease is unknown (61). On the other hand, hypothetically, this might be an important research area. Moreover, several preliminary experimental and clinical studies suggest an anti-tumor and anti-metastatic effect of anticoagulants (45, 46) and this is the subject of ongoing research.

This survey has inherent limitations, since the published papers on the prognostic significance of thrombocytosis in gynecologic malignancies are based on retrospective studies. Consequently, the data here presented concerning the prognostic implications of thrombocytosis in gynecologic malignancies must be interpreted with some caution.

References


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