Thrombocytosis in solid tumors: review of the literature

Çağatay ARSLAN[1], Hasan Şenol COŞKUN[2]

[1] Department of Internal Medicine, Süleyman Demirel University School of Medicine,
[2] Department of Medical Oncology, Süleyman Demirel University School of Medicine, Isparta, TURKEY

Turk J Haematol 2005;22(2): 59-64

Received: *09.11.2004* ***Accepted:*** *26.02.2005*

INTRODUCTION

The relation of thrombocytosis with malignant disorders is known for a century[1]. Frequency of thrombocytosis and thrombocyte count varies in different malignant diseases. It is especially seen in lung, colon, gynecological, and renal cell cancer. The specific mechanism by which thrombocytosis develops in malignancies remain speculative and several hypothesis have been proposed on this subject. In recent years humoral mediators are suggested to play role in the pathogenesis of thrombocytosis occur with the response of host against the malignant tissue. Excess amount of cytokines were found to be associated with thrombocytosis in cancers. Interleukin-6 (IL-6), IL-1, vascular endothelial growth factor (VEGF), macrophage colony stimulating factor (M-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and granulocyte colony stimulating factor (G-CSF), and tumor necrosis factor α (TNF-α) are some of the cytokines studied in malignancy associated thrombocytosis. Thrombocytosis might be a sign of poor prognosis and cause morbi-motality in cancers. It can be in relation with different processes occur during the course of malignant tumors as cell invasion and metastasis.

Solid tümörlerde trombositoz: literatür taraması

Anahtar Kelimeler: Solid tümör, Trombositoz, Sitokin.

Key Words: Solid tumors, Thrombocytosis, Cytokines.

THROMBOCYTOSIS and METASTASIS

Biological behavior of cancer cells and the relation with thrombocytes are not well explained. Thrombocytes might be associated with metastasis, protection of tumor cells from the host immune system, invasion of tumor cells, and angiogenesis in malignant tissue[2]. It was reported that thrombocytosis itself is a poor prognosis marker in cancer. It was considered that thrombocytes might

play role in the formation of tumor thrombi and pathogenesis of metastasis in solid tumors[3]. Platelets have been shown to protect tumor cells by shielding them from the host's immune system[4]. Interaction of tumor cells with thrombocytes is an important process in hematological metastasis. P selectin on activated platelets has an important role in tumor growth and metastasis[4]. Suggesting the role of thrombocytes in tumor metastasis anti-platelet agents and anticoagulants were studied and reported to inhibit the experimental or spontaneus metastasis[3]. Thrombocytosis might act in metastasis in the steps of;

1. Duration and stabilisation of tumor cells in blood vessels,

2. Promoting the proliferation of tumor cells,

3. Contribution to the extravasion of tumor cells and endothelial retraction,

4. Excess of interaction of extracellular matrix and tumor cells. Several cytokines are shown to play role in each of these steps.

MALIGNITY, INFLAMMATION and THROMBOCYTOSIS

Induction of inflammation particular to the malignant tissue and generating cytokines is one of the possible casuses suggested about thrombocytosis in solid tumors. There are an excess number of studies about cytokines in malignancy associated thrombocytosis but certain cause of thrombocytosis in cancers is still not known. Some authors suggest that rapid growing tumors, besides angiogenic factors, also release thrombopoietic cytokines. IL-6 which is produced in malignant tumors and inflammatory tissues, potently stimulates platelet production[5]. The level of IL-6 was found to be associated with levels of C-reactive protein (CRP) and white blood cell (WBC) counts[5]. IL-6 levels are generally positively correlated with WBC counts and CRP levels. Platelet counts were also reported to be increased in the patients with higher CRP levels and WBC counts[5]. Tuberculous pleurisy is a serious disease that stimulates the inflammatory process generously. It was shown that cytokines might also be produced in tuberculous pleurisy in excessive amounts as pleural mesothelioma and thrombocytosis might occur in higher counts[6]. It was reported that IL-1ß and IL-6 play role in reactive thrombocytosis seen in lung cancer not independently but as mediators of inflammation[7]. However in solid tumors different mediators and in excess amounts are synthesized and secreted from malignant cells and surrounding tissues in different quality and quantity from benign conditions. One of the studies showed if thrombocytosis accompanies with pelvic mass in women the diagnose was usually a malignant disease[8]. It might be related with the higher amounts of inflammatory reaction in malignant conditions. The inflammatory cytokines generate in increased levels in advanced stage disease probabely because of the increased interaction of tumor cells and host immune system. In the sera and ascites of the patients with ovarian carcinoma IL-6 levels were reported to be positively correlated with platelet counts[9]. When solid tumors were compared with essential thrombocytemia it was reported that IL-1α and IL-6 levels were elevated in correlation with thrombocyte counts in solid tumors but not in essential thrombocytemia[10]. IL-6 levels were reported to be elevated in reactive thrombocytosis but not in essential thrombocytemia in another study[11]. Thus thrombocytosis might occur on some different pathway in primary thrombocytosis.

Secondary thrombocytosis might appear after splenectomy, in relation with corticosteroid treatment, bacterial or viral infections, surgery or tissue injury, iron deficiency, in recovery phase from the anti-neoplastic treatment and as a result of acute phase response in several conditions[12]. However dif-

ferent mechanisms might play role in the etiopathogenesis of the thrombocytosis related to solid tumors else from the inflammatory cytokines. For instance iron deficiency and iron deficiency anemia are seen frequently in patients with solid tumors. It is known that both iron deficiency and anemia may contribute to thrombocytosis. But the exact mechanism was not clarified. Thrombocytosis was reported to be more frequent and in higher counts in bronchial carcinoma patients with anemia and lower serum iron levels[13]. Eryhtropoietin (EPO) was reported to be in charge with thrombocytosis generated in iron deficiency[14].

DISEASE STAGE and THROMBOCYTOSIS

Thrombocytosis is accepted as an independent poor prognostic marker in solid tumors[4,5]. It was found that higher platelet counts were associated with advanced tumor stage and decreased survival rates in vulvar, oesephageal and gastric cancers[4,5,15]. Increased number of tumor cells interacting with host tissue might stimulate any pathway responsible in development of thrombocytosis in increased levels resulting the higher counts of platelets. Thrombocytosis was reported as a marker of subclinical tumor burden in cervix carcinoma[16,17]. In endometrial carcinoma it was found that patients with thrombocytosis were in advanced stage, with decreased survival and increased risk of recurrence[18,19]. Thrombocytosis was seen more frequently in metastatic breast carcinoma than the loco-regional disease[20]. In endometrial carcinoma it was reported that thrombocytosis was more frequent in advanced disease, unfavorable grade, deep myometrial invasion, and lymph-vascular space invasion[19]. The relation of thrombocytosis and tumor prognosis was studied by different researchers. Thrombocytosis was shown as a bad prognostic sign in a number of solid tumors as; lung, ovarian, follicular thyroid, breast, renal cell, colon, upper gastrointestinal tract cancers and endometrial carcinoma[4,5,21-30].

CYTOKINES, GROWTH FACTORS and ADHESION MOLECULES

It is considered that cytokines generating in reactive thrombocytosis in solid tumors may take role in ethiopathogenesis of thrombocytosis. A number of cytokines were studied about the pathogenesis of thrombocytosis in solid tumors. But IL-6 is the one that most data present about the role in thrombocytosis. Serum levels of IL-6 arise in malignancies especially rapidly progressing tumors. VEGF is another cytokine that is considered to be responsible in solid tumor associated thrombocytosis and also in pathogenesis of metastasis. Serum IL-6 and VEGF levels were found positively correlated in advanced cancers[31]. Thrombocytes store VEGF and so prevent from circulating freely and inducing the development of new blood vessels except at sites where coagulation takes place. It was shown that IL-6 plays role in thrombocytosis and also in the storage of VEGF in trombocytes. Levels of IL-6, GM-CSF, and G-CSF were found elevated in patients with advanced malignancies and thrombocytosis. However the plasma concentrations were found lower than those required for in vitro induction of megakaryocytic differentiation[32]. Thus there may be thrombopoietins that have not yet been identified in plasma of individuals with malignant diseases. Thrombocytosis were reported to be more frequent and in higher counts in metastatic breast carcinoma than loco-regional disease in which serum IL-6 and VEGF levels were found to be positively correlated with thrombocyte counts[33]. Anemia and dose-related thrombocytosis were observed as side effects in a phase-1 trial of subcutaneous recombinant human (rh) IL-6 treatment in patients with refractory cancer[34]. Thrombocytosis, anemia, and neutrophilia were also reported during rh IL-2 treatment[35]. Rh IL-1ß is being used in renal cell carcinoma patients. Thrombocytosis was shown during rh IL-1ß treatment in these patients[7]. In a study of soft tisue sarcomas thrombocytosis was seen in 14.5% of patients, and thrombocyte co-

unts and tumor stage were positively correlated with serum IL-2, IL-6, IL-8, M-CSF, and VEGF levels[36]. Treatment with GM-CSF after bone marrow transplantation and some chemotherapeutics as vincristin were also reported sporadically to cause thrombocytosis[37,38]. These data support that thrombocytosis in solid malignancies might be mediated by tumor derived humoral factors.

THROMBOPOIETIN

Liver is known as the predominant organ for thrombopoietin (TPO) production[39]. There is a feedback mechanism in TPO syntesis and its target cells maintaining normal thrombocyte counts in healthy people. Direct promotion of megakaryocytopoies may be mediated by tumor-derived humoral factors. Increase in circulating IL-6 and TPO levels may cause reactive thrombocytosis in inflammatory diseases and cancer. Administration of rh IL-6 to cancer patients results in a corresponding increase in TPO levels[40]. Thrombopoietic substances are primarily responsible in thrombocytosis in myeloproliferative disorders. TPO and IL-6 are related with reactive thrombocytosis in tumor patients. However serum TPO levels were found increased but IL-6 and IL-11 did not change in thrombocytopenia following myelosupressive chemoterapy[41]. It was shown that stimulation of hepatic cells in cell culture media with IL-6 causes increment of TPO levels[40]. Thrombocytosis is seen frequently in hepatoblastoma patients. However there were not any relation found between thrombocytosis and TPO levels in some of the hepatoblastoma patients[17]. It was thought that tumor cells secrete IL-1ß and some other mediators in hepatoblastoma for production of IL-6 from surronding fibroblasts and endothelial cells[42,43]. Tumors expressing G-CSF and GM-CSF have ben showed that they have megakaryocyte potentiating activity due to IL-6 and cause thrombocytosis[44].

In Conclusion

Thrombocytosis is a risk factor for thromboses which have particular importance in cancer patients and cause the excessive rate of morbi-mortality. The measurement of platelet counts may be a useful clinical marker associated with the prognosis of solid tumors. It also seems to play role in metastase pathogenesis and seems to be related with the spread of malignant diseases. We the clinicians meet thrombocytosis in cancer patients in daily practice frequently and it is still a mystery maybe as a cornerstone in the nature of cancer. It is clear that there is need for much more detailed studies on this subject.

REFERENCES

1. Riess L. Zur pathologischen anatomie des bluttes. Arch Anat Physiol Wissench Med 1872;39:237-49.
2. Trikha M, Nakada MT. Platelets and cancer: implications for antiangiogenic therapy. Semin Thromb Hemost 2002;28:39-44.
3. Honn KV, Tang DG, Crissman JD. Platelets and cancer metastasis: a causal relationship? Cancer Metastasis Rev 1992;11:325-51.
4. Ikeda M, Furukawa H, Imamura H, Shimizu J, Ishida H, Masutani S, Tatsuta M, Satomi T. Poor prognosis associated with thrombocytosis in patients with gastric cancer. Ann Surg Oncol 2002;9:287-91.
5. Shimada H, Oohira G, Okazumi S, Matsubara H, Nabeya Y, Hayashi H, Takeda A, Gunji Y. Thrombocytosis associated with poor prognosis in patients with oesephageal carcinoma. J Am Coll Surg 2004; 198:737-41.
6. Nakano T, Chahinian AP, Shinjo M, Tonomura A, Miyake M, Togawa N, Ninomiya K, Higashio K. Interleukin 6 and its relationship to clinical parameters in patients with malignant pleural mesothelioma. Br J Cancer 1998;77:907-12.
7. Alexandrakis MG, Passam FH, Perisinakis K, Gonotakis E, Margatinis G, Kyriakou DS, Bouros D. Serum proinflammatory cytokines and its relationship to clinical parameters in lung cancer patients with reactive thrombocytosis. Respir Med 2002;96:553-8.
8. Kerpsack JT, Finan MA. Thrombocytosis as a predictor of malignancy in women with a pelvic mass. J Reprod Med 2000;45:929-32.
9. Gastl G, Plante M, Finstad CL, Wong GY, Federici MG, Bander NH, Rubin SC. High IL-6 levels in ascitic fluid correlate with reactive thrombocytosis in patients with epithelial ovarian cancer. Br J Haematol 1993;83:433-41.
10. Alexandrakis MG, Passam FH, Moschandrea IA, Christophoridou AV, Pappa CA, Coulocheri SA, Kyriakou DS. Levels of serum cytokines and acute phase proteins in patients with essential and cancer-

related thrombocytosis. Am J Clin Oncol 2003;26: 135-40.

11. Hollen CW, Henthorn J, Koziol JA, Burstein SA. Serum interleukin-6 levels in patients with thrombocytosis. Leuk Lymphoma 1992;8:235-41.
12. Vora AJ, Lilleyman JS. Secondary thrombocytosis. Arch Dis Child 1993;68:88-90.
13. Bouvenot G, Bartolin R, Dugue P, Heim M, Delboy C, Charpin J. Thrombocytosis and primary bronchial carcinoma. Study about 164 patients with bronchial carcinoma (author's transl). Sem Hop 1979;55: 26-9 [Article in French].
14. Akan H, Guven N, Aydogdu I, Arat M, Beksac M, Dalva K. Thrombopoietic cytokines in patients with iron deficiency anemia with or without thrombocytosis. Acta Haematol 2000;103:152-6.
15. Hefler L, Mayerhofer K, Leibman B, Obermair A, Reinthaller A, Kainz C, Tempfer C. Tumor anemia and thrombocytosis in patients with vulvar cancer. Tumour Biol 2000;21:309-14.
16. De Jonge ET, Viljoen E, Lindeque BG, Amant F, Nesland JM, Holm R. The prognostic significance of p53, mdm2, c-erbB-2, cathepsin D, and thrombocytosis in stage IB cervical cancer treated by primary radical hysterectomy. Int J Gynecol Cancer 1999;9: 198-205.
17. Hernandez E, Donohue KA, Anderson LL, Heller PB, Stehman FB. The significance of thrombocytosis in patients with locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol 2000;78:137-42.
18. Scholz HS, Petru E, Gucer F, Haas J, Tamussino K, Winter R. Preoperative thrombocytosis is an independent prognostic factor in stage III and IV endometrial cancer. Anticancer Res 2000;20:3983-5.
19. Gucer F, Moser F, Tamussino K, Reich O, Haas J, Arikan G, Petru E, Winter R. Thrombocytosis as a prognostic factor in endometrial carcinoma. Gynecol Oncol 1998;70:210-4.
20. Benoy I, Salgado R, Colpaert C, Weytjens R, Vermeulen PB, Dirix LY. Serum interleukin 6, plasma VEGF, serum VEGF, and VEGF platelet load in breast cancer patients. Clin Breast Cancer 2002;2:311-5.
21. Taucher S, Salat A, Gnant M, Kwasny W, Mlineritsch B, Menzel RC, Schmid M, Smola MG, Stierer M, Tausch C, Galid A, Steger G, Jekesz R; Austrian Breast and Colorectal Cancer Study Group. Impact of pretreatment thrombocytosis on survival in primary breast cancer. Thromb Haemost 2003;89: 1098-106.
22. Pedersen LM, Milman N. Diagnostic significance of platelet count and other blood analyses in patients with lung cancer. Oncol Rep 2003;10:213-6.
23. O'Keefe SC, Marshall FF, Issa MM, Harmon MP, Petros JA. Thrombocytosis is associated with a significant increase in the cancer specific death rate after radical nephrectomy. J Urol 2002;168:1378-80.
24. Symbas NP, Townsend MF, El-Galley R, Keane TE, Graham SD, Petros JA. Poor prognosis associated with thrombocytosis in patients with renal cell carcinoma. BJU Int 2000;86:203-7.
25. Lavie O, Comerci G, Daras V, Bolger BS, Lopes A, Monaghan JM. Thrombocytosis in women with vulvar carcinoma. Gynecol Oncol 1999;72:82-6.
26. Menczer J, Schejter E, Geva D, Ginath S, Zakut H. Ovarian carcinoma associated thrombocytosis. Correlation with prognostic factors and with survival. Eur J Gynaecol Oncol 1998;19:82-4.
27. Pedersen LM, Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. Eur Respir J 1996;9:1826-30.
28. Higashihara M, Sunaga S, Tange T, Oohashi H, Kurokawa K. Increased secretion of interleukin-6 in malignant mesothelioma cells from a patient with marked thrombocytosis. Cancer 1992;70:2105-8.
29. Olm M, Obiols G, Garcia-Pascual L, Simo R, Mesa J. Thrombocytosis and follicular thyroid carcinoma. J Clin Pathol 1991;44:439.
30. Nather A, Mayerhofer K, Grimm C, Hefler L, Leodolter S, Obermair A, Joura EA. Thrombocytosis and anaemia in women with recurrent ovarian cancer prior to a second-line chemotherapy. Anticancer Res 2003;23:2991-4.
31. Salgado R, Vermeulen PB, Benoy I, Weytjens R, Huget P, Van Marck E, Dirix LY. Platelet number and interleukin-6 correlate with VEGF but not with bFGF serum levels of advanced cancer patients. Br J Cancer 1999;80:892-7.
32. Estrov Z, Talpaz M, Mavligit G, Pazdur R, Harris D, Greenberg SM- Kurzrock R. Elevated plasma thrombopoietic activity in patients with metastatic cancer-related thrombocytosis. Am J Med 1995;98:551-8.
33. Benoy I, Salgado R, Colpaert C, Weytjens R, Vermeulen PB, Dirix LY. Serum interleukin 6, plasma VEGF, serum VEGF, and VEGF platelet load in breast cancer patients. Clin Breast Cancer 2002;2:311-5.
34. Olencki T, Finke J, Tubbs R, Elson P, McLain D, Herzog P, Budd GT, Gunn H, Bukowski RM. Phase 1 trial of subcutaneous IL-6 in patients with refractory cancer: clinical and biologic effects. J Immunother 2000;23:549-56.
35. Rossini F, Brivio F, Mingozzi S, Lissoni P, Pioltelli P. Thrombocytosis, neutrophilia and anemia during interleukin-2 therapy. Haematologica 1991;76:439-40.
36. Ruka W, Rutkowski P, Kaminska J, Rysinska A, Steffen J. Alterations of routine blood tests in adult patients with soft tissue sarcomas: relationships to cytokine serum levels and prognostic significance. J Ann Oncol 2000;12:1423-32.
37. Krzemien S, Cedrych I, Holowiecki J. Thrombocythemia in a patient after bone marrow autotransplantation with the use of human recombinant granulocyte-monocyte colony growth factor. Pol Tyg Lek 1994;49:300-2 [Article in Polish].

38. Malhotra OP, Mohan A. Vincristine induced thrombocytosis. J Assoc Physicians India 1994;42:258.
39. Jelkmann W. The role of the liver in the production of thrombopoietin compared with erythropoietin. Eur J Gastroenterol Hepatol 2001;13:791-801.
40. Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, Zoller H, Theurl I, Widder W, Molnar C, Ludwiczek O, Atkins MB, Mier JW, Tilg H. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood 2001;98:2720-5.
41. Heits F, Katschinski DM, Wilmsen U, Wiedemann GJ, Jelkmann W. Serum thrombopoietin and interleukin 6 concentrations in tumour patients and response to chemotherapy-induced thrombocytopenia. Eur J Haematol 1997;59:53-8.
42. Yamaguchi H, Ishii E, Hayashida Y, Hirata Y, Sakai R, Miyazaki S. Mechanism of thrombocytosis in hepatoblastoma: a case report. Pediatr Hematol Oncol 1996;13:539-44.
43. von Shweinitz D, Hadam MR, Welte K, Mildenberger H, Pietsch T. Production of interleukin-1 beta and interleukin 6 in hepatoblastoma. Int J Cancer 1993:12;53:728-34.
44. Suzuki A, Takahashi T, Nakamura K, Tsuyuoka R, Okuno Y, Enomoto T, Fukumoto M, Imura H. Thrombocytosis in patients with tumors producing colony-stimulating factor. Blood 1992;80:2052-9.

Address for Correspondence:

Çağatay ARSLAN, MD

Department of Internal Medicine
Süleyman Demirel University School of Medicine
Isparta, TURKEY