Diagnostic value of thrombocytosis and high CA 125 level in women with adnexal masses

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Summary

Aim: The aim of this study was to determine the diagnostic value of thrombocytosis and high CA 125 levels in women with benign and malign adnexal masses. Thrombocytosis (platelet counts > 400 × 10^9/l) has been identified as a poor prognostic factor in many cancers including certain gynecologic malignant tumors such as endometrial, cervical, and ovarian cancers. *Methods:* Medical charts of 180 patients with adnexal masses were retrospectively reviewed and analyzed for the association of preoperative thrombocytosis and high CA 125 level with other clinical prognostic factors. *Results:* Of the 180 participants, 68 (68% of malignant adnexal masses) had thrombocytosis and 74 patients (74% of malignant adnexal masses) had elevated CA 125 levels. The patients with preoperative thrombocytosis were found to have greater elevations of CA 125 levels, more advanced stage disease, and higher grade tumors. *Conclusion:* Presence of thrombocytosis and high CA 125 alone and in combination may be used as a prognostic factor in the management of women with adnexal masses since they are already used as clinical tests for several purposes.

Key words: Thrombocytosis; CA125; Adnexal masses.

Introduction

In gynecology, the adnexa refer to the region adjoining the uterus and contain the ovary and Fallopian tube, as well as associated vessels, ligaments, and supporting connective tissue. Some of adnexal masses can regress spontaneously while others require a surgical procedure for histopathologic diagnosis and treatment. A mass in the adnexa may be symptomatic or discovered incidentally [1, 2].

Pathology in the adnexal area may arise from the uterus, bowel, retroperitoneum, or metastatic disease from another site, such as the breast or stomach [1]. Adnexal masses often include simple ovarian cysts, tubal pregnancies, and benign or malignant (cancerous) tumors. As tubal neoplasms are rare, adnexal masses generally remind us of ovarian tumors. The masses related to the tubes generally originate from inflammation [2].

Thrombocytosis is considered as platelet count greater than 400 × 10^9/l, consistent with published criteria [3-11]. Malignant cells produce cytokines such as IL-6 and other growth factors capable of inducing platelet production, and platelets in turn may contribute to tumor growth and metastases. Platelets are a rich source of both platelet-derived growth factor (PDGF) and thrombospondin. PDGF has been shown to function as a potent mitogen for a variety of cell types. Thrombospondin is an adhesive glycoprotein that supports the adhesion of tumor cells to the endothelium, and may promote metastasis through urokinase-type plasminogen activator mediation of cell invasion. Preoperative thrombocytosis may favor the diagnosis of malignancy in women undergoing surgical evaluation of pelvic masses [12, 13].

The original CA 125 as a tumor marker test is a homologous double-determinant (OC 125 monoclonal antibody based) assay for the quantification of tumor associated mucin-like CA 125 molecules present in the serum. It is found in small amounts like below 35 U/ml in the vast majority of cases. Therefore, its cutoff level for "normal" has been arbitrarily set at 35. CA 125 is a protein produced in response to mainly irritation of the peritoneal cavity. Anything that irritates the peritoneal cavity, the pleural cavity, even the pericardial sac, has a potential to cause an elevation of the CA 125. Thus, many benign disease processes may cause an increase in the level of CA 125. Some of these conditions are gynecological such as endometriosis, fibroids, and even menstruation. Other cancers such as colon cancer metastatic to the peritoneal cavity, metastatic stomach cancer, and pancreatic cancer besides ovarian can increase CA 125 levels [14, 15].

There is limited data evaluating usefulness of thrombocytosis and high CA 125 level in gynecologic practice to differentiate the types of adnexal masses. The aim of this study was to evaluate the diagnostic value of thrombocytosis and high CA 125 levels in patients with a benign or malign adnexal mass.

Materials and Methods

This retrospective study included 180 women undergoing gynecologic surgery for an adnexal mass at the Dr. Zekai Tahir Burak Women's Hospital after approval of the local ethics committee. Patients that were not subjected to preoperative examination of platelet and CA 125 level, patients with an internal disease that could cause thrombocytosis, those with asplenism, those who take medicine that could cause thrombocytosis, and

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Table 1. — *Histopathologic types of adnexal masses in the study population*.

Benign (n = 80)	n (%)	Malign (n = 100)	n (%)
Simple cyst	27 (33.5%)	Serous cystadenocarcinoma	46 (46%)
Serous cystadenoma	12 (15%)	Mucinou cystadenocarcinoma	23 (23%)
Mucinous cystadenoma	8 (10%)	Endometrioid carcinoma	1 (1%)
Mature teratoma	8 (10%)	Clear cell carcinoma	3 (3%)
Thecoma of the ovary	6 (7.5%)	Undifferentiated carcinoma	5 (5%)
Endometrioma	6 (7.5%)	Borderline ovarian tumor	3 (3%)
Intraligamentary myoma	4 (5%)	Dysgerminoma	3 (3%)
Tuboovarian abscess	3 (3.75%)	Endodermal sinus tumor	2 (2%)
Fibroma	3 (3.75%)	Immature teratoma	1 (1%)
Dermoid cyst	2 (2.5%)	Malign lymphoma	2 (2%)
Chronic ectopic pregnancy	1 (1.25%)	Granulosa cell tumor	6 (6%)
		Epidermoid carcinoma	1 (1%)
		Malign mixed Müllerian tumor	3 (3%)
		Metastatic tumors	1 (1%)

Table 2. — *Number and percentage of benign and malign adnexal masses according to age groups of the study population*.

Age group	Benign (n = 80) n (%)	Malign (n = 100) n (%)
< 20	12.5% (10)	4 (4)
21-30	16.25% (13)	13 (13)
31-40	17.50% (14)	9 (9)
41-50	21.25% (17)	28 (28)
51-60	13.75% (11)	17 (17)
61-70	18.75% (15)	22 (22)
71-80	0	6 (6)
≥ 81	0	1 (1)

patients in postpartum and postoperative status were not included in the study. Patients with thrombocyte number > 400,000/mm^3 were diagnosed as having thrombocytosis. Serum CA level 125 > 35 UI/ml was considered high.

We collected demographic, clinical, and histopathologic data and FIGO stage of ovarian cancer of the study subjects. The study subjects were divided into benign and malign adnexal mass groups according to the histopathologic diagnosis.

Statistical analyses

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of thrombocytosis and high CA 125 levels were calculated. After categorization of patients according to age ≤ 48 or 48 years, these calculations were repeated. In patients with a benign or malign adnexal mass, the association of thrombocytosis and high CA 125 levels were evaluated with Pearson's correlation analysis; $p < 0.05$ was considered significant.

Results

We included clinical data of 180 patients with adnexal masses in the study. Mean age of patients with a benign or malign adnexal mass was 44.2 (16-68 years) and 49.7 (16-81 years), respectively (Table 1).

Table 3. — *Number and percentage of patients according to thrombocytosis and high CA 125 level alone and in combination in the study population*.

	Benign (n = 80)	Malign (n = 100)	Significance
Thrombocytosis	11 (13.8%)	68 (68%)	$p < 0.001$
High CA 125 level	42 (52.5%)	74 (74%)	$p < 0.05$
Thrombocytosis plus high CA 125 level	10 (12.5%)	65 (65%)	$p < 0.001$

Table 4. — *Sensitivity, specificity, PPV and NPV of thrombocytosis, high CA 125 level, and thrombocytosis plus high CA 125 level in patients aged less than 48 or higher*.

	Age group	Thrombocytosis	High CA 125 level	Thrombocytosis plus high CA 125 level
Sensitivity	< 48	71%	73%	64%
	≥ 48	65%	75%	65%
Specificity	< 48	80%	41%	89%
	≥ 48	94%	59%	86%
PPV	< 48	78%	56%	85%
	≥ 48	95%	72%	88%
NPV	< 48	73%	60%	71%
	≥ 48	64%	59%	62%

In patients with a benign adnexal mass, the most common histopathologic types were simple ovarian cyst and serous cystadenoma. In patients with a malign adnexal mass, the most common types of tumor were serous and mucinous cystadenocarcinoma (Table 2).

The highest benign and malign adnexal mass ratios were found in women aged 41-50 years. In women aged more than 40 years, the malignity of the adnexal mass was higher compared to that found in women aged less than 40 years (Table 3).

In patients with malign adnexal masses, the ratios of thrombocytosis, high CA 125 level, or thrombocytosis plus high CA 125 level were significantly higher than those in patients with benign adnexal masses ($p < 0.05$) (Table 4).

Overall, in women aged < 48 or ≥ 48 years, the presence of thrombocytosis or high CA 125 alone and in combination provided comparable sensitivity and specificity (Table 5).

Overall, the ratio of thrombocytosis and higher CA 125 levels were increased according to the stage of ovarian cancer (Table 6).

In patients with adnexal masses, the sensitivity of high CA 125 level was the highest compared to thrombocytosis and thrombocytosis plus high CA 125 level. The specificity of thrombocytosis plus high CA 125 level was the highest compared to thrombocytosis and high CA 125 level. Overall, sensitivity, specificity, PPV and NPV of thrombocytosis and high CA 125 level in patients aged 48 years or higher were similar.

Discussion

In this retrospective study, we evaluated the clinical data of 180 women undergoing surgery for an adnexal

Table 5. — *Ratios of thrombocytosis and high CA 125 level in patients with malign adnexal mass according to stage of ovarian cancer*.

	Thrombocyte number		CA 125 level	
Stage n = 100	≤ 400,000/mm^3	> 400,000/mm^3	≤ 35 U/ml	> 35 U/ml
I (n = 31)	19 (61.3%)	12 (38.7%)	13 (41.9%)	18 (58.1%)
II (n = 12)	2 (16.7%)	10 (83.3%)	4 (33.3%)	8 (66.7%)
III (n = 41)	7 (17.1%)	34 (82.9%)	5 (12.2%)	36 (87.8%)
IV (n = 16)	4 (25%)	12 (75%)	4 (25%)	12 (75%)

Table 6. — *Sensitivity, specificity, PPV and NPV of thrombocytosis, high CA 125 level, and thrombocytosis plus high CA 125 level in patients with malign adnexal mass*.

	Sensitivity	Specificity	PPV	NPV
Thrombocytosis	68%	86%	86%	68%
High CA 125 level	74%	48%	59%	59%
Thrombocytosis plus high CA 125 level	65%	88%	87%	67%

mass. We assessed the diagnostic value of presence thrombocytosis, high CA 125 level, and thrombocytosis plus high CA 125 level to rule out malign tumors. Simple ovarian cysts and serous cystadenoma were the most common benign masses. The most common malign types of tumor were serous and mucinous cystadenocarcinoma. The highest benign and malign adnexal mass ratios were between age 41 and 50 years. The malignity of adnexal masses was higher at age 40 years or higher. For malign adnexal mass cases, the ratios of thrombocytosis and high CA 125 level alone or in combination were higher compared to those found in benign adnexal mass. Overall, in women aged less than 48 years or higher, the presence of thrombocytosis and high CA 125 alone and in combination provided similar sensitivity and specificity. According to the increase of stage of ovarian cancer, the ratio of thrombocytosis and higher CA 125 levels were increased. In patients with adnexal masses, the sensitivity of high CA 125 level was higher compared to those found with thrombocytosis and thrombocytosis plus high CA 125 level. The specificity of thrombocytosis plus high CA 125 level was higher compared to those found with thrombocytosis and high CA 125 level.

Van Calster *et al*. [16] evaluated likelihood curves of six subgroups (endometriomas and abscesses, other benign tumors, borderline tumors, Stage I invasive cancers, Stage II-IV invasive cancers, and metastatic tumors) of ovarian pathology based on CA 125 and menopausal status in 3,511 patients presenting with a persistent adnexal mass who underwent surgical intervention. According to their data, endometriomas and abscesses were the only benign pathologies with median CA 125 levels above 20 U/ml and borderline and invasive Stage I tumors had relatively low median CA 125 levels. They found that the CA 125 distributions of Stage II-IV invasive cancers and benign tumors other than endometriomas or abscesses were well distinguished; but the distributions of the other subgroups overlapped. They demonstrated that those findings were comparable for premenopausal and postmenopausal patients. They concluded that the clinical value of CA 125 was limited for preoperative discrimination between benign and malignant ovarian pathology, and that CA 125 may be used in a different way according to other clinical findings to increase its usefulness in patients with adnexal masses.

Liu *et al*. [17] reviewed the management of adnexal masses that were commonly encountered in gynecologic practice which were causing both diagnostic and management challenges. They reported that this was partly because of the fact that the majority of adnexal masses identified represented benign entities not requiring active intervention; however, a small subset had malignant potential. They concluded that for the best diagnostic and management strategies, effectively triage risk for malignancy was required by having a thorough understanding of the entities in the differential diagnosis, and carefully considering the clinical context for each individual patient. They suggested that optimal selection and interpretation of diagnostic tests were enhanced by both an accurate clinical risk assessment and an understanding of the inherent accuracy of diagnostic tests according to evidence-based management algorithms to optimize outcomes for women with adnexal masses.

Nolen and Lokshin [18] suggested that the goal of effective population-based screening for ovarian cancer remains elusive despite intense efforts aimed at improving biomarker and imaging modalities. While dozens of potential serum biomarkers for ovarian cancer have been identified in recent years, none have yet overcome the limitations that have hindered the clinical use of CA 125. Avenues of opportunity in biomarker development are emerging as investigators are beginning to appreciate the significance of remote, as well as local or regional, sources of biomarkers in the construction of diagnostic panels, as well as the importance of evaluating biomarkers in prediagnostic settings. As the list of candidate biomarkers of ovarian cancer continues to grow, refinements in the methods through which specific proteins are selected for further development as components of diagnostic panels are desperately sought. Such refinements must take into account both the bioinformatic and biological significance of each candidate. Approaches incorporating these considerations may potentially overcome the challenges to early detection posed by the histological heterogeneity of ovarian cancer.

Verheijen *et al*. [19] studied the use of cancer antigen 125 (CA 125) in the follow-up of patients with epithelial ovarian cancer after complete response to primary treatment. As it has been suggested to refrain from CA 125 altogether, the European Society of Gynaecological Oncology report has also reviewed possible disadvantages, even possible harm, and potentially missed opportunities when such policy would be implemented. They concluded that indeed routine use of CA 125 does not provide patient benefit in survival or quality of life. They noted that the lack of benefit of CA 125 monitoring has only been proven for a specific subset of ovarian cancer

patients with serous histology and frequent follow-up visits including imaging and in a clinical environment where, particularly, surgery for recurrent disease and clinical studies on new second-line agents will not be considered. They warned not to stop tumor marker follow-up in other than epithelial ovarian cancers and in follow-up of patients who not have been treated with chemotherapy.

Mury *et al*. [20] studied the role of pre- and postoperative CA 125 levels in patients with ovarian cancer. Despite radical surgery and chemotherapy, most patients with ovarian cancer will develop recurrence and die due to progressive disease. To stratify patients for optimal therapy, prognostic and predictive factors are needed. Although CA 125 serum levels differed significantly before and after surgery in early and advanced stage ovarian cancer and preoperative CA 125 values correlated with surgical outcome in advanced stage disease, they advised not to stop tumor marker follow-up in other than epithelial ovarian cancers and in follow-up of patients who have not been treated with chemotherapy.

In a study by Li *et al*. [21], the prognostic value of thrombocytosis in epithelial ovarian cancer was evaluated in 183 women. They found that thrombocytosis was an independent negative prognostic factor for overall survival in patients with advanced stage ovarian epithelial cancer. In another study by that group of researchers [22], incidence of thrombocytosis in patients with uterine papillary serous carcinomas was evaluated. They concluded that thrombocytosis might identify patients at greater risk for recurrence. Our findings, in accordance with those data, supported diagnostic value of thrombocytosis alone and in combination with high CA 125 levels since thrombocyte counting is a routine procedure for women evaluated for several gynecologic diseases. Careful interpretation and assessment of simple clinical data provide important clues to diagnose many difficult cases.

In conclusion, presence of thrombocytosis and high CA 125 alone and in combination may be used as a prognostic factor in the management of women with adnexal masses since they are an already used clinical test for several purposes. Further investigation is needed to elucidate the clinical value of the presence of these tests in a large group of women with adnexal masses grouped according to histopathologic diagnoses.

References

[1] Hoffman M.S.: "Differential diagnosis of the adnexal mass". In: UpToDate, Falk S.J. (ed.), UpToDate, Waltham, MA, 2011.

[2] Teng N., Simons E.J.: "Adnexal tumors. Available at: http://emedicine.medscape.com/article/258044-overview".

[3] Pedersen L.M., Milman N.: "Diagnostic significance of platelet count and other blood analyses in patients with lung cancer". *Oncol. Rep*., 2003, *10*, 213.

[4] O'Keefe S.C., Marshall F.F., Issa M.M., Harmon M.P., Petros J.A.: "Thrombocytosis is associated with a significant increase in the cancer specific death rate after radical nephrectomy". *J. Urol*., 2002, *168*, 1378.

[5] Costantini V., Zacharski L.R., Moritz T.E., Edwards R.L.: "The platelet count in carcinoma of the lung and colon". *Thromb. Haemost*., 1990, *64*, 501.

[6] Gücer F., Moser F., Tamussino K., Reich O., Haas J., Arikan G. *et al*.: "Thrombocytosis as a prognostic factor in endometrial carcinoma". *Gynecol. Oncol*., 1998, *70*, 210.

[7] Lerner D.L., Walsh C.S., Cass I., Karlan B.Y., Li A.J.: "The prognostic significance of thrombocytosis in uterine papillary serous carcinomas". *Gynecol. Oncol*., 2007, *104*, 91.

[8] Hernandez E., Donohue K.A., Anderson L.L., Heller P.B., Stehman F.B.: "The significance of thrombocytosis in patients with locally advanced cervical carcinoma: a Gynecologic Oncology Group study". *Gynecol. Oncol*., 2000, *78*, 137.

[9] Zeimet A.G., Marth C., Müller-Holzner E., Daxenbichler G., Dapunt O.: "Significance of thrombocytosis in patients with epithelial ovarian cancer". *Am. J. Obstet. Gynecol*., 1994, *170*, 549.

[10] 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.

[11] Chalas E., Welshinger M., Engellener W., Chumas J., Barbieri R., Mann W.J.: "The clinical significance of thrombocytosis in women presenting with a pelvic mass". *Am. J. Obstet. Gynecol*., 1992, *166*, 974.

[12] Gastl G., Plante M., Finstad C.L., Wong G.Y., Federici M.G., Bander N.H., Rubin S.C.: "High IL-6 levels in ascitic fluid correlate with reactive thrombocytosis in patients with epithelial ovarian cancer". *Br. J. Haematol*., 1993, *83*, 433.

[13] Kerpsack J.T., Finan M.A.: "Thrombocytosis as a predictor of malignancy in women with a pelvic mass". *J. Reprod. Med*., 2000, *45*, 929.

[14] Kenemans P., Yedema C.A., Bon G.G., von Mensdorff-Pouilly S.: "CA 125 in gynecological pathology - a review". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 1993, *49*, 115.

[15] Gadducci A., Cosio S., Carpi A., Nicolini A., Genazzani A.R.: "Serum tumor markers in the management of ovarian, endometrial and cervical cancer". *Biomed. Pharmacother*, 2004, *58*, 24.

[16] Van Calster B., Valentin L., Van Holsbeke C., Zhang J., Jurkovic D., Lissoni A.A. *et al*.: "A novel approach to predict the likelihood of specific ovarian tumor pathology based on serum CA-125: a multicenter observational study". *Cancer Epidemiol. Biomarkers Prev*., 2011, *20*, 2420.

[17] Liu J.H., Zanotti K.M.: "Management of the adnexal mass". *Obstet. Gynecol*., 2011, *117*, 1413.

[18] Nolen B.M., Lokshin A.E.: "Protein biomarkers of ovarian cancer: the forest and the trees". *Future Oncol*., 2012, *8*, 55.

[19] Verheijen R.H., Cibula D., Zola P., Reed N.: "Cancer Antigen 125: Lost to Follow-Up?: A European Society of Gynaecological". *Oncol. Int. J. Gynecol. Cancer*, 2012, *22*, 170.

[20] Mury D., Woelber L., Jung S., Eulenburg C., Choschzick M., Witzel I. *et al*.: "Prognostic and predictive relevance of CA-125 at primary surgery of ovarian cancer". *J. Cancer Res. Clin. Oncol*., 2011, Vol. *137*, 1131.

[21] Li A.J., Madden A.C., Cass I., Leuchter R.S., Lagasse L.D., Karlan B.Y.: "The prognostic significance of thrombocytosis in epithelial ovarian carcinoma". *Gynecol. Oncol*., 2004, *92*, 211.

[22] Lerner D.L., Walsh C.S., Cass I., Karlan B.Y., Li A.J.: "The prognostic significance of thrombocytosis in uterine papillary serous carcinomas". *Gynecol. Oncol*., 2007, *104*, 91.

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