EJGO European Journal of Gynaecological Oncology

Thrombocytosis in patients with primary peritoneal carcinoma

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Summary

Purpose: Serous primary peritoneal carcinoma (PPC) is histologically identical and clinically similar to epithelial ovarian carcinoma (OvC). In OvC thrombocytosis was found to be a marker of advanced disease and poor prognosis in most studies. Thrombocytosis in PPC has hitherto not been assessed. The purpose of the present investigation was to assess the prevalence of thrombocytosis in PPC patients, its association with prognostic factors, and survival. *Material and Methods:* The pretreatment thrombocyte count and selected clinical data in Stage IIIC histologically confirmed consecutive PPC patients, and a comparison group of Stage IIIC OvC patients diagnosed during January 2004 to December 2015, were abstracted from medical records. *Results:* The study included 21 PPC and 42 OvC patients. The rate of thrombocytosis in PPC patients was significantly higher (57.1% *vs*. 16.7%; $p < 0.001$) and the five-year survival was lower than that of OvC patients. Among the PPC patients, there was a considerable, statistically non-significant, higher rate of grade 3 tumors and of patients with postoperative residual disease in those with thrombocytosis compared to those without it. A borderline significantly higher rate of < 65 years old patients was found in those with thrombocytosis compared to those without it. The five-year survival rate was not different among those with and those without thrombocytosis. Conclusion: The rate of thrombocytosis is higher in PPC than in OvC patients. In spite of the considerable excess of PPC patients with poor prognostic factors in those with thrombocytosis, their survival was not different than of those without thrombocytosis.

Key words: Thrombocytosis; Primary peritoneal carcinoma; Prognostic factors; Survival.

Introduction

Thrombocytes have multiple functions and they play an important role in malignancies as well. According to two recent reviews, thrombocytosis, i.e. a platelet count ≥ 400,000/mm^3, at the time of diagnosis in patients with solid tumors is associated with poor survival in many tumors [1, 2]. The increase in platelet counts in these tumors is due to various tumor secreted cytokines. These cytokines, and especially IL-6 acting as an autocrine growth factor, are overproduced in a variety of malignancies. A potent platelet activator agonist, thrombin, is also generated by tumor cells. Activated platelets release multiple proteins that may stimulate angiogenesis, thus promoting tumor growth and metastasis. Consequently a vicious cycle is created in which tumors increase platelet counts that augment tumor growth and metastases that in turn further increase platelet counts. In addition activated platelets adhere to tumor cells and secrete immunoregulatory molecules that prevent their contact with the host's immune system protecting them from immune destruction by natural killer cells.

Serous primary peritoneal carcinoma (PPC) is a peritoneal malignancy that involves only the peritoneal surfaces with minimal or no involvement of the ovaries. It is histologically identical to advanced stage serous ovarian carcinoma (OvC). The treatment and clinical course of this malignancy are also similar to those of OvC. Nevertheless, epidemiologic, clinical, and biomolecular differences between the two neoplasms have been reported [3-5].

The effect of pretreatment thrombocytosis on outcome in various gynecological malignancies, has been previously reviewed [6, 7]. In OvC thrombocytosis was found to be a marker of advanced disease and poor prognosis in most studies [8-11] and its prevalence ranges from 22.4% to 62.5% [8, 9, 11, 12]. However, to the best of the present authors' knowledge, no study to date has assessed thrombocytosis specifically in PPC. The aim of the present study was to assess the prevalence of thrombocytosis in PPC, its association with prognostic factor, and its effect on survival.

Materials and Methods

After Institutional Review Board approval, the pretreatment thrombocyte count and selected clinical data were abstracted from medical records of consecutive histologically confirmed Stage IIIC PPC patients diagnosed during the period from January 2004 to December 2015. For comparison, the same data were abstracted from medical records of Stage IIIC histologically confirmed OvC patients. Two consecutive OvC patients diagnosed in every year of the study period adjacent to each PPC patient were included in the study. Thus to each PPC patient two OvC patients were matched by year of diagnosis.

Revised manuscript accepted for publication April 26, 2016

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVIII, n. 5, 2017
doi: 10.12892/ejgo3693.2017

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Table 1. — *Selected characteristics of patients with primary peritoneal and ovarian carcinoma.*

	Primary peritoneal carcinoma		Ovarian carcinoma		
	No.	%	No.	%	*p*
Total	21	100.0	42	100.0	
Thrombocyte count					<0.001
No thrombocytosis	9	19.1	35	83.3	
Thrombocytosis	12	57.1	7	16.7	
Age at diagnosis (years)					
< 65	7	33.3	24	57.0	NS
65+	14	66.7	18	43.0	
Main complaint					NS
Abdominal pain	10	47.6	21	50.0	
Abdominal distention	7	33.3	8	19.0	
Routine Examination	0	0	12	28.5	
Other	4	19.1	1	2.5	
Complaint duration (months)					NS
≤ 1	8	38.1	18	43.0	
2+	13	61.9	12	28.5	
Routine examination	0	0.0	12	28.5	
Unknown	1	4.7	2	4.8	
Initial treatment type					NS
Cytoreductive surgery	7	33.3	23	54.8	
Neoadjuvant chemotherapy	10	47.6	16	38.1	
Chemotherapy only	4	19.1	3	7.1	
Residual disease					NS
None	6	28.5	22	52.4	
Present	11	52.4	17	40.5	
No surgery	4	19.1	3	7.1	
CA125 level (u/ml)					NS
≥ 1,000	10	47.6	16	38.0	
< 1,000	11	52.4	26	62.0	
Five-year survival	38.8%		52.4%		0.068

Table 2. — *Selected prognostic parameters and survival according to the presence of thrombocytosis in patients with primary peritoneal carcinoma.*

	Total No. 100.0%	No thrombocytosis No.	%	Thrombocytosis No.	%	*p*
Age (years)						0.08
< 65	7	1	14.3	6	85.7	
65+	14	8	57.1	6	42.9	
Grade*						NS
3	17	5	33.3	10	66.7	
1,2	2	2	100	0	0	
Residual disease **						NS
None	6	4	66.7	2	33.3	
Present	11	5	45.4	6	54.6	
Five-year survival		50.0%		31.2%		0.62

* Two patients had only cytologic diagnosis.
** Four patients had chemotherapy only.

In patients who underwent primary surgery, the diagnosis of PPC was determined according to the criteria of the Society of Gynecologic Oncologists [13]. In patients who had neoadjuvant chemotherapy, the diagnosis of malignancy was established by core needle biopsy or cytologic assessment of aspirated ascitic fluid. In these patients the diagnosis of PPC was made when the largest diameter of the ovaries was not greater than three cm on pretreatment imaging by transvaginal ultrasound and computed tomography.

Differences between PPC and OvC patients were tested by the chi square test for categorical variables and the Fisher's exact test for small cells. Survival was calculate by the Kaplan-Meier method and compared by the log-rank test. None of the PPC or OvC patients had diseases associated with thrombocytosis.

Results

The study included 21 PPC and 42 OvC patients. The mean follow up of the PPC patients was 33.6 ± 33.4 months (range 1-128 months). Table 1 presents selected characteristics of the PPC and OvC patients. The rate of thrombocytosis in PPC patients was significantly higher than in OvC patients (57.1% *vs*. 16.7%; $p < 0.001$). A borderline significantly lower five-year survival rate of PPC compared to OvC patients was observed (38.8% *vs*. 52.4% respectively; $p = 0.068$). No significant differences between PPC and OvC patients were found with regard to age at diagnosis, main complaint, complaint duration, pretreatment CA125 level, initial treatment type, and the presence of postoperative residual disease.

Selected prognostic parameters and survival according to the presence of thrombocytosis in patients with PPC are shown in Table 2. A borderline significantly higher rate of < 65-year-old PPC patients was found in those with thrombocytosis compared to those without it (85.7% *vs*. 14.3% respectively; $p = 0.078$). There was considerable, but statistically non-significant, higher rate of grade 3 tumors and of patients with postoperative residual disease in those with thrombocytosis compared to those without it. The five-year survival rate of patients without thrombocytosis was higher than of those with thrombocytosis (50.0% *vs*. 31.2%, respectively), but the difference was not significant.

Discussion

We found that in spite of similar characteristics, the rate of thrombocytosis in Stage IIIC PPC patients was significantly higher than in those with IIIC OvC. The survival of PPC patients was less favorable than that of OvC patients. Among the present PPC patients, there was considerable, although statistically non-significant, higher rate of younger patients. That older age may be associated with lower likelihood of thrombocytosis was also found in studies of thrombocytosis in OvC patients [14, 15].

In view of the considerable excess of PPC patients with poor prognostic factors, such as higher grade and the presence of postoperative residual disease, in those with thrombocytosis, one could have expected a less favorable survival in these patients and yet the survival of patients with throm-

bocytosis was not significantly different than of those without thrombocytosis. The reason for this is obscure. The lack of significant difference between those with and those without thrombocytosis in the present study is most probably due to the small sample size. However, it is noteworthy that in one OvC study, there were also no differences in survival between patients with and without thrombocytosis [15].

Several studies of thrombocytosis in OvC that included PPC patients have been reported. However, in these studies the rate of thrombocytosis was not given separately for the PPC patients. [8, 16, 17]. To the best of our knowledge, this study is the first that assessed thrombocytosis, its association with prognostic factors, and survival specifically in PPC patients.

While many similarities exist between PPC and OvC, some differences do exist between these two neoplasms. Eltabach *et al.* [3] compared the epidemiologic features of 50 women with PPC with those of 503 women with OvC diagnosed in one institution. They found that women with PPC were significantly older had later menarche and were less likely to have used perineal talc powder. Barda *et al.* [4] in an Israeli population based study compared 95 PPC patients with 117 FIGO Stage III-IV epithelial OvC patients matched by age and continent of birth. A higher rate of abdominal distention, of volume of ascites, of malignant cells in ascitic fluid and lower rate of pelvic palpable mass, and personal breast cancer history were found in the PPC compared with the OvC group. The overall survival was similar but in optimally cytoreduced patients (≤ two cm), survival was better in the OvC group. The differences between PPC and OvC has recently been extensively reviewed by Sorensen *et al.* [5]. According to the studies reviewed by them, PPC patients were older, had higher parity and poorer survival compared to OvC, and in contrast to OvC patients, PPC patients may be of multifocal origin. In the present study we found that PPC and OvC patients also differ with regards to the rate of patients with thrombocytosis.

The disadvantages of the present study are inherent in its retrospective nature and its small sample size. The advantage of this study is that the patients were treated in one institution by the same medical team. Larger studies are needed in order to confirm the present results.

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