Original Article-I

Significance of Haemostatic Markers in Ovarian Carcinoma

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ABSTRACT

Background: **Most cancer patients with metastatic disease have abnormal coagulation parameters. Although many abnormal blood coagulation tests have been reported in malignancies, there is little agreement regarding which tests are most useful to predict disease progression and hence this study was undertaken.**

Methods: **In this prospective study, baseline and special coagulation tests were performed on 23 patients with ovarian adenocarcinoma. The baseline tests were PT, APTT, TT and platelet count. The special tests included factor VIII, factor IX and fibrinogen assay and semiquantitative measurement of D-dimer and FDP levels The cases were grouped into early and advanced disease groups. The results of the coagulation tests were analysed using suitable statistical methods. The results were compared between limited and advanced disease by chi square and Mann Whitney U test**

Results: **The percentage of cases with increased D-dimer and fibrin degradation products (FDP) values were higher in the advanced disease compared to early disease. Two cases in stage IV had DIC. The PT, APTT, TT and platelet count did not show any statistically significant differences between the early and advanced disease groups. Factor VIII, factor IX and fibrinogen levels were not significantly different between two groups.**

Conclusion: Elevated D dimer & FDP are associated with advanced stage ovarian adenocarcinoma

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INTRODUCTION

The haemostatic system is involved in the growth and spread of malignant disease. During cancer progression, it has been observed that coagulation activation becomes more pronounced and may eventually result in disseminated intravascular coagulation.[1] Tumour cells release coagulation factors directly leading to activation of coagulation pathway and also activates the fibrinolytic system. Thrombin leads to fibrin formation which acts as a growth factor for tumour cells and facilitates tumour angiogenesis. Ovarian cancer cells appear to be capable of both thrombin formation and induction of fibrin degradation which is essential for the spread of malignancy.[1]

There is considerable evidence that haemostatic system is involved in the growth and spread of malignant disease. The coagulation activation becomes more pronounced during cancer progression and may eventually result in disseminated intravascular coagulation. The haemostatic abnormalities associated with cancer pose a major challenge to the clinician which may be in the form of thrombosis or excessive bleeding. Even in the absence of overt clinical events, patients with carcinoma

commonly present with abnormalities in blood coagulation. Although several tests have been developed to assess the haemostatic alterations, this study has been carried out to identify the coagulation abnormalities using simple, relatively inexpensive coagulation tests that can be performed in any routine laboratory. In addition, if these tests can provide information on the extent and progression of the disease, it would be of great clinical utility. Comparative literature based on Indian data is not available thereby warranting this study.

MATERIAL AND METHODS

In this prospective study twenty three consecutive new cases of adenocarcinoma of ovary were studied between Jan-dec. 2004. The clinical details of the patient including the age, presenting complaints, relevant history to rule out any bleeding disorder, liver disease, history of drug intake, physical examination, provisional clinical diagnosis, histopathological / cytological diagnosis, and details of treatment. were obtained. Information regarding histological diagnosis, tumour differentiation and post-surgical staging were recorded. Details of investigations like – liver function tests, tumour marker levels, baseline haematological and coagulation parameters, radiological, US/ Scan CT scan, MRI and bone scan were noted in relevant cases. The presence of metastatic disease was determined by one or more of the following: physical examination, chest X ray, US Scan of abdomen and pelvis, CT scan, bone scan, fine needle aspiration cytology or other tissue / cytological diagnosis.

All cases with biopsy proven diagnosis of adenocarcinoma of the ovary in the age group 21–90 years. were included at the time of diagnosis. Patients on anticoagulant therapy, subjects taking oral contraceptives, those with liver disease, inherited bleeding disorder and pregnant women were excluded

The coagulation tests were performed at the time of diagnosis prior to surgery in all the cases. The baseline coagulation tests included : platelet count, PT, APTT and TT. The ranges that were taken as normal are: platelet count 1.5-4 lakh/µl, PT 15 – 17 sec, APTT 15 – 17 sec and TT 17 – 19 sec. The special coagulation tests performed were the factor VIII and IX levels, fibrinogen assay D-dimer and FDP assay. The ranges that were taken as normal are Factor VIII and IX assay 50– 150IU/dl, fibrinogen assay 146–350mg/dl, FDP < 5 µg/ml and D-dimer < 500 ng/ml The clotting factor VIII and IX assay were measured by one stage factor assay.[2] The fibrinogen assay was measured by the Clauss method. The D-dimer and FDP assay were measured by semi quantitative latex agglutination immunoassay test. The cases were grouped into stages I to IV. Stage I and II were considered as limited stage disease and stage III and IV as advanced disease.

The study was approved by the institutional ethical review board and informed consent was obtained from all cases.

Statistical Methods: Chi-square distribution test was applied to compare the results of the baseline and special coagulation tests across the four stages and between limited and advanced disease groups using incidence data. Mann Whitney U test which is a non parametric tests was applied between limited disease and advanced disease to test the variation at p= 0.05.

RESULTS

A toal of 23 cases adenocarcinoma ovary were studied; 5 cases were stage I, stage II-1, stage III-7 and 10 cases were in stage IV. Thus, there were 6 cases in early stage and 17 in advanced stage of malignancy.

Baseline coagulation tests like PT, APTT and TT did not show any significant differences between the stages of the disease. Of 23 cases, 13% of the cases had thrombo-cytopenia and 17.3% had thrombocytosis. Factor VIII levels were elevated in 56.5% of the cases, and Factor IX levels in 17.3%. 95% of the cases had elevated fibrinogen levels. D-Dimer and FDP levels were increased in 47.5% of the cases.

The mean and range for the coagulation parameters were as follows: Platelet count 2.55 $\pm$ 1.03 10^9/L PT 17.11 $\pm$ 3.23 sec, APTT 30.35 $\pm$ 5.87 sec, TT 16.61 $\pm$ 1.11 sec, Factor VIII assay 250. 76 +/-141.97 IU/dl, Factor IX assay 121.84

± 53.79 IU/dl and fibrinogen assay 576 ± 135.92 mg/dl. FDP and D-dimer were measured across a range.

Factor VIII, factor IX and fibrinogen levels also did not show significant difference between early Vs advanced disease groups. D-dimer and FDP levels showed statistically significant differences between early and advanced disease groups. (Table 1) None of the cases in the early disease group showed an increase in the D-dimer and FDP values, whereas 64.7% of the cases in the advanced disease group showed an increase in the D-dimer and FDP levels. (Table 2). All cases in stage 1 and 2 (early disease) had normal FDP and D-dimer levels. 2 cases in stage IV had DIC. The diagnosis of DIC was made on the basis of presence of elevated levels of FDP / D-dimer and thrombocytopenia.

DISCUSSION

Abnormalities of the so-called "routine" blood coagulation tests have been described in up to 92% of cancer patients.[3] The most common abnormalities are elevation of clotting factor levels like fibrinogen, factor V, VIII, IX and XI, elevated fibrinogen/fibrin degradation products and thrombocytosis. In the present study, all the cases had more than 3 abnormal coagulation tests. Thrombocytopenia was observed in 13% and thrombocytosis in 17.3% of the cases. The prevalence of thrombocytosis in invasive epithelial ovarian carcinoma (EOC) was found to

Table 1 Comparison of D-dimer and FDP levels according to stage

	Across stages	Early vs advanced disease	
Test	Chi square P <0.05	Chi square P <0.05	Mann Whitney P< 0.05
D-dimer	9.48	8.83	84/18
FDP	11.71	7.44	84/18

Table 2 Comparison of High D-dimer and FDP levels in Early vs. advanced disease

Ovary n=23	*Early disease n=6*		*Advanced disease n=17*	
	No.	**%**	No.	%
Increased D-dimer	0	0	11	64.7
Increased FDP	0	0	11	64.7

be significantly higher than in benign controls (24.3% vs 2.9%) in a study of 82 patients with ovarian cancer by Menczer et al.[4] In another study of 130 patients with ovarian carcinoma by Zeimet et al, thrombocytosis was reported in 38%.[5] The incidence of thrombocytopenia has been reported to vary from 4% in patients with inoperable lung cancer to 11% in a large series of patients with a variety of tumours.[6]

Thrombocytosis occurs more frequently in untreated cases and is most commonly associated with carcinoma of the pancreas, lung, gastrointestinal tract, breast and ovary. It may also be explained by the existence of low grade DIC and overcompensation. Platelet counts tend to increase in the months before death. It has been suggested to be a poor prognostic indicator in patients with lung cancer and gynaecological cancers.[7, 8]

The plasma levels of many of the clotting factors including factor I, V, VII, VIII, IX and XI have been found to be increased in patients with cancer [9] Increased fibrinogen levels have been associated with rapid tumour growth , widespread metastasis and reduced survival in patients with colorectal, breast, gastric and lung cancer. Hyperfibrinogenemia may reflect the presence of a subclinical compensated form of DIC. Khoo et al measured D-dimer levels in patients with ovarian cancer before surgery and during chemotherapy for 12 months. Serial D-dimer levels were found to have a high sensitivity for the detection of tumours in patients with subclinical disease (91%) as well as for predicting progression of disease (100%)[10]

The hemostatic and fibrinolytic status in 60 patients with ovarian cancer and benign ovarian cysts was determined by Koh et al[11]. Hypercoagulation, increased platelets, and enhanced fibrinolysis were seen in patients with preoperative ovarian cancer compared to patients with benign ovarian cysts. Enhanced thrombin generation, evidenced by increased F1+2 and decreased antithrombin III (ATIII) levels with further enhanced fibrinolysis by elevated D-dimer, was seen in advanced cancer. The authors suggest that these two parameters might be useful as systemic prognostic markers in survival outcome from the disease for the first 24 months in advanced ovarian cancer, in addition to the known correlation with the International Federation of Gynecology and Obstetrics (FIGO) stage.

Koh et al [12] evaluated 35 patients of EOC FIGO stage I/II n = 11, stage III / IV, n = 24) for hemostatic parameters relating to survival outcome by 36 months of disease by Fibrinogen, von Willebrand Factor (vWF), antithrombin III (ATIII), and D-dimer levels were determined for their association with disease outcome by 12 months, 24 months and 36 months. Elevated fibrinogen, vWF, and D-dimer together with reduced ATIII levels were found to be associated with poor survival outcome by 12 months of disease. Moreover, elevated vWF and D-dimer with reduced ATIII levels was strongly implicated with poor survival outcome by 36 months from diagnosis. It is therefore suggested that fibrinogen, vWF, ATIII, and D-dimer (DD) levels be used together as prognostic markers for disease outcome especially in patients with advanced ovarian cancer within 36 months of disease-von templehoff in a study of 60 patients with untreated ovarian cancer (FIGO stage I-IV) reported significant correlation between FIGO stage and D-dimer and fibrinogen levels. [1]

Gadducci et al measured D-Dimer and CA 125 in 39 patients with EOC at different times from first surgery. Both median DD and CA 125 levels were significantly higher in the 20 patients with clinically evident disease than in the 37 patients without clinical evidence of disease The sensitivity, specificity and diagnostic accuracy of D-Dimer in the assessment of clinical disease status were 65%, 62% and 63%, respectively.[13]

In the present study, D-dimer and FDP levels were increased in 47.5% of the cases. None of the cases in the early disease group had an increase in the D-dimer and FDP values, whereas 64.7% of the cases in the advanced disease group had an increase in the D-dimer and FDP levels suggesting that these parameters strongly correlate with disease stage and may be used as haemostatic markers of advanced malignancy. However, there is scope for further analysis with larger sample size and serial follow up.

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