

Evaluation of Plasma D-Dimer Level as a Predictive Marker of Advanced Carcinoma Breast

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Abstract

Purpose: Evaluation of plasma d-dimer level as a predictive marker of advanced carcinoma breast.

Background: The relationship between malignancy and thrombosis is known for over 100 years. Thrombocytosis, an increase in fibrinogen and fibrin degradation products like D-dimer, a rise in factors V, VII, VIII, IX, and XI levels, and a decrease in antithrombin III, are seen in cancer patients. Extracellular remodeling of fibrin is essential for angiogenesis in tumors, and activation of intravascular fibrin formation and degradation has been shown to occur in the plasma of breast cancer patients.

Material and methods: This study was conducted in the Department of Surgery in I.G.M.C. Shimla & included 90 patients admitted in surgery ward/ presenting in the O.P.D. Patients were randomized into three equal groups of 30 patients each. Group 1 included patients of Diagnosed breast Carcinoma and Group 2 included patients of Diagnosed Benign breast diseases and Group 3 included Healthy females. Plasma D- Dimer value of all groups were compared. Modified radical mastectomy was performed of Group 1 patients. HPE of breast specimen done and pathological examination report were analysed with Plasma D- Dimer value.

Results: Plasma D-Dimer value was normal i.e. <0.25 mg/l in all Group 2 & Group 3 patients, while in Group 1 it was increased in 90% of the patients.

There was statistically significant correlation between Mean values of plasma D- Dimer and advancing stage of disease, tumour size histological grade and lymphovascular invasion.

Conclusion: Plasma D-Dimer level is elevated in breast carcinoma, especially in those with advanced stage. Increased D-Dimer level is an important marker of clinical stage, lymphovascular invasion, lymph node involvement & tumor metastasis. So Preoperative Plasma D-Dimer may prove to be a safe, convenient and easily available predictive marker of advanced breast carcinoma.

Keywords: Carcinoma; Thrombosis; Antithrombin

Introduction

The relationship between malignancy and thrombosis is known for over 100 years [1]. Thromboembolism is present in almost half of the cancer patients at autopsy. Thrombosis in cancer often is migratory may involve superficial veins and relatively unusual sites. The hypercoagulable state in malignancy is due to a complex interaction of tumor cells and their products with the host cells leading to various degrees of impairment of the normal defense mechanisms that ordinarily protect the host against thrombogenesis. Tumor cells can activate directly the blood clotting cascade and cause thrombosis or can induce procoagulant properties and inhibit the anticoagulant ones of the vascular endothelial cells, platelets, monocytes and macrophages [1].

There is ample evidence that the components of the coagulation/fibrinolytic system play an important role in cancer biology and angiogenesis. Fibrin deposition and remodeling in extracellular matrix of the tumor is an important initial step in tumor metastasis. For a tumor to successfully metastasize from its primary location, it must undergo several obligate steps, including the invasion into either the lymphatic or vascular lumen, transportation through the circulation, and establishment of viability in target tissues. Cross linked fibrin in the extracellular matrix serves as a stable framework for endothelial cell migration during angiogenesis and tumor cell migration during invasion. It is reported that various abnormalities, including thrombocytosis, an increase in fibrinogen and fibrin degradation products like D-dimer, a rise in factors V, VII, VIII, IX, and XI levels, and a decrease in antithrombin III, are seen in cancer patients. Extracellular remodeling of fibrin is essential for angiogenesis in tumors, and

activation of intravascular fibrin formation and degradation has been shown to occur in the plasma of breast cancer patients.

This study was done with an attempt to evaluate role of D-dimer in patients of carcinoma breast, in predicting lymph node metastasis in carcinoma patients and to look for relationship of these markers with histopathologic parameters which are known to have predictive and prognostic value in carcinoma breast.

Material and Methods

In our study Patients were randomized into three equal groups of 30 patients each. Group 1 included patients of Diagnosed breast Carcinoma and Group 2 included patients of Diagnosed Benign breast diseases and Group 3 included Healthy females.

Blood collection

Blood samples from carcinoma breast patients, benign breast disease patients and healthy females were taken (1.8 ml. Blood from antecubital vein and mixed with 0.2 ml citrate) before surgery.

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Received May 19, 2015; Accepted June 25, 2015; Published June 27, 2015

Citation: Bhavesh D, Kapil Dev N, Sudershan S, Jaswal S (2015) Evaluation of Plasma D-Dimer Level as a Predictive Marker of Advanced Carcinoma Breast. J Clin Case Rep 5: 547. doi:10.4172/2165-7920.1000547

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D-Dimer: D-dimer was measured using Nyco card D-Dimer single test which is an in vitro test for rapid determination of D-dimer in plasma. Normal value of plasma D-dimer in healthy women is <0.25 mg/l.

TNM staging: Clinical staging using TNM classification was performed in carcinoma breast patients. This includes Tumor size, node status and metastatic workup including USG abdomen and chest X Ray. The American Joint Committee on cancer (AJCC) TNM staging system was used for staging of the patients.

Histopathological characterisation

After enrollment onto the study carcinoma breast patient undergo surgery and level III axillary dissection was done. Pathological Breast specimen and axillary lymph nodal tissue was examined for the following characteristics:

1. Tumor size: Gross examination of specimen after serial sectioning.
2. Histological grade: Modified scarff-Bloom-Richardson system (grade 1 to grade 3 according to differentiating of tumor)
3. Lymphovascular invasion.
4. Number of lymphnodes.
5. Number of lymph nodes positive for metastasis.

Results

The Age of the patients in Group 1, ranged from 30 to 78 years with a mean age of 51.6 years. In Group 2, from 13 to 36 years with a mean age of 24.8 years and In Group 3, from 17 to 65 years with a mean age of 42.76 years. In Group 1, 7 (23.33%) patients were premenopausal and 23 (76.67%) patients were post-menopausal. In Group 2, 30(100%) patients were premenopausal. In Group 3, 17 (56.67%) patients were premenopausal and 13 (43.33%) patients were postmenopausal.

In group 1 patients Rt. Sided breast lump was more common accounting for 56.67%. Most common location of breast lump was UOQ (60%). Most of these lumps had nodular surface, irregular margins, were hard in consistency and were not fixed to chest wall and overlying skin. Axillary lymph nodes were palpable in 60% of the patients while 40% had no clinically palpable lymph nodes. Anterior group was involved in 30% of patients. Central group was involved in 10% of patients. Most of the lymph nodes were non-tender, mobile and not fixed to each other or overlying skin.

In Group 1, 3 (10%) patients had D-Dimer value < 0.25 mg / l, 9 (30%) patients had D-Dimer value between 0.25-0.5 mg/l, 14 (46.67%) patients had D-Dimer value between 0.5-1.0 mg/l and 4 (13.33%) patients had D-Dimer value between 1.0 mg/ to 2.0 mg/l. In Group 2 and Group 3, 30 (100%) patients had D-Dimer value less than 0.25 mg/l (Table 1).

In stage I, 1 patient had normal plasma D-Dimer level i.e. less than 0.25 mg/l. In stage IIA, out of 4 patients 1 patient had normal D-Dimer level and 3 patients had D-Dimer levels more than 0.25 mg/l. In stage IIB, out of 7 patients 1 patient had normal plasma D-Dimer level and 6 patients had D-Dimer levels more than 0.25 mg/l. In stage IIIA, out of 5 patients 1 patient had normal plasma D-Dimer level and 4 patients had plasma D-Dimer levels more than 0.25 mg/l. In stage IIIB, stage IIIC and stage IV all patients had plasma D-Dimer levels more than 0.25 mg/l. This shows that plasma D-Dimer levels increase with advancement of stage (Table 2).

D-Dimer (mg/l)	No. of patients		
	Group 1 (Percentage)	Group 2 (Percentage)	Group 3 (Percentage)
<0.25	3(10.00%)	30(100%)	30(100%)
0.25-0.5	9(30.00%)	-	-
0.5-1.0	14(46.67%)	-	-
1.0-2.0	4(13.33%)	-	-
Total	30	30	30

Table 1: Comparison of D-Dimer (mg/l) levels in different groups.

TNM Stage	No. of Patients	D-Dimer (mg/l)
Stage I	1	0.1
Stage IIa	4	0.1
		0.3
		0.5
		0.7
Stage IIb	7	0.1
		0.3
		0.4
		0.4
		0.5
		0.8
Stage IIIa	5	0.9
		0.2
		0.4
		0.5
		0.6
Stage IIIb	11	0.9
		0.3
		0.4
		0.4
		0.4
		0.5
		0.5
		0.5
		0.7
		0.7
0.9		
Stage IIIc	1	1.0
Stage IV	1	1.1

Table 2: Plasma D-Dimer values as per different stages of group 1 patients (Clinical).

In stage 1, 1(3.33%) patient had mean D-Dimer (mg/l) value 0.1. In stage II A, 4 (13.33%) patients had mean D-Dimer value 0.4. In stage II B, 7 (23.33%) patients had mean D-Dimer value 0.49. In stage III A, 5 (16.67%) patients had mean D-Dimer value 0.52. In stage III B, 11 (36.67%) patients had mean D-Dimer value 0.65. In stage III C, 1 (3.33%) patient had mean D-Dimer value 1.1. In stage IV, 1(3.33%) patient had mean D-Dimer value 1. The increase in mean value of D-Dimer with advancing stage of disease was found to be significant (p value 0.011). So it is clear that plasma D-Dimer levels increases with the advancement of the disease (Table 3).

In Group 1, 3 (10%) patients with tumour size T1 had mean plasma D-Dimer (mg/l) value 7.74, 10 (33.33%) patients with tumor size T2 had mean plasma D-Dimer value 29.17, 4 (13.33%) patients with tumor size T3 had mean plasma D-Dimer value 8.93, 13(43.33%) patients with tumor size T4 had mean plasma D-Dimer value 54.17. The increase in

mean value of D-Dimer with increasing tumor size was significant (p value.023) (Table 4).

In Group I, 5 (16.67%) patients with histological grade I had mean plasma D-Dimer (mg/l) value 1.7, 10 (33.33 %) patients with histological grade II had mean plasma D-Dimer value 2.8 and 15 (50%) patients with histological grade III had mean plasma D-Dimer value 12.4.

The difference between mean value of D-Dimer value according to Histological grade was highly significant (p value.002) (Table 5).

In Group I, 19 (63.33%) patients lymphovascular invasion was present having mean plasma D-Dimer (mg/l) value 4.2 and in 11 (36.67%) patients lymphovascular invasion was absent, having mean plasma D-Dimer value 12.7. The difference between mean value of D-Dimer according to Histological grade was highly significant (p value 0.00017) (Table 6).

Discussion

The levels of factor VIII and D-dimer are reported to be considerably high in cancer patients compared to healthy control subjects [2]. Procoagulant activity has been shown to be associated

with stage of the disease [3]. In our study plasma D-Dimer of breast cancer, benign breast diseases & healthy females were compared and there was no increase in level of D-Dimer in benign breast diseases patients and healthy females but there was elevated level of plasma D-Dimer in breast cancer patients and its value increases as stage increases [4].

Our study showed that there is progressive increase in D-dimer levels as the stage of disease progresses. This increase is found to be statistically significant [4-7].

There was statistically significant relationship found between D-dimer according to increase in tumor size [6,7]. There was significant relationship between D-dimer and Factor VIII levels and histologic grade of the tumor. Similar results were reported by other studies when D-dimer and Factor VIII levels were compared with histologic grade of tumor [5,6]. Peritumoral lymphatic vessel and vascular invasion (LVI) has been demonstrated to have prognostic significance for the risk of local and distant recurrence. At 20 years of follow-up, Rosen et al. noted a correlation between lymphovascular invasion and the risk of recurrence and death the recurrence rate for women with LVI-positive stage I disease was 38% compared with 22% for those with LVI-negative disease. To survive, metastatic cancer cells must leave the primary tumor, migrate into the lymphovascular system, and establish a new blood supply at their metastatic site. Fibrin remodeling is almost certainly involved in all steps of metastasis and has been proven to play a crucial role in new vessel formation. In a study done by Blackwell et al. [7] linear regression modeling showed a tight relationship between the presence of lymphovascular invasion and elevated D-dimer levels. This relationship suggests a possible, yet unproven, biologic mechanism for the entrance of D-dimer fragments into the circulation. In present study we found statistically significant relationship of D-dimer levels with Lymphovascular invasion by the tumor cells, this relationship suggests a possible role of these markers as prognostic factors in carcinoma Breast.

TNM Stage	No. of patients (Percentage)	D-dimer (Mean) (mg/l)
Stage I	1(3.33%)	0.1
Stage II A	4(13.33%)	0.4
Stage II B	7(23.33%)	0.49
Stage III A	5(16.67%)	0.52
Stage III B	11(36.67%)	0.65
Stage III C	1(3.33%)	1.1
Stage IV	1(3.33%)	1
P value		0.011(Significant)

Table 3: Comparison of D-Dimer in different stages of group 1 patients (Clinical).

Tumour Size	No. of patients (Percentage)	D-Dimer (Mean) (mg/l)
T1	3(10%)	7.74
T2	10(33.33%)	29.17
T3	4(13.33%)	8.93
T4	13(43.33%)	54.17
P value		0.023 (Significant)

Table 4: Comparison of D-Dimer according to increasing tumour size in group1 patients.

Histological Grade	No. of patients (Percentage)	D-Dimer (Mean) (mg/l)
I	5(16.67%)	1.7(10.06)
II	10(33.33%)	2.8 (16.57)
III	15(50%)	12.4 (73.37)
P value		0.002 (Significant)

Table 5: Comparison of D-Dimer according to histological grade in group1 patients (Pathological).

Lymphovascular invasion	No. of patients (Percentage)	D-dimer(Mean) (mg/l)
Present	19(63.33%)	4.2
Absent	11(36.67%)	12.7
P value		0.00017 (Significant)

Table 6: Comparison of D-Dimer according to lymphovascular invasion in group1 patients (Pathological).

Conclusion

The diagnosis and treatment of carcinoma breast requires a multi-disciplinary approach involving the surgeon, radiologist, pathologist and medical oncologist. Treatment planning and survival depends on stage of disease at the time of diagnosis. Lymph node metastasis is the most important prognostic factor.

This study clearly shows that plasma D-Dimer levels are elevated in carcinoma breast patients. Increased D-Dimer levels are an important marker of clinical stage, lymphovascular invasion, lymph node involvement and tumour metastasis.

Further studies may prove plasma D-Dimer levels to be a safe, cost effective, convenient and easily available preoperative predictive marker of advanced breast carcinoma.

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