Coagulation Abnormalities in Breast Cancer

Manjunath B.D.[a], Abhishek G.[b], Prem Kumar A.[c]

[a]Assistant Professor [b]Postgraduate Student [c]Assistant Professor, Department of General Surgery, Bangalore Medical College and Research Institute, Bangalore, Karnataka 560002, India.

Abstract

Introduction: Breast cancer is the commonest cancer in Indian female population. India faces a potential breast cancer epidemic over the next decade as women adopt western lifestyles by marrying and bearing children later in life. An emerging literaturesupports hemostatic elements as an important patientfactor that facilitates the metastatic potential of breastcancer including platelets, coagulation, and fibrinolysis. Hence this study was taken up to assess the coagulation abnormalities in patients of breast cancer.

Materials and Methods: The study was a prospective, case control study carried out with patients presenting with complaints of lump in the breast which were later confirmed to be malignant after triple assessment. Data was collected by history taking, physical examination, haematological investigations including coagulation profile, imaging tests (mammogram, ultrasound and/or MRI), andFNAC or core needle biopsy.

Results: Platelet count, Bleeding and clotting times, PT, INR, APTT and fibrinogen were found to be comparable in patients with breast cancer when compared with controls. D-Dimers were found to be significantly elevated (odds ratio = 10.54, p = 0.03) in patients with breast cancer when compared with controls. D-Dimers were elevated in cases with locally advanced and advanced breast carcinomas.

Conclusion: Locally advanced and advanced breast carcinomas may present with an elevated levels of d-dimers indicating a compensated state of DIC.Detection of D-Dimers may offer a differential analysis over other laboratory tests for DIC.

Keywords: Carcinoma Breast; Disseminated Intravascular Coagulation; Prothrombin Time; Activated Partial Thromboplastin Time; D-Dimers; Coagulation Abnormalities.

Introduction

Incidence of breast cancer is on the rise in India and it is now the most common cancer in most cities in India, and 2nd most common in the rural areas after cervical cancer. India faces a potential breast cancer epidemic over the next decade as women adopt western lifestyles by marrying and bearing children later in life.

Trousseau first reported over 100 years ago that cancer patients have an increased incidence of coagulopathies [1]. Since Trousseau published his findings, thromboembolic disorders have been documented at elevated frequencies in patients with a wide variety of tumors such as lung, pancreas, stomach, and colon tumors [2]. The coagulation disorders of non-hematological malignancies like breast, prostate, ovary, lung, stomach tumors can cause either excessive clotting and bleeding or the combined abnormalities of excessive clotting direct to utilization of coagulation factors and secondarily guide to excessive bleeding [3,4].

The coagulation mechanism is carried out by the coagulation factors, coagulation inhibitory factors and fibrinolytic systemswhich play an essential role in hemostasis [5,6]. D-dimers are produced as a result of fibrin degradation by plasmin and its concentration increasesduring thrombolysis. Due to high credibility of D-dimers, monoclonal antibodies can be used with

plasma samples, thereby distinguishing fibrinolysis from fibrinogenolysis and advising an advantage over most usual assays for FDP [7-9].

Disseminated intravascular coagulation (DIC) is a consumptive coagulopathy characterized by consumption of platelets, blood clotting factors V and VIII, fibrinogen resulting in their decreased circulatory levels and increased FDP circulatory levels as a result of secondary or compensatory fibrinolysis [10,11]. Thrombin and platelet functions are further inhibited by high levels of circulating fibrin complexes and FDP's, thus continuing widespread bleeding tendency [12]. D-dimer and FDP tests are highly effective in diagnosing DIC[13,14].

Thrombosis in cancer is frequently migratory and involves superficial veins at somewhat typical positions [15]. Non-specific mechanisms likeinflammation and tissue injury result in expression of tissue factors (TF). The tumor may also induce the expression of TF due to monocytes and tissue macrophages or express pro-coagulant activity directly, giving them the capacity to produce thrombin even in the presence of other coagulation proteins. Elevated TF expression has been in breast cancer patients [16]. Other pro-thrombotic mediators like cysteine protease that activate factor X have been identified in tumor cells [17]. TF expression may also be increased by hypoxic conditions that act as a stimulus for VEGF production, thus mediating tumour metastasis [18].

Prothrombin time (PT) and activated partial thromboplastin time (APTT) may be increased or decreased, although hyperfibrinogenemia is common. Probability of elevated FDP in cases with metastases is higher when compared to cancer confined to a small area [19].

Cancer patients may also suffer from the impediment of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura (HUS/TTP), renal failure, micro-angiopathic hemolytic anemia and severe thrombocytopenia [20-23].

Increased association of systemic venous thromboembolism has been observed in women with breast cancer. Treatments modalities for breast cancer like chemotherapy, hormonal therapy and surgery contribute to this hypercoagulable state. The role of coagulation pathway including tissue factor (TF) and thrombin, as an important regulator of malignant transformation, tumor angiogenesis, and metastasis is being supported by strong evidence.

Inspite of our understanding being modest with regard to the role of hemostasis in breast cancer progression, the mechanisms and pathways highlighting the tumor-promoting effects of platelets, coagulation, and fibrinolysis are being increasingly identified. The current evidencesare not just confined to breast cancer models that support the role of the hemostatic system in cancer progression, although are limited with regard to efficacy of targeting the hemostatic system [24].

In this study, the main aim was to assess the coagulation abnormalities in patients of breast cancer in its different stages.

Methodology

The study was a prospective, case-control study conducted at Victoria and Bowring & Lady Curzon hospital, Bangalore Medical College & Research Institute from January 2016 – December 2017. All patients with complaints of lump in the breast which was confirmed to be a carcinoma after subjecting the patient to triple assessment were included in the study. Patients not willing for treatment were excluded from the study.

Patients

A total of 60 subjects were included in the study. The selected subjects were divided into two groups. Group I (case group) Inclusion Criteria: It included 30 breast cancer patients, all patients with breast cancer and patients without the personal and family history of bleeding diathesis. Exclusion Criteria: Patients with all hematological malignancies (leukemia, lymphoma, multiple myeloma), family history of bleeding diathesis, liver disease, renal disease and patients having history of chemotherapy and radiotherapy. Group II (control group): It included 30 healthy subjects with age, sex and socio-economically matched controls from hospital staff or relative of the patients. They did not have any history of liver disease or bleeding diathesis.

Laboratory Investigations

The blood samples were analyzed for general haematological investigations and coagulation profile. General Hematological Investigations: Hemoglobin, total leukocyte count, differential leukocyte count, platelets count were performed on the samples collected from the subjects. Specific Hematological investigations: Platelet count, bleeding time, clotting time, PT, INR, APTT, Fibrinogen Assay, D-Dimer Detection was also done for collected samples.

Demographic details of each patient was recorded. History included presenting complaints, age of the patient, associated complaints of pain in the lump or ulceration over the skin, nipple retraction or nipple discharge.

History of associated comorbid conditions like diabetes mellitus and hypertension were also noted.

Clinical examination of the patient was carried out according to the standard method of examination as described previously. A clinical staging of the breast carcinoma was done based on those findings.

After clinical evaluation the patients were subjected to appropriate non-invasive and invasive investigations.

Those women with a palpable breast lump underwent a fine needle aspiration cytology or a tru-cut biopsy from the lesion for histopathological confirmation of the type of carcinoma.

Metastatic workup was done for all patients with locally advanced breast carcinoma. Surgical intervention was decided mainly on the stage of the disease.

After the initial evaluation including the routine blood investigations and pre anaesthetic evaluation the patients who were deemed fit for surgery underwent modified radical mastectomy.

Statistical Analysis

Data was managed and analyzed by using statistical software packages for social sciences (SPSS) v21. For categorical variables, different codes were assign to them. Arithmetic mean (x), Odds Ratio and Probability Value (P value) analysis were performed.

Results

A total of 60 subjects were included in this study from November 2015 to May 2017. Out of 60 subjects, 30 were cases of breast carcinoma confirmed by triple assessment. 30 were age and sex matched controls.

The mean age of cases was 51.6 years and controls was 51.27 years. The age distribution of both cases and controls are shown in Table 1.

Clinical Features

Side Involvement: Out of the 30 subjects under our study 17 (56.6%) had carcinoma of the left breast and 13 (43.3%) had carcinoma of the right breast.

Quadrant Involved: There is a higher incidence of breast carcinoma in the upper outer quadrant of the breast due to the increased amount of breast tissue present in this quadrant. In our study also the highest percentage of tumors were found in the upper outer quadrant (80%) followed by upper inner (6.6%), central (6.6%), lower outer (3.3%) and lower inner (3.3%). Stages at presentation: Majority of the patients presented us to in stage II i.e. 56.6%, 16.6% of the cases were still in stage I, 26.6% of the patients were in stage III and 3.3% of the patients presented when there was already evidence of distant metastases. The same is described in Table 2.

Table 1: Age distribution

Age (in years)	Cases	Controls
21-30	1	0
31-40	4	5
41-50	12	9
51-60	8	11
61-70	4	4
71-80	1	1
Total	30	30

Table 2: Stages at presentation

TNM Stage	Number of Cases	Percentage
STAGE IA	1	3.3%
STAGE IB	4	13.3%
STAGEIIA	11	36.6%
STAGE IIB	6	20%
STAGE IIIA	7	23.3%
STAGE IIIB	0	0%
STAGE IIIC	1	3.3%
STAGE IV	1	3.3%
TOTAL	30	100%

Table 3: Histopathological report

HPE Report	Number of Cases	Percentage
Invasive ductal carcinoma	25	83.3%
Invasive lobular carcinoma	2	6.6%
Medullary carcinoma	1	3.3%
Colloid carcinoma	1	3.3%
Metaplastic carcinoma	1	3.3%

Table 4: Coagulation profile

Investigations	Cases	Controls
Haemoglobin	11.92	12.12
Total count	8857.3	8938
Platelets	2.86	3.03
Bleeding time	2'20"	2'28"
Clotting time	5'31"	5'15"
Prothrombin time	11.4	11.3
INR	1.03	1.02
aPTT	28.2	28.2
Fibrogen	235.43	228.83
d-dimers	385.13	196.56

Table 5: Elevated D-dimers in different stages of breast cancer

TNM Stage	Number of Cases	Percentage
Stage IA	0	0%
Stage IB	0	0%
Stage IIA	0	0%
Stage IIB	2	25%
Stage IIIA	1	12.5%
Stage IIIB	4	50%
Stage IIIC	0	0%
Stage IV	1	12.5%
TOTAL	8	100%

Histopathological Variants

Out of the 30 operated cases 83.3% of the tumors turned out to be intraductal carcinoma and the rest were lobular, medullary colloid and metaplastic carcinoma. The incidences of various histopathological types are described in Table 3.

Coagulation Profile

Comparative data of pre-operative coagulation profile showed normal and comparable hemoglobin, white blood cell count, platelet count, bleeding and clotting times, prothrombin time, INR, aPTT and fibrinogen level. D-Dimers were significantly elevated in 8 cases while only 1 control showed elevated levels, *Odds ratio being 10.54 with a p value of 0.03.* The data is shown in Table 4.

All the cases who showed elevated D-Dimers were mostly locally advanced or advanced breast cancers (Stages III and IV). Only 2 out of 8 early breast cancer cases showed coagulation abnormalities. This distribution is described in Table 5.

Discussion

Carcinoma of the breast is the commonest malignancy of females worldwide. It is the most frequent cancer and cause of cancer deaths in developed and developing countries. Breast cancer accounts for 23% of all newly occurring cancers in women worldwide and represents 13.7% of all cancer deaths.

Breast cancer is the second most common cancer after cervical cancer in India with 115,251 new diagnoses seen in 2008, the second most common cause of cancer related deaths with 53,592 breast cancer deaths in 2008, leading site of cancer in metropolitan cities of India.

In the developing countries of Asia, the health care

burden on account of breast cancer has been steadily mounting. It is expected that in the coming decades, these countries would account for majority of new breast cancer patients diagnosed globally. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India.

According to the National Cancer Registry Program (2001-2004) of Indian Council of Medical Research (ICMR), breast cancer was most common in all registries in urban centres except Barshi. The complete details of cancers in various cities like Mumbai, Delhi, Bangalore, Bhopal, Kolkata, Chennai, Ahmedabad etc. can be found on the PBCR (Population Based Cancer Registry).

Breast cancer accounts for 25% to 32% of all female cancers in all these cities. This implies that practically, one fourth (or even approaching one thirds) of all female cancer cases are breast cancers.

In our study, we have noticed normal levels of hemoglobin, total leucocyte count, platelet count, bleeding and clotting times, PT, INR, aPTT and fibrinogen in all cases. Some cases of locally advanced breast cancer and advanced breast cancer showed elevated D-Dimers suggesting a possibility of a compensated state of disseminated intravascular coagulation.

Conclusion

Breast cancer is fast becoming an epidemic in developing countries where it not only results in a huge economic and emotional burden for the family but for the nation as well. There is no absolute or definitive way to prevent breast cancer. Hence the easiest way to reduce this disease burden would be by incorporating screening and risk reduction.

Screening will help in identifying early non-invasive cancers and allow for treatment before they become invasive or help in identifying invasive cancers at an early treatable stage. Locally advanced and advanced breast carcinomas may present with an elevated levels of D-dimers indicating a compensated state of DIC. Detection of D-Dimers may offer a differential analysis over other laboratory tests for DIC.

Whether D-Dimers can be used as a marker or guide to assess metastatic potential of the disease needs to be evaluated by further large scale studies.

Drugs targeting coagulation cascade may be used in future to reduce the metastatic potential or reduce the burden of the disease.

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