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Evaluation of Haemostatic Abnormalities among Sudanese Patients with Haematologic and Solid Malignancy

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Abstract Cancer is a broad group of various diseases, all involving unregulated cell growth. Both experimental and clinical studies have evidenced an association between cancer and haemostasis. This study aimed to evaluate the haemostatic property among cancer patients in Sudan by determining D-dimer level, activated partial thromboplastin time (APTT), prothrombin time (PT) and platelets count. Following informed consent, one hundred and twenty subjects were enrolled in this cross-sectional study: Sixty patients with haematologic or solid malignancies (pathologically confirmed) attending Alzara hospital; and age and sex matched sixty normal subjects as controls. D-Dimer was measured using i-CHROMA^{TM} system, APTT and PT were measured using coagulometer (Sysmex CA 50), and Platelets count was measured by automated cell counter (Sysmex Kx21). The results of the cancer patients were as follows: mean D-Dimer level was 2196.32±2110.95 ng/ml, mean APTT was 35.7±6.6 seconds, mean PT was 13.7±1.3 seconds and mean platelets count was 249.6±142.3 X10^9/L; while for the control: mean D-Dimer level was 213.65±103.57ng/ml, mean APTT was 29.6±2.2 seconds, mean PT was 12.2±0.8 seconds and mean platelets count was 279.7±77.9 X10^9/L. Mean D-Dimer level was significantly higher among cancer patients than the controls (p value (0.000). mean APTT and PT were also higher among cancer patients than the controls (p value 0.000, for both parameters). There was a significant association between the D-Dimer levels and the plasma clotting times (APTT and PT). In conclusion, our study confirms the hypercoagulable state among various types of malignancies in Sudan, which has been determined by elevated D-Dimer levels.

Keywords D-Dimer level, Cancer Patients, Sudan

1. Introduction

Cancer is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body [1]. Despite major advancements in the basic biology of cancer and new therapeutic interventions, cancer still remains among the deadliest diseases of the modern age [2].

Both experimental and clinical studies have evidenced an association between cancer and haemostasis [3]. It has been estimated that approximately 15% of all cancer patients develops thrombosis during the course of their disease [4]. In fact, the occurrence of cancer is usually associated with various clinical thrombotic syndromes, including local and systemic venous and arterial thrombosis [5]. Additionally, thrombosis is often diagnosed as the first clinical manifestation of a tumor and has been reported as the second leading cause of death of patients with cancer [6-8].

Malignant cells can interact with the haemostatic system in multiple ways [9], but the two principal categories of interaction are the capacity to produce and release procoagulant and fibrinolytic activities, as well as inflammatory cytokines [10,11]; and direct interaction with other blood cells, i.e., endothelial cells, platelets, and monocytes [9].

Abnormal coagulation activation promotes endothelial adhesion and metastatic spread, as well as tumor cell growth and tumor cell survival [2]. It is widely recognized that the majority of cancer patients present with one or more abnormalities of laboratory coagulation tests. The most frequent abnormalities include increased levels of fibrinogen, factors V, VIII, IX, X, fibrin (ogen) degradation products (FDPs) and thrombocytosis [12].

Despite the well-established link between cancer and venous thrombosis, anticoagulation is not routine care for these patients [13]. Evaluation of the coagulation profile among cancer patients may help understanding the association of cancers with the coagulation abnormalities,

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also can help in the prediction and management of the complications that arise from the coagulation abnormalities in such patients. This study aimed to evaluate the haemostatic properties among cancer patients in Sudan by determining D-Dimer level, activated partial thromboplastin time (APTT), prothrombin time (PT) and platelets count.

2. Material and Methods

One hundred and twenty subjects were enrolled in this cross-sectional study: Sixty patients with haematologic or solid malignancies (pathologically confirmed) attending alzara hospital; and age and sex matched sixty normal subjects as controls. Patients with history of chemotherapy, use of anticoagulant drugs, surgery or trauma within the last 4 weeks, patients on steroid, and those with known hereditary coagulation disorders, homocysteinaemia, rheumatologic, renal, liver, and heart problems were excluded from this study.

Informed consent was obtained from each subject before enrollment in the study. Five ml of venous blood was collected from each subject: 2.5 ml in 3.8% trisodium citrate (9:1 vol/vol), kept on ice until centrifugation at 2500g for 30 minutes at 4°C, plasma samples were immediately frozen and stored at - 80°C for subsequent coagulation analysis; and 2.5 ml in EDTA for the platelets count. Laboratory analysis was performed at the Department of Haematology, Faculty of Medical Laboratory Sciences, Alneelain University.

D-dimer was measured using i-CHROMA™ system (Boditech – Korea). The test uses the sandwich immunodetection method. D-Dimer is bound with an antibody in buffer and the antigen-antibody complexes are captured by antibodies that have been immobilized on the test strip as sample mixture migrates through nitrocellulose matrix. Signal intensity of fluorescence on detection antibody reflects the amount of the antigen captured and is processed by *i*-CHROMA™ Reader to show D-Dimer concentration in the specimen. The working range of *i*-CHROMA™ D-Dimer test is 50 – 10,000 ng/ml. APTT and PT were measured using coagulometer (Sysmex CA 50) which rely on scattered light detection method. Platelets cell count was performed by automated cell counter (Sysmex KX-21N).

Statistical analysis was performed using statistical package for social science (SPSS) software. Evaluation of patient's data was performed using the t-test and Pearson correlation test. Results with p value < 0.05 were considered statistically significant.

3. Result

Fifty-eight percent (n = 34/60) of patients had haematologic malignancy (76.4% (n = 26/34) acute myeloid leukaemia, 11.8% (n = 4/34) chronic myeloid leukaemia, 5.9% (n = 2/34) chronic lymphoid leukaemia, and 5.9% (n = 2/34) acute lymphoid leukaemia); and 42% (n = 26/60) had solid malignancies (61.4% (n = 16/26) breast, 19.3% (n = 5/26) prostate and 19.3% (n = 5/26) pancreas. Cancer patients included 25 male and 35 female, and the median age was 43 years, with minimum age of 15 and maximum of 75 years. All patients were tested for D-Dimer level, APTT, PT and platelets count.

Mean D-Dimer level for the patients was 2196.32±2110.95 ng/ml, the levels were elevated in 88% (n = 53/60), and were always normal among the control group with a mean level of 213.65±103.57 ng/ml. Mean D-Dimer level was significantly higher among cancer patients than the controls (p value 0.000). No significant difference was observed in the D-Dimer levels between patients with haematologic malignancies and those with solid malignancies (p value 0.302). Although most of the patients had normal APTT (93%) and PT (97%), mean APTT and PT were higher among patients than the controls (p value 0.000, for both parameters) (table 1). Most of the patients (87%) had normal platelets counts, 10% had thrombocytopenia and 3% had an elevated count. No significant difference was observed in mean platelets count between patients and controls (p value 0.155) (Table 1). The study found a significant association between the D-Dimer levels, and APTT (p value 0.012) and PT (p value 0.002).

Table 1. D-Dimer level, APTT, PT and platelets count results between cancer patients and controls

	Cancer patients	Controls	P value
Number	60	60	
Male/female	25/35	25/35	
D-Dimer mean±SD (ng/ml)	2196.32±2110.95	213.65±103.57	0.000
APTT mean±SD (seconds)	35.7±6.6	29.6±2.2	0.000
PT mean±SD (seconds)	13.7±1.3	12.2±0.8	0.000
Platelets mean±SD (X109/L)	249.6±142.3	279.7±77.9	0.155

4. Discussion

Cancer can confer a prothrombotic or hypercoagulable state through an altered balance between the coagulation and fibrinolytic systems [9]. Many studies have been conducted to assess the function of the haemostatic system in patients with cancer. In this study we utilized a quantitative approach for the determination of D-dimer level, APTT, PT and platelets counts. The study included 60 Sudanese cancer patients, their D-dimer levels, APTT, PT and platelets counts were measured and compared with 60 age and sex matched normal subjects as controls. We observed higher D-dimer levels among cancer patients when compared with the normal healthy controls. Similar findings, with higher

D-Dimer level had previously been reported [14-16]. D-dimer is the major breakdown fragment of fibrin and a good biochemical marker of thrombogenesis and fibrin turnover, increased D-dimer level in plasma is an indirect marker of hypercoagulation activation and thrombolysis [14]. Elevated plasma D-dimer levels can be seen in cancer patients because procoagulant factors in various types of cancer lead to constitutive activation of the coagulation cascade which results in thrombin generation and fibrin formation [17]. D-dimer levels have been found to rise proportionally to the extent and severity of disease in patients with various types of malignancy [17, 18], and has been suggested as a measure of disease status in patients with malignant neoplasms [14, 15, 19, 20]. Most of our patients (88%) have an elevated D-Dimer levels, and may be at a high risk of some haemostatic complication however, D-dimer levels, in patients with cancer, may also be elevated in response to other conditions, such as trauma, surgery, and inflammatory processes, thereby the interpretation of an elevated D-Dimer level as a risk marker for the disease progression and coagulation complication among the cancer patients must be taken after the exclusion of such conditions. Mean APTT and mean PT were significantly higher in malignancy cases when compared to healthy controls, and also were directly associated with D-Dimer levels. This finding is in agreement with other study [21] (Mohammed et al., 2013). This finding most probably is explained by the competition of the FDP for the fibrinogen binding sites of thrombin, and thus slows down clot formation by preventing the conversion of fibrinogen to fibrin leading to prolonged plasma clotting times. Our study highlights abnormalities within the haemostatic properties with a hypercoagulable state, which has been determined by elevated D-Dimer levels among various types of malignancies in Sudan.

5. Conclusions

This study evaluated the haemostatic properties among cancer patients in Sudan by determining D-Dimer level, activated partial thromboplastin time (APTT), prothrombin time (PT) and platelets count, and confirmed the hypercoagulable state among various types of malignancies in Sudan, which has been determined by elevated D-Dimer levels.

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