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Estimation of Protein C and Measurement of Coagulation Changes among Sudanese Patients with Solid Malignancy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Activation of the coagulation cascade frequently occurs in cancer by a number of mechanisms, including the generation of tumor necrosis factor, tumor pro-coagulant and tissue factor.
Aim: The purpose of this study was to investigate the plasma level of PC, FIB, DD and evaluate the PT, INR, APTT, and platelets count in Sudanese patients with some solid malignant tumors.
Methods: A total of 165 individuals (both sex 52% male and 48% female) of Sudan origin 125 patients diagnosed as solid malignant tumors (40% Breast, 24.8% Prostate, 10.4% uterine cervix, 7.2% rectum, 5.6% ovarian, 4,8%esophageal, 4.8% lungs and 2.4% colon) and 40 apparently

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healthy control subjects were prospectively enrolled in the study. The exclusion criteria of the study were the presence of a medical history of hematological malignancies or coagulation-related diseases, severe hepatic and/or renal insufficiency, significant cardiovascular disease, or receiving any anticoagulant therapy. Platelets were count by Sysmex Kx21, XRC used for PT, PTT, FIB, Snibe maglumi 2000 was used for D-dimer and ELISA was used for PC.

Results: There were significant statistical differences between the study parameters in the patients compared with apparently healthy controls. The mean of (platelets count, PT, INR and APTT) was (295±125)cell/L, (22.9±2.82)sec, (1.49±0.206)% and (45.3±5.74) sec, in patients with solid malignant tumors vs (350±80.0) cell/L, (17.4±1.48)sec,(1.13±0.104)% and (38.0±5.28)sec in control group p-value (0.011), (0.000), (0.000) and(0.000) respectively. Then mean of PC, FIB and D-dimer (8.20±2.81)pg/ml, (297.9±75.1)mg/dl, and (1.08±1.26) µg /ml in patients with solid malignant tumors vs (9.57±3.40) pg/ml, (288.6±57.2) mg/dl, and (0.482±0.223) µg /ml in control group p-value (0.011), (0.409), and (0.000) respectively.

Conclusion: In this study, the study variables (Platelets count, PT, INR, APTT, PC, and DD) showed significant statistical difference between the patients with solid malignant tumors and apparently healthy controls, but the FIB level results show insignificant different, our finding suggest that these study variables can play important role in pathogenesis of the hypercoagulable state in cancer patients and the significant difference in platelets count, PT and APTT may early indication of bleeding tendency, further investigations (platelets function tests and coagulation factors assay) should be done to avoid risk of bleeding.

Keywords: Hemostatic system; solid malignant tumors; coagulation profile.

ABBREVIATIONS

APTT : Activated Partial Thromboplastin Time
CA-125 : Cancer Antigen 125
DD : D-Dimer; FIB: Fibrinogen
INR : International Normalization Ratio
APC : Activated Protein C
PLTs : Platelets
PT : Prothrombin Time.

1. INTRODUCTION

“The hemostatic system is responsible for limiting blood loss upon vascular injury and is designed to rapidly react to breaches in the endothelial cell lining. Components of this system are subject to powerful regulatory mechanisms including various anti-hemostatic actions of the endothelium, anti-hemostatic actions from proteins in plasma, and blood flow that removes activated hemostatic proteins from the growing thrombus. Hemostatic abnormalities can lead to excessive bleeding, thrombosis or other cardiovascular diseases” [1,2]. “In circulation, the predisposition to thrombosis depends on the balance between procoagulant and anticoagulant systems. Various genetic defects that affect any gene in these systems have been associated with an increased risk of venous thrombosis” [3]. “The prevalence of venous thromboembolism (VTE) in patients with active cancer has been reported as four to seven times higher than those without cancer and is increasing with cancer status. This is because the cancer patients have increased thrombotic risk due to the malignancy itself or chemotherapy” [4,5].

“Activation of the coagulation cascade frequently occurs in cancer by a number of mechanisms, including the generation of tumor necrosis factor, tumor pro-coagulant and tissue factor” [6]. “Cancer patients may have increased risk of thrombosis and may be associated with high levels of coagulation markers such as fibrinogen and D-dimer as thrombogenesis markers, although the activation of coagulation cascade contributes to tumor progression and metastasis, cancers induce a hypercoagulable state that promotes venous thromboembolism (VTE), which is a frequent complication and a leading cause of morbidity and death in patients with cancer” [7]. “After activation by thrombin, fibrinogen is cleaved to fibrin monomers that are rapidly combined to form a fibrin matrix. Besides the critical role of fibrinogen in hemostasis, this protein is also important in tumor biology. It is well documented that fibrinogen and the cross-linked fibrin reside inside the tumor stroma. This deposition is indicative of the extravascular activation of the hemostatic mechanism, a process favored by the increased vascular permeability of the newly formed tumor vessels” [8]. “Protein C is activated by the thrombin-thrombomodulin complex, to form activated protein C (APC) on the surface of the vascular endothelial cells. Once protein C is activated,

free protein S in the plasma serves as a cofactor along with phospholipids and calcium, to inactivate factor V and factor VIIIa at specific polypeptide arginine cleavage sites" [9]. "This results in impaired prothrombin activation, thereby exerting their anti-coagulant action by reducing thrombin generation. In the setting of protein C or protein S deficiency, the coagulation cascade continues unchecked with the overactivity of factor V and factor VII, resulting in excessive thrombin production" [10,11].

2. METHODS

In this study one hundred and sixty five individuals were included; 125(75.8%) Sudanese patients with different age groups mean age group (23±13.4) years diagnosed as solid malignant tumors (50 breast 40%, 31 prostate 24.8%, 13 uterine cervix 10.4%, 9 rectum 7.2%, 7 ovarian 5.6%, 6 esophageal 4.8%, 6 lungs 4.8% and 3 colon 2.4%) and 40 (24.2) apparently healthy control groups were matching in age and sex. The exclusion criteria of the study were the presence of a medical history of hematological malignancies or coagulation-related diseases, severe hepatic and/or renal insufficiency, significant cardiovascular disease, or receiving any anticoagulant therapy. Venous blood sample (6 ml) was collected from patients with solid malignant tumors according to different type of tumor and healthy controls. Of these, 3 ml blood sample were collected in tri sodium citrate container for measuring PT, PTT, Fibrinogen level D-dimmer level, and a 3ml blood samples were collected in EDTA tubes for platelets count. Sysmex Kx21 used for platelets count, XRC (full automated thrombolyzer) used for PT, PTT, FIB and Snibe maglumi 2000 was used for D-dimer. ELISA is assay that quantify PC antigen using an antibody specific to PC (SUNLONG BIOTECH) South Korea. Sandwich-ELISA. Statistical assessment was carried out with a statistical package for social sciences (SPSS).

3. RESULTS

The current study show significant statistical differences between the study parameters in the patients compared with apparently healthy controls .The mean of (platelets count, PT, INR and APTT) was (295±125)cell/L, (22.9±2.82)sec, (1.49±0.206)% and (45.3±5.74) sec , in patients with solid malignant tumors vs (350±80.0) cell/L, (17.4±1.48)sec,(1.13±0.104)% and (38.0±5.28) sec in control group p- value (0.011), (0.000), (0.000) and(0.000) respectively Table 1.Then mean of PC, FIB and D-dimer (8.20±2.81)pg/ml, (297.9±75.1)mg/dl, and (1.08±1.26) µg /ml in patients with solid malignant tumors vs (9.57±3.40) pg/ml, (288.6±57.2) mg/dl, and (0.482±0.223) µg /ml in control group p- value (0.011), (0.409), and (0.000) respectively Table 2.

Table 1. Mean of clotting profile levels in blood among Sudanesepatients with some solid malignant tumors compared to control

Clotting profile	Mean ± SD Case	Mean ± SD Control	P value
	N=125	N=40	
PT seconds	22.9±2.82	17.4±1.48	**0.000** ^{S}
APTT seconds	45.3±5.74	38.0±5.28	**0.000** ^{S}
INR%	1.49±0.206	1.13±0.104	**0.000** ^{S}
PLTs count $_{cell/l}$	295±125	350±80.0	**0.011** ^{S}

Table 2. Mean of D-dimer and Fibrinogen levels in blood among Sudanese patients with some solid malignant tumors compared to control

Clotting profile	Mean ± SD Case	Mean ± SD Control	P value
	N=125	*N=40*	
D.dimer $_{µg/ml}$	1.08±1.26	0.482±0.223	**0.000** ^{S}
Protein C $_{pg/ml}$	8.20±2.81	9.57±3.40	**0.011** ^{S}
Fibrinogen $_{mg/dl}$	297.9±75.1	288.6±57.2	0.409 ^{NS}

4. DISCUSSION

"Cancer can be complicated by hypercoagulability resulting in intravascular fibrin deposition and depletion of clotting factors and platelets. Cancer-related coagulopathies may present with an insidious and sustained manifestation, whereby consumption of platelets or coagulation factors (and bleeding as a consequence) may be the dominant feature. At the same time patients with systemic cancer-related coagulopathies have a several-fold increased risk of thromboembolic complications" [12]. "PT and PTT evaluate the time it takes for the extrinsic and intrinsic pathways to take effect, respectively. D-dimer is a reactive marker of the hemostatic balance and an end product of the plasmin degradation process of the cross-linked fibrin clot; Systemic values of D-dimer are an index of fibrin turnover in the circulation" [13]. "Various solid tumor patients, including lung, prostate, uterine cervix, and colorectal cancer patients are found with elevated D- dimer level in the plasma. In patients with colorectal cancer, D-dimer level has been shown to correlate with depth of tumor invasion at the time of surgical excision. Plasma D dimer level has also been shown to directly correlate with other tumor markers, including CA-125 and carcinoembryonic antigen" [14]. The current study showed that platelets count was decreased in patients with solid malignant tumors compared with control groups p-value (0.011)this agreement with study done in Italy by Castaman and Pieri who found that the thrombocytopenia is a common finding in cancer patients, while in solid tumors it occurs often as a consequence of chemotherapy treatment [15]. Our study proved that the PT, APTT and D-dimer significantly higher in patients compare with healthy control with p-value (0.000, 0.000 and 0.000) respectively, this is in line with [16,17] who found the PT, APTT, PLTs and D-dimer levels higher in freshly diagnosed lung and colorectal cases were compared with healthy controls and [18] who reported that levels of D-dimer increase significantly in patients with gastric, colorectal, lung ,ovarian and breast cancer. The present study finds there is no significant different in FIB level between the patients and controls. The current study revealed that significant decreased in PC level in the patients compared to control subject's p-value (0.011). The activated form of PC plays an important role in regulating anticoagulation, inflammation, and cell death and maintaining the permeability of blood vessel walls in humans.

5. CONCLUSION

In this study, the study variables (Platelets count, PT, INR, APTT, PC, and DD) showed significant statistical difference between the patients with solid malignancy and apparently healthy controls, but the FIB level results show insignificant different, our finding suggest that these study variables can play important role in pathogenesis of the hypercoagulable state in cancer patients. The significant difference in platelets count, PT and APTT may early indication of bleeding tendency, further investigations (platelets function tests and coagulation factors assay) should be done to avoid risk of bleeding and further studies should be conducted using large sample size and different population to obtain more accurate results.

CONSENT AND ETHICAL APPROVAL

This study was approved by the faculty of medical laboratory sciences, Omdurman Islamic University, and informed consent was obtained from each participant before sample collection.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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