Haemostatic Changes Associated with Thrombosis in Long Term Hemodialysis Treatment

Hanan G. Abd El-Azeem[1], Eman Nasr Eldin[1], Adel HM Mekawy[2], Ahmad F. Thabet[2], Nahla Mohamed Elsherbiny[3].

Departments of [1]Clinical Pathology; [2]Internal Medicine and [3]Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Egypt
emannasr2000@yahoo.com.

Abstract: In end-stage renal disease, particularly when treated with haemodialysis, the function of platelets, coagulation and fibrinolytic systems can be disturbed; those patients may show both thrombotic complications and bleeding abnormalities. Thus, it is essential to investigate haemostatic alterations in patients on hemodialysis so that adequate regime for anticoagulant therapy could be implemented. Haemostatic changes in patients on hemodialysis may result from alterations in vessel wall integrity and platelet function, and reduced blood flow in the native arteriovenous fistula. We study the haemostatic abnormalities associated with thrombosis in long term hemodialytic patients to determine whether coagulation and fibrinolysis are enhanced or not in 42 uremia patients on chronic regular hemodialysis treatment (20 of them had history of thrombotic events "group I" and the remaining 22 patients showed no history of thrombosis" group II") and 20 apparently health control group. Plasma levels of some blood coagulation-fibrinolysis parameters were measured including platelet count, prothrombin time/concentration (PT/PC), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen and D-Dimer, platelet aggregation (induced by adenosine diphosphate, collagen, Ristocetin, and Arachedonic acid), and the levels of natural anticoagulant protein C, protein S and antithrombin-III (AT-III). The mean platelet count was normal in all studied groups, while higher mean value of platelet count was observed among patients in group I than group II. Prolonged PT/sec., aPTT/sec and TT in patients groups were observed; those differences were statistically highly significant in comparison with healthy controls ($p < 0.001$). The mean plasma fibrinogen (g/l) concentration was normal in all groups although levels above normal limits were noted in group I, fibrinogen level was significantly higher ($p < 0.05$) in group I patients than in normal controls. The mean value of D-dimer (ng/ml) was significantly higher in group I than group II and in comparison with control group ($p < 0.001$). We did not find differences between group I patients and control group as regard platelet aggregation induced with all agents, while there were statistically significant difference were observed between group II and control except for collagen. In contrast, the level of natural anticoagulants (protein C, protein S and AT III) were significantly reduced in patients groups than control and they were statistically significant, and the levels were lower in group I than group II. In conclusion, our results showed that the long term haemodialysis procedure affects the haemostatic process and may contribute to a thrombotic tendency. Careful weighing of risks and benefits of pharmacological prevention of thrombosis in patients on hemodialysis is crucial and this area certainly warrants further investigation.

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1. Introduction

Although renal failure has classically been associated with a bleeding tendency, thrombotic events are common among patients with end-stage renal disease (ESRD) (Jalal et al., 2010). It is widely believed that not only chronic renal disease but also the haemodialysis process by itself activates platelets, coagulation and fibrinolysis (Sloand and Sloand , 1997, Kawabata et al., 1998). The haemodialysis procedure could influence haemostasis by two distinct pathways: first, by the effect of the dialysis membrane, the composition of the dialysis circuit, and changed rheology, and second, by the effect of added anticoagulants (Aggarwal et al., 2004). Noticeably, these factors have been significantly changed in the last decade (Rios et al., 2010).

Cardiovascular mortality and morbidity are higher in patients with chronic renal disease than in the general population (Aggarwal et al., 2002). Patients with chronic renal disease are in the highest risk group for thromboembolic disease and many clinical trials have demonstrated the greater safety and efficacy of low-molecular-weight heparin

(LMWH) versus unfractionated heparin (UFH) (Malhotra et al., 2001; Lai et al., 2010).

A variety of thrombosis-favoring hematologic alterations have been demonstrated in these patients. In addition, "non-traditional" risk factors for thrombosis, such as hyperhomocysteinemia, endothelial dysfunction, inflammation, and malnutrition, are present in a significant proportion of chronic dialysis patients (Naumnik et al., 2003).

Since activated platelets and coagulation could contribute to the occurrence of atherothrombotic events in haemodialysis patients, one could speculate that the haemodialysis procedure itself facilitates the development of atherothrombotic events (Sirolli et al., 2002). On the other hand, activation of fibrinolysis may lead to bleeding complications (Galbusera et al., 2009).

Hemodialysis vascular access thrombosis, ischemic heart disease, and renal allograft thrombosis are well-recognized complications in these patients. While deep venous thrombosis and pulmonary embolism are viewed as rare in chronic dialysis patients. Several ESRD treatment factors such as recombinant erythropoietin (EPO) administration (Wirtz et al., 1992), dialyzer bioincompatibility (Windus et al., 1996), and calcineurin inhibitor administration may have prothrombotic effects (Casserly and Dember, 2003).

This unanswered issue was the rationale for performing the present study in which we examine the abnormalities in the haemostatic pathway in patients with chronic renal failure on regular haemodialysis sessions to identify factors associated with thrombotic events.

2. Patients and Methods

Blood samples were obtained from 42 patients with CRF (19 females, 23 males; mean age 58 years, range 48–70) treated by chronic haemodialysis (at least 6 months); 20 of them had history of thrombotic events "group I" and the remaining 22 patients showed no history of thrombosis" group II". All patients had native vessels as a vascular access. All patients were treated by haemodialysis three times per week and received regular doses of low-molecular heparin before haemodialysis and no patient used aspirin or warfarin. Plasma levels of some blood coagulation-fibrinolysis parameters were measured including platelet count, prothrombin time/concentration (PT/PC), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen and D-Dimer, platelet aggregation (induced by adenosine diphosphate, collagen, Ristocetin, and Arachedonic acid), and the levels of natural anticoagulant protein C, protein S and antithrombin III. The results were compared with those obtained in a group of normal volunteers [twenty healthy subjects (9 females, 11 males; mean age 42 years, range 30–54) as controls].

Blood Sampling

Whole blood was obtained from venous needles without venous stasis was collected on:

- Tri potassium- EDTA containing tubes for standard hematology parameters (platelet count) were immediately prepared for testing on an automated blood cell counter (Beckman Coulter).
- Trisodium citrate 3.2% containing tube was centrifuged for 15 to 20 min at 3,000 *rpm* for measurements of coagulation and fibrinolytic parameters including PT/PC , aPTT, TT and AT-III [using Sysmex CA-1500- Siemens], fibrinogen was determined using STArt4- Diagnostica Stago, D-dimer, Protein C and protein S were measured by enzyme linked immunosorbent assay (ELISA) technique (Diagnostica Stago – France).
- Trisodium citrate 3.2% containing tube for platelet aggregation studies using adenosine diphosphate (ADP), collagen, ristocetin, and arachedonic acid (AA) (Crono-log company, USA) immediately prepared for testing using platelet aggregation profiler ® (PAP-4CD Bio/Data corporation) aggregometer. Platelet-rich plasma (PRP) was prepared by centrifugation of citrated blood at 1,000 *rpm* for 15 min at 20 °C.

Results were expressed as percentages of the maximal aggregation obtained after 5 min of stimulation.

Statistical Methods

Measured variables were expressed as mean±SD. Statistical analysis was done to compare the data between studied groups using t-test. P value < 0.05 was considered statistically significant and highly significant if $p < 0.001$. Statistical analyses were performed by the SPSS version 11).

3. Results

Markers of both coagulation and fibrinolysis activation (Table 1 & Figure1):

As regard Platelet count the mean platelet count were normal in patients groups, although mild thrombocytopenia occurred in several patients in both groups and thrombocytosis was observed in few patients in group I.

Higher mean value of platelet count was observed among patients in group I than group II with no statistically significant difference, while there was statistically significant differences when compared with controls, (216.7±122.5 and 169.4±63.8 *vs.* 284.1±37.8; range 91-535 and 79-291 *vs.* 225-336 $X10^3$/l; $p < 0.01, < 0.001$) in both groups respectively.

Longer PT/sec. and lower PC (%) in patients groups were observed, those differences were statistically significant between patients groups (15.4±1.4 *vs.* 14.4±1.0 and 68.1±12.8 *vs.* 76.6±9.7; $p < 0.05$) and were significantly increased in comparison with healthy controls (15.4±1.4 and 14.4±1.0 *vs.* 12.8±0.2; $p < 0.001$)

No statistically significant difference was observed between both patients groups as regard

aPTT/sec (37.6±11.6 *vs.* 36.3±7.6; $p > 0.05$); aPTT/sec was longer among patients groups compared with controls and the differences were statistically highly significant (37.6±11.6 and 36.3±7.6 *vs.* 26.6±2.2; $p < 0.001$).

There were statistically significant difference between both patients groups as regard TT/sec (21.4±2.7 *vs.* 19.1±3.0; $p < 0.05$); TT/sec was longer among patients groups compared with controls and the differences were statistically significant (21.4±2.7 and 19.1±3.0*vs.* 17.6±1.2; $p < 0.001$ & $p < 0.05$ respectively).

The mean plasma fibrinogen concentration was normal although levels above normal limits were noted in a few group I patients. Fibrinogen was significantly higher in group I than group II and normal controls fibrinogen levels (3.4±0.8 *vs.* 2.94±0.6 and 3.4±0.8 *vs.* 2.89±0.6; $p < 0.05$). The mean value of D-dimer (ng/ml) was significantly higher in group I than group II (391.9±144.5 *vs.* 231.7±132.7; $p < 0.001$) and in comparison with control group (391.9±144.5 and 231.7±132.7 *vs.* 97.3±13.6; $p < 0.001$).

In patients, platelet aggregation (induced by adenosine diphosphate, collagen and arachedonic acid and ristocetin) did not differ significantly in both groups and when comparing group I with the control, while there were statistically significant difference were observed between group II and control except for collagen (Table 2 & Figure 2).

Table 1. Screening test for coagulation and fibrinolytic system in different study groups

	CRF with thrombosis Group I N=20 *Mean±SD*	CRF without thrombosis Group II N=22 *Mean±SD*	Control N=20 *Mean±SD*	*P-value*
Platelet count	216.7±122.5	169.4±63.8	-	*NS*
	216.7±122.5	-	284.1±37.8	*
	-	169.4±63.8	284.1±37.8	**
PT (sec.)/ PC (%)	15.4±1.4/68.1±12.8	14.4±1.0/76.6±9.7	-	*
	15.4±1.4/68.1±12.8	-	12.8±0.2/96.0±3.5	**
	-	14.4±1.0/76.6±9.7	12.8±0.2/96.0±3.5	**
aPTT (sec.)	37.6±11.6	36.3±7.6	-	*NS*
	37.6±11.6	-	26.6±2.2	**
	-	36.3±7.6	26.6±2.2	**
TT (sec.)	21.4±2.7	19.1±3.0	-	*
	21.4±2.7	-	17.6±1.2	**
	-	19.1±3.0	17.6±1.2	*
Fibrinogen (g/l)	3.4±0.8	2.94±0.6	-	*
	3.4±0.8	-	2.89±0.6	*
	-	2.94±0.6	2.89±0.6	*NS*
D-Dimer (ng/ml)	391.9±144.5	231.7±132.7	-	**
	391.9±144.5	-	97.3±13.6	**
	-	231.7±132.7	97.3±13.6	**

PT: prothrombin time, PC: prothrombin concentration, aPTT : activated partial thromboplastin time, TT: thrombin time, NS: not significant, *: significant ($p < 0.05$), **: highly significant ($p < 0.001$).

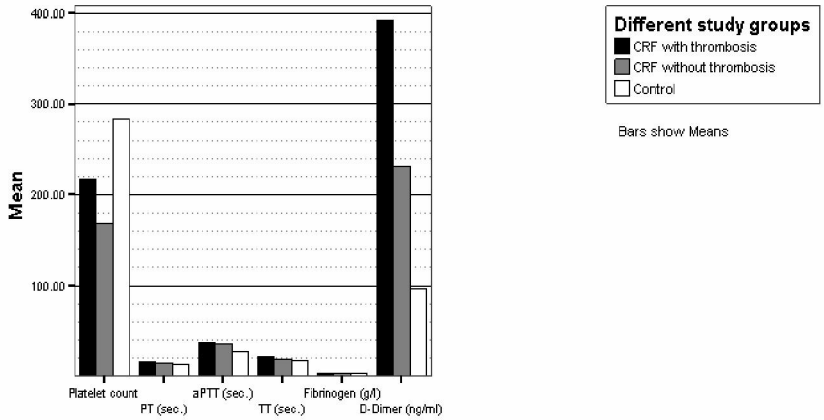

Figure 1.Plasma levels of some blood coagulation-fibrinolysis parameters

Table 2. Platelet aggregation test in different study groups.

	CRF with thrombosis Group I N=20 *Mean±SD*	CRF without thrombosis Group II N=22 *Mean±SD*	Control N=20 *Mean±SD*	*P-value*
ADP	68.6±23.4	45.9±29.8	-	*
	68.6±23.4	-	72.3±14.1	*NS*
	-	45.9±29.8	72.3±14.1	**
Collagen	64.9±21.6	61.8±26.4	-	*NS*
	64.9±21.6	-	72.5±6.9	*NS*
	-	61.8±26.4	72.5±6.9	*NS*
AA	64.4±24.5	43.2±28.3	-	*
	64.4±24.5	-	69.1±5.2	*NS*
	-	43.2±28.3	69.1±5.2	*
Ristocetin	72.3±16.4	58.0±26.9	-	*
	72.3±16.4	-	78.7±12.9	*NS*
	-	58.0±26.9	78.7±12.9	*

ADP: adenosine diphosphate, AA: arachedonic acid, NS: not significant, *: significant ($p < 0.05$), **: highly significant ($p < 0.001$).

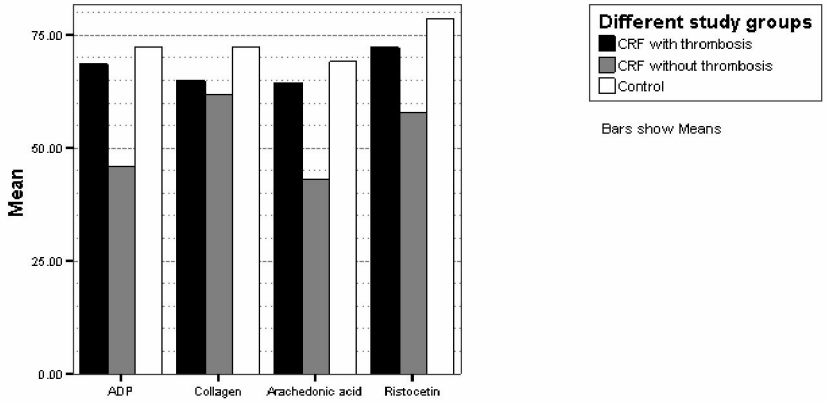

Figure 2. Platelet aggregation test in different study groups.

- In contrast, lower level of natural anticoagulants (protein C, protein S and AT-III) were observed in patients groups than control and they were statistically significant. The levels were lower in group I than group II and the differences between patients group were statistically highly significant for protein C (65.6±19.5vs. 93.2±18.3; $p < 0.001$), significant for protein S (68.6±10.6 vs. 76.3±10.9; $p < 0.05$), and not significant for AT-III (Table 3& Figure 3).

Table 3. Natural anticoagulant levels in different study groups.

	CRF with thrombosis Group I N=20 *Mean±SD*	CRF without thrombosis Group II N=22 *Mean±SD*	Control N=20 *Mean±SD*	*P-value*
Protein C	65.6±19.5	93.2±18.3	-	**
	65.6±19.5	-	106.7±15.6	**
	-	93.2±18.3	106.7±15.6	*
Protein S	68.6±10.6	76.3±10.9	-	*
	68.6±10.6	-	105.5±14.8	**
	-	76.3±10.9	105.5±14.8	**
AT-III	67.5±11.4	70.9±11.6	-	*NS*
	67.5±11.4	-	102.1±15.5	**
	-	70.9±11.6	102.1±15.5	**

AT: antithrombin, , NS: not significant, *: significant ($p < 0.05$), **: highly significant ($p < 0.001$)

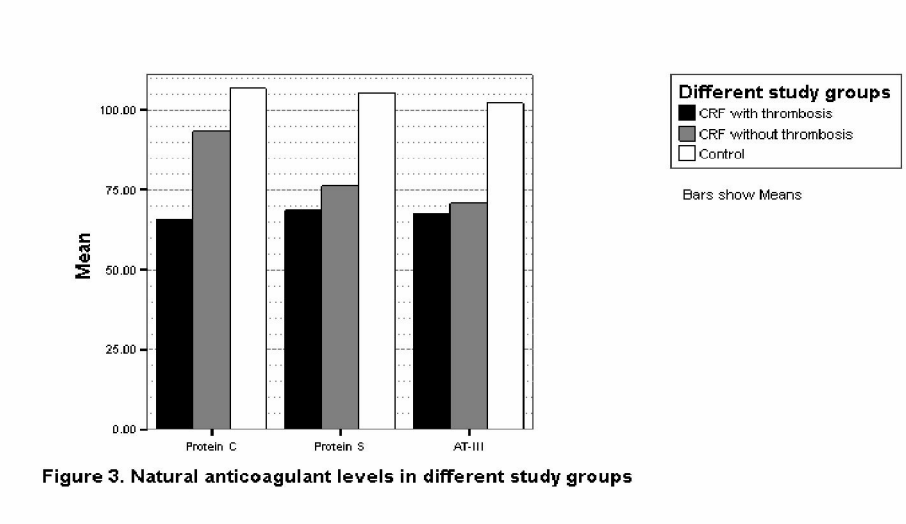

Figure 3. Natural anticoagulant levels in different study groups

4. Discussion

Chronic kidney disease (CKD) is a growing global health problem. CKD is typically associated with a prothrombotic tendency in the early stages of the disease, whereas in its more advanced stage, that is, end-stage renal disease, patients suffer from a prothrombotic tendency leading not only to possibly fatal conditions like ischemic heart disease or stroke (Irish, 1998), but also to thrombosis of the vascular access and, in many cases, a bleeding diathesis most frequently manifested by epistaxis and ecchymosis (Rios et al., 2010). The exact etiology behind the coexistence of these conflicting haemostatic disorders is poorly understood (Jalal et al., 2010).

Vascular complications represent 20-25% of all hospitalized patients on hemodialysis. Changes in the haemostatic system may play a major role in the pathogenesis of cardiovascular complications and vascular thrombosis; during haemodialysis, platelets, coagulation and fibrinolytic systems could be importantly affected due to several known (e.g. alterations in vessel wall integrity and platelet function, reduced blood flow in the native arteriovenous fistula, velocity of procedure, type of membrane, artificial vascular access, circuit composition, and the type of anticoagulation) and unknown factors (Naumnik et al., 2003; Aggarwal et al., 2004) .

Thus, it is essential to investigate haemostatic alterations in patients on hemodialysis so that adequate regimes for anticoagulant therapy could be implemented. The aim of the present study was to explore the effect of long term haemodialysis on the haemostatic system including some of coagulation,

fibrinolytic system, natural anticoagulant and platelet aggregation activation (induced by several agents).

Our results were in agreement with the majority of studies, which mostly showed activation of coagulation after haemodialysis procedure in some points, but are in line with other studies that showed lack or only low activation of coagulation during haemodialysis procedure (Irish, 1998; Naumnik et al., 2003) . Very likely, this seems to be due to the differences between previously used and improved, currently used modern procedures of haemodialysis by biocompatible membranes and better anticoagulation with low-molecular weight heparins (Vaziri et al., 1994).

Platelet count first increased then significantly decreased with increased serum creatinine in conservatively treated chronic uremias. The transient thrombocytopenia often seen with dialysis is thought to be due to the contact activation and deposition of platelet and fibrin on the dialysis membrane (Posadas et al., 2011). Blood and dialyzer membrane interaction can cause significant thrombocytopenia through the activation of complement system (Olafiranye et al., 2011)

Previous studies reported that neither platelet count nor platelet half life altered in uremia (Andrassy and Ritz, 1985). Our result revealed that the mean platelet number was normal, mild thrombocytopenia occurred in several patients in both groups and thrombocytosis observed in group I, the mean platelet number statistically lower in patients group than control group and it was higher among CRF patients presented with thrombotic complications.

This result found that the mean PT, aPTT, and TT were prolonged in patients groups than control and these differences were statistically significant. Increased levels of FDP (D-Dimer) can interfere with thrombin-fibrinogen reaction resulting in prolongation in the TT and aPTT.

Fibrinolysis is evidently activated during the modern haemodialysis procedure. The role of haemodialysis on fibrinolytic parameters has been investigated in several studies (Opatrny et al., 1991; Nakamura et al., 1992; Martin-Malo , 1993; Ishii et al., 1996). It seems that increased activation of fibrinolysis is the consequence of extra-corporeal circulation and that it is related to dialysis membrane biocompatibility (Opatrny et al., 1991; Martin-Malo , 1993). Synthetic membranes appear to be more biocompatible than others (Cianciolo et al., 2001; Sirolli et al., 2002). It might be that factors other than membranes are also important for fibrinolysis activation. The increase in fibrinolytic activity after haemodialysis may contribute to an increased bleeding tendency present in some susceptible haemodialysis patients (Kurz et al., 1985).

Fibrinogen level in our patients with thrombosis was significantly higher than control group. Elevated levels of fibrinogen was previously reported (Sagripanti et al., 1993) in some patients with CRF, the value increased almost with increased serum creatinine level to 10 mg/ 100ml due to new formation associated with a reactive process, which might also be extrarenal and afterward fell even with increased creatinine levels (Amiral et al., 1995); that might be due to a decreasing new formation in severe renal insufficiency (Boaz et al., 1999).

Also D- Dimer level was significantly higher in patients group than control this in agreement with Erdem and coworkers (1995), whom reported that D-Dimer were elevated in patients receiving dialysis implicated the dialysis procedures as a contributor to procoagulant activity.

Protein C deficiency has been described in ESRD patients with claciphylaxis, and a linked functional protein C deficiency with the development of deep venous thrombosis in dialysis patients was reported (Erdem et al., 1995).

The possible changes of natural anticoagulants (PC, PS, and AT III) were investigated, in accordance with Faioni *et al.* (1991) we found reduced protein C level in uremic patients, other studies reported that the effect of dialysis on protein C activity are conflicting partial normalization, reduction, and no change following dialysis treatment have been demonstrated (Kant et al., 1992).

The same finding were observed as regard Protein S and AT III, where lower significant levels of protein S was detected among patients group which might be attributed to peritoneal ultrafiltration of this factor (Kant et al., 1992).

The artificial circuit, changed rheology, and heparin might activate platelets (Kawabata et al., 1998; Aggarwal et al., 2004). These effects could be counterbalanced by defective aggregation of platelets due to ESRD (Aggarwal et al., 2002). Contradictory results have been reported in regard to the effect of haemodialysis on platelet aggregation (Sloand and Sloand , 1997; Malhotra et al., 2001), probably related to the complex interaction of the vessel wall, and different compositions of the dialysis circuit and anticoagulants on platelet function (Cianciolo et al., 2001; de Sa et al., 2001). Diminished platelet degranulation, reduction in stored platelet ADP and serotonin, and decreased platelet thromboxane are among the abnormalities that have been demonstrated *in vitro* studies of platelets from CRF patients (Remuzzi et al., 1983).

In this study we found diminished platelet aggregation response in uremic patients than control group and these differences were significant to ADP, AA, and ristocetin.

The detection of an abnormality of platelet AA metabolism in uremic patients has given a new possible clue in understanding the pathogenesis of uremic

thrombocytopathy (Remuzzi Gand Pusineri, 1988). Šabovi and coworkers (2005) results did not show differences in platelet aggregation before and immediately after haemodialysis procedure, suggesting that the haemodialysis procedure probably does not significantly activate platelets.

In comparison with healthy controls, haemodialysis patients with thrombosis had

an evidently activated coagulation system and activated fibrinolysis than those without thrombotic complication.

In conclusion, these results suggest that coagulation and fibrinolysis are enhanced in long term haemodialysis patients. Haemostatic abnormalities existed in patients on maintenance hemodialysis might contribute to thrombotic complications.

Thus, it is essential to investigate hemostatic alterations in patients on hemodialysis so that adequate regimes for anticoagulant therapy could be implemented, To date pharmacological prevention of thrombosis in patients on hemodialysis has been a major therapeutic challenge, as direct data are lacking on the management of anticoagulation in dialysis patients, so careful weighing of risks and benefits is crucial and this area certainly warrants further investigation.

Corresponding author
Dr. Eman Nasr Eldin
Departments of Clinical Pathology; Faculty of Medicine, Assiut University, EGYPT.
emannasr2000@yahoo.com.

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