Original Research Article

Correlation of prothrombin time and activated partial thromboplastin time with serum immunoglobulins in newly diagnosed patients with plasma cell dyscrasias: an experience from tertiary care centre

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ABSTRACT

Background: Plasma cell dyscrasia (PCD) is the term used to describe the disorders characterized by neoplastic proliferation of plasma cells with the abnormal production of immunoglobulins (Ig). Patients with multiple myeloma frequently have abnormal coagulation tests. Aim of the present study were to correlate prothrombin time (PT) and Activated Partial Thromboplastin time (aPTT) with Ig concentrations in patients with newly diagnosed with PCD and to compare PT and aPTT values in untreated and treated patients diagnosed with PCD

Methods: This study was conducted in the department of clinical hematology of SKIMS, a tertiary care hospital in northern India from 2015 to 2016. Patients diagnosed with PCD were advised for coagulogram (PT, aPTT) as a base line investigation. A total of 72 patients were included in the study.

Results: 37% of multiple myeloma cases (newly diagnosed) and 22% of light chain disease patients presented with prolonged PT whereas none of the patients in treated cases of PCD had prolonged PT. The mean Ig concentration was significantly higher in patients with prolonged PT and aPTT compared to that of patients with normal PT and aPTT values. In IgA myeloma, the mean immunoglobulin concentration was 3643 mg/dL with a mean PT and aPTT values of 18.8s and 36.6 (p value: 0.006). The mean free light chain concentration in kappa (k) light chain myeloma was 1727 mg/L with a mean PT value of 20.5 s, mean aPTT value of 37.4 s (p-value: 0.026).

Conclusions: Patients with newly diagnosed myeloma presented with prolonged PT as compared to the treated cases. Also, mean Ig concentration was significantly higher in patients with prolonged PT and aPTT compared to that of patients with normal PT and aPTT values.

Keywords: aPTT, PT, Multiple myeloma

INTRODUCTION

Plasma cell dyscrasia is the term used to describe the disorders characterized by neoplastic proliferation of plasma cells with the abnormal production of immunoglobulins. Thrombotic and haemorrhagic complications frequently have been observed in patients with monoclonal gammopathy, Waldenstroms macroglobulinemia, amyloidosis and multiple myeloma (MM).[1] Patients with multiple myeloma frequently have abnormal coagulation tests, including thrombin time (64%), fibrin degradation products (32%), platelet

aggregation tests carried out with different agonists (30-55%), and bleeding time (22%).[2] The pathophysiology of the coagulopathy in multiple myeloma is multifactorial.[3] The pathogenesis of the observed clotting abnormalities in these patients is probably complex.[4,5] The high blood concentration of the M-protein with its impact on fibrin polymerization process, may be the cause of the prolongation of not only PT, aPTT, but also TT.[6]

The possible mechanisms by which coagulopathy could develop in patients with dysproteinemias include:

- Paraprotein interference with the normal function of coagulation factor (s) (i.e. by complexing with specific clotting factors);
- Enhancement of the clearance of coagulation facto r (s) by the reticuloendothelial system;
- Anticoagulant activity of paraproteins;
- Impaired normal platelet function;
- Excessive fibrinolysis; and
- Hyperviscosity per se. In all of these situations, the development of coagulopathy necessitates the presence of paraproteins in the plasma.[7-11]

The main aim of this study was to correlate prothrombin time (PT) and activated partial thromboplastin time (aPTT) with Immunoglobulin concentrations in patients with newly diagnosed plasma cell dyscrasias and to compare prothrombin time (PT) and activated partial thromboplastin time (aPTT) values in untreated and treated patients diagnosed with plasma cell dyscrasias.

METHODS

This study was conducted in the Department of Clinical Hematology of Sheri-Kashmir Institute of Medical Sciences (SKIMS) Soura, a tertiary care hospital in northern India from July 2015 to September 2016.

This was a prospective study where patients diagnosed with plasma cell dyscrasias were advised for coagulogram (PT, aPTT) as a base line investigation. A total of 72 patients were included in the study, of which 20 were treated and 52 were newly diagnosed (as per WHO guidelines) cases of plasma cell dyscrasia (PCD). The presence of M-protein was confirmed by Agarose gel electrophoresis of serum and followed by identification and quantification of a specific immunoglobulin involved in the monoclonal gammopathy using single radial immuno diffusion.

Interpretation of Agarose gel electrophoresis was made by the shape (deflected/bowed) of the precipitin arc, its location (mobility) in the gel, and the amount (density) of precipitate making up the line were taken into account in delineating in different paraprotein types and for determining their light chain status by comparison to normal arc from normal control serum. The prothrombin time and activated partial thromboplastin time was determined by Quick's method using Ceveron automated

coagulation analyzer. Prothrombin time (PT) reference value was between 12 to 18 seconds and activated partial thromboplastin time (aPTT) value was 26-34 seconds.

Quantitative data was tabulated in Mean±SD form and comparative analysis was done by Pearson co-relation. P value <0.05 was considered significant. All the analysis was done by using SPSS-22 software.

RESULTS

A total of 72 patients diagnosed with plasma cell dyscrasias (PCD) were enrolled in the study over a period of 15 months out of which 52 were newly diagnosed with PCD and 20 were treated (Table 1 and 2).

Table 1: Distribution of patients newly diagnosed with PCD.

Group	Number	Percentage
Multiple myeloma	37	71
Plasmacytoma	04	7.6
Light chain disease	09	17.3
MGUS	02	3.8
Total	52	100

Table 2: Distribution of treated patients with PCD.

Group	Number	Percentage
Multiple myeloma	18	90.0
Plasmacytoma	01	5.0
Light chain disease	01	5.0

Laboratory investigations of newly diagnosed and treated cases are shown in Table 3 and 4.

Table 3: Hemogram in patients newly diagnosed with PCD.

Group	Mean hemoglobin (g/dL) ±SD	Mean TLC (x103/µL) ±SD	Mean platelet count (x103/µL) ±SD
Multiple myeloma	8.67±2.4	8.67±2.4	136.5±64.9
Other PCD	9.8 ±2.6	6.3±2.3	±95.8

Table 4: Hemogram in treated patients of PCD.

Mean Hemoglobin (g/dL) ±SD	Mean TLC (x103/ µL) ±SD	Mean platelet count (x103/µL) ±SD
11.4±1.9	6.5±2.4	66

Bone marrow aspiration carried in all the newly diagnosed cases showed plasmacytosis in 48 cases (92%) of which severe bone marrow plasmacytosis of >60% was observed in 36 patients (72%) (Table 5 and Figure 1).

Table 5: Bone marrow aspiration of newly diagnosed cases.

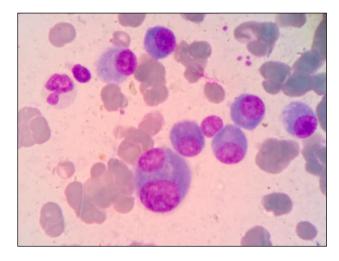| Group	Bone marrow plasmacytosis >60%	Bone marrow plasmacytosis 10%-60%
Multiple myeloma	32	07
Other PCD	04	05
Total	36	12

Figure 1: Bone marrow aspirate showing plasma cells with binucleate forms also seen (Leishman's stain, 100X).

Most of these cases showing severe plasmacytosis had increased serum immunoglobulin concentrations with prolonged Prothrombin time (PT) and activated partial thromboplastin time (aPTT) time (Table 6) compared to the cases with plasmacytosis of <60% indicating that prolonged PT and aPTT was associated with disease severity.

Table 6: Comparison of bone marrow plasmacytosis with serum immunoglobulin concentrations, PT and aPTT values in newly diagnosed PCD patients.

Bone marrow plasmacytosis (%age)	Mean Ig concentration (mg/dL)	Mean PT (s)	Mean aPTT (s)
>60%	7249	18.9	39.7
<60%	2849	16.8	30.0

37% of multiple myeloma cases (newly diagnosed) and 22% of light chain disease patients presented with prolonged prothrombin time (PT) (Table 7) whereas none of the patients in treated cases of PCD had prolonged PT (Table 8). Out of 37 newly diagnosed cases 28 were IgG myeloma and 8 were IgA myeloma and one case of IgM was seen. Distribution of patients with prolonged PT and APTT in these different iso-types of multiple myeloma

(Table 9) and mean values of prolonged PT and aPTT in these types is shown (Table 10).

Table 7: Coagulation profile in untreated patients with PCD.

Group	PT (≥18 s)	PT (≤18 s)	APTT (≥34 s)	APTT (≤34 s)
Multiple myeloma	37% (14/37)	62% (23/37)	40.5% (15/37)	59% (22/37)
Light chain myeloma	22% (02/09)	77% (07/09)	44% (04/09)	55% (05/09)
Plasmacytoma	-	100% (04/04)	25% (01/04)	75% (03/04)
MGUS	-	100% (02/02)	50% (01/02)	50% (01/02)

Table 8: Coagulation profile in treated patients with PCD.

Group	PT ≥18 s	PT ≤18 s	aPTT ≥34 s	aPTT ≤ 34s
Multiple myeloma	---	100% (18/20)	30% (06/20)	60% (12/20)
Plasmacytoma	---	5% (1/20)	5% (1/20)	---
Light chain disease	----	5% (1/20)	5% (1/20)	---

Table 9: Distribution of patients with prolonged PT and APTT in different iso-types of multiple myeloma.

Group	PT ≥18 s	PT ≤ 18 s	APTT ≥34 s	APTT ≤ 34s
IgG myeloma	35.7% (10/28)	64% (18/28)	42% (12/28)	57% (16/28)
IgA myeloma	50 % (04/08)	50% (04/08)	37.5% (03/08)	62.5% (05/08)

Table 10: PT and APTT values in different groups of PCD.

Group	Mean of PT >18s	Mean of APTT >34s
IgG	22.7±7.04	51.0±23.18
IgA	18.8±0.99	36.6±1.4
K	20.5±2.9	37.4±3.6
Λ	----	40.3±3.18

The mean immunoglobulin concentration was significantly higher in patients with prolonged PT and aPTT compared to that of patients with normal PT and aPTT values (Table 11). In patients with plasmacytoma, since the tumor was localized and no M-protein was detected on electrophoresis, immunoglobulin concentrations were not available.

Table 11: Comparison of mean Ig conc. in patients with normal PT, aPTT and patients with prolonged PT, aPTT.

Immunoglobulin isotype	Normal range	Mean conc. of Ig in patients with prolonged PT	Mean conc. of Ig in patients with normal PT	Mean conc. Of Ig in patients with prolonged APTT	Mean conc. of Ig in patients with normal APTT
IgG (mg/dL)	710-1500	10475	4119	8600	4731
IgA(mg/dL)	90-310	3643	3657	4629	3141
fKLC (mg/L)	3.5-19	1727	433	879	431
fλLC(mg/L)	5.7-26	3410	2399	1712	1995

Also, the number of patients in IgM myeloma was small l (only one case), the immunoglobulin details were not included in the study. The mean immunoglobulin concentration (10475 mg/dL) was highest in IgG iso-type with mean PT value of 22.7s, mean aPTT value of 51.0 s and a p-value of 0.114 (>0.05 statistically insignificant). In IgA myeloma, the mean immunoglobulin concentration was 3643 mg/dL with a mean PT and aPTT values of 18.8s and 36.6 respectively. The p-value in IgA myeloma was 0.006 and was statistically significant. λ light chain myeloma patients presented with only prolonged aPTT values (mean 40.3s) with mean free light chain concentration of 3410 mg/L and p-value of 0.309 which was statistically insignificant (>0.05 statistically insignificant).

Table 12: Correlation of immunoglobulin concentration with prolonged PT and prolonged APTT.

Immunoglobulin type	Mean conc. of immunoglobulin (mg/dL)	Mean of prolonged PT (s)	Mean of prolonged APTT(s)	p value
IgG	10475	22.7±7.04	51.09±23.18	0.114
IgA	3643	18.8±0.99	36.6±1.4	0.006 (S)*
K free light chain	1727	20.5±2.9	37.4±3.6	0.026 (S)*
Λ free light chain	3410	----	40.3±3.18	0.309

(s): Statistically significant

The mean free light chain concentration in kappa (k) light chain myeloma was 1727 mg/L with a mean PT value of 20.5 s, mean aPTT value of 37.4s and a p-value of 0.026 which was statistically significant (Table 12).

DISCUSSION

A total of 72 cases were included in the study of which 52 were newly diagnosed patients and 20 treated patients of PCD. Of the total patients in both the untreated and treated cases, the most common group included patients diagnosed with multiple myeloma. The most common coagulation abnormality was prolonged aPTT (40.3%) followed by prolonged PT (30.7%) in newly diagnosed PCD patients. Teng et al also reported prolonged aPTT as the most common coagulation abnormality followed by prolonged PT in their study on IgG and IgA myeloma patients.[12]

Overall 30.7% of patients newly diagnosed with PCD had a prolonged PT of >18 s (reference range 12-18s). 37% of multiple myeloma and 22% of light chain disease patients presented with prolonged prothrombin time (PT). Prolonged aPTT of >34s (range 26-34s) was found in 40.5% of multiple myeloma patients, 44% light chain disease patients, 25% plasmacytoma patients and 50% of

MGUS patients. Overall 40.3% of patients in newly diagnosed PCD presented with prolonged aPTT of >34s. An isolated prolonged PT was found in 7.6% of patients, an isolated prolonged aPTT in 17.3 % and 23% presented with both prolonged PT and aPTT. 11.5% (6/52) patients presented with low APTT of <26 s.

In a study conducted by Pandey et al, an isolated prolonged PT (>15 s) was found in 25% patients, and 4% patients had prolonged PT and aPTT.[13] An isolated prolonged aPTT (>36.9s) was present in two patients (<1%) and decreased APTT was observed in five patients (2%). In the present study, the mean prolonged PT in IgG was 22.7 s and in IgA myeloma it was 18.8 s, were as it was 20.5 s in kappa light chain myeloma.

The mean prolonged aPTT in IgG myeloma was 51s and in IgA myeloma it was 36.6s whereas for kappa (κ) and Lambda (λ) light chain myeloma, it was 37.9s and 40.3s respectively.

Among treated cases 18 cases were of multiple myeloma, of which 30% presented with prolonged aPTT, 5% of the treated cases of plasmacytoma and 5% of light chain diseases presented with prolonged aPTT. None of the patients in treated cases of PCD had prolonged PT. On

follow-up, almost all patients in treated group of PCD with prolonged aPTT had an active disease at the time of sampling, indicating a greater impact of paraprotein on aPTT.

The mean immunoglobulin concentration was highest in IgG iso-type (mean 10475mg/dL) with mean PT value of 22.7s and mean aPTT value of 51.0 s. In IgA myeloma, the mean immunoglobulin concentration was 3643mg/dL with a mean PT and aPTT values of 18.8s and 36.6s. This correlation was statistically significant. λ light chain myeloma patients presented with only prolonged aPTT values (mean 40.3s) with mean free light chain concentration of 3410 mg/L and p-value of 0.309 (statistically insignificant). The mean free light chain concentration in k light chain myeloma was 1727mg/L with a mean PT value of 20.5 s, mean aPTT value of 37.4s and a p-value of 0.026 which was statistically significant. So, mean immunoglobulin concentration in our study was significantly higher in patients with prolonged PT and aPTT compared to that of patients with normal PT and aPTT values and was positively correlated with the studies conducted by Pandey et al, Huang H et al and Teng et al.[12,13,14]

CONCLUSION

Patients with newly diagnosed myeloma presented with prolonged prothrombin time as compared to the treated cases. Also, mean immunoglobulin concentration was significantly higher in patients with prolonged PT and aPTT compared to that of patients with normal PT and aPTT values.

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