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BIOCHEMICAL AND ELECTROPHORETIC EVALUATION OF CLINICALLY SUSPECTED MULTIPLE MYELOMA

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ABSTRACT

Multiple Myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic cancers, typically occurring in elderly patients. A study was conducted on 25 (n=25) subjects clinically suspected multiple myeloma cases considered as study group and 25 (n=25) healthy volunteer individuals taken as control group. The biochemical parameters such as serum total protein, serum albumin, serum calcium and serum creatinine levels in both study and normal healthy subjects were evaluated that may be useful in the diagnosis of the disease. Mean and SD values of serum total proteins, serum creatinine and serum calcium were significantly high in study cases compared to control group and are statistically significant ($p < 0.05$, 0.001). Whereas, serum albumin levels showed slight decrease and are not statistically significant ($p > 0.05$). Present study showed abnormal eletrophoretic pattern in multiple myeloma cases, with M band identified in the gamma region. Increased serum total protein indicates the increased paraprotein production. Increased serum calcium and serum creatinine levels in the study group indicate bone resorption and renal damage respectively. The nature of complex interpretations have yet to be elucidated and improving our understanding of these interpretations may provide us with new opportunities to identify novel therapeutic approaches to treating both the bone destruction and the myeloma disease itself.

KEYWORDS: ***Multiple myeloma, serum albumin, serum calcium, serum creatinine, serum total protein.***

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INTRODUCTION

Multiple Myeloma is a plasma cell dyscrasia that can have various clinical presentations. Signs and symptoms often reflect plasma cell infiltration into organs but can be subtle. Multiple Myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic cancers, typically occurring in elderly patients. The most common presenting symptom is the bone pain. Osteolytic bone lesions and/or compression fractures are hallmark of the disease and cause significant morbidity. Anemia occurs in 70% of the patients at diagnosis and is the primary cause of fatigue. Renal dysfunction occurs in 50% and hypercalcemia in 25% of the patients[1]. Prevalence of the disease is low which constitutes 1% of all cancers[2]. The term "Multiple Myeloma" was first introduced by a Russian doctor Rusitzky[3] to describe the presence of multiple tumours originating in the bone. In 1937, after the discovery of hyper proteinemic state in multiple myeloma, Tiselius[4] used an electrophoretic technique to separate serum globulins into three components, alpha, beta and gamma, which led to a Nobel Prize. The term multiple myeloma (MM) describes a characteristic feature, found at multiple sites within the bone marrow (myelo-) with accumulations of tumor (-oma) cells. Normally plasma cells constitute 1% in the bone marrow but as the disease advances, tumor load in bone marrow increases up to 80% depending on the severity. These malignant plasma cells synthesize monoclonal antibodies and release it in to circulation. As a result high concentration of monoclonal immunoglobulin termed as paraprotein are present in bone marrow as well as in serum and urine or both[5]. Bone pain related to multiple lytic lesions is the most common clinical presentation. The prevalence of the disease varies according to gender, age, and race or ethnicity. The median age at diagnosis of MM is 62 years[6]. MM is more common among men than women, occurs more frequently with increasing age, and develops twice as often among black individuals than among white individuals[7]. With the advent of facilities and understanding, the members are increasing even in India and younger age group between 45 to 60 years is being seen. The exact etiology of MM remains unclear. Occasionally it is possible to identify members of the same family with MM, although no evidence suggests a hereditary basis for the disease[8]. A precursor cell arises in patients with MM when one or more exogenous stimuli induce cytogenetic changes in the B-cell lineage at the lymph node[9]. The MM cell establishes itself in the bone marrow by adhering to stromal cells and inhibiting osteoblastic activity and osteocalcin production. Increased osteoclastic activity plus inhibited osteoblastic activity results in osteoporosis, painful lytic lesions and hypercalcemia[10]. The MM cell clone produces excess of monoclonal protein (M protein) which is also called paraprotein and free light chain proteins. The M proteins may be recognized as IgA, IgD, IgG, IgE or IgM, depending on their heavy chain class. This excess of M protein is responsible for the hyper viscosity syndrome; paradoxically haemorrhage and susceptibility of infections are relatively common. The light chain proteins are designated as kappa or lambda, which may precipitate and deposit, producing organ damage. These monoclonal light chains appear in the urine, and are called Bence Jones proteins. Bence Jones proteins may provoke a diversity of renal lesions, depending on the intrinsic physical or chemical properties of the light chain[11]. Renal failure occurs in nearly 25% of myeloma patients, Hypercalcemia is the most common cause of renal failure. Glomerular deposits of amyloid, hyperuricemia, recurrent infections, and frequent use of nonsteroidal anti-inflammatory agents for pain control, use of iodinated contrast dye for imaging, bisphosphonate use, and occasional infiltration of the kidney by myeloma cells all may contribute to renal dysfunction. Bone lesions, fractures, renal failure, infections, anemia, hypercalcaemia and occasionally clotting abnormalities neurologic symptoms and vascular manifestations of hyper viscosity are the common findings in MM. Hall mark of MM is detection of M Protein in the serum or urine. As a result of paraproteinemia (increased abnormal immunoglobulin in serum) total serum protein concentration and serum albumin may alter in MM. Paraproteins appears as single narrow sharp discrete spike (M band) in gamma globulin region detected by serum protein electrophoresis[7]. In evaluation of paraprotein in serum, hypercalcemia has been considered to play a significant role in the pathogenesis of MM. Serum protein M spike was found in 1939[12], [13] found that the incidence of MM is higher in US black population than the whites. [14]stated that MM is rare among persons of Asian descent with the incidence of one to two cases per 100,000 populations. [15] reported that the risk of developing MM appears to be higher in populations of lower socio-economic status, particularly where diagnostic services are unavailable. [16]explored the risk of MM to be higher in those employments in the nuclear industry, sheet metal and agricultural occupations and jobs in which workers are exposed to wood dust. [17] observed higher incidence of MM among nuclear industry workers than general populations. [18]Published a proportional mortality study of 1043 subjects from Farmers and horticulturists directly exposed to the pesticide DDT may have an increased risk of developing MM. This substance tends to accumulate in the ecosystem and has various toxic effects in many vertebrates. Farmers are exposed to multiple herbicides and fertilizers that could increase their risk[18]. The clinical presentation of MM seems to be changing, probably as a result of diagnostic services that detect the disease in earlier stages. However, 30% of new cases are diagnosed incidentally during evaluation for seemingly unrelated problems, one third of the patients are diagnosed after a pathologic fracture commonly of the axial skeleton[19]. The present study was aimed to evaluate the biochemical parameters and electrophoretic pattern in clinically suspected Multiple Myeloma (plasma dyscrasias) patients. The evaluation of paraprotein by serum protein electrophoresis and supported by immuno fixation electrophoresis (IFE). The estimation of serum total protein, serum albumin, serum calcium and the serum creatinine levels may help in the diagnosis and understanding the course of the disease.

MATERIALS AND METHODS

The present study was undertaken in the Department of Biochemistry, MNR Medical College and Hospital, Sangareddy, Medak, Telangana, India. The study was conducted from August, 2009 to March, 2010. The case

group consisted of 25 (n=25) subjects clinically suspected multiple myeloma cases consisting both male and female patients aged between 40 to 55 years were included in the study. 25 (n=25) healthy volunteer individuals consisting of male and female subjects aged between 40 to 55 years were taken as control group. The study group (n=25) subjects were obtained from Care Hospital, Hyderabad, Telangana, India and normal healthy volunteers (n=25) (control samples) were obtained from MNR Hospital, Sangareddy, Medak, Telangana, India, during the same period. Blood samples were collected under aseptic conditions from both the study subjects and normal healthy individuals. The ethical clearance was taken as per the guidelines of the institute. 3ml of blood from the cubital vein was collected in a plain sterile bottle after consent has been taken from both the study and normal healthy subjects. Serum was separated from the blood samples by centrifugation at 3000rpm for 10 minutes. The present study included evaluation of paraprotein pattern in both study and normal healthy subjects by serum protein electrophoresis (agarose gel electrophoresis)[20]. The serum samples were also estimated for Serum total proteins by Biuret method, Serum albumin by Bromo Cresol Green method, Serum creatinine by Jaffes alkaline picrate method and Serum calcium by Ortho Cresolphthalein Complexone kit method using SPAN Auto chem 2011.

STATISTICAL ANALYSIS

The data was subjected to descriptive statistical analysis to find out Mean and Standard Deviation values and One Way Analysis of Variance (One Way ANOVA) to decipher the intra and inter group variations of the study subjects from both control and experimental groups. p value less than 0.05 and 0.01 was considered statistically significant.

RESULTS AND DISCUSSION

The present study included a total of 50 (n=50) subjects, of which 25 subjects (n=25) consisted of clinically suspected multiple myeloma cases (study group) and 25 subjects (n=25) consisted of healthy volunteer individuals (control group), both included male and female cases aged between 40 to 55 years respectively (Table 1 and Fig. 1). The mean (Mean±SD) age of the patient group was 48.04 ± 4.18 and that of control group 47.92 ± 4.82. [6] reported high incidence of multiple myeloma after 40 years.

Table 1
Age distribution among controls and cases.

Parameter	Mean ± SD Controls (n=25)	Mean ± SD Cases (n=25)
Age (years)	47.92 ± 4.82	48.04 ± 4.18

SD- Standard Deviation

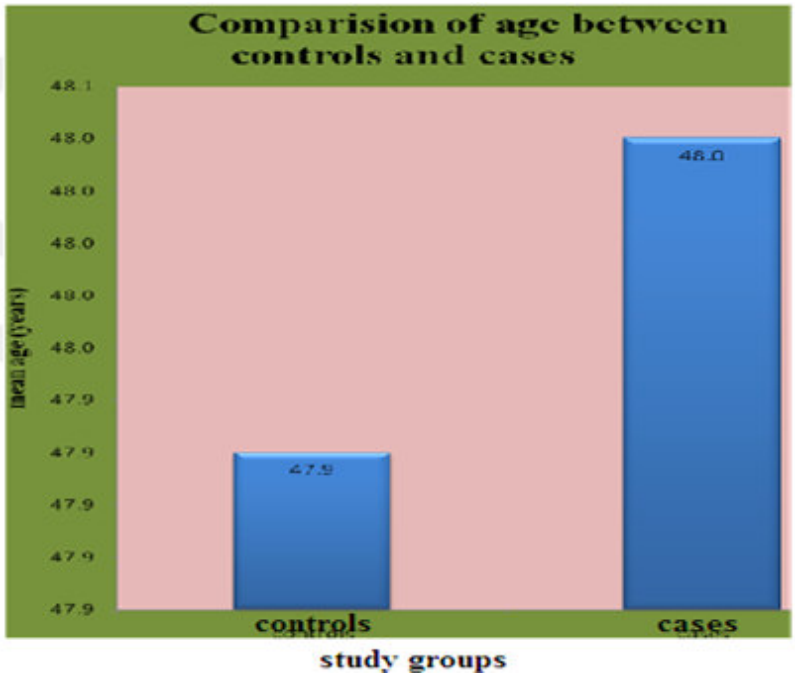

Figure 1
Comparison of age between controls and cases

Multiple myeloma is a neoplastic disease characterized by the proliferation of single clone of plasma cells derived from B cell. Multiple myeloma clinically presents with paraproteinemia as a result of excessive production of monoclonal immunoglobulin (monoclonal protein) in the bone marrow that infiltrates multiple organs and produce organ dysfunction which leads to bone pain, fracture, renal failure, susceptibility to infections, and hypercalcemia. In the present study MM characterization is based on biochemical and

electrophoretic evaluation of paraproteins in which serum proteins were separated. This mobility pattern was visually interpreted and quantified by densitometer. Densitometry tracings showed relative percentage of each protein fraction. The biochemical parameters such as serum total protein, serum albumin, serum creatinine and serum calcium evaluated in control and study cases are presented in Table 2 and 3 respectively.

Table 2

Age, gender, serum total protein, serum albumin, serum creatinine and serum calcium evaluated in control group (n=25)

S.NO	ID. Nos	AGE	SEX	SERUM TOTAL PROTEIN (gm/dl)	SERUM ALBUMIN (gm/dl)	SERUM CREATININE (mg/dl)	SERUM CALCIUM (mg/dl)
1	214609	55	F	7.4	4.5	0.8	10.1
2	213985	50	F	6.5	5.2	0.6	9.7
3	214810	47	M	6.4	5.4	1.0	10.0
4	214603	43	M	6.2	3.8	0.9	9.4
5	214792	47	F	7.2	4.5	0.9	9.9
6	213992	54	M	7.4	5.2	0.9	11.0
7	1525938	45	F	7.0	4.1	0.8	9.0
8	1541750	41	F	6.7	4.7	0.9	9.1
9	214233	51	F	6.1	4.2	1.1	10.3
10	210810	55	M	7.2	5.3	1.0	9.2
11	213989	50	F	6.3	3.6	0.7	8.9
12	1541814	46	F	6.8	4.4	0.9	9.2
13	1539532	51	M	6.7	4.6	0.8	9.7
14	1539683	50	M	7.4	4.1	1.1	10.2
15	1541273	55	F	6.4	4.0	0.8	9.1
16	20346	40	F	7.0	4.7	0.9	9.1
17	1540870	46	F	7.2	4.2	1.0	9.4
18	216339	43	F	6.1	3.7	0.9	9.3
19	214685	55	M	6.7	5.3	1.1	9.6
20	1541271	50	M	7.0	4.4	1.0	10.3
21	201462	47	M	6.3	4.7	0.8	9.3
22	211733	43	M	7.6	4.3	0.4	9.1
23	21329	40	M	7.2	5.1	0.8	9.2
24	284365	44	M	6.9	4.1	0.9	9.8
25	M-130	50	M	7.0	4.2	1.0	9.0

Table 3

Age, gender, serum total protein, serum albumin, serum creatinine and serum calcium evaluated in study group (n=25)

S.NO	ID Nos	AGE	SEX	SERUM TOTAL PROTEIN (gm/dl)	SERUM ALBUMIN (gm/dl)	SERUM CREATININE (mg/dl)	SERUM CALCIUM (mg/dl)
1	CM-16	52	F	8.5	4.3	1.2	9.7
2	CM-N-195	47	F	9.5	5.5	0.9	12.2
3	CM-O5040	43	F	7.4	3.1	1.9	9.9
4	CM-O8619	50	M	9.9	4.6	2.0	11.9
5	CM-O7170	47	M	8.7	4.2	1.8	11.1
6	CM-O7540	53	M	7.8	4.1	1.1	10.9
7	CM-O4351	50	F	8.0	3.5	1.4	10.7
8	CM-O6451	52	F	7.4	4.1	1.1	9.8
9	CM-5282-12	45	F	8.0	2.6	1.3	9.3
10	CM-1307-7	55	M	8.4	3.4	1.0	11.4
11	CM-O5812	51	M	7.8	3.1	0.9	10.2
12	CM-O9352	52	M	7.0	2.2	4.4	12.7
13	CM-O6467	46	F	7.9	3.4	1.1	11.4
14	CM-O7306	50	F	7.9	2.7	1.4	10.8
15	CM-N-68	41	M	7.8	2.8	1.7	10.8
16	CM-O6771	45	M	10.8	4.3	3.1	11.3
17	CM-647-5	44	M	7.6	3.1	1.1	10.4
18	CM-O9515	47	M	8.0	4.5	2.4	13.2
19	CM-1110-11	45	F	7.7	3.7	0.9	10.7
20	CM-N-9	41	F	9.1	2.6	3.2	11.7
21	CM-O9579	46	M	7.6	2.8	2.0	11.2
22	CM-O743	50	M	8.2	3.3	2.7	10.6
23	CM-O7043	54	F	8.2	4.3	2.0	11.2
24	CM-O7431	53	F	9.2	3.3	2.3	11.4
25	CM-3785	42	M	7.2	2.9	1.3	10.6

Serum total protein was measured to know the abnormal monoclonal protein production in study subjects in comparison to controls. The statistical analysis data of serum total protein showed statistically significant differences between the two groups studied (Table 4, Fig. 2A).

Table 4
Serum total protein, serum albumin, serum creatinine and serum calcium in study group subjects control group

Parameter	Controls (n=25) Mean ± SD	Cases (n=25) Mean ± SD	p value	Interpretation
Serum total protein (gm/dl)	6.8 ± 0.44	8.2 ± 0.88	0.01*	S
Serum albumin (gm/dl)	4.5 ± 0.52	3.5 ± 0.79	0.08	NS
Serum creatinine (mg/dl)	0.9 ± 0.15	1.8 ± 0.86	0.00**	S
Serum calcium (mg/dl)	9.6 ± 0.53	11.0 ± 0.91	0.00**	S

S= Statistically significant, NS=Not statistically significant;
**** statistically significant P value less than 0.05;***
***** statistically significant P value less than 0.01***

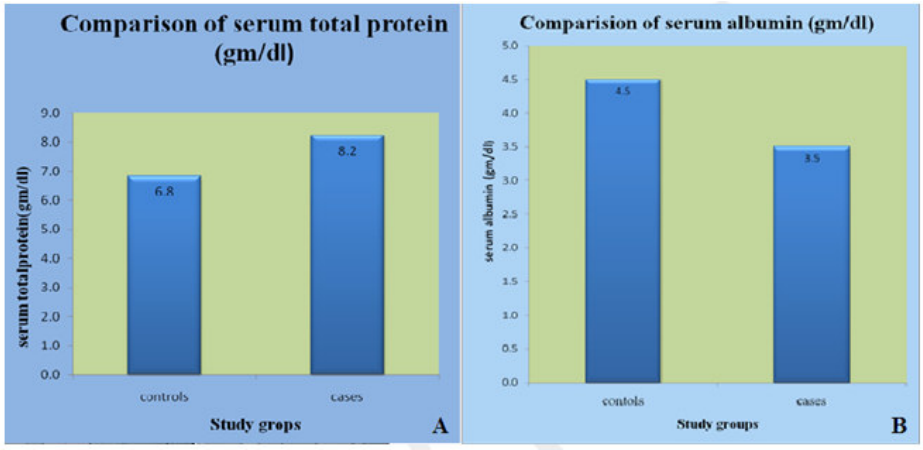

Figure 2
A- Serum total protein, B- Serum albumin in controls and study group subjects

The mean and SD values of serum total proteins in cases (8.2±0.88) were significantly increased when compared to controls (6.8±0.44) and are statistically significant (p = 0.01). [21]stated that there is significant increase in the total protein concentration (p = 0.01) in the multiple myeloma cases. In the present study the paraprotein was observed as discrete M band in the gamma region (Fig. 3B, D) of multiple myeloma patients which reveals considerable increase in gamma globulin fraction due to paraprotein production in comparison to normal healthy control group individuals (Fig. 3A, C). [22]also reported that the high concentrations of gamma globulin in MM patients are due to increased production of abnormal immunoglobulins termed as paraproteins.

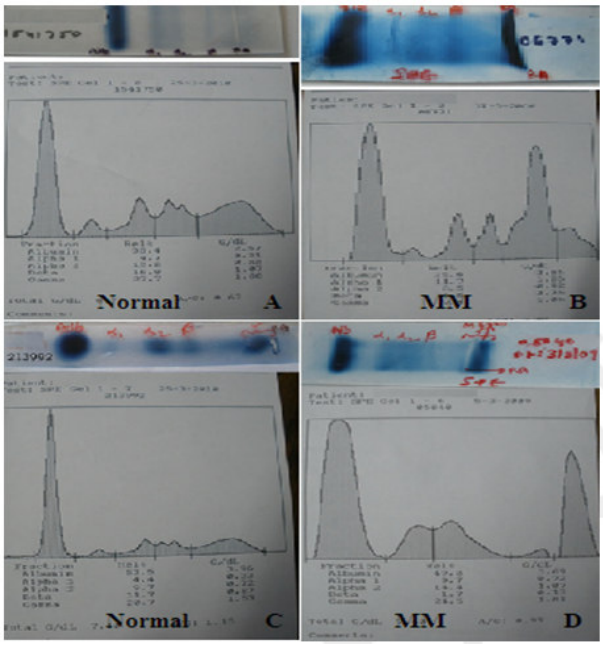

Figure 3
A, C- Serum protein electrophoretic patterns in normal healthy individuals; C, D- Serum protein electrophoretic patterns in the suspected multiple myeloma subjects

Serum total protein and serum albumin levels were estimated as the indicators of progression of the disease. Estimation of serum creatinine levels was important in MM as an indicator of renal function. Serum calcium level was estimated as the indicator of bone material status, degree of bone lytic lesions and pathological fractures. Serum albumin is largest protein component of human serum. Serum albumin was measured to know the nutritional status, general status of health and disease progression in cases. The statistical analysis data of serum albumin showed no statistical significant differences between the two groups studied (Table 4, Fig. 2B). The mean value of serum albumin in study cases showed considerable reduction (3.5±0.79) compared to control group (4.5±0.52) and were not statistically significant (p = 0.08). According to [23]hypoalbuminemia is seen in multiple myeloma. The values in both the groups were within normal limits. This is in accordance with the study of [24], who suggested that serum albumin values are within normal limits in subjects suffering from multiple myeloma being statistically not significant (p = 0.08). Serum creatinine is an important marker of renal function and is estimated in both study cases as well as controls. The mean and SD values of serum creatinine showed 2 fold increases in study group subjects (1.8±0.86) over controls (0.9±0.15). The increases were statistically significant (p = 0.00) (Table 4, Fig. 3A) and are in agreement with the earlier results[25]. Serum calcium is an important indicator to identify bone material status. The mean and SD values in both the groups (Table 4) showed significant difference between the two groups (p = 0.00). Mean and SD values of serum calcium in the study cases (11±0.91) were greater than that of controls (9.6±0.53) (Fig. 3B) and are statistically significant (p = 0.00). In multiple myeloma there is an increased osteoclastic activity and inhibited osteoblastic activity that leads to tumor induced bone destruction, which results in hypercalcemia. Earlier reports[1] showed significant (p = 0.00) rise in serum calcium in patient group compared to control.

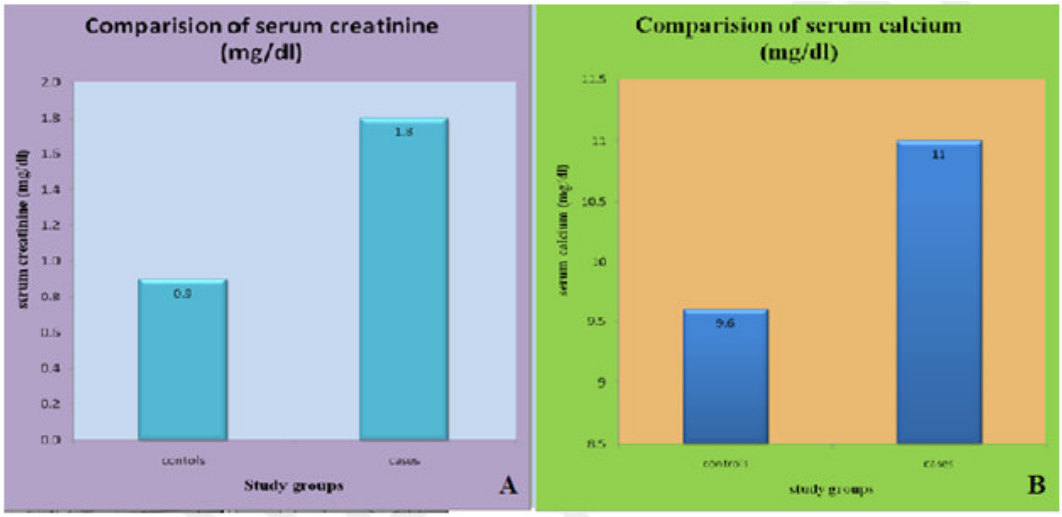

Figure 4
A- serum creatinine levels, B- serum calcium levels in control and case group

Hypercalcemia is the most common cause of renal failure. Glomerular deposits of amyloid, cast nephropathy, hyperuricemia, recurrent infections and frequent use of nonsteroidal anti-inflammatory agents for pain control, use of iodinated contrast dye for imaging, bisphosphonate use, and occasional infiltration of the kidney by myeloma cells all may contribute to renal dysfunction[7]. Mean and SD values of serum total proteins, serum creatinine and serum calcium are significantly high in study cases when compared to control group (Table 4) and are statistically significant. Whereas, serum albumin levels showed slight decrease and are not statistically significant (p > 0.05). Present study showed abnormal eletrophoretic pattern present in multiple myeloma, in which M band was identified in the gamma region when compared to normal electrophoretic patterns observed in normal healthy individuals. Increased serum total protein indicates the increased paraprotein production. Increased serum calcium indicates the bone resorption and increased serum creatinine levels in case group indicates renal damage. A serum protein electrophoresis can identify a monoclonal (M) protein, and a serum immunofixation confirms the presence of immunoglobulin.

CONCLUSION

Serum protein electrophoresis has a significant role in the diagnosis of suspected multiple myeloma. Estimation of serum total protein has a role in assessment of paraprotein production. Assessment of bone lesions and bone mineral status using serum calcium has a significant role in the multiple myeloma cases. Evaluation of serum creatinine is used as an indicator of renal function. These resulted biochemical parameters alert the clinicians to investigate along the lines of MM.

CONFLICT OF INTEREST

Conflict of interest declared none.

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