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Multiple Myeloma: An Experience from an Exclusive Tertiary Care Renal Referral Centre

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Original Research Article

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Abstract: Multiple myeloma is hematological malignancy characterized by a clonal proliferation of malignant plasma cells in the bone marrow secreting a monoclonal immunoglobulin. Approximately 20% of patients with newly diagnosed myeloma present with renal failure and it is the second most common cause of death in these patients. This study was undertaken to review the spectrum of cases of myeloma from an exclusive renal centre. Renal disease was present in all patients before myeloma was diagnosed. All the 36 patients showed 'M'spike in serum electrophoresis and deranged renal function. Renal diseases consisted of mainly of acute renal failure (51%), chronic renal failure (36%) and nephrotic syndrome (13%). Thus, acute renal failure is the most common renal disease preceding the diagnosis of myeloma. Hence it is necessary to look for potential renal impairment in myeloma patients as reversal of renal function can be achieved with chemotherapy and hemodialysis treatment.
Key words: myeloma, electrophoresis, renal.

INTRODUCTION

Multiple myeloma is characterized by a clonal proliferation of malignant plasma cells in the bone marrow secreting a monoclonal immunoglobulin [1]. This hematological malignancy accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers. It is the second most common adult hematological malignancy, and is the most common cancer with skeleton as its primary site. Although multiple myeloma is a malignancy that predominantly affects bone marrow and bone, involvement of extra-osseous tissues is becoming increasingly common both at initial presentation and follow-up.

Most common initial presentations include anemia (73%), bony lesions (80%), and renal impairment (20–40%). Complications include neurologic and hematologic complications, infections, renal insufficiency, and lytic bone lesions[2]. Approximately 20% of patients with newly diagnosed myeloma present with renal failure and is second most common cause of death in these patients. Up-to 50% of newly diagnosed patients present with decrease in GFR and many require dialysis. Despite progress in therapy regimes the median survival rates with conventional treatment remain no more than 2- 3 years.

The diagnosis of patient with multiple myeloma is based on certain clinical and laboratory findings such as: presence of skeletal lesions (e.g., lytic lesions), diffuse osteopenia, vertebral compression fractures, anemia, pancytopenia, hypercalcemia and renal disease. The laboratory diagnosis requires 10 to 15% plasma cell involvement on bone marrow biopsy and 'M' protein spike in the gamma, beta, or alpha-2 regions with concentration greater than 3 g per dL on electrophoresis. The nature of the monoclonal protein is then characterized and confirmed by immunofixation electrophoresis (IFE). The purpose of the study was to review the cases of multiple myeloma from exclusive renal referral centre.

MATERIALS AND METHODS

A retrospective analysis of 36 patients of myeloma presenting with renal failure were included in the study at Institute of NephroUrology, Bangalore were included in the study.

Baseline demographics, clinical history of the patients along with routine urine examination and biochemical parameters at the time of presentation/ biopsy were also analyzed. Creatinine clearance (Crcl) was estimated in all the patients by modification of diet in renal disease (MDRD) formula by an online calculator.

For serum electrophoresis, 5ml blood was drawn in plain tube and sera was separated after the

sample had clotted and stored till further analysis. While for urine electrophoresis 50 ml of random urine sample was collected and stored for analysis.

All biochemical investigation was done on Abbott integrated chemistry immunoassay analyzer (Ci4100). Serum Protein electrophoresis and Immunofixation electrophoresis was done on Helena Biosystems using SAS-MX SP-10 SB and SAX-MX IFE-1 kit respectively. The results were analyzed using Helena software PT version 3.0.

The serum protein fractions analyzed included total protein, albumin, α1-globulin, α2-globulin, β1-globulin, β2-globulin, and γ- globulin. Laboratory parameters evaluated included hemoglobin, serum calcium, creatinine, and lactate dehydrogenase levels and the erythrocyte sedimentation rate.

The current diagnostic criteria and staging method for newly diagnosed multiple myeloma a patient is as follows: Diagnostic Criteria. They include at least 10% clonal bone marrow plasma cells, serum, or urinary monoclonal protein.

Myeloma-related organ dysfunction (CRAB criteria) is as follows: hypercalcemia [serum calcium > 11.5 mg/dL (2.88 mmol/L)]; renal insufficiency [serum creatinine > 2 mg/dL (177 umol/liter)]; anemia [hemoglobin < 10 g/dL or >2 g/dL] below the lower limit of the normal range); bone disease (lytic lesions, severe osteopenia, or pathologic fracture).

The raw data was entered and analyzed on GraphPad software. The mean values of the different parameters were compared between normal and myeloma patients. P-values were compared to detect significant statistical differences between mean values at a level of $p>0.05$.

RESULTS AND DISCUSSION

Out of 36 cases 27 were males and 9 females with average age of 56.42± 6.14 years. Diagnosis of was confirmed by two or more of the following four features: lytic bone lesions, serum or urine monoclonal peak, Bence Jones proteinuria, and ≥ 20% plasma cells in marrow.

Renal disease was present in all patients before myeloma was diagnosed. Renal diseases consisted of mainly of acute renal failure (51%), chronic renal failure (36%) and nephrotic syndrome (13%).

In all the patients the SPEP showed 'M' spike in gamma region, beta region while UPEP was done in 18 cases these entire cases showed M spike in gamma zone. Serum protein electrophoresis revealed a localized band in agarose gel or a sharp peak in the densitometer tracing in 36 patients consistent with finding of multiple myeloma. The band migrated in the gamma zone in 81%, beta zone in 18%, between alpha-2 and beta zones in 1%. The concentration of the serum M-protein was lower than 1.0 g/dL in 8% of patients and was lower than 3 g/dL in 34% and remaining patients had a peak more than 3g/dl. In 15 cases serum immunofixation studies were done, the most common type of heavy chain produced in myeloma is IgG followed by free light chains (predominently kappa light chains). After confirmation of myeloma, the patients were referred for chemotherapy with supportive therapy and hemodialysis. More than half of the total number of patients did not complete chemotherapy because of death or lost to follow-up.

Table-1: The comparative data between normal and myeloma patients

	normal	myeloma
Age (years)	61.2±10.8	56.42±6.14
hemoglobin(g/dL)	7.8 ±1.8	7.4±2.1
Serum creatinine (mg/dL)	6.48±3.45	4.12±2.68
Serum calcium (mg/dL)	7.82±0.85	9.16±0.68
Total protein (g/dL)	6.34±1.88	8.10±3.18

The reported incidence of Multiple myeloma in North America is 4.8 per 100000 population for men and 3.3 per 100000 for women. In India the exact incidence in is not known but based on data available from 6 population based cancer registries (covering <0.3% of the population), the reported incidence varies from 0.3 to 1.9 per 100000 for men and 0.4 to 1.3 per 100000 for women[3].

The diagnosis of multiple myeloma is based on certain clinical and laboratory findings such as: presence of skeletal lesions (e.g., lytic lesions, diffuse osteopenia, vertebral compression fractures), anemia, pancytopenia, hypocalcemia and renal disease]. The laboratory diagnosis requires ≥ 10% plasma cell involvement in bone marrow biopsy and M-protein spike in the gamma region with concentration greater than 3g per dL in electrophoresis. In the laboratory serum protein electrophoresis is given more attention especially the gamma region which is mainly composed of immunoglobulins[4]. Many conditions can cause an increase in gamma region, but those with a homogenous spike like a peak are of significance. These are called paraproteins or M (monoclonal) proteins and sometimes

also seen in beta or alpha-2 regions also. Similarly in urine electrophoresis also a homogenous spike like a peak is seen. An additional point considered is size of the M-protein spike. Although spike is usually greater than 3 g per dL in patients with multiple myeloma, up to one fifth of patients may have an M-protein spike of less than 1g per dL. Thus, the size of the M-protein spike is not helpful in excluding multiple myeloma. In our study, all patients had renal failure with anemia and 'M' spike in serum electrophoresis.

Most of the myeloma patients have a large amount of Bence-Jones protein (monoclonal free kappa or lambda chain) in their urine and may not have an M-protein spike in serum protein electrophoresis. Consequently, urine protein electrophoresis is recommended for all patients suspected of having a plasma cell dyscrasia. In one series, serum protein electrophoresis showed a spike or localized band in only 82 percent of patients with multiple myeloma. The remainder had hypogammaglobulinemia or a normalappearing pattern. In our study, all the myeloma patients showed a spike or localized band on serum protein electrophoresis and spike in urine electrophoresis from the respective patients.

The kidney acts as a filter, eliminating only a few molecules and leaving most of the proteins in the bloodstream. Renal failure in myeloma is due to an elevated serum concentration of monoclonal free light chains which affect the glomerular basement membrane, tubules, or the interstitium. Free light chains from the circulation are filtered by glomerular filtration and either pass directly into the tubules or are transported into the mesangium. These may deposit along the glomerular basement membrane or within the tubular basement membrane, either in the form of fragments or intact chains. Their deposition leads to obstruction, amyloid formation, and inflammation.

The most common causes of renal failure in multiple myeloma are due to: Monoclonal immunoglobulin deposition disease due to deposition of light chains (LCDD) or heavy chains (HCDD). Cast nephropathy is due to the formation of casts in the distal tubules, caused by the deposition of light chains and Tamm-Horsfall protein leading to secondary tubulointerstitial nephritis.

Therefore, it is necessary to rapidly reduce blood levels of free light chains in order to facilitate the recovery of renal function. Up to 50% of newly diagnosed patients present with decrease in GFR and many require dialysis. Despite progress in therapy regimes, the median survival rates of myeloma patients with conventional treatment remain no more than 2- 3 years. At least half of the patients with multiple myeloma will develop renal failure through the course of their disease.

The United Kingdom Medical Research Council Multiple Myeloma trials between 1980 and 2002, results showed that renal failure contributed to 28% of documented early mortality. At diagnosis, 30%-40% of patients had serum creatinine above the upper limit of normal, and up to 10% of these patients required dialysis[5].. Half of these patients will respond to supportive treatment with reversibility of renal impairment, but 2%-12% will progress to end stage renal disease (ESRD) and require dialysis. In our study the mean age of myeloma patients presenting with renal failure was higher than the patients without myeloma. Development of unexplained renal failure in an elderly individual, in association with disproportionate anemia even in absence of skeletal lesions should alert the physician to the diagnosis of multiple myeloma.

Our results suggest that serum electrophoresis especially in patients with unexplained renal impairment, is of utmost importance and also important tool for monitoring the clinical course of myeloma and monitoring for para proteins. As acute renal failure is the most common renal disease preceding the diagnosis of myeloma in our series, it is necessary to look for potential renal impairment in myeloma patients as reversal of renal function can be achieved with chemotherapy and haemodialysis treatment.

CONCLUSION

As acute renal failure is common renal disease preceding the diagnosis of myeloma, serum electrophoresis as an inexpensive and widely available test should be used as an screening test routinely especially in patients with renal impairment.

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