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Renal Function in Patients with Multiple Myeloma

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Abstract

Background. Multiple myeloma is associated with renal disease and only 52% of patients have normal renal function at the time of diagnosis. If renal disease is present, prognosis and outcome are poor. The aim of our study was to evaluate the degree of renal impairment at the time of diagnosis of multiple myeloma and its relationship with biochemical parameters.

Methods. Study included patients with multiple myeloma in a period 2006 – 2008. We analysed: demographic data, type and stage of multiple myeloma, degree of renal impairment and biochemical parameters.

Results. In the follow up period of two years there were 62 patients (40 males and 22 females) with multiple myeloma, with mean average age of 65,8 ± 7,92. The most common type of multiple myeloma was immunoglobulin G - 77,4% (48 patients), IgA was presented with 9,6% and IgM with 12,9%. There were significant differences (p <0, 01) between groups in gender (more males then females), but no significant differences in age. There was no statistically significant difference between the separate male/female groups of different myeloma patients (X^2=8,205, df=2, p-0,0165 p<0,05). 38,7 percent of patients have had renal impairment at the time of diagnosis as suggested by the low creatinine clearance. There were no significant differences between groups considering the renal impairment, but the renal impairment was more common in patients with light-chain multiple myeloma. From the 62 patients, 5 of them had dialysis. There was no significant correlation between creatinine clearance and Calcium levels, p-n.s. 19, 3% of patients had serum calcium level of >2, 60 mmol/L. During study period 23 patients died and 5 of them required dialysis. Mean average age was 71,75 years and the death rate was significantly higher for males rather then for females (17 males died in the follow up period).

Conclusion. The study reported that IgG myeloma was the most common type of myeloma. The presence of renal impairment in patients with multiple myeloma was present in more than 30% of the patients and 5 of them required hemodialysis treatment. The presence of renal failure also affects the outcome of therapy in multiple myeloma and the 37% of patients out of the total number died.

Keywords: multiple myeloma, renal impairment, dialysis, outcome.

Introduction

Multiple myeloma is a progressive neoplastic expansion of clonal plasma cells¸ who originated from a single B cell¸ which often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. Other common clinical findings include anemia, hypercalcaemia, and renal insufficiency [1]. Most frequently it occurs in male population after >40 years of age (3-4 people per 100 000 in the US. Male-female ratio app. 1, 6:1). Myeloma is more common in African Americans than Caucasians. Only 52% of patients had normal renal function at the time of diagnosis. Different factors influence on multiple myeloma occurrence: gene predisposition, exposure to radiation, benzene, and other organic solvents, herbicides, and insecticides may play a role, chronic antigen stimulation. Primary sites of renal injury in multiple myeloma are:

A. Glomerular: primary (AL) amyloidosis – 30%, monoclonal immunoglobulin deposition, 19%, miscellaneous (cryoglobulinemia, proliferative glomerulonephritis, etc.).

B. Tubular: cast nephropathy (myeloma kidney) - 41%, distal tubular dysfunction, proximal tubule dysfunction or acquired Fanconi's syndrome.

C. Interstitial: plasma cell infiltration, interstitial nephritis – 10% [2].

In some patients overly produced monoclonal light chains (or rarely excess heavy chains) can develop two other disorders: primary amyloidosis (AL amyloidosis), monoclonal immunoglobulin deposition disease. In AL amyloidosis, the circulating light chains are taken up and partially metabolized by macrophages. Light chain deposition disease is pathogenetically similar, except that the light chain fragments do not form fibrils and the deposits are Congo red negative. Patients with these disorders typically present with the nephrotic syndrome, rather than renal failure as in myeloma kidney [3,4].

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Cast nephropathy is the single most common diagnosis, accounting for 40 to >60 percent of the cases. It is the result of monoclonal immunoglobulin light chains (κ or λ), which are secreted into the urine. The term myeloma kidney or myeloma cast nephropathy refers to a disorder in which monoclonal urinary immunoglobulin light chains (Bence-Jones proteins) lead to acute or chronic renal failure (renal injury) [5,6]. Light chains are freely filtered across the glomerulus and then largely reabsorbed by the proximal tubular cells. Light chain excretion has normal rate of <30 mg/day and a pathologic rate from 100 mg to 20 g/day.

Two factors are likely to be of primary importance: intratubular cast formation and direct tubular toxicity. Light chains can precipitate in the tubules, leading to densing and obstruction [7,8]. Casts contain: light chains, Tamm-Horsfall mucoprotein (THMP, also called uromodulin) and other filtered proteins. THMP is a protein of uncertain function. It is normally secreted by the cells of the thick ascending limb of the loop of Henle. It constitutes the matrix of all urinary casts [9].

Tubular injury can promote the development of renal failure, at least in part by enhancing cast formation. Some patients with multiple myeloma develop signs of tubular dysfunction without renal failure.

Diagnosis of myeloma kidney

Suspected in any patient over age 40, who presents with otherwise unexplained acute or subacute renal failure. A large proportion of patients will not have a previously diagnosed multiple myeloma or other monoclonal gammopathy. The diagnosis is usually made based on suggestive clinical features, and the presence of elevated quantities of monoclonal free light chains in both the plasma and urine [10]. Potential contributors to acute renal failure should be explored and addressed if present, such as volume depletion and hypercalcemia. Serum protein electrophoresis and free light chain assay should be obtained on every patient. A 24 hour urine collection and serum should be sent for protein electrophoresis and immunofixation to confirm the identity of the monoclonal protein and determine the amount of albuminuria (negative or trace-positive dipstick should be tested with sulfosalicylic acid (SSA). Prognosis is primarily determined by the response of the myeloma to chemotherapy. Dialysis has become an accepted treatment in end-stage renal disease due to myeloma.

The aim of this study was to determine the degree of renal impairment at the time of diagnosis of multiple myeloma and its relationship with hematological and biochemical parameters.

Patients and methods

All patients with multiple myeloma included in a study admitted in Clinical Center University of Sarajevo between January 2006 to January 2008. Multiple myeloma was diagnosed if any two of the following criteria were evident: plasma cells infiltrate of the bone marrow of greater than 15%, presence of serum or urinary monoclonal paraprotein and radiographic evidence of osteolytic skeletal lesions.

Renal function was evaluated by measuring creatinine clearance (CrCl) at the time of diagnosis. Three subgroups were defined as follows: no renal impairment, with CrCl > 60 ml/min/1,73 m^2 .Moderate renal impairment with CrCl between 60 ml/min/1,73 m^2 and 25 ml /min/1,73 m^2. Severe renal impairment with CrCl < l5 ml/min/l,73 m2. Five (5) patients were treated in the follow up period with hemodialysis, because of the end stage renal failure. Demographic information and clinical data including type of multiple myeloma, presence of Bence-Jones proteinuria and renal function were also included.

Statistical analysis

Data were expressed as mean values with standard deviation (SD). Hi test was used to evaluate the relationship between CrCl and serum Calcium levels, confirmed with ANOVA. In all analysis p value < 0, 05 was considered significant.

Results

Study follow up period was two years. There were 62 patients in our study cohort, mean age was 65,8 + 7,92 years, and there was higher number of males (40 - 64,5%) than females (22-35,5%). There was no statisically significant difference between the separate male/female groups of different myeloma patients (X^2=8,205, df=2, P=0,0165 <0,05).

The most common type is IgG multiple myeloma (77,4%) followed by IgM (12,9 %) and IgA (9,6%), Table 1.

38,7 percent of patients have had renal impairment at the time of diagnosis as suggesteed by the low CrCl. 19,3% of patients had serum calcium level of >2, 60 mmol/L (Table 2 and Figure 1). Furthermore, there was no significant correlation between types of multiple myeloma and CrCl. 66,6% patients (n=16) with CrCl <60 ml/min/1,73m^2 belong to IgG type of multiple myeloma. Light-chain myeloma was more frequently associated with renal impairment. However, there was no significant correlation between CrCl and Calcium levels, p=n.s. (Table 3). From the total number of 62 patients, Bence-Jones proteinuria was found in 57 (91,9%), 20 females and 37 males patients. Dialysis was recommended for patients with end-stage renal disease, uremic symptoms and hypervolemia. Three patients continued with chronic hemodialysis program and two patients died (Table 4). Furthermore, there was no significant correlation between types of multiple myeloma and CrCl. 66,6% patients (n=16) with CrCl <60 ml/min/1,73m^2 belong to IgG type of multiple myeloma. Light-chain myeloma was more frequently associated with renal impairment. However, there was no significant correlation between CrCl and Calcium levels, p=n.s. (Table 3). From the total number of 62 patients, Bence-Jones proteinuria was found in 57 (91,9%), 20 females and 37 males patients. Dialysis was recom-

mended for patients with end-stage renal disease, uremic symptoms and hypervolemia. Three patients continued with chronic hemodialysis program and two patients died (Table 4).

Table 1. Types of multiple myeloma

Type of multiple myeloma	% of patients	N = M/F
IgG	77,4	31/17
IgA	9,6	1/5
IgM	12,9	8/0

Table 2. Creatinine clearance levels and characteristics of patients with different types of multiple myeloma

Types of multiple myeloma	Number of patients	Creatinine clearance <60 ml/min/1,73m^2	Creatinine clearance >60 ml/min/1,73m^2	P value	Ca level <2,10 mmol/L	Ca level 2,10 – 2,6 mmol/L	Ca level >2,6 mmol/L
IgG	48	16	32	ns	6	21	5
IgA	6	4	2	ns	5	10	3
IgM	8	4	4	ns	3	5	4
Total	62	24	38		14	36	12
	100%	38,7%	61,2%		22,5%	58,0%	19,3%

Table 3. Relationship between creatinine clearance and Calcium levels

	Creatinine clearance <60 ml/min/1,73 m^2 with Ca level >2,6 mmol/L	Creatinine clearance >60 ml/min/1,73 m^2 with Ca<2,6 mmol/L
N = patients	13	49
Mean	51,8	53,2
Std. deviation	29,7	28,5
P	0,883 (ns)	0,879 (ns)

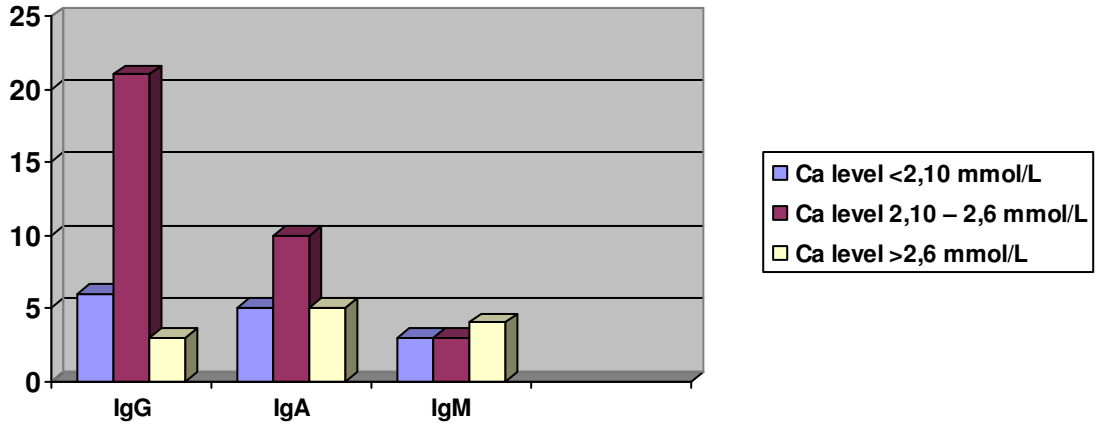

Fig. 1. Distribution of patients by Ca levels in different diagnosis

Table 4. Characteristics of patients requiring hemodialysis

Patient No.	Age/ years	Gender	Type	Outcome
1	47	F	IgM	HD
2	64	M	IgA	died
3	50	M	IgG	died
4	74	M	IgM	died
5	80	F	IgM	HD

Mortality rate and age of patients with various MM types is presented in Table 5. In addition, mortality rate was significantly higher for males compared to females, p<0.001, (Table 6).

Table 5. Mortality rates and mean age for patients with different types of multiple myeloma

Types of multiple myeloma	Number of died patients	Mean average age
IgG	11	73±8,53
IgA	5	74,8±2,8
IgM	8	68,1±11,46

Table 6. Patients outcome by gender

Outcome	Males	Females
Died	17 (43,59%)	7 (30,43%)
Alive	22 (56,41%)	16 (69,56%)
Total	**39**	**23**

Discussion

The present study has focused on the importance of renal failure at the time of diagnosis of multiple myeloma and patient outcome. We found that 38,7% of patients had CrCl <60 ml/min/1,73m^2. This is in accordance with the data from literature [11,12].

The ideal way to evaluate renal function is to measure the GFR by the inulin clearance on radio labeled markers. It is very difficult to carry out this measurement, and therefore we measured CrCl by ml/min/1,73m^2. We also classified patients in three groups based upon CrCl at the time of diagnosis. The literature indicates [13-15] that as many as 50% of patients with multiple myeloma have some degree of renal insufficiency, although in the majority renal function will improve in response to medication as rehydration, correction of hypercalcemia, on discontinuing usage of nephrotoxic drugs. Improvement of renal function occurred for most patients during the first three months, which was also found by Alexanian at al. [16]. Improvement was more common when renal failure was moderate, but occurred irrespective of treatment response. In this study five patients (8%) required dialysis. Torra *et al*. [17] found the proportion of patients requiring dialysis in their case series was some what higher than 12 (7%). One study evaluated mortality of 140 patients with multiple myeloma and found that the median survival time was 22 months both for patients with renal failure treated with dialysis and those with lesser degrees of renal failure.

Conclusions

The study reported that IgG myeloma was the most common type of myeloma.

The presence of renal impairment in patients with multiple myeloma was found in more than 30% of the patients and 5 of them required hemodialysis treatment.

The presence of renal failure also affects the outcome of therapy in multiple myeloma and a substantial proportion of patients (37%) out of the total number died.

Conflict of interest statement. None declared.

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