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Kidney Damage in Multiple Myeloma: Clinical, Biological, Histological and Therapeutic Aspects at the Chartres Hospital Center

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Abstract

Introduction: Multiple myeloma is a haematological malignancy characterised by monoclonal plasma cell proliferation in the bone marrow, which synthesises a serum and/or urinary monoclonal protein, associated with one or more manifestations including (anaemia, hypercalcaemia, bone lesions, renal failure). The aim of our work was to determine the prevalence, clinico-biological, histological and therapeutic manifestations of renal damage during multiple myeloma. **Methodology:** This is a retrospective descriptive study spread over a period of 2 years from 01 January 2020 to 31 December 2021 carried out in the nephrology department of the louis pasteur hospital of the CH of Chartres. All patients treated for multiple myeloma with renal involvement were included, whether the renal involvement was revelatory or diagnosed during the follow-up of the multiple myeloma. **Results:** We collected 20 cases of myeloma. Renal involvement was present in 19 cases (95%). The mean age was 68.78 ± 10.77 years with extremes ranging from 44 to 82 years. Males were more prevalent, with an M/F sex ratio of 3.75. The most common antecedent condition was hypertension in 14 cases (73.7%) and diabetes in 4 cases (21.1%). The circumstances of discovery were renal failure in 16 cases (84.2%), followed by bone pain in 6 cases (31.6%). Renal involvement was dominated by renal failure in 18 cases (94.7%), hypercalcaemia in 14 cases (73.7%), para protein in 9 cases (47.4%), haematuria and leukocyturia in 5 cases (26.3%). On plasma protein electrophoresis, 11 cases (57.9%) had kappa light chain multiple

myeloma, 8 cases (42.1%) had lambda light chain multiple myeloma. We noted 9 cases (69%) of myelomatous cylinder nephropathy at renal biopsy, Randall's disease in 2 cases (15%), AL amyloidosis and acute tubular necrosis in 1 case (8%). First-line chemotherapy treatment was dominated by the combination of Velcade, cyclophosphamide and dexamethasone in 5 cases (79%). **Conclusion:** Renal involvement in myeloma is still common; it may be isolated and precede the first signs of myeloma by several months; the most common histological forms are myelomatous cylinder nephropathy and Randall's disease.

Keywords

Multiple Myeloma, Renal Involvement, Chartres Hospital

1. Introduction

Multiple myeloma is a haematological malignancy characterised by monoclonal plasma cell proliferation in the bone marrow which synthesises a serum and/or urinary monoclonal protein, associated with one or more manifestations including anaemia, hypercalcaemia, bone lesions, and renal failure [1] [2].

It accounts for around 10% - 15% of haematological cancers worldwide, making it the second most common cancer after lymphoma. It is responsible for 15% - 20% of haematological cancer deaths and around 2% of all cancer deaths [3].

Renal involvement in myeloma can be classified either according to the primary site affected, the histological type or the pathophysiological mechanism involved; there are clinical and prognostic differences between these renal pathologies [4].

In the nephrology setting, the most common circumstances in which monoclonal gammopathies of renal significance are discovered are Fanconi syndrome, nephrotic syndrome, dyscalcaemia, anaemia or renal failure.

According to the literature, around 50% of myeloma patients have or will have kidney damage. Tubular damage is the most common, accounting for more than 80% of kidney damage (tubulopathymyelomatous, Fanconi syndrome and acute tubular necrosis) because it is directly linked to the presence of FLC in the urine; followed by glomerular damage (AL amyloidosis, monoclonal Ig deposition diseases, GNMP and GIT, around 10 to 15%) and interstitial damage (plasma cell infiltration), which accounts for around 4% [5].

In Russia in 2015, Zakaharova. EV reported 60% renal damage in a cohort of 282 subjects with plasma cell dyscrasia [6].

In Morocco in 2013, Ben-Tebbaa. His doctoral thesis in medicine found 42% renal involvement during myeloma [7].

In Senegal in 2017, Khalid Z, in his doctoral thesis in medicine, reported 49% renal involvement in myeloma in a multicentre study of 175 cases [8]. New therapeutic protocols have emerged, in particular proteasome inhibitors and monoclonal antibodies, which have improved renal response in patients with the possibility of access to haematopoietic stem cell transplants. However, light chain

purification techniques have not proved effective and some teams are tending to abandon them due to the lack of consensus [9].

The increasing incidence of incurable chronic diseases such as myeloma, for which renal failure is one of the key prognostic criteria, and the absence of previous studies on this subject at Chartres Hospital, were our main reasons for choosing this study.

The aim of this study was to investigate the clinical, biological, histological and therapeutic aspects of renal damage in multiple myeloma.

2. Material and Methods

The nephrology and haemodialysis department of the Hôpital Louis Pasteur, CH Chartres, was used as the setting for this study. This was a retrospective study spread over a 2-year period from 01 January 2020 to 31 December 2021.

All records of adult patients treated for multiple myeloma with renal involvement were included in this study, whether the renal involvement was revealing or diagnosed during follow-up of the myeloma, biopsied or not, and regardless of the clinical picture.

Incomplete records, any renal involvement not attributable to myeloma and records of patients with monoclonal gammopathy of non-renal significance were not included.

The data were collected on **Appendix**.

Our variables were quantitative and qualitative, divided into the following categories.

Socio-demographic data: prevalence, age, sex.

Clinical and paraclinical data: history, circumstances of discovery, manifestations of renal damage, plasma protein electrophoresis, histological classification of renal lesions.

▪ Plasma protein electrophoresis with blood immunofixation enabled us to detect monoclonal immunoglobulin, hypergammaglobulinemia and hyopogammaglobulinemia.

▪ The renal biopsy allowed us to characterize the renal attacks (tubular, glomerular, interstitial or other attacks) and its indication was in front of any:

- Patients with acute renal failure KDIGO 1 or 2 associated with an albuminuria to creatinuria ratio of between 3 and 30 mg/mmol;

- Patients with acute renal failure KDIGO 3, proteinuria and haematuria, or albumin/creatinine ratio greater than 30mg/mmol.

Therapeutic data: includes management of acute renal failure and treatment of plasma cell clones.

Data were collected manually on pre-established survey forms and entered into World, Excel and PowerPoint, then analysed using epi info 7.2 software.

Ethical considerations:

The agreement of the department managers was obtained before the start of the surveys. A working protocol was drawn up and validated by the hospital

authorities. Free informed consent was obtained from the written patients included in this study, respecting confidentiality and anonymity in accordance with medical ethics.

3. Results

3.1. Sociodemographic Data

We collected 20 cases of multiple myeloma during the study.

Renal involvement was present in 19 patients (95%).

The mean age was 68.78 ± 10.77 years, with extremes ranging from 44 to 82 years.

The most common age groups were 60 - 69 and 70 - 79 (31.6% each).

The male sex was the most dominant with a sex ratio M/F of 3.75 (Table 1).

Table 1. Socio-demographic characteristics of patients.

Characteristics	Workforce	%
Prevalence		
Kidney disease	19	95
No disease	1	5
Age		
40 - 49	1	5.3
50 - 59	2	10.5
60 - 69	6	31.6
70 - 79	6	31.6
80 - 89	4	21.1
Average age: 68.78 ± 10.7 years	Extreme 44 to 82 years	
Sex		
Male	15	79
Female	4	21
Sex ratio M/F: 3.75		

3.2. Clinical and Paraclinical

The most common antecedent condition was hypertension in 14 cases (73.7%) and diabetes in 4 cases (21.1%). The circumstances of discovery were renal failure in 16 cases (84.2%) followed by bone pain in 6 cases (31.6%).

Revealing signs of renal damage were renal failure in 94.7% of cases, hypercalcaemia in 73.7%, para protein in 47.4%, urine sediment abnormalities such as haematuria in 26.3% of cases, and leucocyturia in 26.3% of cases. The serum protein profile showed 11 cases (57.9%) of kappa light chain multiple myeloma, 8 cases

(42.1%) of lambda light chain multiple myeloma. At renal biopsy we found 9 cases (69%) of myeloma cell nephropathy, 2 cases (15%) of Randall's disease, AL amyloidosis and acute tubular necrosis 1 case (8%) each (Table 2).

Table 2. Distribution of patients according to clinical and paraclinical data.

Characteristics	Workforce	%
History		
Hypertension	14	73.7
Diabetes mellitus	4	21.1
Chronic kidney disease	3	15.8
Ischaemic heart disease	3	15.8
Gammapathy	2	10.5
No previous history	2	10.5
Polycystic kidney disease	1	5.3
CDD myeloma		
Renal insufficiency	16	84.2
Bone pain	6	31.6
Anemia (THb < 11 g/dl)	5	26.5
Nephrotic syndrome	3	15.8
Gammapathy	2	10.5
Manifestations of renal impairment		
Renal failure	18	94.7
Hypercalcaemia (≥2.75 mmol/l)	14	73.7
Para protein	9	47.4
Leukocyturia (leukocytes > 10/mm^3)	5	26.3
Haematuria (> 10 red blood cells/mm^3)	5	26.3
Serum protein profile		
MM CLL kappa	11	57.9
MM CLL lambda	8	42.1
Histological data		
NCM	9	69
Randall MIDD	2	15
Amyloidosis AL	1	8
Acute tubular necrosis	1	8

3.3. Therapeutic Treatment

We have 16 cases (81.2%) of rehydration, 6 cases (31.6%) of discontinuation of NSAIDs, 6 cases (31.6%) of extra renal purification,5 cases (26.3%) of urine alkanization and 4 cases (25.2%) of transfusion.

Treatment of the plasma cell clone was dominated by VCD in 15 cases (79%), RD in 3 cases (16%) and VD in 1 case (5%) (Table 3).

Table 3. Breakdown of patients according to treatments received.

Characteristics	Number	%
ARF treatment		
Rehydration	16	81.2
Discontinuation of NSAIDs	6	31.6
Extra renal purification	6	31.6
Alkalisation	5	26.3
Transfusion	4	25.2
Chemotherapy protocol		
VCD	15	79
Revlemide/Dexamethasone	3	16
Velcade/Dexamethasone	1	5

4. Discussion

During our study period, we collected 20 cases of myeloma, of which 19 (95%) had renal involvement. This result is much higher than that found by Khalid. Z *et al.* in Senegal in 2017, who reported a prevalence of 49% of renal involvement [8]. This difference can be explained by the existence of health care, which made it easier to carry out all the necessary investigations, and by the inequality of the sample. The mean age was 68.78 ± 10.77 years, with extremes ranging from 44 to 82 years. The age groups most affected were [60 - 69 years] and [70 - 79 years], each accounting for 31.6%. Our results are lower than those of several African authors (Fall, S) [10], which could be explained by the fact that this study was carried out on a population with a higher life expectancy.

There was a predominance of males in 15 cases (79%), with a sex ratio of 3.75. The predominance of males in our study is consistent with several African and European studies. The predominance of males in our study is consistent with several African and European studies [11]-[13], since in general men are more often affected than women because of their more frequent exposure to chemicals such as pesticides and tobacco, which are considered to be the main risk factors for myeloma.

High blood pressure and diabetes were the most common cardiovascular

antecedents, with frequencies of 14 cases (73.7%) and 4 cases (21.1%) respectively. These results are simply due to the fact that they represent the 2 leading causes of CKD in France and in the world; but what is not so clear is that diabetes is a major risk factor.

In addition, the literature does not establish a formal link.

In our study, renal failure was the most frequent finding, followed by bone pain, with 16 cases (84.2%) and 6 cases (31.6%) respectively.

The manifestations of renal damage were dominated by renal failure in 18 cases (94.7%) with a mean creatinine level of 420 ± 236 micromole/l, resulting in KDIGO 3 ARF, followed by hypercalcaemia in 14 cases (73.7%).

This result can be explained by the fact that acute renal failure in myeloma can generally be severe and naked, with no accompanying signs other than deterioration in general condition or bone pain, and that hypercalcaemia remains the most frequent finding of renal damage in myeloma.

The serum protein profile showed 11 cases (57.9%) of kappa light chain multiple myeloma and 8 cases (42.1%) of light chain multiple myeloma.

Our results are similar to those reported by El Mezouar (2010) who found 56.25% of Kappa type myeloma and 43.75% of Lambda type [14].

This can be explained by the fact that κ light chains are physiologically synthesised first during allelic exclusion and the cell produces 2/3 κ light chains before 1/3 λ light chains.

9 cases (69%) followed by Randall's syndrome 2 cases (15%); Our result is identical to the data in the literature and also to that reported by Béhdi Benmoussa *et al.* in 2021 in Morocco, who reported a predominance of myelomatous cylinder nephropathy with 54% and 25% for Randall's syndrome [15]. This result is in line with the profile of our patients, who essentially had light chain myeloma, a large tumour mass, tubular proteinuria with few cases of nephrotic syndrome.

For the emergency management of ARF, we had 16 cases (81.2%) of rehydration, 6 cases (31.6%) of discontinuation of NSAIDs, and 6 cases (31.6%) of extrarenal purification.

Treatment of the plasma cell clone was dominated by the VCD protocol in 15 cases (79%), followed by RD in 3 cases (16%).

The limitations of the study are summarized by the non-interpretability of urine protein immunofixation due to the presence of blood, the small sample size, the retrospective study and the non-biopsy cases.

5. Conclusions

Renal damage in myeloma remains frequent at the Chartres Hospital, in the nephrology department of the Louis Pasteur Hospital.

Renal failure and hypercalcaemia continue to be the presenting symptoms.

Myelomatous cylinder nephropathy remains the most common histological disorder.

The most commonly used combination therapy was VCD followed by RD.

A larger-scale prospective study would be desirable, with a view to identifying other aspects of renal damage in myeloma.

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What We Know about This Subject

Multiple myeloma is a malignant haematological disease that accounts for around 10% - 15% of haematological cancers. myelomatous cylinder nephropathy is the most frequently encountered histological disorder.

What This Work Provides

Knowledge of the epidemiology of kidney damage at Chartres Hospital during our study period.

Authors' Contributions

All authors participated in data collection, analysis and drafting of the manuscript. The final manuscript was read and accepted by all authors.

Conflicts of Interest

The authors declare no conflict of interest.

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Appendix

Survey sheet:

I-N°:.....

Age:..... Sex: Male □ Female □

II- HDM:

a-Discovery of renal involvement: Before MM □ With MM □ After MM □

b-Circumstances of discovery of multiple myeloma:

Renal failure Bone pain □ Gammapathy □ Nephrotic syndrome □ Anemia □ Proteinuria □ Other.....

III-ATCD AND COMORBIDITY:

a-HTA □ Diabetes □ Chronic kidney disease □ Heart disease □ Other...

b-Exposure to toxic products: pesticides □ herbicides □ fertilizers, □

Dyes □ NSAIDs □ Smoking □ Iodinated contrast media □

IV: Clinical and paraclinical data:

General signs: Asthenia.....□ Weight loss.....□ Fever.....□ Anorexia □

Existence of a bone syndrome: □ Existence of an anemic syndrome:.....□ Neurological signs:.....□ Other revealing complications:.....□

EPP: Protidemia.....□ Albumin.....□ Alpha1.....□ Alpha2.....□ Beta1.....□ Beta2.....□ Gamma.....□

Peak: yes □ no □

Immunofixation: IgG..... IgA….. IgM..... IgE..... IgD..... kappa Lambda

IgA..... IgG..... IgM…... IgD..... Kappa:..... Lambda:.....

k/l ratio…...

-Myelogram: Plasmocytes ≤ 10% □ 10_30% □ 30_60% □≥60% □

Anemia (Hb < 10 g): yes no Hb rate:…... WBC:…... Platelets:…...

Calcemia: normal…... hypocalcemia…... hypercalcemia…...

Bone damage: yes □ no □

Topography: fractures lyses demineralization Tassement

Creatininemia:…... Creatinine clearance (MDRD):

Beta 2 microglobulin:…...

In urine

- 24h PU: EPPU: Yes □ No □

- Immunofixation PU: Yes □ No □ Kappa Lamba K/L

- Bence Jones proteinuria: yes □ no □

- Hematuria: yes no Leukocyturia: yes □ no □

Abdominal ultrasound: Yes □ No □ RG size: …... RD size: …...

Differentiation: Good Fair Poor

-PBR: Yes □ No □

Glomerulopathy A C3: □ Myelomatous tuberculopathy: □

Randall (MIDD) □

Amyloidosis AL □ Fanconi □ Cryoglobulin □

Glomerulonephritis immunotactoid □

GNMP □ IgA nephropathy□ NTA □ Plasma cell infiltration □

Fibrillary glomerulosclerosis □

- Bone marrow biopsy: done □ not done □

VI-TREATMENT:

1-Emergency treatment:

a-hypercalcemia: yes □ no □

Rehydration □ Biphosphonate □

b-ARF and complications:

NSAIDs □ discontinuation □ Rehydration □ Urine alkalinization □

FLC purification □

2-Treatment of plasma cell clones:

a-protocol of chemo:

MP: yes □ no □; RD: yes □ no □ CTD: yes □ no □;

VTD: yes □ no □

VCD: yes □ no □; VD: yes □ no □; MPT: yes □ no □;

VAD: yes □ no

b-Bone marrow transplant: yes □ no □ eligibility criteria age under 65.....

c-Immunotherapy: yes □ no □

Daratumabe: yes □ no □ ;VRD: yes □ no □

3-Associated treatments: yes □ no □

Radiotherapy: yes □ no □

Surgery: yes □ no □

ATB: yes □ no □

NB:

We can no longer increase the sample size as the work has already been presented to a member of the jury and then validated.

The study did not address the prognostic aspect of the patients.