Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/19169
DOI URL: http://dx.doi.org/10.21474/IJAR01/19169

RESEARCH ARTICLE

EXPLORING KIDNEY INVOLVEMENT IN MULTIPLE MYELOMA:FIRST DESCRIPTIVE COHORT IN SOUTHERN MOROCCO

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Manuscript Info

Manuscript History
Received: 31 May 2024
Final Accepted: 30 June 2024
Published: July 2024

Abstract

Introduction: Multiple Myeloma (MM) is a malignant and a clonal proliferation of plasma cells that secrete a monoclonal immunoglobulin or its fragment. Renal involvement is common in MM, secondary to the production of monoclonal immunoglobulins (IgM) with intrarenal deposition of light chains. This renal involvement can exacerbate the already poor prognosis due to tumor progression. The aim of our study is to describe the epidemiological, clinical, biological, therapeutic, and evolutionary aspects of renal involvement in MM.

Patients and Methods: We conducted a prospective descriptive study based on the analysis of 22 cases of MM treated at the Nephrology Department of University Hospital Center of Agadir over a period of 4 years (April 2020 - March 2024). The study included all patients meeting the International Myeloma Working Group (IMWG) 2014 classification criteria.

Results: The average age of our patients was 59.4 years, with a male-to-female ratio of 1.44. The average consultation delay was 2 months. Clinical manifestations were predominantly general deterioration, osteoarticular symptoms, and mucocutaneous pallor, present in the majority of our patients. Biological assessments revealed anemia in all cases, severe in half of them. Hypercalcemia was present in the majority of cases (72.7%). Hyperproteinemia was noted in 45% of patients, being significant (>100 g/L) in half of them. Hypoalbuminemia was observed in more than three-quarters of the patients. Severe renal failure was present in 77.2% of patients, with an average serum creatinine level of 66 mg/L. Infectious syndromes were found in half of the patients at admission, primarily urinary (60%) or pulmonary (40%) infections. A monoclonal peak was observed in 77.3% of patients, mainly in the gamma-globulin zone. The myelogram was significant in all cases. Immunofixation revealed a predominance of kappa light chains (62%).. Radiological osteolytic lesions were found in 77.3% of cases. All patients had high tumor mass myeloma.

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Kidney biopsies were not systematically performed, being done in only 2 patients. Therapeutically, chemotherapy was initiated in most patients. Dialysis was indicated in 8 cases (36.3%), and was successful in 6 out of 8 patients. Renal response was complete in 9 cases (40.9%), partial in 3 cases (13.6%), and minor in 6 cases (27.3%). Worsening renal function was observed in 4 patients (18.2%), with 2 patients progressing to chronic dialysis. Infectious complications were noted in 14 patients during their follow-up (63.6%). Hematological toxicity from chemotherapy was observed in 9 patients (40%). with a follow-up period of 22 months, 9 patients are in complete remission, 7 patients have died, and 6 patients were lost to follow-up.

Discussion and Conclusion: Multiple Myeloma remains an incurable disease. However, the advent of new therapies has significantly improved its prognosis. Early diagnosis and management is essential for rapidly restoring renal function and preventing serious complications.

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Introduction:-

Multiple myeloma (MM) is a malignant clonal proliferation of plasma cells that excessively and inappropriately produces an immunoglobulin or its fragments. It constitutes 10% of malignant haematologic diseases and primarily affects the elderly [**1**]. The diagnosis is based on clinical and biological evidence, as well as bone marrow exploration. The International Myeloma Working Group (IMWG 2014) has defined MM using the CRAB criteria (calcemia, renal injury, anemia, and bone lesions). Since 2014, three additional criteria have been established: clonal marrow plasmacytosis >10%, affected/unaffected light chain ratio >100, or more than one focal bone lesion on imaging [**1-2**]. Nearly 50% of patients have impaired renal function at diagnosis. The classic lesion in multiple myeloma is myeloma cast nephropathy, characterized by the precipitation of light chains in tubules. Kidney damage also includes conditions such as amyloidosis and Fanconi syndrome [**2**].

Patients are classified using the Durie-Salmon Staging System, which categorizes them into three groups based on tumor mass, with renal function defining low or high-risk subgroups [**3**]. Therapeutic decisions are based on this classification. Therefore, coordinated management by hematologists and nephrologists is essential. Chemotherapy protocols are tailored to age, comorbidities, and prognostic factors, but symptomatic treatment remains crucial. It targets dehydration, hypercalcemia, infections, and urine alkalinization [**4**]. Despite therapeutic advancements, it is a fact that MM remains incurable. While patient survival has increased, the median survival in MM is approximately six years [**5**].

Our study aims to investigate renal complications associated with MM in our population, determining their epidemiological, clinical-biological, therapeutic, and evolutionary profiles.

Patients and Methods:-

This is a monocentric, descriptive cohort study conducted over a 4-year period, from early April 2020 to late March 2024, in the nephrology and haematology departments of Souss Massa University Hospital Center of Agadir. We included all patients who developed renal complications at the time of diagnosis or during the follow-up of MM. MM was diagnosed in line with the new IMWG criteria. We evaluated the renal response to therapy for all patients using the IMWG standards [**6**] (**Table I**).

Tableau I:- Criteria for Defining Renal Response to Treatment According to the IMWG 2016 [6].

RenalResponse	**BeselineeGFR*** (ml/min/1.73 m²)	**Best CrClResponse**
Complete Response	< 50	≥ 60 ml/min
Partial Response	< 15	30-59 ml/min
Minor Response	< 15 15-29	15-29 ml/min 30-59 ml/min

CrCl: Creatinine Clearance. **eGFR**: estimated Glomerular Filtration Rate.

*eGFR is based on the Modification of Diet in Renal Disease formula, or the Chronic Kidney Disease Epidemiology Collaboration equation.

Our study included a total of 22 patients. We examined their demographic, clinical, biological, and radiological profiles, therapeutic choices, and haematological and renal outcomes over an average follow-up period of 20 months.

The results were entered and analysed using Jamovi software.

Results:-

Among 22 cases of MM with renal involvement included, the average age was 59.4 years (range: 29-78 years-old). The majority of our patients were aged 50 years or older (90%) (**Fig. 1**). The male-to-femalesex ratio was 1.44.

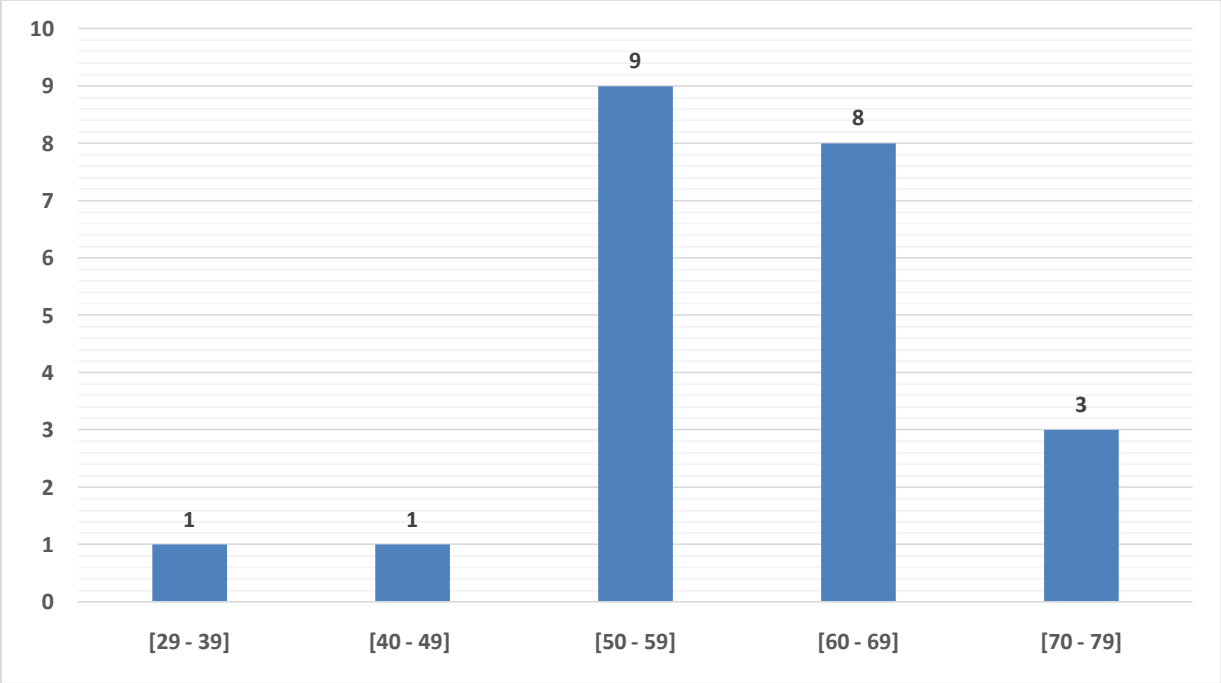

Figure 1:- Distribution of Patients by Age.

The average time between the onset of symptoms and diagnosis was two months, with a range of two weeks to six months. In 60% of cases, renal involvement was the initial indicator of the disease. All patients presented with general malaise, varying degrees of fatigue, anorexia and weight loss at the time of diagnosis. Followed by bone pain in 81% of cases and cutaneous-mucosal pallor in 77%. Neurological symptoms were observed in 68% of our patients, most commonly presenting as lumbosciatica and paresthesia of the lower limbs. Dehydration was noted in 60% of our patients (**Figure 2**).

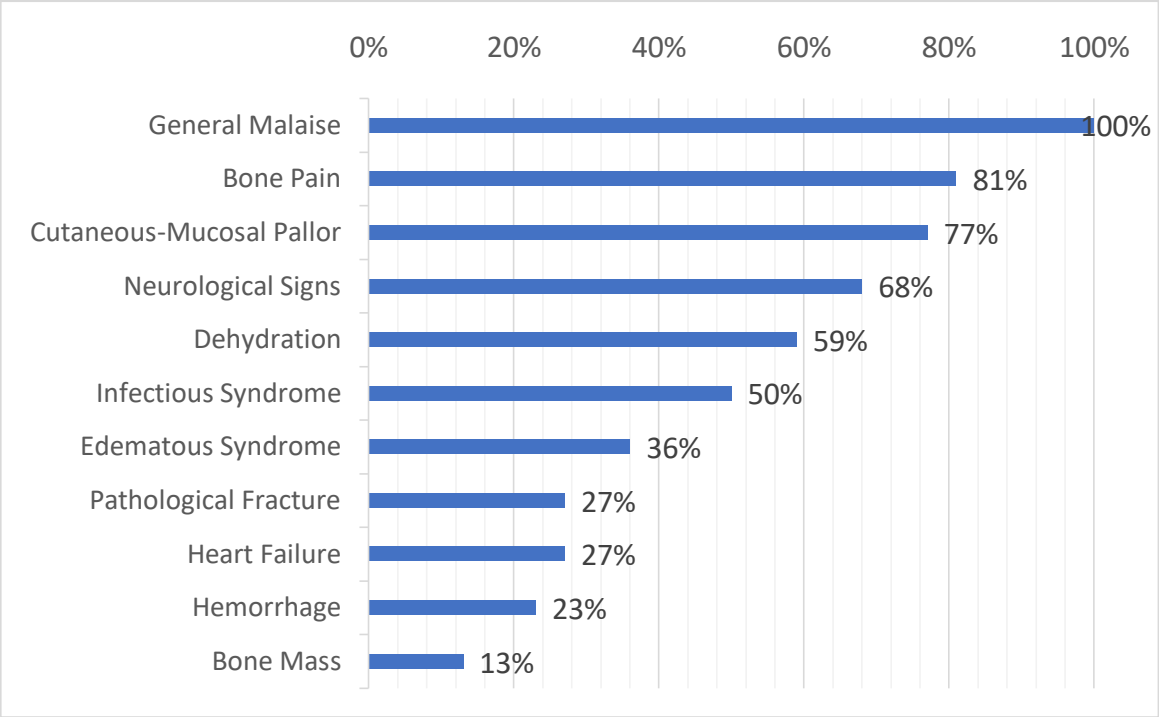

Figure 2:- Distribution of Clinical Signs Noted in Our Patients.

Biological abnormalities were characterized by anemia, which was present in all patients. It was severe, with haemoglobin levels below 7.5 g/dl in 50% of the cases. Additionally, hypercalcaemia was observed in the majority of cases (72.7%). Hyperproteinemia was also noted in 45% of patients, with levels exceeding 100 g/l being significant in 50% of these cases.

Hypoalbuminemia was found in more than three-quarters of the patients. The rest of the abnormalities observed in the biological assessment are shown in Table II.

Tableau II:- Biological Assessment of Our Patients.

Biologicalassessment		**Frequency (Percentage)**
Hemoglobin g/dl	<7,5	12 (54,5 %)
	7,5 – 10	5 (22,7 %)
	10-12	5 (22,7 %)
Leukocytes	Leukocytosis	11 (50 %)
Platelets	Thrombocytosis	1 (4,5 %)
	Thrombocytopenia	**8 (36,5 %)**
Calcium	Normal	6 (27,3 %)
	Hypercalcemia	**16 (72,7 %)**
ProteinLevel	Hyperproteinemia 80-100 g/l	**5 (22,7 %)**
	Hyperproteinemia>100 g/l	**5 (22,7 %)**
	Hypoproteinemia	6 (27,3 %)
AlbuminLevel	Hyperalbuminemia	1 (4,5 %)
	Hypoalbuminemia	**17 (77,3 %)**
		Mean (min-max)
SerumCreatinin (mg/l)		66 mg/l (14 – 223)
eGFR (Glomerular filtration rate) mL/min		16 ml / min (2 – 56)
β2Microglobulin(mg/dl)		23.9 mg/l (3.3 – 56)
Lactate dehydrogenase (U/L)		536 IU / l (250 – 1236)

A biological inflammatory syndrome was noted in 82% of cases, with an average C-reactive protein (CRP) level of 84 mg/l (range 11-202) and an average erythrocyte sedimentation rate (ESR) of 119 millimeters in the first hour. An

infection was present in half of the patients upon admission to the department. These were mainly urinary tract infections (60%) or respiratory tract infections (40%). Serum β2-microglobulin was measured in 16 patients (72.7%). It was high in the majority of cases (93.7%). The mean value was 23.9 mg/l (range 3.3 - 56 mg/l). Lactate dehydrogenase (LDH) levels were elevated in half of the cases, with an average of 536 IU/l (range 250 - 1236).

At the renal level, renal failure was present in all patients on admission to our unit. It was severe AKIN III in the majority of cases (77.2%), moderate in 13.6% and mild in 9% (**Figure 3**). The average creatinine level was around 66 mg/l (range 14-223).

All cases presented acute renal failure (ARF), associated with an underlying chronic diabetic nephropathy in 2 patients, and chronic obstructive pathology in 1 patient. Proteinuria was positive in 17 patients (77.2%), with an average of 1.24g/24h (0.6-12.3 g/24h).

Serum protein electrophoresis showed a monoclonal peak in 17 patients (77.3%). This was a gamma-globulin peak in 13 patients (59% of cases), a beta-globulin peak in 5 patients (22.7%), and an alpha-globulin peak in just one patient. Hypogammaglobulinemia was observed in 9 patients. The coexistence of two peaks on serum protein electrophoresis (SPE) was noted in two patients (**Fig 4**).

Serum protein immunofixation, performed in 21 out of 22 patients, identified free kappa light chains (FLC κ) in 13 patients (62%) and free lambda light chains (FLC λ) in 5 patients (23.8%). Both kappa and lambda light chains were found in three patients (14,2%).0 Bence Jones proteinuria was tested in 16 patients and was positive in 14 cases (87.5%).

Cytogenetic analysis, including FISH, was performed on 3 patients and did not reveal any genetic abnormalities.

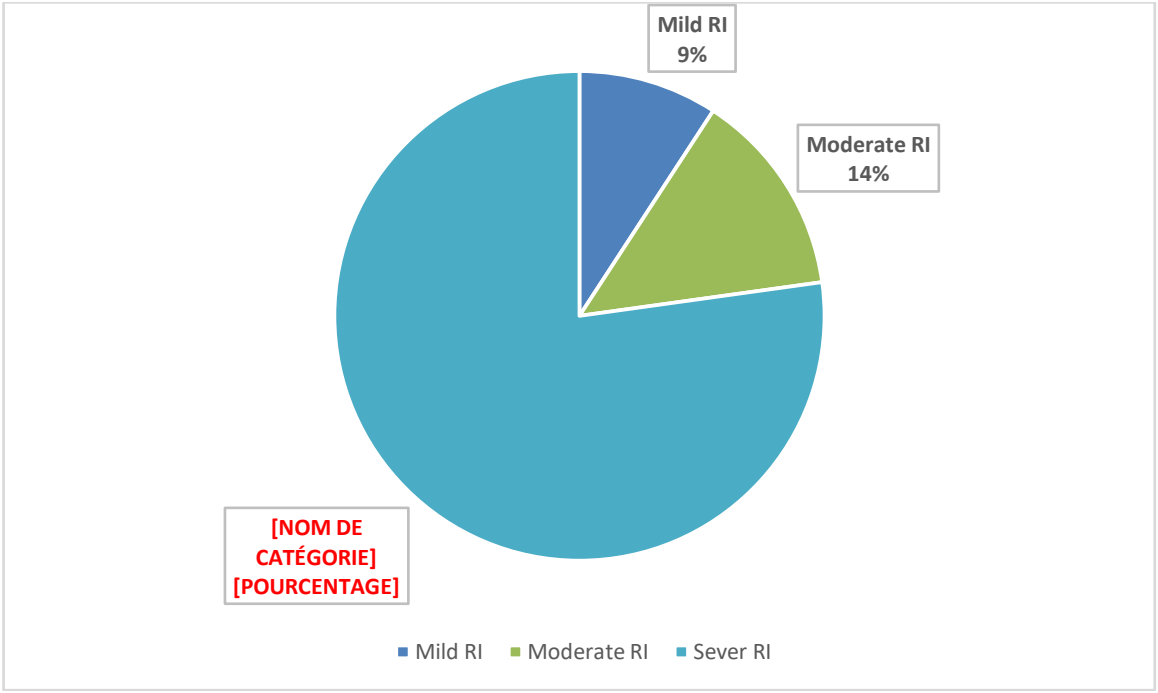

Figure 3:- Distribution of Renal Impairment (RI) by Severity.

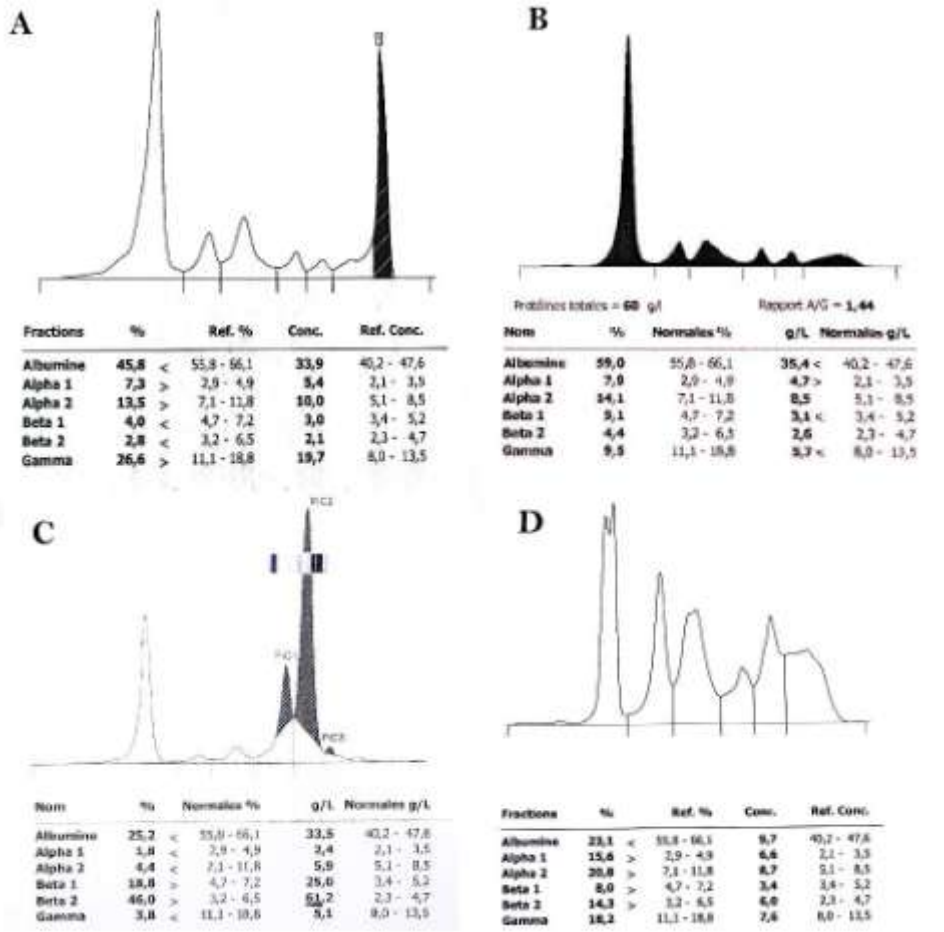

Figure 4: Serum electrophoretic profiles found in our patients: **A**: gamma globulin peak, **B**:hypogammaglobulinemia,**C**: 2 beta globulin peaks associated withhypogammaglobulinemia, **D**: 2 alpha and beta globulin peaks with bisalbuminemia.

Regarding renal involvement, in half of the cases we made the diagnosis of myeloma casts nephropathy (MCN) based on suggestive clinical and biological elements: a context favouring the formation of intratubular casts (dehydration), proteinuria composed mainly of light chains, positive Bence Jones proteinuria and low albuminuria on urine protein electrophoresis(**Figure5**). This entity (MCN) was confirmed by renal biopsy (RB) in one case. AL amyloidosis was identified in 6 patients (27.2% of cases), with one case confirmed by RB and 5 cases by biopsy of the accessory salivary glands.

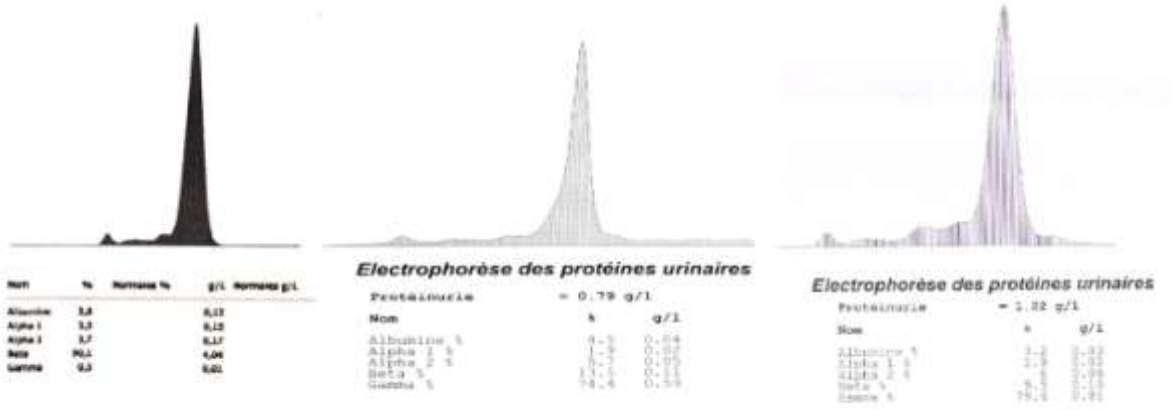

Figure 5:- Electrophoresis of urinary proteins carried out in our patients, showing low albuminuria and a predominance of gamma or betaglobulins in the urine.

Standard radiography showed osteolytic lesions in 77.3% of cases, associated with pathological fractures in 18%. A compression fracture image was observed in one patient. Lumbosacral CT-scans were performed in five patients, showing a lytic mass in three patients and diffuse osteolytic lesions in one patient. Thoraco-abdominopelvic CT scans were done in five patients, revealing multifocal lytic lesions in four of them. Lumbosacral MRI was performed in six patients. It showed spinal tumor infiltration in four cases, a vertebral compression fracture in one case, and lytic lesions in two patients. All our patients had high tumor burden myeloma (Salmon and Durie class 3B). The ISS prognostic classification was assessed in 16 patients. 13 of them (59%) were classified as stage 3, and three patients (13.6%) were classified as stage 2.

Therapeutically, 14 patients received level one analgesics. Four of them needed level 2 analgesics. Hypercalcemia treatment involved IV hyperhydration with isotonic saline in 16 patients (72.7%). Bisphosphonates, which slow bone resorption, were administered to six patients (59%). 16 patients received red blood cell transfusions (72.7%). Only one patient was also treated with erythropoietin. Dialysis was required in eight cases (36.3%).

Chemotherapy was administered as follows: the CTD protocol (cyclophosphamide, thalidomide, dexamethasone) in eight patients (36.3%), the VCD protocol (Velcade/bortezomib, cyclophosphamide, dexamethasone) in 45.5% of cases (10 patients), and the VMP protocol (Velcade, melphalan, prednisone) in two patients (9%). One patient died before starting chemotherapy, and one newly diagnosed patient had not yet initiated chemotherapy. Five patients (22.7%) underwent autologous stem cell transplantation.

Clinically evolutionary, a good hematologic response was achieved in 36% of cases. Renal response was complete in nine cases (40.9%), partial in 3 cases (13.6%), and minor in six cases (27.3%). Worsening renal function was observed in four patients (18.2%). Chronic dialysis was required for two patients (9%). For the other dialyzed patients (27%), they were weaned from dialysis. Infectious complications were noted in 14 patients during their follow-up (63.6%). Haematological toxicity from chemotherapy was observed in 9 patients (40%). With a follow-up of 22 months, 9 patients are in complete remission, 7 patients have died and 6 patients were lost to follow-up.

Discussion:-

Multiple myeloma is primarily considered to be a neoplasm of the elderly, with a peak incidence between 65 and 70 years of age. Diagnosis is rarely made before the age of 40 [**7**]. The average age of around 60 years and the male predominance observed in our study have also been reported in most series [**8, 9, 10**].

Multiple myeloma (MM) typically begins with the presence of an asymptomatic low-mass plasma cell clone, known as monoclonal gammopathy of undetermined significance (MGUS), which often progresses to an intermediate myelomatous state called indolent MM (or smoldering myeloma, SMM), which is also asymptomatic, before progressing to symptomatic MM [**10**]. The presence of MGUS is therefore the strongest risk factor associated with the development of MM [**11**]. The discovery of the disease at an advanced stage (large tumour mass) in our patients is explained by the delay in diagnosis in our context, due to the low economic level of the population and the unavailability of biological tests in certain regions of southern Morocco.

The revealing symptoms are predominantly bone pain (80% of cases), usually intense and located in sites of active hematopoiesis, namely the axial skeleton, impacting functional capacities. Bone involvement sometimes leads to pathological fractures or neurological symptoms due to spinal compression. General health deterioration is often present at an early stage [**2, 7, 12**]. In our study, bone pain was also very common (81% of the cases) and was associated with general health deterioration in all cases, thus worsening the condition of our patients.

Marrow infiltration by tumor plasma cells induces a maturation defect in other hematopoietic lineages. Anemia, classically normocytic and normochromic, is the most common sign observed in patients at diagnosis [**2**]. In our study, anemia was present in all cases, severe in half of the cases. We could not establish a link between the plasma cell count and the severity of the anemia. Hypercalcemia was found in 72.7% of our patients. Its frequency varies according to studies (**Table III**); Several mechanisms are implicated, the main one being an increase in osteoclastic activity induced locally by myelomatous cells. It can worsen renal impairment due to the dehydration it causes.

Tableau III:-Frequency of Hypercalcemia in Various Studies.

Studies	**Frequency**
Benmoussa M, Rabat 2021 [13]	28%

Laidouni O, Rabat 2020 [14]	50%
Idrissia A, Fès 2016 [15]	53%
Ben-Tebbaa I, Marrakech 2013 [10]	59,4%
Our study	72,7%

The SPEP (serum protein electrophoresis) showed a monoclonal gamma spike in 77.3% of cases. Similar results are described by other authors (**Table IV**). However, the absence of a monoclonal spike in a significant number of cases highlights the lack of sensitivity of this test for detecting monoclonal gammopathies, especially in light chain MM, necessitating the use of immunofixation of proteins. This was confirmed in a study of light chain multiple myeloma conducted in Rabat in 2020, where hypogammaglobulinemia was observed in 64% of cases and normal SPEP in 35.7% of cases [**14**].

Tableau IV:- SPEP Profile According to Studies.

Studies	Presence of a Monoclonal peak	Gammapeak	Hypo gamma
Ben-Tebbaa I, Marrakech 2013 [10]	84%	55%	-
Idrissia A, Fès 2016 [15]	63%	36,7%	-
Gaougaou N [16]	82%	69%	6%
Bouaouche S, Marrakech 2017 [17]	87,5%	67,5%	6,5%
Our study	77,3%	59%	41%

Approximately 55% of MM cases present with IgG type immunoglobulin, and 25% present with an IgA type. Regarding light chains, the κ type is twice as common as the λ type [**10**]. Our findings were consistent with those found in the literature (**Tab V**). Free light chains can appear in urine late when the kidney's reabsorption capacities are exceeded [**18**].

Table V:- Distribution of immunoglobulin isotypes in serum protein IF.

Study	IgG	IgA	LC Kappa
Bouaouche S, Marrakech 2017 [17]	67,5%	17,5%	12,5%
Gaougaou N [16]	56%	20%	10%
Idrissia A, Fès 2016 [15]	36,7%	22,2%	37,8%
Benmoussa M, Rabat 2021 [13]	40%	12,7%	45,5%
Our study	50%	20%	62%

According to the new IMWG criteria, the definition of renal involvement in symptomatic MM is based on a plasma creatinine level greater than 2 mg/dL or a glomerular filtration rate less than 40 mL/min [**19**]. The incidence of renal involvement in MM is fairly high, reaching 50% at diagnosis [**2, 20**]. Its severity can vary, sometimes necessitating immediate dialysis. The high frequency of acute renal failure in our patients (80%) compared to literature data, found in 21%, 40%, and 50% of cases in respective studies [**9, 21, 22**], reflects relatively early diagnosis in our department and excellent collaboration with the hematology department. Renal failure can be promoted by various factors, including dehydration, hypercalcemia, tubular precipitations of light chains, and the consumption of medicinal plants specific to our region [**23**]. Myeloma kidney disease is typically characterized by proteinuria consisting of more than 70% of light chains. Other components include low-molecular-weight proteins and albumin. The presence of albuminuria exceeding 1g/day is often linked to a glomerular dysfunction caused by amyloidosis or light chain deposition disease [**24**].

The necessity of performing a kidney biopsy for the diagnosis of myeloma kidney disease is controversial. Acute renal failure with an identified aggravating factor such as high tumor mass, hypercalcemia, or dehydration is sometimes considered sufficiently characteristic for a myeloma tubulopathy diagnosis without needing histological proof [**6**]. However, some authors argue/ discuss that the discovery of combined histological involvement in a significant number of kidney biopsies which can alter the prognosis, justifies the need for precise histological diagnosis [**25**]. In our study, only two patients underwent a kidney biopsy, which was indicated due to suspected renal amyloidosis. Congo red stain confirmed the diagnosis of amyloidosis in one case. The other case was identified as isolated myeloma kidney disease (**Figure 6**)

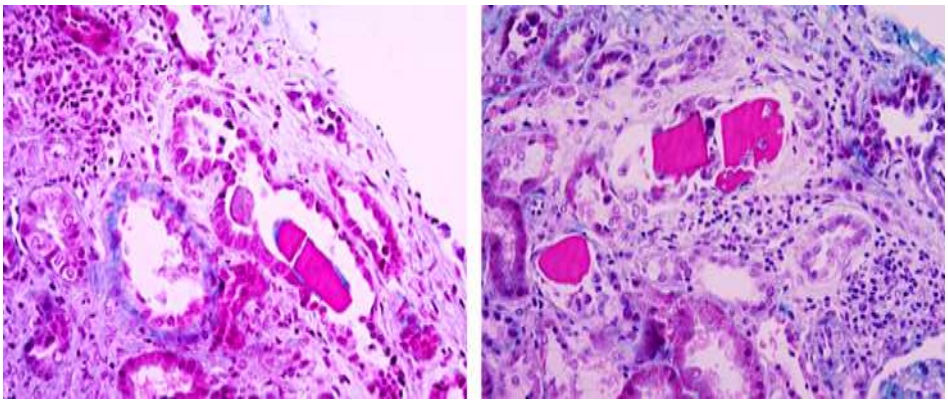

Figure 6:- Photomicrograph of the renal biopsy shows amyloid deposition, appearing as red-green cracked intra-tubular substance, with a surrounding macrophagic reaction and peritubular interstitial inflammatory infiltrate.

In the majority of multicenter studies, Stage IIIB is the most frequent in most series conducted in Morocco, with reported incidences of 54.5% [**13**], 89.2% [**9**], and 91% [**8**]. Our results are consistent with the literature and show a predominance of stage III at the time of diagnosis. This could be explained by delayed consultation or diagnosis.

Effective nephrological management of these patients requires rapid intervention to normalize renal dysfunction. The primary goal is to restore tubular flow, thereby reducing the concentration of monoclonal light chains and preventing intra-tubular obstruction [**26**]. Management strategies include hyperhydration with isotonic saline solution (0.9% NaCl) to maintain a high urine output (2 to 3 liters/day), while avoiding the use of loop diuretics. Treatment of hypercalcemia involves the use of bisphosphonates and possibly calcitonin if the initial response is insufficient. Stopping non-steroidal anti-inflammatory drugs and renin-angiotensin system blockers is also recommended [**27**]. The use of hemodialysis varies across different Moroccan series (**Table VI**), and our study observed its use in 36% of cases, which is often lower than reported in other series.

Tableau VI:- Use of Hemodialysis According to Various Series.

Study	**Use of Hemodialysis**
Bouterfas B [21]	56%
Kortobi L et al. [9]	64,3%
Benmoussa M, Rabat 2021 [13]	35,4%
Dimopoulos M A et al. [26]	10%
Our study	36%

The interest in clearing free light chains through plasmapheresis or hemodialysis using a very high-permeability membrane, in terms of improving renal function, remains controversial. While a dramatic reduction in free light chains in patients undergoing plasmapheresis or hemodialysis with a very high permeability membrane has been observed in several studies, there was no significant difference in overall survival, dialysis dependence, or improvement in renal response [**28**].

The use of new chemotherapeutic agents (such as thalidomide, bortezomib or lenalidomide) has significantly improved individual prognosis and outperformed conventional chemotherapies. Currently, it is estimated that around 60-70% of complete responses are achieved, with median survival up to 10 years [**29**].

The comparison of renal response should be made separately according to whether renal failure is acute or chronic. In our study, the outcome was favourable for patients with acute renal failure, with 40.9% of them achieving a complete response. (**Table VII**). This reflects the rapid intervention in our department.

Tableau VII:-Renal response according to studies.

Studies	**Complete Renal Response**	**Partial Renal Response**	**Minor Response**	**Progression to Chronic Kidney Disease**
Idrissia A, Fès 2016 [15]	21,3%	36,5%	**--**	**--**

Kortobi L et al [9]	9,5%	40,4%	--	31%
Benmoussa M, Rabat 2021 [13]	10,5%	36,8%	52,6%	25,5%
Ben-Tebbaa I, Marrakech 2013 [10]	41,8%	37,5%	--	--
Our study	40,9%	13,6%	27,3%	18,2%

Analyzing the factors associated with renal response was not possible due to the small size of our sample. Several factors have been associated with poor prognosis in the literature, including the severity of initial kidney failure and the rate of proteinuria[**30**]. A good renal prognosis has been observed in patients with an initial GFR greater than 30 mL/min and in those treated with Bortezomib, according to the works of Benmoussa et al. [**13**] and Dimopoulos et al. [**6**]. This prognosis depends on the early diagnosis, the initiation of an effective chemotherapy to quickly reduce the production of monoclonal immunoglobulins, and removing circulating light chains through throw proper techniques. Infectious complications are the most frequent. They are promoted by humoral immunity deficits and cellular immunity deficits, high-dose corticosteroids and chemotherapy-induced immunosuppression [**2**]. In our study, 14 patients had an infections complication during their follow-up (63.6%), most often a urinary tract infection (60%). Neurological complications were observed in 40% of patients, typically presenting as neurological deficits due to spinal compression.

According to studies, the causes of death in patients with multiple myeloma are represented by tumour progression (36.1%), cardiovascular problems (17.2%), and infections (14.7%) [**31**]. In our study, with a follow-up period of 22 months, 9 patients are in complete remission, 7 patients have died, and 6 patients were lost to follow-up.

Conclusion:-

Renal involvement is common in multiple myeloma and is often an indicator of high tumour burden. Effective management of renal complications requires early diagnosis and prompt initiation of treatment to restore renal function and improve outcomes. Advances in therapeutic agents have significantly improved the prognosis for patients with renal impairment associated with multiple myeloma. The use of High Cut-Off haemodialysis, which can more effectively remove light chains from the blood, has proved beneficial in further improving renal recovery. Moreover, treatment of infectious complications is critical. Continuous collaboration and communication between haematologists and nephrologists are crucial for optimizing care in patients with renal complications secondary to multiple myeloma.

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