Renal involvement as the first symptom of multiple myeloma

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Abstract

Background . Renal involvement is a common complication of multiple myeloma (MM). However, most studies have focused on renal failure in MM, and little information is available about the other renal manifestations in MM and their association with immunophenotypes and renal pathology. **Methods .** We retrospectively analyzed the clinical, laboratory and pathology data of 283 MM patients treated in Sichuan Provincial People's Hospital, West China, between January 1990 and May 2017. The patients were divided into a renal involvement group (n = 200) and a non-renal involvement group (n = 83). **Results.** In the renal involvement group, 90 (45.0%) patients were diagnosed with MM in the Nephrology department, and isolated proteinuria, renal failure and nephrotic syndrome were detected in 90(45.0%), 94 (47.0%) and 58 (29.0%) patients, respectively. 135 patients with renal involvement underwent immunofixation electrophoresis, and IgG, IgA, IgD, IgE, pure light chain and nonsecretory MM were detected in 52 (38.5%), 32 (23.7%), 1 (0.7%), 1 (0.7%), 45(33.3%) and 4 (3.0%) patients, respectively. 47 patients without renal involvement also underwent immunofixation electrophoresis, and IgG and IgA MM were found in 24 (51.0%) and 18 (38.3%) patients, respectively. Severe anemia and hypertension, hypercalcemia and pure light chain were more frequent in patients with renal involvement ($P < 0.05$). 9 patients with renal involvement were performed renal biopsy, and cast nephropathy, renal amyloidosis were proved in 5 and 4 patients, respectively. **Conclusions.** Renal involvement was common at MM diagnosis and had diverse clinical manifestations. The most common clinical manifestations include renal failure, isolated albuminuria and nephrotic syndrome. Nephrologists should rule out MM in patients presenting with renal involvement.

Introduction

Multiple myeloma (MM) is a neoplastic, plasma-cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, the presence of monoclonal protein in the blood or urine and associated organ dysfunction. Renal involvement is one of the main clinical manifestation threatening complication in MM patients[1, 2] Tsakiris DJ et al.[3] reported that MM was the most common neoplasm causing end-stage renal disease, and the first malignancy to be considered an indication for dialysis. Studies on renal involvement in MM tend to focus on renal failure. Impaired renal function is a marker of poor prognosis[4]. Multiple pathogenic mechanisms can contribute to kidney injury in MM patients; some mechanisms are the result of nephrotoxic monoclonal Ig deposition in the kidneys and others are independent of Ig deposition[5].

However, renal involvement in MM has diverse manifestations, which include isolated proteinuria, proteinuria combined with hematuria, renal failure and renal tubular interstitial involvement. Little is known about the proportion of the different manifestations of renal involvement in MM. Studies on the relationship between immunofixation electrophoresis and renal involvement in MM patients have mainly analyzed immune phenotypes and renal failure. Patients with light chains were significantly more prone to develop renal failure (42%–52%) than patients with IgG (22%) or IgA (31%)[6]. However, the relationship between other results of immunofixation electrophoresis and renal involvement is unclear. Furthermore,

we have found that most cases of MM with renal failure were reported from Departments of Hematology. Some MM patients with renal involvement as the first manifestation may be admitted in Departments of Nephrology, and the clinical features of these patients need to be studied. The first symptom of MM varies among patients, and therefore, MM can be diagnosed in different hospital departments. However, few data are available on the proportion of the various presenting symptoms of MM and of the different departments in which MM is diagnosed. In addition, little information is available on MM with renal involvement in the Chinese population. Therefore, to explore the incidence, manifestations of renal involvement, clinical, pathological characteristics and immunofixation electrophoresis features in MM in the Chinese population, we retrospectively studied 283 MM patients admitted to the Sichuan Provincial People's Hospital in West China, between January 1990 and May 2017. Here, we present the results of our analysis.

Materials And Methods

This study involved 283 MM patients who were treated in Sichuan Provincial People's Hospital, West China, between January 1990 and May 2017. Our study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital.

MM was diagnosed if any two of the following criteria were met: at least 10% clonal plasma cells in the bone marrow, serum or urinary monoclonal protein and radiographic evidence of osteolytic skeletal lesions[7]. In patients with true nonsecretory myeloma, the diagnosis was based on the presence of 30% monoclonal plasma cells in the bone marrow or the presence of a biopsy-proven plasmacytoma[7]. The clinical stages of the patients were classified according to the staging system of Durie-Salmon[8]. Only patients without previous diagnosis of MM were included into analysis. Patients with persistent proteinuria, hematuria, nephrotic syndrome, acute renal injury (AKI) and renal failure were clinically diagnosed with myeloma nephropathy. And patients with evidence of other renal diseases were excluded (for example advanced diabetes and hypertension with possible nephropathy, analgesic drug abuse, lupus, rheumatoid diseases, etc.) Proteinuria is defined as urine ACR values ≥ 30 mg/g or $>1+$ proteinuria on dipstick[9]. Nephrotic syndrome is defined as ACR values ≥ 2000 mg/g (≥ 200 mg/mmol) or $>3+$ proteinuria on dipstick with serum albumin <25 g/L (25 g/L). Hematuria is defined as the presence of red blood cells in the urine—including gross hematuria and microscopic hematuria (as defined as greater than or equal to 3 RBCs per HPF)[10]. AKI is defined as increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 hours; or increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours[11]. According to the International Myeloma Working Group diagnostic criteria, renal failure was also defined as a serum creatinine level ≥ 177 μ mol/l[12].

Clinical parameters such as the department in which the diagnosis was confirmed, gender, age, blood pressure, hemoglobin, blood urea nitrogen, serum creatinine, total protein, albumin, globulin, calcium, blood uric acid, urine routine and 24-h urinary protein were collected at the time of diagnosis. The percentage of plasma cells in the bone marrow, radiographic detection of lytic bone lesions in the skull

and pelvic bones and results of serum immunofixation electrophoresis and renal biopsy were also recorded. Patients were divided into a renal involvement group ($n = 200$) and a non-renal involvement group ($n = 83$) according to their renal clinical manifestations and laboratory findings.

Statistical analysis was performed using a standard statistical software package (SPSS 22.0, SPSS Inc.).

Continuous variables were expressed as mean and standard deviation. Categorical variables were presented as median with interquartile ranges (IQR). The values between groups were analyzed by independent sample T test and non-parametric test. P values < 0.05 were considered statistically significant.

Results

Clinical characteristics of MM with or without renal involvement

The departments in which the diagnosis of MM was confirmed have been shown in Table 1. In the renal involvement group, 90 (45.0%) patients were admitted to the Department of Hematology, 90 (45.0%) patients were admitted to the Department of Nephrology and 12 (6.0%) patients were admitted to the Department of Orthopedics. The remaining patients were admitted to various departments, such as Oncology and Cardiology. In the non-renal involvement group, 56 (67.5%) patients were admitted to the Department of Hematology, 17 (20.5%) to the Department of Orthopedics and 6 (7.2%) to the Department of Oncology.

We compared the clinical characteristics at the time of diagnosis between the MM patients with and without renal involvement (Table 2). Patients with renal involvement had a higher systolic blood pressure (130.2 ± 18.7 mmHg vs. 122.7 ± 14.2 mmHg, $P = 0.002$), a lower hemoglobin level (84.9 ± 22.9 g/l vs. 94.1 ± 28.7 g/l, $P = 0.008$) and a higher calcium level (2.4 ± 0.4 mmol/l vs. 2.3 ± 0.2 mmol/l, $P = 0.012$) than the levels in patients without renal involvement. Stage III disease was present in 110 (55.0%) patients in the renal involvement group and only 30 (36.2%) patients in the non-renal involvement group. No significant differences were detected in gender, age, albumin, proportion of plasma cells and incidence of bone destruction between patients with and without renal involvement.

Characteristics of renal involvement in MM

We have summarized the incidence and manifestations of renal involvement in MM in Table 3. Renal involvement was present in 200 (70.7%) of the total 283 patients at the time of diagnosis. The most common manifestation of renal involvement was proteinuria and/or hematuria: 90 (45.0%) patients presented with isolated proteinuria and 67 (34.0%) with proteinuria and hematuria (including 58[29.0%] patients with 24-h urinary protein excretion ≥ 3.5 g). In addition, 94 (47.0%) patients presented with renal failure(including 26[13%]patients presented with AKI). Some patients presented with only microscopic hematuria, and some non-diabetic patients presented with urinary sugar excretion.

Characteristics of immunofixation electrophoresis and renal involvement

A total of 182 patients underwent immunofixation electrophoresis. The results of immunofixation electrophoresis in patients with and without renal involvement have been summarized in Table 4. In the renal involvement group, 135 patients underwent immunofixation electrophoresis, and IgG, IgA, IgD, IgE, nonsecretory and simple light chain was detected in 52(38.5%), 32(23.7%), 1(0.7%), 1(0.7%), 4(3.0%) and 45(33.3%) patients, respectively. In the non-renal involvement group, 47 patients underwent immunofixation electrophoresis; IgG, IgA, IgD, nonsecretory and simple light chain disease was detected in 24(51.0%), 18(38.3%), 2(4.3%), 1(2.1%), and 2(4.3%) patients, respectively. There have found statistically significant in the distribution of λ chain disease between renal involvement and no- renal involvement group. No significant differences were observed in the distribution of IgG and IgA disease between the two groups. We further analyzed the relationship between clinical and immune phenotypes among the 135 patients with renal involvement who underwent immunofixation electrophoresis. We found that patients with IgA disease presented with mainly proteinuria and renal failure, while patients with pure light chain disease, whether κ or λ chain disease, presented with significantly proteinuria with hematuria, increased 24-h urinary protein excretion and renal failure (Table 5).

Characteristics of renal pathology and renal involvement

There were 9 patients with renal involvement underwent renal biopsy. The results of renal biopsy have been summarized in Table 6. In the cast nephropathy group, 24-h urinary protein 8.5 ± 1.9 (g/24h), was higher than that in amyloidosis group. The patients with cast nephropathy had a higher calcium (2.3 ± 0.2 mmol/l vs. 2.0 ± 0.1 mmol/l) and creatinine level ($325.4 \pm 344.5 \mu\text{mol/L}$ vs. 71.8 ± 9.8) than the levels in patients with renal amyloidosis. In the cast nephropathy group, the serum immunofixation electrophoresis detected only simple light-chain, while immunoglobulin in amyloidosis group, IgG type, Simple light-chain type and non-secretory were detected in 1(25.0%), 2(50.0%), and 1(25.0%), respectively.

Discussion

MM is an age-related disease. In most studies, the reported age at onset is approximately 65 years. [Palumbo A et al.\[13\]](#) reported only 37% of patients with newly diagnosed disease are aged < 65 years, 26% are aged 65-74 years, and 37% are aged $\geq$ 75 years. [Jalaeikhoo H et al. \[14\]](#) reported the mean age was 61.98 ± 11.44 years (range = 30–88 years), and the male: female ratio was 1.73. Our results were consistent with these findings: in our study, the median age at onset was 63 years, and the male: female ratio was 1.5:1. The youngest patient in our study was 36 years old.

In our study, 90(45.0%) patients were admitted to the Department of Nephrology. And MM patients with renal involvement as the first symptom often do not exhibit the typical clinical manifestations of myeloma, such as hyperglobulinemia. From the Table 2, we could find that patients with renal involvement had a lower globulin level than the levels in patients without renal involvement. In the non-renal involvement group, 17(20.5%) patients presented with bone pain as the first manifestation and were admitted in the Department Orthopedics. Other patients were admitted in the Departments of Oncology,

Cardiology, Ophthalmology, Neurology, etc. The reason for this diversity in symptoms is that amyloid deposition in different organs or tissues causes dysfunction of these organs and tissues and leads to specific symptoms. In an analysis of light chain deposition disease (LCDD), Pozzi C et al.[15] found that 35% of LCDD cases were associated with extrarenal manifestations involving the heart (21%), which presented as congestive heart failure and arrhythmias, and the liver (19%), which could lead to portal hypertension. Involvement of the lung (pulmonary cystic disorder), gastrointestinal tract and neurological system was less frequent. The above findings indicate that the presenting symptoms of MM are diverse and can easily be misdiagnosed; therefore, every physician should be familiar with these symptoms.

Renal failure in MM is one of the most common complications, and 50% of MM patients are reported to have renal failure at the time of diagnosis[16, 17]. Jalaeikhoo H et al.[14] reported that in a group of 345 patients, serum creatinine levels were (2.04 ± 2.56) mg/dL, range in $(0.6-26.6)$ mg/dL. MacLennan IC et al.[18] reported that in a group of 1,205 patients, serum creatinine levels were $>130 \mu\text{mol/l}$ in 42% of patients, $>200 \mu\text{mol/l}$ in 20% and $>300 \mu\text{mol/l}$ in 12%. Korbet SM et al.[19] reported that renal insufficiency (serum creatinine of ≥ 1.3 mg/dl) is found at presentation in almost 50% of patients with myeloma, and severe renal insufficiency (serum creatinine ≥ 2.0 to 2.5 mg/dl) is seen in ≈ 15 to 20% of cases. In our study, however, the most common type of renal involvement was proteinuria and/or hematuria, followed by renal failure. In all, 94 (47.0%) patients presented with renal failure (including 26[13%] patients presented with AKI, the result is similar to those previously reported[16-18]. Moreover, MM patients with renal involvement had a higher degree of anemia, hypercalcemia and hypertension than patients without renal involvement. The incidence of stage III disease was also significantly higher in the renal involvement group than in the non-renal involvement group. These data suggested that MM with renal involvement is a more serious condition, and this conclusion is consistent with the findings of other studies[18]. Suzuki K et al.[20] reported that hypercalcemia associated with osteolysis by myeloma cells is also causes of renal dysfunction.

We analyzed the relationship between renal involvement and the results of immunofixation electrophoresis. In total, 182 patients, of which 135 were in the renal involvement group, underwent immunofixation electrophoresis. IgG, IgA, IgD, IgE nonsecretory and simple light chain was present in 52, 32, 1, 1, 4 and 45 patients, respectively, in the renal involvement group. IgG and IgA MM was found in 24 and 18 patients in the non-renal involvement group. Greipp PR et al.[8] reported the immunophenotyping results of 10,750 MM patients. They found that the IgG type accounted for 60% of patients, while the IgA, IgD and light chain types accounted for 24%, 3% and 11% of patients; the remaining 2% of patients had other immunophenotypes. Immunofixation electrophoresis of large samples of MM serum from abroad showed that IgG type accounted for 52%, and the IgA, IgM, IgD, kappa, and lambda types accounted for 21%, 0.5%, 2%, 9% and 7% of patients[21]. Our results were similar to these findings; the main immunophenotype of MM was IgG, followed by IgA and pure light chains.

Next, we analyzed the association of immunofixation electrophoresis results with clinical phenotype in patients with renal involvement. We found that 19 (36.5%) of the 52 patients with IgG MM and 22 (68.8%) of the 32 patients with IgA MM in the renal involvement group presented with renal failure. 11(21.2%)

patients with IgG MM were presented with AKI. In this group, patients with pure light chain types (n = 45) presented with massive proteinuria and renal dysfunction, and 20 (44.4%) of these patients had a 24-h urinary protein excretion of >3.5 g/24 h. Korbet SM et al. reported proteinuria is observed in ~80% of cases, it most often consists of light chains, and light-chain proteinuria can be massive (~10 g/d)[19], which was higher than our study. In the literature, MM presenting as nephrotic syndrome is not common, although light chain and IgD MM can present as nephrotic syndrome[22]. It has been reported that patients of MM produce only light chains account for 40–60% of severe myeloma-associated kidney injury[23]. Consistent with this, our data also showed that patients with pure light chain MM were more prone to renal failure. The major cause of renal failure in patients with pure light chain disease is the overproduction of nephrotoxic light chains. Heher EC et al.[5] reported that mechanisms are the result of nephrotoxic monoclonal Ig deposition in the kidneys and others are independent of Igs. However, in our data 36.5% patients with IgG MM and 68.8% patients with IgA MM in the renal involvement group presented with renal failure, indicating that the development of renal failure is not dependent solely on the concentration of light chains. Wirk B et al.[24] reported that patients with large amounts of serum free light chains can have normal renal function, and patients with small concentrations of serum free light chains can present with renal failure. IgD and IgE overproduction is rare in MM. Only one patient in our study had IgD and IgE MM, which manifested as isolated proteinuria and renal failure. Tsakiris DJ et al.[3] reported that IgD MM is almost invariably associated with Bence Jones light chain proteinuria and renal failure.

Renal biopsies in MM patients with renal dysfunction help defining the types of renal injury, which can influence the extent of aggressive therapy and predict possible outcome[25]. The single center of Mayo Clinic analyzed 190 cases of multiple myeloma kidney pathology, and the results showed that MCN accounted for 45%, renal amyloidosis 29%, and light chain deposition 26%[26]. Su YT et al.[27] reported that the 46 cases of MM, cast nephropathy, renal amyloidosis and light-chain deposition disease accounted for 52.2%, 32.6%, and 4.3% patients, respectively. In our data, 9 patients with renal involvement were performed renal biopsy, cast nephropathy and renal amyloidosis were proved in 5 and 4 patients, respectively. 4/80.0% cases of light chain cast nephropathy were presented with AKI.

The main limitation of our study was that there was small sample size underwent renal biopsy. In our cohort, if a clinical diagnosis have already been established by other ways(eg, diagnosis of MM based on bone marrow findings and lytic bone lesions), nephrologist may not recommend MM patients with renal involvement undergo renal biopsy. Diagnosis of multiple myeloma does not require renal biopsy, however, a biopsy based diagnosis is important in the evaluation of patients with myeloma because each of the renal lesions has its own therapeutic and prognostic implications. In the future, we will recommend that MM patients with renal involvement undergo routine renal biopsy in our department. Another limitation of our work was that our study was lack of the clinical follow-up data of MM patients. The effect of immunosuppression on both renal disease and the hematologic disease and the prognostic effect of different clinical and histopathological parameters in predicting end-stage renal disease were not discussed. Basit A et al.[28] reported that ISS stage and renal failure have a significant impact on prognosis of MM patients. In our study the most common type of renal involvement was isolated

proteinuria and/or hematuria. Is there also a bad renal prognosis among those patients who present with isolated proteinuria and/or hematuria at onset ? In future, we need to collect follow-up data and assess the prognostic significance of these clinical parameters.

Conclusions

In summary, this is the first study to report the proportion of MM patients who presented with renal involvement as the first manifestation and were admitted in the Department of Nephrology. These patients often did not exhibit the typical clinical manifestations of myeloma. We have also reported, in detail, the characteristics of immunofixation electrophoresis, and manifestations of renal involvement. These data should help nephrologists have deeper understanding of MM associated with renal involvement.

Abbreviations

MM: multiple myeloma

MCA: myeloma cast nephropathy

LCDD: light chain deposition disease

AKI: Acute renal injury

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital (Chengdu, China), and all the patients signed informed consents to participate in this study.

Consent for publication

Not applicable.

Availability of data and material.

All data and material were obtained from Sichuan Provincial People's Hospital.

Competing interests

The authors report no conflicts of interest.

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Authors' contributions

Data collection (Yongjing D, Wei Wang, Ping Zhang, Xiang Zhong, Chen Shasha), study design (Wei Wang, Guisen Li, Li Wang), statistical analyses (Yongjing D, Wei Wang), writing (Yongjing D & Wei Wang).

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Tables

Table 1. Hospitals departments in which multiple myeloma was diagnosed

Departments	Renal involvement group (n=200)	Non-renal involvement (n=83)
Hematology	90[45.0%]	56[67.5%]
Nephrology	90[45.0%]	0[0%]
Orthopedics	12[6.0%]	17[20.5%]
Oncology	2[1.0%]	6[7.2%]
Cardiology	2[1.0%]	1[1.2%]
Ears nose throat	1[0.5%]	0[0%]
Ophthalmology	0[0%]	1(1.6%)
Neurology	0[0%]	1(1.6%)
Ache branch	1[0.5%]	0[0%]
Urinology	1[0.5%]	0[0%]
Endocrinolgy	1[0.5%]	0[0%]

Table 2. Clinical characteristics of multiple myeloma patients with and without renal involvement

	Renal involvement group(n=200)	Non-renal involvement(n=83)	<i>P</i> value
Age (years)	62.9±9.5	63.0±11.5	0.866
Systolic blood pressure (mmHg)	130.2±18.7	122.7±14.2	0.002
Diastolic blood pressure (mmHg)	77.1±10.3	73.5±9.6	0.818
Hemoglobin (g/L)	84.9±22.9	94.1±28.7	0.008
Total protein (g/L)	77.3±22.5	84.8±16.8	0.333
Albumin (g/L)	35.6±6.8	37.0±8.6	0.219
Immunoglobulin (g/L)	41.6±15.1	47.2±18.5	0.575
Calcium (mmol/L)	2.4±0.4	2.3±0.2	0.012
Bone marrow plasma cell (%)	30.2±17.9	32.7±19.9	0.186
Soft tissue lesions (%)	133(66.5%)	54(65.1%)	0.890
Clinical stage (%)			
	33(16.5%)	33(39.8%)	<0.01
	57(28.5%)	20(24.0%)	0.378
	110(55.0%)	30(36.2%)	0.004

Table 3. Clinical manifestations of renal involvement in multiple myeloma (n = 200)

Clinical manifestation	Incidence (%)
Isolated proteinuria	90(45.0%)
Proteinuria with hematuria	67(34.0%)
Nephrotic syndrome	58(29.0%)
Isolated microscopic hematuria	11(6.0%)
Renal failure	94(47.0%)
AKI	26(13.0%)
Urinary glucose positive	7(3.5%)

Table 4. Distribution of immune phenotypes in multiple myeloma patients with and without renal involvement

	Renal involvement group (n = 135)	Non-renal involvement (n = 47)	<i>P</i> value
IgG	52(38.5%)	24(51.0%)	0.169
IgA	32(23.7%)	18(38.3%)	0.060
IgD	1(0.7%)	2(4.3%)	0.164
IgE	1(0.7%)	0(0%)	
npa	24(17.8%)	0(0%)	
nlda	21(15.6%)	2(4.3%)	0.045
n-secretory	4(3.0%)	1(2.1%)	1.000

Table 5. Relationship between clinical phenotypes and results of immunofixation electrophoresis in the renal involvement group

	Isolated proteinuria	Proteinuria with hematuria	Nephrotic syndrome	Renal failure	AKI
	15(28.8%)	18(34.6%)	9(17.3%)	19(36.5%)	11(21.2%)
	11(34.4%)	7(21.9%)	8(25.0%)	22(68.8%)	2(6.3%)
	1(100.0%)	0(0%)	0(0%)	0(0%)	0(0%)
	0(0%)	0(0%)	0(0%)	1(100.0%)	0(0%)
na	5(20.8%)	10(41.7%)	13(54.2%)	11(45.8%)	4(16.7%)
bda	8(38.1%)	10(47.6%)	7(33.3%)	13(61.9%)	2(9.5%)
	2(50.0%)	1(25.0%)	0(0%)	1(25.0%)	0(0%)
story					

Table 6. Relationship between clinical phenotypes and results of renal biopsy in the renal involvement group

	Cast nephropathy	Renal amyloidosis
	N=5	N=4
Male (%)	3(60.0%)	1(25.0%)
Age (years)	52[50.5,62]	57(41,65.5)
Hemoglobin (g/L)	100.2±27.7	123.7±15.5
24-h urinary protein(g/24h)	8.5±1.9	1.8±0.5
Creatinine (μmol/L)	325.4±344.5	71.8±9.8
Globulin (g/L)	28.4±10.4	24.5±4.7
Calcium (mmol/L)	2.3±0.2	2.0±0.1
Bone marrow plasma cell(%)	9.9±5.1	8.9±7.1
Bone lesions (%)	2(40.0%)	1(25.0%)
Clinical stage (%)		
I	1(20.0%)	3(75.0%)
II	3(60.0%)	1(25.0%)
III	1(20.0%)	0(0%)
Immune phenotypes		
IgG	0(0%)	1(25.0%)
Simple light-chain type	5(100.0%)	2(50.0%)
Kappa	3(60.0%)	2(50.0%)
Lambda	2(40.0%)	0(0%)
Non-secretory	0(0%)	1(25.0%)