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Renal manifestations in multiple myeloma and in primary amyloidosis

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ONE of the important clinical features of plasmacytic dyscrasias is the frequency of renal complications.[1] In patients who have multiple myeloma, acute or chronic renal failure may be produced by the precipitation of Bence Jones (light chain) proteins in the renal tubules. Moreover, patients with this disease are subject to a number of other renal abnormalities, including hypercalcemia, hyperuricemia, infection, and amyloid deposition in the glomeruli. Primary amyloidosis, another plasma cell dyscrasia, is frequently manifested as a nephrotic syndrome. Multiple myeloma and primary amyloidosis have been grouped together for the purpose of this report because of their close relation.[2-4] Waldenstrom's macroglobulinemia may have renal complications resembling those of multiple myeloma[5] but will not be included in this review.

Material and method of study

The records of 72 consecutive cases of multiple myeloma and 14 cases of primary amyloidosis seen at the Cleveland Clinic between August 30, 1965, and August 1, 1968, were reviewed. Particular attention was given to renal excretory function, degree and type of proteinuria, serum protein electrophoresis, serum calcium levels, as well as biopsy or autopsy findings. Proteinuria of any degree was recorded when it was more than 0.1 g per 24 hours. This low level of proteinuria was selected because of the finding of Bence Jones proteins in small amounts in the urine of some patients. The electrophoresis was done on paper at a pH of 8.6 with a barbital buffer. The urine specimens were first concentrated by pervaporation.

All cases that satisfied the usual criteria for the diagnosis of multiple myeloma were classified as such, regardless of the presence or absence of amyloid. Patients with primary amyloidosis had the diagnosis substantiated by biopsy in all cases and had no evidence of multiple myeloma.

The median survival was expressed in months from the time of diagnosis. Although a significant number of the patients are still living, the survival times are presented to be able to compare the influence of various complications.

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Results

Proteinuria was found in 51 (70 percent) of the 72 patients with multiple myeloma, and in 12 (86 percent) of the 14 patients with primary amyloidosis (*Table 1*). In patients with multiple myeloma the quantity of protein was generally small to moderate, being less than 4 g per 24 hours in 41 (80 percent) of the 51 patients with proteinuria. In patients with primary amyloidosis, the proteinuria was generally moderate to heavy, and was more than 4.1 g per 24 hours in 6 (50 percent) of the 12 patients with proteinuria. In five cases of amyloidosis, urine protein electrophoresis was performed and the protein was chiefly albumin with no peak in the globulin region. The urine protein electrophoresis in multiple myeloma showed a peak indicative of Bence Jones protein in 34 (90 percent) of 37 patients tested. The three patients whose patterns did not show a peak on urine protein electrophoresis had proteinuria of 0.7, 0.37, and 0.29 g per 24 hours. In two of those patients there was insufficient protein for electrophoresis. In the other patient who had 0.7 g protein per 24 hours, the urine protein electrophoresis showed both albumin and globulin with no monoclonal peak. The heat test for Bence Jones protein was positive in specimens of only 20 (53 percent) of 38 of the patients tested, all of whom had proteinuria.

A clinical diagnosis of nephrotic syndrome,[6] as manifested by proteinuria of more than 6 g per 24 hours and edema, was made in four (23 percent) of the 14 patients with primary amyloidosis, but in only two patients (2.8 percent) among the 71 with multiple myeloma. All patients had biopsy proved amyloid deposition in the renal glomeruli.

Renal insufficiency, as judged from a blood urea nitrogen value of more than 30 mg per 100 ml, and a serum creatinine content of more than 2.0 mg per 100 ml, was found in four (28 percent) of 14 patients with primary amyloidosis. Subsequently, in six of the other 10 patients renal insufficiency developed and they died of uremia. Renal insufficiency was found in 17 (24 percent) of 72 patients with multiple myeloma at the time of the initial examination. In eight of these patients, the azotemia was associated with

Table 1.—Incidence and degree of proteinuria in 86 patients with plasmacytic disease

Proteinuria	Disease, number of patients	
	Multiple myeloma (72 patients)	Amyloidosis (14 patients)
Mild (0.1 to 1.0 g/24 hours)	26	4
Moderate (1.1 to 4.0 g/24 hours)	15	2
Heavy (>4.0 g/24 hours)	10	6
	51 (70 %)	12 (86 %)

only Bence Jones proteinuria. Three of these patients died shortly after admission to the hospital, but the conditions of the other five patients were either improved or stabilized for a significant period. One patient with multiple myeloma had azotemia on the basis of only hypercalcemia (serum calcium content more than 11.5 mg per 100 ml), which was readily reversed by treatment. Six patients with azotemia had both Bence Jones proteinuria and hypercalcemia. In all of those patients renal insufficiency was reversed or stabilized. Renal insufficiency in the other two patients with multiple myeloma was due to prostatic hypertrophy in one patient and of unknown cause in the other.

Azotemia occurred subsequently in seven patients with multiple myeloma. In two patients with Bence Jones proteinuria and in four patients with both Bence Jones proteinuria and hypercalcemia, treatment was unsuccessful and the patients died with renal insufficiency. In one patient with late azotemia, associated both with hypercalcemia and with Bence Jones proteinuria there was a favorable response to treatment.

Among 65 patients with multiple myeloma who had a serum calcium determination there were 19 who each had a value of more than 11.5 mg per 100 ml. Among the 14 patients with primary amyloidosis, serum calcium was measured in only two and was normal in both patients. The hypercalcemia was accompanied by renal insufficiency in seven of the patients with multiple myeloma. In all but one instance, Bence Jones proteinuria was also present. Initial hypercalcemia was readily reversed with high fluid intake and administration of steroids. Hypercalcemia subsequently developed in five patients and in only one patient was it reversed with treatment. Serum uric acid values were high in three patients, but there were no complications of the hyperuricemia.

Specimens obtained by biopsy or at autopsy from the kidneys of 27 patients were available for histologic examination. Among the 14 patients with primary amyloidosis 11 had amyloid deposition in the renal glomeruli. In one patient there were changes of acute pyelonephritis which did not contribute materially to the cause of death. In one patient with generalized amyloidosis, acute cortical necrosis developed after an operation. Three patients with primary amyloidosis had normal renal biopsies and no evidence of renal insufficiency. In contrast, the renal histologic findings available in 13 patients with clinical multiple myeloma revealed amyloid deposition in the renal glomeruli of only two. The picture of "myeloma kidney" as described by Heptinstall,[7] was seen in seven patients, five of whom had azotemia. No renal pathologic changes were present in four patients with multiple myeloma, two of whom had azotemia.

The median survival (*Table 2*) in primary amyloidosis was five months regardless of the presence or absence of azotemia. Of the 10 patients without azotemia, two lived longer than two years, while none of the four patients with azotemia survived as long as 12 months. Among the 61

Table 2.—Comparison of survival times of patients with plasmacytic disease and various complications

Status	Multiple myeloma		Amyloidosis	
	Number of patients	Median survival time, months	Number of patients	Median survival time, months
All patients with adequate follow up	61	>14	14	5
Normal renal function (blood urea nitrogen <30 mg/100 ml; creatinine <2.1 mg/100 ml)	43	>15	10	5*
Azotemia (blood urea nitrogen >30 mg/100 ml; creatinine >2.1 mg/100 ml)	18	3	4	5
Proteinuria only	19	>19	12	5
Hypercalcemia	15	>17	0	--

* Two patients survived longer than 24 months.

patients with multiple myeloma whose progress was adequately documented, the median survival was 15 months. The survival was not influenced by the presence of proteinuria or hypercalcemia alone in the absence of azotemia. By contrast, the 17 patients whose presenting manifestations were symptoms of azotemia had a median survival of only three months.

Discussion

The presence of Bence Jones (light chain) proteinuria, often associated with renal failure, is one of the primary manifestations of multiple myeloma. By contrast, in primary amyloidosis the protein that is in the urine is albumin, although with careful immunologic study[3, 4] an abnormal paraprotein has been demonstrated in the urine or in the serum of the majority of these patients. Light-chain proteinuria may be detected by the heat test, which is much less sensitive than urine protein electrophoresis. In 10 instances in which the heat test was negative, the urine protein electrophoresis demonstrated the presence of Bence Jones protein. Paper electrophoresis also has the advantage of distinguishing albumin from globulin (light chain) which is helpful in the differential diagnosis. The light chains can then be further identified by means of immunoelectrophoresis.

Four patients with primary amyloidosis and two patients with multiple myeloma had the nephrotic syndrome. All six had amyloid deposition in the renal glomeruli. The nephrotic syndrome, however, has been reported to occur in association with multiple myeloma in the absence of amyloid deposition.[8]

Azotemia was common in the patients in the study and was present at the time of the initial examination in four patients with amyloidosis (25 percent), and in 17 patients with multiple myeloma (25 percent). In

patients with multiple myeloma and Bence Jones proteinuria, chronic renal failure usually develops, but acute renal failure may occur.[9, 10] In this series, proteinuria in the absence of renal insufficiency did not have an adverse effect on the median survival, but those patients with azotemia had a poor prognosis, the median survival being three months.

There were five patients with multiple myeloma and relatively acute renal failure. Three of those patients died as a result of the renal failure, and the condition of one patient was stabilized temporarily but death ensued one month later. The status of one patient was stabilized without dialysis and, at his last examination, 14 months after diagnosis, the serum creatinine level was 15.0 mg per 100 ml. The fifth patient recovered completely and is alive four years after diagnosis. Twelve patients with myeloma had moderate renal insufficiency at the time of the initial examinations. Two had azotemia not related to myeloma. The other 10 had azotemia secondary to Bence Jones proteinuria or hypercalcemia or a combination of these two entities. The condition of each of the 10 patients was stabilized with treatment.

The myeloma kidney, characterized by Bence Jones protein precipitates in the renal tubules, atrophy of the renal tubular cells, scattered inflammatory cells, and relatively normal glomeruli,[7] was present in 7 of 13 patients studied. The microscopic changes are seen in patients with renal failure associated with multiple myeloma, but the changes may also be found in some patients in whom there is no measurable impairment of renal function.

The mechanism of renal failure in multiple myeloma is thought to be the precipitation of Bence Jones protein in the renal tubules, which results in mechanical obstruction. However, renal insufficiency is not well correlated with the amount or duration of Bence Jones proteinuria in this series, azotemia being present in 16 of 38 patients with Bence Jones proteinuria. The picture of myeloma kidney was reversed in the majority of patients in this series and is potentially reversible even in advanced cases.[10]

The mechanism of renal failure in primary amyloidosis is probably a replacement of the normal parenchyma with amyloid deposition. In this series, 10 of the 14 patients with primary amyloidosis died from renal failure. The presenting symptoms of four patients were of azotemia, and in six renal insufficiency developed subsequently. Once azotemia developed in the patients with amyloidosis there was generally a progressively downhill course. The median survival was five months, regardless of the presence or absence of azotemia. The survival of those patients initially without azotemia, however, sometimes may be prolonged, as evidenced by two patients who lived longer than two years. Unfortunately there is as yet no effective treatment for primary amyloidosis.

Intravenous urography has been reported to precipitate renal failure in

patients with multiple myeloma,[11, 12] and this procedure is contraindicated in patients with Bence Jones proteinuria. There were no complications in the 12 patients in this series with Bence Jones proteinuria who underwent urography.

The adult Fanconi syndrome has been well documented[13] in association with multiple myeloma and light-chain proteinuria; there were no cases of the syndrome in the present series. The light chains are postulated to act as a specific toxin to the renal tubules.

Hypercalcemia was present in 19 patients (29 percent) with multiple myeloma. Hypercalcemia noted early in the course of multiple myeloma was often associated with mild to moderate renal insufficiency, but the serum calcium value returned to normal rapidly after treatment with steroids and fluid administration. When azotemia was found in association with hypercalcemia this did not appear to affect adversely the median survival of this group. The hypercalcemia in patients who were under treatment for multiple myeloma was quite resistant to therapy. As bed rest encourages a rise in serum calcium values, patients with multiple myeloma should be kept as mobile as possible with supportive measures, including analgesics, back braces, radiation to painful areas, and occasionally prophylactic surgical pinning of bone lesions.

The majority of patients with multiple myeloma in this series were treated with melphalan, or a combination of melphalan and prednisone, in large intermittent doses. A few patients were treated with daily doses of cyclophosphamide. The retrospective nature of this study precluded any comparison of the various regimens in regard to remission rate or survival time. Inasmuch as significant advances have been made in the treatment of multiple myeloma,[14-16] all patients, including those with renal insufficiency, should have the benefit of a vigorous trial on therapy.

Summary

A retrospective study was undertaken of the incidence and type of renal disease in 86 consecutive patients—72 with multiple myeloma and 14 with amyloidosis. Proteinuria was present in 51 (70 percent) of 72 patients with multiple myeloma, and in 12 (86 percent) of 14 patients with amyloidosis. The quantity of proteinuria, in general, was mild to moderate in patients with multiple myeloma, and moderate to heavy in those with amyloidosis. Bence Jones protein was detected in a total of 37 patients (43 percent). The heat test was insensitive, and the urine protein electrophoresis was more reliable for diagnosis. Hypercalcemia (serum calcium > 11.5 mg per 100 ml) was present in 17 patients (21 percent).

The median survival among 62 patients with multiple myeloma was 13 months. The median survival was not decreased in the presence of proteinuria or hypercalcemia. In contrast, those patients with azotemia (blood urea nitrogen > 30 mg per 100 ml) had a median survival of only three

months. Among the 14 patients with amyloidosis the median survival was only five months regardless of the presence or absence of azotemia. There is no known effective treatment for amyloidosis. In this series, initial azotemia in patients with multiple myeloma associated with Bence Jones proteinuria or hypercalcemia was usually reversible with treatment. Renal insufficiency that developed during the course of therapy was in general resistant to treatment.

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