Studies in multiple myeloma

II. Light chains

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In 1848 Bence Jones[1] first reported finding an abnormal protein in the urine of a patient with multiple myeloma. Since that time, tests for detection of this protein have been considered important in the clinical evaluation of patients with this disease. Recent studies have shown this protein to be identical with the light chains of immunoglobulin molecules. Immunoelectrophoresis has enabled investigators not only to detect light chains (L-chains) in serum and urine but to classify them into two major types: kappa and lambda. In a previous report, the general characteristics of multiple myeloma as observed in 98 patients were described.[2] This report documents the occurrence and distribution of light chains (both free and in association with intact Ig molecules) and their prognostic significance in the same group of patients.

Materials and methods

The material for this report was collected from 126 cases of monoclonal gammopathy evaluated from 1965 to 1972. There were 94 patients with myeloma proteins which could be typed for light chains (*Table 1*). Only cases of IgG, IgA, and Bence Jones myelomas were numerous enough for evaluation; two cases of IgD myeloma have been reported.[2]

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Table 1. Multiple myeloma; immunoglobulin classes and light chain types

Ig class	Number	Kappa	Lambda
IgG	43	31	12
IgA	27	13	14
Bence Jones	22	10	12
IgD	2	0	2
Total	94	54	40

The clinical parameters evaluated, diagnostic criteria employed, and laboratory tests performed have been described.[2] Serum or urine specimens or both were analyzed by immunoelectrophoresis in ionagar using a barbital buffer at pH 8.6. Specific antilight chain antisera were obtained commercially* as well as prepared in the laboratory. In many cases, urine specimens were also analyzed with a Bence Jones heat test using the method of Putnam et al.[3] Most patients were treated with melphalan alone or in combination with other drugs.

Results

Incidence and distribution of light chains. The myeloma proteins of all patients included in the study were typed for light chains. The distribution by immunoglobulin class is illustrated in *Table 1*. The ratios of kappa to lambda were 2.6:1 in IgG, 1:1.1 in IgA myeloma and 1:1.2 in Bence Jones myeloma. The overall kappa to lambda ratio for the three major classes was 1.4:1.

In 79 cases, urine specimens were analyzed (*Table 2*). Free light chains were identified in 40, including all specimens from patients with Bence Jones myeloma. Compared with the overall distribution of kappa and lambda types, the ratio of free urinary kappa and lambda chains was reversed, being 1:1.4 (*Table 3*).

Comparison of immunoelectrophoresis to Bence Jones heat test. Urine specimens from 23 patients were analyzed for free light chains by both methods (*Table 4*). Using immunoelectrophoresis, free light chains were detected in three specimens judged negative by the heat test. One of these patients had IgG myeloma, one had IgA myeloma, and the third had Bence Jones myeloma.

Table 2. Incidence of light chains in urine

Ig class	Number	Positive	%
IgG	33	9	27
IgA	24	9	37
Bence Jones	22	22	100
Total	79	40	51

Table 3. Free light chains in urine

Ig class	Number	Kappa	Lambda
IgG	9	4	5
IgA	9	3	6
Bence Jones	22	10	12
Total	40	17	23

Table 4. Detection of light chains in urine

	Bence Jones heat test	Immunoelectrophoresis
Positive	13	16
Negative	10	7
Total	23	23

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Survival related to light chains. Three facets of this problem were studied: (1) survival according to light chain type; (2) survival related to light chain type in those with free light chains in the urine; and (3) survival related to the presence or absence of free urinary light chains (Bence Jones proteinuria) in patients with IgG or IgA myelomas. The time of risk was fixed at 2 years from the date of diagnosis to facilitate comparisons with the work of others. The selection of this time interval is somewhat arbitrary. When the data were analyzed, it became apparent that the numbers in each category were small, and that meaningful conclusions could only be made for survival by light chain type. Fifty patients were at risk for 2 years (*Tables 5 and 6*). Of these, 27 were kappa and 23 were lambda. More patients with type kappa M-proteins appeared to have 2-year survivals than patients with type lambda, although differences between immunoglobulin classes did exist. The number of patients in each category was so small that no meaningful statistical analyses could be performed.

Table 5. Light chain type and 2-year survival

Ig class	Kappa		Lambda	
	Alive	Dead	Alive	Dead
IgG (23)	9	6	1	7
IgA (14)	2	5	6	1
Bence Jones	5	0	3	5
(13)	—	—	—	—
Total (50)	16	11	10	13

Table 6. Light chain type and median survival

	Alive	Dead
Kappa (27)	32	13
Lambda (23)	44	9

Table 7. Light chains, kappa to lambda ratios

Ig class	Overall (92)	Urine (40)
IgG	2.6:1	1:1.2
IgA	1:1.1	1:2.0
Bence Jones	1:1.2	1:1.2
All myelomas	1.4:1	1:1.4

Discussion

The overall distribution of kappa and lambda light chains (*Table 1*) was compared with the distribution of light chains in the urine (*Table 3*). The overall kappa to lambda ratio for IgG myeloma was approximately 2.5:1, but when only urinary light chains were considered, the ratio was almost equal. Similar differences in the kappa to lambda ratio were apparent for light chains in IgA myeloma (*Table 7*). Excretion of free light chains in patients with IgG and IgA myeloma results from excessive production in the malignant plasma cell rather than from breakdown of the whole molecule in the serum.[4] These data appear to indicate that at least some malignant IgG- and IgA-producing plasma cells synthesizing lambda chains are more likely to make excessive amounts than those producing kappa chains. This finding has not been emphasized by others and it is difficult to evaluate its significance. Renal complications of multiple myeloma have been related to the amount and duration of free light chains excreted.[5, 6] In this series the appearance of lambda type light chains in patients

with renal disease would be expected more frequently, not because lambda chains are intrinsically more pathogenic than kappa chains, but because a greater percentage of patients with type lambda myelomas are at risk, i.e., have lambda type Bence Jones proteinuria. If this is true, the results of treatment directed toward the tumor cells should be the same in patients with renal complications regardless of light chain type.

There is no longer any doubt that methods such as immunoelectrophoresis, which rely on specific immunodiffusion techniques for identification, are more sensitive and slightly more specific for the detection of free urinary light chains than the Bence Jones heat test. Concentrations in micrograms per milliliter can be detected by immunoelectrophoresis, whereas levels at least 400 times higher must be present to give a positive heat test.[7] The Bence Jones heat test is, however, less expensive, faster, and somewhat easier to perform. The fact that much greater quantities of protein are necessary for a positive result can also aid in prognosis. Of the 23 specimens analyzed by the heat test, 13 were positive and 11 of these were from patients at risk 2 years. Six of the 11 (55%) died within 25 months of diagnosis. Of the 79 specimens examined by immunoelectrophoresis, 40 were positive, and 23 of these were from patients at risk 2 years. Only 9 of the 23 (39%) died within 25 months. A positive Bence Jones heat test, indicating a greater quantity of urinary protein, seems to be associated with a graver prognosis than a positive immunoelectrophoresis.

It has been stated that patients with IgG or IgA myelomas and Bence Jones proteinuria have a worse prognosis than those without Bence Jones proteinuria.[8, 9] As stated previously, the poor prognosis associated with Bence Jones proteinuria is probably more dependent on the amount and duration of light chain excretion than on the mere detection of light chains in random urine analyses. One of the most important factors in the detection of free light chains is the sensitivity of the procedure. When immunoelectrophoresis is used, Bence Jones proteinuria can be detected when only small amounts of free light chains are present and renal damage has not occurred. If treatment is introduced at this point urinary light chains may be decreased, renal damage may be forestalled, and survival prolonged.[10] Some investigators have shown that survival is much better correlated with objective evidence of renal insufficiency such as increased blood urea than with the presence of light chains.[6, 11]

It is the opinion of some investigators that patients with type lambda myeloma proteins, especially those with Bence Jones myelomas, are less likely to survive 2 years and have a poorer response to treatment[12-14] than those with type kappa myeloma proteins. Others do not support this opinion,[15, 16] but the data in *Table 5* appear to confirm it. Further analysis, however, leads to interesting conclusions which warrant additional comment.

Five of the 16 patients with type kappa M-proteins alive at 24 months died within 30 months compared with only one of the patients with type lambda. When these revised figures

Table 8. Light chain type and 30-month survival

Ig class	Kappa		Lambda	
	Alive	Dead	Alive	Dead
IgG (23)	7	8	1	7
IgA (14)	0	7	6	1
Bence Jones (13)	4	1	2	6
	—	—	–	—
Total (50)	11	16	9	14

are compared, the 30-month survival for all patients is essentially equal, with approximately 60% mortality in each group. The distribution by immunoglobulin class is illustrated in *Table 8*. The data for Bence Jones myeloma support the findings of Bergsagel et al.[13, 14] However, the numbers in each category are small, and any conclusions must remain tentative until more data can be collected. Although 2 years is the usual time interval used to evaluate cases of multiple myeloma, it is an arbitrary designation. As more effective therapeutic regimens are introduced, remissions will lengthen and the period of analysis should perhaps be extended to assess more accurately the effect of treatment.

Summary

Ninety-four cases of myeloma proteins were evaluated to document the incidence and distribution of light chains by immunoglobulin class and to analyze the prognostic significance of kappa and lambda light chains. The overall survival of patients with kappa light chains appeared to be the same as that of patients with lambda light chains, but within each immunoglobulin class, the prognosis varied. Free light chains associated with IgG and IgA myelomas appeared to be lambda type more often than kappa type; the significance of this finding is not clear. The value of the Bence Jones heat test in diagnosis and prognosis is discussed.

References

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