Studies in multiple myeloma

I. Characteristics by immunoglobulin class

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Clinical investigation of multiple myeloma has provided the answers to many questions concerning the natural history of multiple myeloma. However, many other questions have been raised, such as the relationship between elevations of serum and urinary proteins and the type of neoplastic cells producing them. With the introduction of sophisticated immunologic techniques, it was discovered that the tumor cells produced several chemically distinct types of proteins related structurally to whole or fragmentary gamma globulin molecules. Data on these "myeloma" proteins (M-proteins) and their relationship to the manifestations and course of the disease are the basis of this report.

Materials and methods

The material for this study was collected from the clinical records and laboratory reports of patients with monoclonal gammopathy evaluated in the Immunology Laboratory of the Cleveland Clinic from 1965 to 1972. Immunoelectrophoresis and, in most instances, quantitative immunoglobulin determinations were performed.

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Table 1. Monoclonal gammopathies 126 cases

	No. cases	%
Myeloma		
IgG	43	34.2
IgA	27	21.4
Bence Jones	24	19.0
IgD	2	1.6
Nonsecretory	2	1.6
Total	98	77.8
Macroglobulinemia	18	14.2
Heavy chain disease	1	0.8
Monoclonal gammopathy without myeloma		
IgG	8	6.4
IgA	1	0.8
Total	9	7.2

Of the 126 cases of monoclonal gammopathy evaluated, 98 patients had multiple myeloma (*Table 1*). There were too few patients with IgD myeloma for meaningful analysis, but the general features of the two cases will be presented. The two patients in whom no M-protein was identified have been seen only recently and sufficient data are not available for analysis.

The parameters tabulated included age and sex, clinical diagnosis and date of diagnosis, length of follow-up, hemoglobin level, skeletal survey, bone marrow evaluation, serum and urinary protein electrophoresis, serum and urinary protein immunoelectrophoresis, and quantitative levels of immunoglobulin. Most patients were treated with melphalan alone or in combination with other drugs, but the many facets of treatment and response were beyond the scope of this study.

Usual methods of laboratory analysis were employed. Immunoelectrophoresis was performed in ionagar with a barbital buffer at pH 8.6. Sources of antisera for immunoglobulin characterization included various commercially prepared products* as well as material prepared in the laboratory. Quantitative immunoglobulins were measured by the technique of Fahey and McKelvey[1] using commercially prepared materials.† The two most important diagnostic criteria for multiple myeloma were: (1) evidence of an abnormal monoclone as shown by monoclonal M-protein in serum or urine and the presence of sheets or clumps of mature and abnormal plasma cells in a bone marrow aspirate, (2) the presence of "punched-out," lytic bone lesions or pathological fractures related to plasma cell infiltration. Anemia alone was a nonspecific finding but an important feature when considered in conjunction with the main criteria.

Results

The characteristics of IgG, IgA, and Bence Jones types of multiple myeloma are summarized in *Tables 2 through 4*.

IgG myeloma. There were 43 patients in this group, 25 women and 18 men. The mean age at diagnosis was 64 years. One patient had plasma cell leukemia and two had amyloidosis. In 31 instances the M-protein was type kappa and in 12 it was type lambda. Seventy-five percent had characteristic bone lesions. Monoclonal serum pro-

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Table 2. Characteristics of multiple myeloma

Ig class	No. cases	Mean age	Light chains		Bone lesions	Serum M-protein mobility		Anemia	Characteristic bone marrow
			κ	λ		γ	β		
IgG	43	64	31	12	31	39	4	37	36
IgA	27	60	13	14	19	13	12	23	27
Bence Jones	24	55	10	12	21	1	—	24	20

Table 3. Quantitative immunoglobulins

Ig class	No. cases	Range (mg/100 ml)	Median (mg/100 ml)	Other Ig decreased	Other Ig increased or normal
IgG	40	1,900–14,000	5,000	33	7
IgA	24	1,400–7,700	3,250	24	0

teins were observed in all, with most migrating in the gamma region on paper electrophoresis. Anemia and hyperproteinemia were common features but not present in every case. Quantitative immunoglobulin levels before treatment were available in 40 cases (*Table 3*). The levels ranged from 1,900 to 14,000 mg/100 ml (normal 900 to 1,600 mg/100 ml) with a median of 5,000 mg/100 ml. IgA and IgM levels were decreased in 33 patients but were either normal or slightly increased in 7. Characteristic plasma cell infiltration of the bone marrow was present in 36 cases. Of the 43 patients, 23 were at risk for at least 2 years (*Table 4*). The median survival in this group was 20 months; the range 2 to 93 months.

IgA myeloma. Twenty-seven patients had IgA myeloma, 10 women and 17 men. The mean age in this group was 60 years. One patient had plasma cell leukemia; none had amyloidosis. The light chain distribution was 13 kappa and 14 lambda. Most

Table 4. Survival (2 years) by immunoglobulin class

Ig class	No. patients at risk	Alive	Dead	Median survival mos.
IgG	23	10	13	20
IgA	14	8	6	27
Bence Jones	15	9	6	25
Total	52	27	25	24

patients had bone lesions. In 25 patients a well-defined serum M-protein was identified on paper electrophoresis; with a gamma mobility in 13 and a beta mobility in 12. One of the two patients without a well-defined peak had a broad increase in the beta region, and the other had been treated before electrophoresis. As with the IgG myelomas, anemia and hyperproteinemia were common but not always present. Pretreatment serum was available for quantitative Ig analysis in 24 cases. M-protein levels ranged from 1,400 to 7,700 mg/100 ml (normal 60

to 200 mg/100 ml), with a median of 3,250 mg/100 ml. IgG and IgM were decreased in all. In contrast to IgG myeloma, characteristic bone marrow pathology was found in every case. Fourteen patients were at risk for 2 years. The median survival of these patients was 27 months with a range of 11 to 74 months.

Bence Jones myeloma. Bence Jones myeloma was diagnosed in 24 patients, 11 women and 13 men. The mean age was 56 years. One patient had plasma cell leukemia and one had amyloidosis at the time of diagnosis. Kappa type light chains occurred in 10 patients and lambda type in 12. Urinary protein immunoelectrophoresis was not performed (*Table 2*) in two instances, although serum specimens from these patients were examined. Urine paper electrophoresis revealed a well-defined M-protein in both. Bone lesions occurred in more than 80% of cases. A small M-spike with $gamma_1$ mobility was identified in the serum of only one patient. Further studies indicated that this represented free light chains in the serum. All individuals in this group were anemic and none had hyperproteinemia. Pretreatment serum was examined for quantitative Ig levels in 16 cases; IgG, IgA, and IgM were decreased in most; immunoglobulins were normal in only one instance. Twenty patients had characteristic bone marrow pathology. Of the 24 patients, 15 were at risk 2 years. Median survival was 25 months with a range of 1 to 86 months.

IgD myeloma. Two patients, an 80-year-old woman and a 55-year-old man, had IgD multiple myeloma. Neither patient had plasma cell leukemia or amyloidosis at the time of diagnosis. Like most individuals with this type of disease, both had lambda type light chains, decreased immunoglobulin levels, and no recognizable M-protein on serum paper electrophoresis. IgD levels were 87 and 25 mg/100 ml respectively (normal 0.5–3.0 mg/100 ml). One patient died 26 months after diagnosis and the other 4 months after diagnosis.

Discussion

Since 1965, 126 cases of monoclonal gammopathy have been evaluated immunologically. Although the series is small compared with those of cooperative study groups,[2-4] it is relatively large for a single institution. The series also has the advantages of uniformity of procedure and continuity of approach, not often obtainable in series collected from several institutions. Before discussing the characteristics peculiar to multiple myeloma of each immunoglobulin class, certain aspects of the distribution and evaluation of these cases should be described in more detail.

The distribution of cases is similar to that reported by others,[5, 6] except that the incidence of IgG myeloma appears low. The percentage seems especially small, mainly because monoclonal gammopathies of IgG type not associated with multiple myeloma (eight cases) were excluded (*Table 1*). When these cases are included or when the incidence of IgG myeloma is related only to total cases of myeloma (rather than to all monoclonal gammopathies) the number approaches 45%, still slightly lower than the 50% to 55% reported in most other series.

The incidence of Bence Jones myeloma in this series appears increased when compared with early reports,[5, 6] but corresponds well with that in later

publications.[7, 8] This apparent change in frequency probably reflects increased clinical awareness leading to early diagnosis and increased use of a more sensitive procedure such as immunoelectrophoresis to evaluate concentrated urine specimens for free light chains.

It is generally accepted that IgG M-proteins migrate in the gamma region, and IgA peaks occur in the beta region on serum paper electrophoresis. This general rule may not apply in every case, and the data presented here (*Table 2*) emphasize that attempting to classify M-proteins on mobility alone without the aid of immunoelectrophoresis can lead to errors.

Since the first report by Waldenström[9] in 1952, so-called benign monoclonal gammopathy and monoclonal gammopathy not associated with signs and symptoms of multiple myeloma have been reported in increasing numbers. Incidences in the range of 10% to 30% are common.[2, 5] One of the most important features of "benign" monoclonal gammopathy is the finding of normal levels of the other nonmonoclonal immunoglobulins. However, it should be emphasized that normal levels of nonmonoclonal immunoglobulins may occur in patients with multiple myeloma. Seven of the 40 patients with IgG myeloma who were tested had such findings. Only three of these seven patients with IgG myeloma were at risk for 2 years, and all three died within that period, suggesting a less favorable prognosis in this group.

It appears that patients with IgG and Bence Jones myelomas have a lower incidence of bone marrow changes than those with IgA myeloma (*Table 2*). This apparent discrepancy is probably fortuitous, in that there is no reason to suspect from the incidences of anemia and bone lesions or from published reports that bone marrow involvement is any less common in IgG or Bence Jones myelomas than in IgA type disease.

Comparison of the individual classes of multiple myeloma in this series reveals certain patterns. Patients with IgG myeloma included slightly more women than men. The ratio of kappa type to lambda type light chains was almost 3 to 1. Characteristic bone pathology and bone marrow morphology was present in most. The monoclonal protein was easily identifiable and was almost always greater than 2,000 mg/100 ml. Usually, but not always, it migrated in the gamma region on paper electrophoresis. A small but significant percentage of patients had normal or slightly increased levels of IgA and IgM. Two-year survival in this group was approximately 50%.

Patients with IgA myeloma shared many of the features of those with IgG type disease, but certain differences were observed. The sex incidence was reversed with slightly more men than women. The kappa to lambda light chain ratio was nearly equal. Median levels of M-protein were significantly different (3,250 mg/100 ml for IgA as compared with 5,000 mg/100 ml for IgG) and the M-protein often migrated in the beta region on paper electrophoresis. Two-year survival was approximately the same as that for IgG, but the median survival was longer for IgA patients; 27 months compared with 20 months. The above data are in essential agreement with published reports.[3, 10] The few areas of variance (e.g., sex and light chain distribution among the IgG myeloma

cases), can be readily attributed to the sampling error inherent in any small series of this type.

Patients with Bence Jones myeloma were younger than those with IgG or IgA type disease, but there was the same sex distribution and light chain incidence. Hypogammaglobulinemia with monoclonal free light chains in the urine was the rule. A greater percentage had characteristic lytic bone lesions. Overall 2-year survival and median survival in this group was not less than in those with IgG and IgA myelomas. This last finding is in distinct contrast to the experience of others and deserves further analysis.

The figures in *Table 4* indicate a decreased 2-year survival for patients with IgG myeloma compared with those with Bence Jones type disease. When survival in Bence Jones myeloma is compared with survival in IgA myeloma or the combination of IgA and IgG types, the figures are much closer. Further analysis revealed that two of the nine patients with Bence Jones myeloma surviving 2 years died at 26 months, and if the 2-year survival figures are adjusted to exclude these two patients who "got in under the wire" there is no difference in survival. Even so, these data are at variance with many published reports[3, 4, 10] which indicate that in Bence Jones myeloma survival is significantly less than that for IgG or IgA type disease. There is little reason to suspect from other comparisons of IgG, IgA, and Bence Jones myelomas in this series that the sample is so distorted as to account for the above observations. It is more probable that an increased index of suspicion and more sensitive techniques for detection of light chains (Bence Jones protein) contribute to diagnosis of the disease at an earlier stage before massive or prolonged proteinuria lead to irreversible renal damage.[11-13] In this regard the beneficial effect of recently evolved treatment regimens used in most of these patients cannot be discounted. These findings do not confirm the widely held theory that malignant plasma cells producing anything other than whole immunoglobulin molecules are less differentiated and thus account for a poorer prognosis.[14]

Summary

Of 126 cases of monoclonal gammopathies studied between 1965 and 1972, 98 were multiple myelomas. These were analyzed according to immunoglobulin class, light chain type, electrophoretic mobility of the M-protein involved, and also with respect to certain clinicopathologic features such as bone lesions, characteristic bone marrow histology, anemia, and 2-year survival. Our findings agree with the observations of others except that no difference in 2-year survival among the major classes including those with Bence Jones myeloma was noted. This is attributed to earlier diagnosis and more effective treatment secondary to an increased index of suspicion and the use of more sensitive laboratory techniques for detection of free light chains in the urine.

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