MONOCLONAL GAMMOPATHY IN HUMAN NEOPLASIA

PHILIP J. MIGLIORE, MD,* AND RAYMOND ALEXANIAN, MD**

Monoclonal gammopathy unassociated with overt multiple myeloma was detected in 0.65% of 5066 individuals who were referred for the evaluation of known or suspected neoplasia. The incidence, age and sex distributions were similar to those found in a large population of normal adults, suggesting that the association of monoclonal gammopathy with nonreticuloendothelial neoplasms has a fortuitous rather than a cause and effect relationship. The failure of effective treatment of the associated neoplasm to alter favorably the concentration of the serum gammopathy supported this view. This abnormality may represent an early phase in the slow evolution of multiple myeloma; this emphasizes the importance of early recognition and long term evaluation.

THE DISCRETE, HOMOGENEOUS PROTEIN IDENtified on serum electrophoresis as a "paraprotein," "M-protein" or more commonly now as a "monoclonal gammopathy" consists of biochemically distinct and immunochemically specific molecules presumably derived from a single clone of immunoglobulin-producing cells. Because of the common association of monoclonal gammopathy with multiple myeloma and macroglobulinemia of Waldenstrom, such clones in these conditions are presumed to result from malignant transformations.

In recent years monoclonal gammopathy has been recognized in apparently normal individuals as well as in subjects with a variety of diseases, including those with different malignant neoplasms. In the absence of overt multiple myeloma or macroglobulinemia this condition has been variously termed "benign monoclonal gammopathy," "monoclonal gammopathy of unknown etiology," "essential hyperglobulinemia" and "dysimmunoglobulinemia."[17, 19, 20, 23] Numerous case reports have attested to the association of this form of monoclonal gammopathy with neoplasms other than those derived from the reticuloendothelial system, some implying a cause and effect relationship.[6, 7, 10, 11, 16, 17, 21, 22] This relationship was examined in this study which determined the incidence of monoclonal gammopathy in a large number of cancer patients.

MATERIALS AND METHODS

The population studied consisted of 5066 randomly selected patients examined at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston between June 1964 and April 1966. Of the patients surveyed 81% had malignant neoplasms, 5% had benign tumors, 91% were older than 30 years and 56% were women.

All serum specimens submitted for a serologic test for syphilis, representing approximately 57% of all new clinic admissions during this period, were studied. Initial screening for monoclonal gammopathy was performed by an agar gel electrophoresis technique (Fig. 1). When present, the concentration of monoclonal components was determined by microcellulose acetate electrophoresis (Model R-100 Microzone System*). All monoclonal gammopathies were typed by immunoelectrophoresis.[13] Antisera specific for immunoglobulins IgG, IgA and IgM were obtained commercially.** Anti-K and anti-L antisera were prepared in rabbits by serial intramuscular injections of Kappa and Lambda Bence Jones proteins, emulsified in complete Freund's ad-

From the Department of Pathology and the Department of Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Tex.

* Assistant Pathologist, Department of Pathology and Assistant Professor of Pathology, The University of Texas M. D. Anderson Hospital and Tumor Institute.

** Associate Internist, Section of Experimental Hematology, Department of Medicine and Associate Professor of Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute.

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* Beckman Instruments, Inc., Fullerton, Calif.

** Hyland Laboratories, Los Angeles, Calif.

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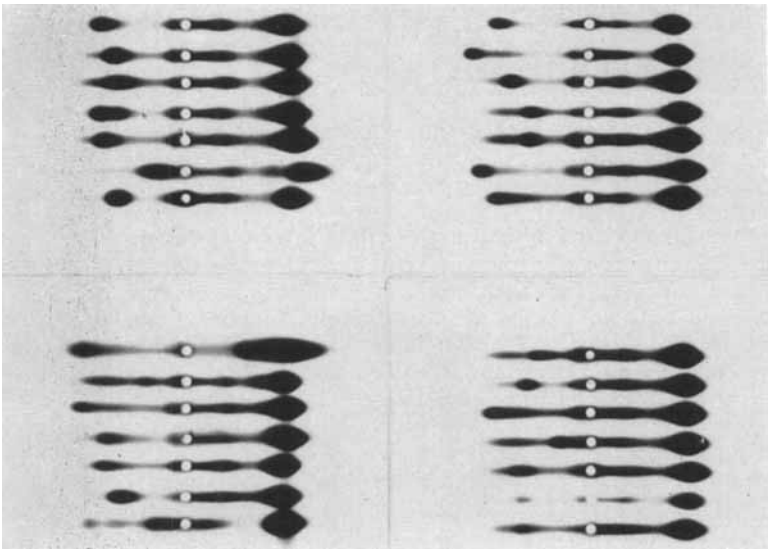

FIG. 1. The albumin fractions (positive pole) are to the extreme right. Each specimen demonstrates a gammopathy which is monoclonal in nature and which can easily be seen in the left half of each pattern as a discrete oval fraction.

juvant. The proteins had been isolated from the urine of patients with multiple myeloma and purified by column chromatography prior to injection.[2]

When possible, patients with monoclonal gammopathy were evaluated further for the presence of multiple myeloma. Additional studies included examination of sternal marrow aspirates, radiographs of the axial skeleton and immunochemical analysis of urine for Bence Jones protein. Periodic follow-up evaluations on 21 patients continued for 1 to 43 months after initial detection of the protein abnormality.

RESULTS

A monoclonal gammopathy was detected in the serum of 56 patients with a variety of neoplasms and suspected neoplasms, an overall incidence of 1.1%. Twenty-three of these patients were referred with known multiple myeloma and excluded from further analysis. Of the remaining 33 patients with unexplained monoclonal gammopathy (0.65%), 27 had malignant neoplasms, most commonly of epithelial origin (Table 1). Twenty-one of the 33 subjects were men. The median age was 65, ranging from 33 to 81. This figure compares with a median age of 60 for 82 patients with multiple myeloma treated at the Anderson Hospital between 1959 and 1966 (age range 33 to 83 years).

Of the 33 monoclonal components detected, 31 were of IgG, 2 of IgM and none of IgA specificity. Among IgG components, 18 demonstrated Kappa specificity (IgGK) and 13 Lambda specificity (IgGL). Both IgM components were of Kappa specificity (IgMK). These components were detected in a median concentration of 1.0 Gm/100 ml, ranging from approximately 0.3 Gm/100 ml to 3.5 Gm/100 ml. In 82 patients with multiple myeloma studied with the same techniques, the median concentration of monoclonal gammopathies was 4.7 Gm/100 ml and ranged from 1.4 to 11.4 Gm/100 ml.

The incidence of unexplained monoclonal gammopathy increased with age, rising from 0.4% in the fourth decade to 2.8% in the ninth (Fig. 2). Between the fourth and ninth decades the incidence among women increased from 0.6 to 1.4% and among men from none to 4.2%.

Additional studies are summarized in Table 1. The percentage of plasma cells in those bone marrows studied exceeded the normal (3%) in only 4 of 20 cases; in no case did plasma cells constitute more than 10% of the cellularity. One marrow was replaced by cells typical of chronic lymphocytic leukemia. In one patient (JM) a single lytic lesion of the ilium was caused by a local plasmacytoma. A second patient with lytic lesions (HB) had bone marrow metastases from his associated carcinoma.

In 20 of 21 patients with available follow-up information, treatment of the primary neoplasm by surgery, radiotherapy or chemotherapy did not favorably alter the concen-

TABLE 1. Summary of Patients with Monoclonal Gammopathy

Patient	Age	Race	Sex	Primary cancer	Gammopathy	Initial conc. Gm/100 ml	Marrow Plasma cells (%)	Bone x-rays	Status of gammopathy
IW	53	C	F	Breast	IgGK	0.5	normal	normal	Unchanged in 38 months
SH	63	C	F	Breast	IgGK	1.0	normal	normal	Unchanged in 29 months
BM	80	C	F	Breast	IgGL	1.7	normal	osteoporosis	Unchanged in 43 months
SO	35	C	F	Breast	IgGL	2.5	7%	normal	Unchanged in 12 months
BD	64	C	F	Breast	IgGK	0.6	normal	osteoporosis	Unchanged in 26 months
HH	63	C	M	Naso-pharynx	IgGK	1.4	*	*	*
CM	58	C	M	Larynx	IgGL	0.5	normal	*	Unchanged in 23 months
WW	60	C	M	Larynx	IgGK	1.0	*	*	*
CG	66	N	M	Lung	IgGL	1.8	normal	lytic lesions skull ?	Unchanged in 32 months
WS	64	C	M	Lung	IgGK	1.2	normal	normal	Unchanged in 26 months
GP	63	C	M	Lung	IgGK	*	*	*	*
CL	62	N	M	Esophagus	IgGK	3.5	normal	*	Dead within 2 months
DB	70	N	F	Rectum	IgGK	0.8	normal	normal	Dead. Unchanged in 12 months
HH	79	C	M	Rectum	IgGK	0.8	5%	osteoporosis	Unchanged in 4 months
WR	69	C	M	Bladder	IgGK	*	*	osteoporosis	Dead. Unchanged in 6 months
HB	80	N	M	Prostate	IgGK	0.8	normal	lytic lesions vertebrae	Dead. Increase to 1.5 Gm/100 ml in 8 months
TS	80	C	M	Prostate	IgGL	2.0	9%	osteoporosis	Trace Bence Jones proteinuria. Increase to 2.5 Gm/100 ml in 15 months
JM	33	C	F	Cervix	IgGL	0.6	normal	lytic lesions ilium & rib	Dead. Increase to 1.5 Gm/100 ml in 22 months
KS	66	C	F	Uterus	IgMK	0.9	*	*	*
AO	73	N	F	Uterus	IgGL	0.9	*	*	*
FN	81	C	M	Lip	IgGK	1.0	normal	normal	Unchanged in 17 months
CM	63	C	M	Skin	IgGK	*	*	*	*
MS	69	C	F	Melanoma	IgGL	1.7	normal	normal	Increase to 2.3 Gm/100 ml in 17 months
ED	55	C	F	Origin unknown	IgGK	0.7	*	normal	*
JR	76	C	M	Chronic lymphocytic leukemia	IgGK	0.8	normal	normal	Unchanged in 8 months
JC	53	C	F	Hodgkin's Disease	IgGL	2.3	normal	*	Dead within 1 month
LW	67	C	M	Lymphoma	IgGL	1.1	*	*	Unchanged in 21 months
WF	74	C	M	None ?	IgMK	*	*	*	*
GJ	51	C	M	None	IgGK	1.1	normal	normal	*
JO	73	C	M	None	IgGL	0.8	6%	normal	Unchanged in 20 months
EJ	58	C	M	None	IgGK	1.3	*	*	*
JP	52	C	M	None	IgGL	1.4	*	*	*
ES	73	C	F	None	IgGK	*	*	*	*

* No data available.

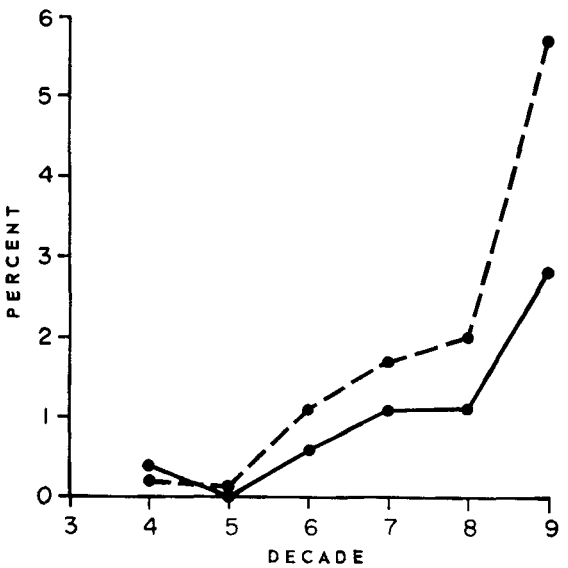

FIG. 2. The overall incidence of unsuspected monoclonal gammopathy in the Anderson Hospital adult cancer population (solid line) compared with that in a general adult population (broken line).[3]

tration of the monoclonal serum peak. In the only exception (JM) a serum IgGL abnormality (0.6 Gm/100 ml) disappeared temporarily after curettement and irradiation of a localized plasmacytoma.

Of four patients who demonstrated progressive increase of at least 0.5 Gm/100 ml in the serum concentration of the monoclonal globulin, two have died. One (JM) probably died of progressive multiple myeloma and the other (HB) of advanced carcinoma. However, postmortem examinations were not performed in either case. A total of nine patients are now dead. Autopsies have been performed on two (CL and JC) and no explanation for the gammopathy was found in either case.

DISCUSSION

The significance of monoclonal gammopathy in the absence of overt multiple myeloma is poorly understood. Although its occurrence in patients without multiple myeloma or other reticuloendothelial malignancies is now recognized, the prevalence in normal individuals, the relationship to various diseases and the significance with respect to the evolution of multiple myeloma are unknown. In a recent analysis of serum electrophoreses from 6995 adults over 25 years of age the incidence of monoclonal gammopathy was found to be 0.9%, increasing with age from 0.2 to 5.7% between the fourth and ninth decades (Fig. 2). In the same decades the incidence in women ranged from 0.5 to 1.6% and in men from none to 9.2%.[3] The similarity of these figures to those found in this analysis of patients with malignant diseases suggests that the association of monoclonal gammopathy with cancer is probably fortuitous and contrasts with the cause and effect relationship implied by some previous reports. This conclusion is further supported by the failure of effective treatment of associated primary neoplasms to alter favorably the level of the serum immunoglobulin abnormality in the patients observed during this study.

The incidence of unexplained monoclonal gammopathy is apparently many times greater than that of overt multiple myeloma, which is estimated to be approximately 0.01–0.02%.[1, 3] Conceivably, many, if not most, people with this condition represent cases of multiple myeloma in an early, latent or "in-situ" phase, the serum protein abnormality preceding the development of more apparent disease by a period of many months to many years. That such a long evolution of multiple myeloma may occur is demonstrated by reports of individuals living as long as 18 years between the initial detection of an immunoglobulin abnormality and the diagnosis of overt multiple myeloma.[8, 12, 15, 18]

Additional support for the concept of early myelomatous disease is suggested from studies of mouse myeloma which have shown a direct correlation between tumor weight and the amount of serum myeloma protein.[9, 14] Most of the individuals evaluated during this study, in comparison with patients with overt myeloma, had serum monoclonal gammopathies in relatively low concentrations, suggesting a low volume of total body "tumor".

Unfortunately, few parameters are available to predict the likelihood that a specific individual with unexplained monoclonal gammopathy will develop overt and progressive plasma cell myeloma. Overt myeloma is more likely to be present in individuals with rapidly increasing levels of monoclonal components or in individuals presenting with IgG components of more than 2.0 Gm/100 ml or IgA components of more than 1.0 Gm/100 ml.[4, 20] However, in individuals with low constant levels of unexplained monoclonal gammopathy, these particular aids are not

helpful. Careful long-term evaluation of all individuals with this abnormality is essential to detect as early as possible the development of progressive myelomatous disease. Recognition of the early phases of multiple myeloma may provide an opportunity to further improve response rates and survival following earlier and more sustained application of effective therapeutic regimens.[5] Consequently, in individuals older than 40, serum electrophoresis should be considered an important screening procedure to aid in the detection of those likely to have or to develop multiple myeloma.

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