M components – a review of 1242 cases

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Among 1242 patients referred for immunologic investigation 1255 M components were detected in the serum. Of these patients 50.9% had multiple myeloma, 18.1% had nonmyelomatous malignant diseases such as macroglobulinemia, lymphoma, leukemia or cancer, 4.3% had connective tissue diseases, 2.5% had primary generalized amyloidosis (PGA) and the rest had various "benign" conditions.

Whereas IgG was the commonest M component in multiple myeloma, connective tissue diseases and the other benign conditions, IgM was the commonest M component in lymphoma and leukemia; Bence Jones proteinemia was most frequently observed in PGA. The ratio of κ to λ light chains varied from 1.7:1 in IgG myeloma to 1:9 in IgD myeloma, and was 1:2.1 in PGA.

Bence Jones protein was detected in 422 (66%) of 640 urine samples tested, the prevalence ranging from more than 70% in multiple myeloma and PGA to as low as 36% in various benign conditions.

It is evident that the class and type of M components and the presence of Bence Jones proteinuria have no definite significance with regard to the diagnosis. Therefore, thorough investigation and follow-up at regular intervals are required when M components are detected.

Chez 1242 patients reçus en consultation pour examen immunologique, 1255 constituants M ont été décelés dans le sérum. De ces patients 50.9% étaient atteints de myélome multiple, 18.1% souffraient de maladies malignes nonmyélomateuses telles que macroglobulinémie, lymphome, leucémie ou cancer, 4.3% avaient des collagénoses, 2.5% souffraient d'amyloïdose primaire généralisée (APG) et les autres présentaient diverses affections "bénignes".

Alors que les IgG représentaient le principal constituant M dans les cas de myélome multiple, les collagénoses et les affections bénignes, les IgM étaient le constituant M le plus fréquent dans les lymphomes et les leucémies; la protéinémie de Bence Jones a été le plus fréquemment observée dans l'APG. Le rapport des chaînes légères κ aux chaînes λ a varié de 1.7:1 dans les myélomes à IgG à 1.9:1 dans les myélomes à IgD et a été de 1:2.1 dans l'APG.

Les protéines de Bence Jones ont été décelées dans 422 (66%) des 640 échantillons d'urine testés, la fréquence variant de plus de 70% dans les cas de myélome multiple et l'APG à moins de 36% dans diverses affections bénignes.

Il est évident que la classe et le type de constituant M et la présence de protéinurie de Bence Jones ne comportent aucune signification définitive en ce qui a trait au diagnostic. Donc, un examen approfondi et une surveillance à intervalles réguliers sont de mise lorsque des constituants M sont décelés.

Immunoglobulins (Ig) are synthesized and secreted by lymphocytes and plasma cells. In physiologic conditions they are synthesized in a harmonious balance, the proportions of the various classes (IgG, IgA, IgM, IgD and IgE) and of the two types of light chains (κ and λ) being fairly constant. Antigenic stimulation, such as infection or immunization, may cause excessive production of Ig (antibodies), which is almost invariably heterogeneous, and give rise to polyclonal hypergammaglobulinemia. On the other hand, when a single clone proliferates abnormally, the produced immunoglobulin is homogeneous and has only one class of heavy chain and one type of light chain. Such a homogeneous (monoclonal) immunoglobulin is called an M component. It is usually seen in serum (or urine) electrophoresis as a narrow band or spike. The diagnosis should be confirmed by immunoelectrophoresis. Occasionally two or three abnormal clones of cells proliferate simultaneously or sequentially, producing two or three different M components.

Until a few years ago M components were usually considered to denote malignant processes; however, they were also found in patients with non-neoplastic diseases and in healthy individuals. Therefore, it seemed important to analyse a large series of patients with M components in relation to diagnosis of their conditions. In this paper we present such an analysis, based on data from 1242 patients with M components.

Material and methods

Between June 1967 and June 1975, 1242 serum and 640 urine samples were referred to our laboratory from hospitals in Toronto and other centres for investigation because M components were suspected. All serum underwent assay for total protein, cellulose acetate electrophoresis, immunoelectrophoresis, immunoquantitation and cryoglobulin assay, as described previously.[1,2] Urine was concentrated, when required, up to 3000 times, by either negative pressure dialysis or concentration against 30% polyvinylpyrrolidone. Antisera against Ig, IgG, IgA, IgM, IgD and Fc and Fab fragments, and immunoquantitation plates for IgG, IgA, IgM and IgD were purchased from Hyland Laboratories, Los An-

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geles, California, and from Meloy Laboratories, Springfield, Virginia. Antisera against IgE, Bence Jones protein types κ and λ, and free κ and λ light chains were produced in our laboratory.

The data reported in this paper were obtained only from cases in which the presence of M components was confirmed and there was sufficient information for a clinical diagnosis.

Results

All but 3 of the 1242 patients had one or more M components in the serum, and altogether 1255 M components were found. The three other patients had Bence Jones proteinuria only. Bence Jones proteinuria was found in 422 (66%) of the 640 urine samples.

Prevalence of M components according to immunoglobulin class and light-chain type is shown in Table I. Classification of M components according to diagnosis (Table II) shows that 50.9% of patients with this abnormality had multiple myeloma and 18.1% had a nonmyelomatous malignant disease.

In malignant plasmacytic diseases (Table III) the prevalence of different classes of M components corresponded approximately to the physiologic concentration of various immunoglobulin classes in the serum, IgG myeloma being the most frequently observed disease. Among the myelomas the ratio of κ to λ light chains of M components varied, ranging from 1.7:1 in IgG myeloma to 1:9 in IgD myeloma (Table IV). The highest prevalence of Bence Jones proteinuria in multiple myeloma was found in light-chain disease and in IgD myeloma, and the lowest in IgA(κ) myeloma.

In Waldenström's macroglobulinemia (Table V) the ratio of κ to λ light chains was 2.5:1 and 58.3% of the urine samples tested contained Bence Jones protein; 16% of the serum samples contained cryoglobulin and a similar proportion contained cold agglutinin. Among the 67 M components found in patients with lymphoma and Hodgkin's disease (Table V) 34 (50%) were of the IgM class; this proportion contrasts with the overall proportion of IgM M components in our series — 13.0% (Table I). In lymphoma the ratio of κ to λ light chains of M components was 2.1:1. Fifty percent of the patients had a lymphocytic type of lymphoma and 20% had a histiocytic type. All patients were in stage III or IV of lymphoma and the average duration of disease when M components were detected was 29.3 months. Anemia, abnormal peripheral blood lymphocytes and lymphomatous involvement of the bone marrow were especially common among patients with IgM M components.

In leukemia (Table VI) a high prevalence (45%) of IgM M components was also noted; the components were found mainly in patients with chronic lymphocytic leukemia, who composed 74% of the group. The ratio of κ to λ

Table I—Prevalence of 1255 serum M components according to class and type

Class and type of M component	No. (and %)
IgG	
κ	459 (36.6)
λ	273 (21.8)
IgA	
κ	102 (8.1)
λ	83 (6.6)
IgM	
κ	83 (6.6)
λ	42 (3.3)
Unidentified	39 (3.1)
BJP*	
κ	66 (5.3)
λ	57 (4.5)
IgD	
κ	1 (0.08)
λ	11 (0.9)
Biclonal†	16† (2.5)
Unidentified‡	7 (0.6)

*BJP = Bence Jones protein.

†Sixteen pairs or 32 M components (excluding cases with Bence Jones proteinemia in addition to whole-molecular M component).

‡Very small but definite spikes of γ mobility, probably IgG.

Table II—Diagnoses in Toronto and New York series of patients with M components

Diagnosis	No. (and %) of patients		
	New York[3]	Toronto (our series)	Total
Multiple myeloma	303 (37.6)	632 (50.9)	935 (45.7)
Macroglobulinemia	66 (8.2)	45 (3.6)	111 (5.4)
Cancer	128 (15.9)	180* (14.5)	308 (15.1)
Amyloidosis	70 (8.7)	31 (2.5)	101 (4.9)
Others†	239 (29.7)	354 (28.5)	593 (28.9)
Total	806 (100.1)	1242 (100.0)	2048 (100.0)

*Includes 72 with cancer, 62 with lymphoma and 46 with leukemia.
†Includes 53 patients with connective tissue disease.

Table III—Classification of malignant plasmacytic diseases by class of M component

Disease	No. (and %) of patients		
	Data of Zawadzki and Edwards[4]	Data of our series	Combined data
IgG myeloma	816	385	1201 (53.0)
IgA myeloma	369	122	491 (21.7)
Light-chain disease	171	106	277 (12.2)
Other myelomas	39	19	58 (2.6)
Macroglobulinemia	194	45	239 (10.5)
Total	1589	677	2266 (100.0)

Table IV—Prevalence of M components and Bence Jones proteinuria in multiple myeloma

Class and type of M component	No. (and %) of patients		Urine	
			No. of samples examined	No. (and %) with Bence Jones protein
IgG				
κ	242	385 (60.9)	151	106 (70.2)
λ	143		100	59 (59.0)
IgA				
κ	65	122 (19.3)	40	21 (52.5)
λ	57		38	26 (68.4)
LCD				
κ	59	106 (16.8)	59	59 (100.0)
λ	47		47	47 (100.0)
IgD				
κ	1	12 (1.9)	1	1 (85.7)
λ	11		6	5
Biclonal	5	(0.8)	—	—
IgM	2	(0.3)	2	1 (50.0)
Total	632	(100.0)	444	325 (73.2)

LCD = light-chain disease — i.e., multiple myeloma with Bence Jones protein in the serum as the only M component.

light chains in the leukemia group was 1.3:1. An increased, but smaller, prevalence (24%) of IgM M components was also noted in patients with cancer (Table VII). The overall ratio of κ to λ light chains in this group was 1.1:1. Of 48 patients with cancer the serum concentrations of immunoglobulins other than M component were greatly decreased in only 7, and in 6 others the concentration of only one immunoglobulin was low.

A different distribution of M components was observed in patients with primary generalized amyloidosis (Table VIII): in 50% of the patients Bence Jones protein was the only M component in the serum (so-called light-chain disease) and the ratio of κ to λ light chains was reversed — 1:2.1.

In connective tissue diseases (Table IX) the majority of M components (70%) were of the IgG class. The ratio of κ to λ light chains was 1.8:1. Bence Jones protein was detected in 41% of the urine samples examined.

The prevalence of M components in 301 patients with various benign diseases is summarized in Table X. The concentration of M components in the serum exceeded 1.0 g/dl in 58, 64 and 18% of patients with IgG, IgA and IgM M components, respectively. The ratio of κ to λ light chains was 1.8:1. In 28 patients in this group Bence Jones protein was detected in the urine; 2 had angioimmunoblastic lymphadenopathy, 1 had lichen myxedematosus, 1 had essential cryoglobulinemia, 3 had chronic, ill-defined anemia and the rest had conditions unrelated to plasmacytic dyscrasias, such as osteoarthritis or arteriosclerotic cardiovascular disease. All these patients were older than 45 years and most were older than 60 years. Among 197 of these patients the serum concentrations of two immunoglobulins other than M component were decreased in 6% and the concentration of one immunoglobulin was low in 21%; the other patients had normal or increased concentrations.

Table V— Prevalence of M components in Waldenström's macroglobulinemia and in lymphomatous diseases

Class and type of M component	No. of patients: Waldenström's macroglobulinemia (n = 45)	No. of patients: Lymphoma (n = 53) and Hodgkin's disease (n = 11)
IgG		
κ	—	17
λ	—	5
IgA		
κ	—	5
λ	—	2
IgM		
κ	30	16
λ	12	11
Unidentified	3	5
Biclonal	—	3*
Urine		
BJP	14	7
No BJP	10	9

*IgG(λ) + IgG(λ); IgA(κ) + IgM(κ); IgG(κ) + IgM(κ).

Discussion

The prevalence of M components in a general population over 25 years of age was found to be 0.9%.[5] In that survey of 6995 persons all 64 with M components were examined and only 7 were found to have a malignant disease. Further clinical information was obtained in 55 of the 64 individuals 5½ years later. Of the 16 who had died only 5 had had malignant diseases. No change in the serum concentration of M components was detected in the 39 survivors and malignant disease had not developed in any.[6] Thus, in 91% with M components the condition was still benign after 5½ years.

Among 13 400 healthy young adults in another study the prevalence of M components was 0.15%.[7] Of 20 individuals with M components only 4 had malignant diseases. Surveys of two large series of hospital patients (7200 and 5327 patients, respectively) showed the

Table VI—Prevalence of M components in leukemia*

Class and type of M component	CLL (n = 34)	AML (n = 4)	AMML (n = 3)	ABCL (n = 2)	ALL (n = 1)	AL (n = 1)	CML (n = 1)	Total (n = 46)
IgG								
κ	8	—	1	2	1†	—	—	12
λ	5	1	1	—	—	—	—	7
IgA								
κ	—	—	—	—	—	—	—	—
λ	2	—	—	—	—	—	—	2
IgM								
κ	7	1	—	—	—	1	—	9
λ	8	—	—	—	—	—	—	8
Unidentified	3	—	—	—	—	—	1	4
BJP	1 (κ)	—	—	—	—	—	—	1
Urine								
BJP	8	2‡	1‡	—	—	—	—	11
No BJP	3	1	2	—	—	—	—	6

* Abbreviations: CCL = chronic lymphocytic leukemia; AML = acute myeloblastic leukemia; AMML = acute myelomonocytic leukemia; ABCL = acute blast cell leukemia; ALL = acute lymphoblastic leukemia; AL = aleukemic leukemia; CML = chronic myelogenous leukemia.
†Biclonal with IgG(λ).
‡No M components in serum.

Table VII—Prevalence of M components in cancer

Site or type of neoplasia	No. of patients	Class and type of M component: IgG κ	IgG λ	IgA κ	IgA λ	IgM κ	IgM λ	Unidentified	BJP
Breast	12	8	3	—	—	—	1	—	—
Metastatic cancer	11	2	3*	1	—	2	—	2	1 (λ)
Colon	10	4	2	1	2	1	—	—	—
Lung	9	2	2	—	2	2	—	1	—
Urinary bladder	4	—	2	—	1	—	—	1	—
Prostate	3	—	1	—	—	1	—	1	—
Malignant melanoma	3	2	—	—	—	1	—	—	—
Ovary	2	—	1	—	—	—	—	1	—
Skin, basal cell	2	—	1	1	—	—	—	—	—
Pancreas	2	1	—	1	—	—	—	—	—
Thyroid	2	1	1	—	—	—	—	—	—
Kidney	1	1†	—	—	—	—	—	—	—
Uterine cervix	1	—	1	—	—	—	—	—	—
Hepatoma	1	—	1	—	—	—	—	—	—
Tongue	1	—	1	—	—	—	—	—	—
Larynx	1	—	1	—	—	—	—	—	—
Kaposi's sarcoma	1	1	—	—	—	—	—	—	—
Stomach	1	1	—	—	—	—	—	—	—
Lip	1	1	—	—	—	—	—	—	—
Oropharynx	1	—	—	—	—	—	—	1	—
Gastric neurofibrosarcoma	1	—	—	—	—	—	1‡	—	—
Seminoma	1	—	—	—	—	1	—	—	—
Neuroblastoma	1	—	1	—	—	—	—	—	—
Total	72	24	21	4	5	8	2	7	1

*One biclonal with IgA(λ).
†One biclonal with IgA(κ).
‡With cryoglobulin.

same prevalence of M components — 0.8%.[8-10]

It seems, therefore, that when an M component is detected incidentally, especially in a young individual, the chance that the condition is benign is high. The fact that in our series 50.9% of the patients had multiple myeloma and 18.1% had nonmyelomatous malignant diseases does not contradict this statement. Our series was composed mainly of hospital patients referred for special studies. A similar observation was made in other referral centres[3,11-13] but, since the referral policy varied, the proportion of patients with benign conditions associated with M components varied too, ranging from 16.5[13] to 53%.[12] In our series the prevalence of such benign conditions was 31%, identical to that reported by Isobe and Osserman.[3] However, malignant disease is seen to develop in some patients with these benign conditions associated with M components if the follow-up period is sufficient.

Patients with multiple myeloma have made up 38 to 73% of large series of individuals with M components.[3,12,13] The majority of M components in multiple myeloma belong to the IgG class.[11] Approximately two thirds of M components have κ light chains, but the ratio of κ to λ light chains varies in different classes of M components and among various diseases. For example, in our patients with IgG myeloma 63% of M components had κ light chains, whereas the frequency in IgA myeloma was 53% and in IgD myeloma, 8%. M components with κ light chains predominated in Waldenström's macroglobulinemia, cancer, lymphoma, leukemia and connective tissue diseases. In contrast, M components with λ light chains predominated in primary generalized amyloidosis.

Comparison of diagnoses in our series with those in a similar series from New York[3] (Table II) showed a lower proportion of multiple myeloma and a higher proportion of amyloidosis in the latter.

The distribution of various classes of M components in nonmyelomatous malignant diseases differed from that in multiple myeloma. In lymphoma and leukemia almost half the M components belonged to the IgM class. The proportion of IgM M components in patients with cancer and with connective tissue diseases was also higher (24 and 23%, respectively) than the proportion in the whole series (13.0%). A much higher prevalence of Bence Jones proteinemia was observed in primary generalized amyloidosis (48%) than in multiple myeloma (17%). The prevalence of Bence Jones proteinemia in nonmyelomatous neoplastic diseases was very low. Patients who could not be classified into any of the groups of diseases in which M components are usually detected were classified as "others" or as having "unclassified benign" conditions. In this group the proportion of IgM M components was low (6.4%) and no Bence Jones proteinemia was detected. In approximately half of these patients the serum

Table VIII—Prevalence of M components in primary generalized amyloidosis

Class and type of M component	No. of patients (n = 31)
IgG	
κ	3
λ	8*
IgA	
κ	1
λ	3
IgM	
λ	1
BJP	
κ	6
λ	9
Urine	
BJP	24
No BJP	7

*Four serum samples also contained BJP(λ).

Table IX—Prevalence of M components in connective tissue diseases

Disease	No. of patients	Class and type of M component: IgG κ	IgG λ	IgA κ	IgA λ	IgM κ	IgM λ	Unidentified	Urine: BJP	Urine: No BJP
Rheumatoid arthritis	28	13	8	2	1	2	1	1	11	9
Systemic lupus erythematosus	4	3	—	—	—	—	—	1	0	2
Scleroderma	3	2	1	—	—	—	—	—	—	—
Felty's syndrome	3	—	1	—	—	1	1	—	—	—
Dermatomyositis	2	—	—	—	—	2*	—	—	1	1
Wegener's granulomatosis	1	—	—	—	—	—	1	—	0	1
Sjögren's syndrome	1	—	—	—	—	—	—	1	0	1
Peetoom-Meltzer syndrome	1	—	—	—	—	1*	—	—	0	1
Collagen disease, unclassified	6	4†	2	—	—	—	—	—	1	2
Seronegative arthritis	4	3	—	—	1	—	—	—	0	2
Total	53	25	12	2	2	6	3	3	13	19

*With cryoglobulins.
†One biclonal with IgG(λ).

concentration of M components exceeded 1.0 g/dl at the time of detection, and in many the concentration exceeded 2.0 g/dl.

Among the patients with cancer and M components, carcinoma of the breast, colon and lung, and generalized metastatic cancer with no evident primary focus were the most frequent types of cancer, affecting 58% of the whole group. In the series of Isobe and Osserman[3] the commonest tumours associated with M components were adenocarcinoma or adenomatous polyp of the rectosigmoid colon, and prostatic and breast cancers, accounting for more than two thirds of the group. In another series stomach and skin cancer were frequently observed.[14]

Bence Jones proteinuria was found in more than 70% of the patients with multiple myeloma, and in other diseases the prevalence varied from 36 to 77%; the overall prevalence was 66%. Therefore, the finding of M component or Bence Jones proteinuria, or both, cannot distinguish a neoplastic process from a benign condition. Nor is the serum concentration of M components helpful, although in multiple myeloma and Waldenström's macroglobulinemia the concentration is usually higher than in other diseases. The concentrations of immunoglobulins other than M components are usually decreased in multiple myeloma and macroglobulinemia. Low concentrations of immunoglobulins were observed only rarely in the groups of patients with cancer and unclassified benign disorders. No depression of immunoglobulin production was noted in patients with connective tissue disorders and M components.

Table X—Prevalence of M components according to class and type in unclassified benign conditions*

Class and type of M component	No. (and %) of patients (n = 301)
IgG	
κ	141 (47.0)
λ	78 (25.5)
IgA	
κ	25 (8.4)
λ	12 (4.0)
IgM	
κ	14 (4.7)
λ	5 (1.7)
Unidentified	15 (5.0)
Biclonal†	4 (1.3)
Unidentified	7 (2.3)
Urine	
BJP	28 (36.0)
No BJP	48 (64.0)

* Chronic liver disease (18), peripheral neuropathy (5), various anemias (12), idiopathic cryoglobulinemia (3), chronic cold agglutinin disease (3), myelofibrosis (3), lichen myxedematosus (1), angioimmunoblastic lymphadenopathy (2) and others (254).
†IgG(κ)+IgG(λ); IgG(λ)+IgG(λ); IgA(κ)+IgG(κ); IgG(λ)+ IgM(λ).

It is not clear whether suppression of immunoglobulin production is definite evidence of a malignant process. It seems, however, that patients with M components and low concentrations of immunoglobulins should be checked repeatedly for malignant disease, and the finding of an M component always warrants extensive investigation. A diagnosis of "benign" M components should be made by exclusion only; malignant disease may develop in patients with these seemingly benign conditions. Therefore, all patients with M components should be followed up for long periods. Transient appearance of M components has been described,[15] and we have observed this in a few patients.

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