LABORATORY AND CLINICAL CHARACTERIZATION OF MONOCLONAL GAMMOPATHY IN TAIWANESE

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Background and Purpose: To investigate the prevalence of monoclonal gammopathy, the frequency of associated diseases, and the laboratory features useful in the differential diagnosis and prediction of associated complications.
Materials and Methods: From January 1994 through December 1998, 11,510 serum samples and 1,555 urine samples from 10,974 Taiwanese patients requiring electrophoresis study were examined for the presence of monoclonal protein by electrophoresis on cellulose acetate membrane and immunofixation electrophoresis (IFE).
Results: Two hundred and eighty seven cases (2.6%) of monoclonal gammopathy were found. Of these, 136 (47.4%) had multiple myeloma, 84 (29.3%) had monoclonal gammopathy of undetermined significance (MGUS), 53 (18.5%) had other lymphoproliferative disorders (LPD), eight (2.8%) had polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin pigmentation (POEMS) syndrome, and six (2.1%) had cryoglobulinemia. Immunoglobulin A (IgA) monoclonal protein was more often associated with myeloma than LPD (25 *vs* 3.8%, $p = 0.002$); monoclonal light chains were more often associated with myeloma than MGUS (17% *vs* 3.6%, $p = 0.006$). Biclonal gammopathy was more often associated with MGUS than myeloma (10.7 *vs* 1.5%, $p = 0.014$). Hypogammaglobulinemia was common in patients with myeloma (70%) but rare in patients with LPD (20%, $p < 0.001$) and in those with MGUS (5%, $p < 0.001$). Concomitant polyclonal hypergammaglobulinemia was rare in patients with myeloma (5%), but common in patients with LPD (53%, $p < 0.001$) or MGUS (27%, $p < 0.001$). Patients with λ chain myeloma had the highest risk (100%) of developing renal insufficiency. Our myeloma patients were also at increased risk of developing myelomatous pleural effusions than previously reported.
Conclusions: The lower frequency of MGUS in this study than previously reported may have been due to differences in patient selection, laboratory methods, and the presence of local diseases. The presence of POEMS syndrome and cryoglobulinemia, the very high association of λ chain myeloma with renal failure, and the higher occurrence of myelomatous effusion than previously reported probably reflected local disease patterns.

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Key words:
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Monoclonal proteins are immunoglobulins of a single light and/or heavy chain class, which form discrete bands on electrophoresis of serum or urine. They may arise from malignant or benign proliferation of B lymphocytes. To distinguish between malignant monoclonal proteins, such as those resulting from multiple myeloma or other lymphoproliferative disorders (LPD), from those resulting from monoclonal gammopathy of

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undetermined significance (MGUS), the frequency of the associated diseases and the clinical and laboratory characteristics of each disease category must be known. The overall incidence of monoclonal gammopathy and the frequency of associated diseases among ethnic Chinese have rarely been reported [1]. However, during the last 14 years, the number of deaths due to multiple myeloma in Taiwan has increased 3.7-fold [2]. In this study, we examined serum and urine samples that were submitted to our laboratory at National Taiwan University Hospital for electrophoresis over a 5-year period, to identify patients with monoclonal gammopathy. This paper describes the frequency of malignant monoclonal gammopathy, other related diseases such as LPD, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin pigmentation (POEMS) syndrome, cryoglobulinemia, and MGUS among these patients. We also analyzed laboratory findings that may be useful in differential diagnosis, and in the prediction of complications of monoclonal gammopathy.

Materials and Methods

From January 1994 through December 1998, 11,510 serum samples and 1,555 urine samples from 10,974 patients were sent to the Department of Laboratory Medicine of National Taiwan University Hospital for electrophoresis. Electrophoresis was carried out when requested by attending physicians, and, thus, was performed on a selective basis. Indications for electrophoresis included back pain, recurrent infection, peripheral neuropathy, anemia, proteinuria, renal failure, abnormal concentration of serum globulins, hypercalcemia, or skeletal roentgenograph lesions.

Protein electrophoresis

Serum or urine protein electrophoresis was performed using the Sebia processor system (Sebia, les Moulineaux, France) on cellulose acetate membrane (Sebia EPU kit). To detect Bence Jones protein in the urine, a sample from the urine collected over 24 hours was submitted.

Immunofixation electrophoresis

Serum or urine samples were subjected to immunofixation electrophoresis (IFE) when demonstrating monoclonal bands, a decrease in gamma globulins, or when the possibility of a small monoclonal protein could not be excluded. IFE was performed on agarose gel (Paragon SPE and IFE kit, Beckman Immunosystems, Brea, CA, USA).

Viscosity

Hyperviscosity syndrome was diagnosed when a patient had bleeding from gums or nasal mucosa with normal platelet counts, together with ocular / neurologic manifestations (such as blurred vision, diplopia, impaired hearing, abnormal gait, sudden change in consciousness or mentality) or digital gangrene [3]. Viscosity was measured using a Silenus viscometer (Melbourne, Australia) at 37°C. The normal value for plasma viscosity was 1.24 ± 0.07 centipoises (cP) (mean ± standard deviation).

Differential diagnosis of monoclonal gammopathy

The diagnostic criteria for myeloma were more than 10% plasma cells in bone marrow aspirates or plasmacytoma on biopsy, serum monoclonal protein or Bence Jones proteinuria, and osteolytic lesions on bone survey.

POEMS syndrome was diagnosed if a patient with monoclonal gammopathy had sensory motor polyneuropathy, and at least two of the following: endocrinopathy, hyperpigmented skin, or hepatosplenomegaly.

The diagnosis of Waldenstrom's macroglobulinemia was based on a serum monoclonal immunoglobulin M (IgM) spike, and plasmacytoid lymphocytic infiltration of bone marrow or lymph nodes.

Essential cryoglobulinemia was diagnosed if a patient had cryoglobulinemia and monoclonal gammopathy, but no myeloma, macroglobulinemia, lymphoma, or other related diseases. Secondary cryoglobulinemia was defined as the presence of cryoglobulins in patients with myeloma or macroglobulinemia.

MGUS was diagnosed when a patient with serum or urine monoclonal protein had no evidence of myeloma, macroglobulinemia, lymphoma, chronic lymphocytic leukemia, POEMS syndrome, primary amyloidosis, or cryoglobulinemia.

Statistics

The frequency distribution of the laboratory parameters between the groups was analyzed using Fisher's exact test.

Results

Monoclonal gammopathy was found in 287 (2.6%) of the 10,974 patients (Table 1).

Multiple myeloma

Among the 136 patients with myeloma, at least 17 (12.5%) were farmers. Five patients (3.7%) had the

Table 1. Classification of monoclonal gammopathy and demographic data in 287 patients

Diagnosis	No. of patients (%)	M, F	Age range (yr) (mean ± SD)
Multiple myeloma	136 (47.4%)	91, 45	22–86 (62.0 ± 12.8*)
POEMS syndrome	8 (2.8%)	7, 1	37–62 (47.0 ± 7.1)
Lymphoproliferative disorders	53 (18.5%)	44, 9	22–84 (60.6 ± 13.9)
Waldenstrom's macroglobulinemia	12	9, 3	
Non-Hodgkin's lymphoma	31	25, 6	
Immunoproliferative small intestinal disease	1	1, 0	
Chronic lymphocytic leukemia	9	9, 0	
Essential cryoglobulinemia	6 (2.1%)	1, 5	24–60 (46.2 ± 16.5)
Type I	2	1, 1	
Type II	4	0, 4	
MGUS	84 (29.3%)	50, 34	18–92 (58.3 ± 16.2)
Total	287 (100%)	193, 94	

*p = 0.001 myeloma *vs* POEMS; p = 0.004 myeloma *vs* cryoglobulinemia. POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin pigmentation syndrome; MGUS = monoclonal gammopathy of undetermined significance.

initial manifestation of solitary plasmacytoma and 129 (94.9%) had classical multiple myeloma at various stages (9.6% at stage I, 30.1% at stage II, and 60.3% at stage III). Two (1.5%) presented with plasma cell leukemia. Sixteen patients (11.8%) developed hyperviscosity syndrome. Plasma viscosity was measured in 13 patients; all had elevated viscosities with a mean of 1.94 cP (range, 1.47–2.77). The mean concentration of myeloma proteins in patients with hyperviscosity syndrome was significantly higher than that in patients without (80.2 ± 20.9 *vs* 48.9 ± 31.6 g/L, $p < 0.001$), although there was a considerable overlap (range, 52.4–130 *vs* 33.8–125 g/L). Bence Jones proteinuria was detected in 66.4% of 113 patients with myeloma other than light chain disease (Table 2). Fifty-eight (42.6%) patients had chronic renal insufficiency with a serum creatinine concentration of more than 2 mg/dL. Patients with light chain myeloma were more prone to develop renal insufficiency than other patients (83 *vs* 34%, $p < 0.001$). All 14 patients with λ chain myeloma developed renal insufficiency compared to 55.6% of the nine patients with k chain myeloma ($p = 0.029$). Six patients (4.4%) developed myelomatous pleural effusion; two (1.5%) had myelomatous ascites. All patients were at an advanced stage (III) when effusions/ascites developed.

POEMS syndrome

POEMS syndrome was diagnosed in eight (2.8%) patients. They were relatively young (37–62 yr; median, 46 yr) and all except one were men. Endocrinopathies were found in six of these patients, including hypothyroidism in five, hypogonadism in five, hypoadrenalism in one, and diabetes mellitus in one; osteosclerotic bone lesions were found in four; angiofollicular lymph node hyperplasia (Castleman's disease) in two; IgAλ

Table 2. Comparison of laboratory findings between patients with myeloma, other lymphoproliferative disorders (LPD), and monoclonal gammopathy of undetermined significance (MGUS)

Laboratory finding	Myeloma (n = 136)	LPD (n = 53)	MGUS (n = 84)
No. with paraprotein			
IgG	75 (55.1%)	21 (39.6%)	55 (65.5%)
κ:λ	52:23	14:7	39:16
IgM	1 (0.7%)	22 (41.5%)	5 (6.0%)
κ:λ	1:0	20:2	4:1
IgA	34 (25%)	2 (3.8%)	12 (14.3%)[a]
κ:λ	17:17	0:2	10:2
IgD	1 (0.7%)	0	0
κ:λ	0:1		
Light chain	23 (16.9%)	4 (7.5%)	3(3.6%)[b]
κ:λ	9:14	2:2	1:2
Biclonal	2 (1.5%)	4 (7.5%)	9 (10.7%)[c]
κ:λ	2:1	4:3	8:5
Total κ:λ	81:56	40:16	62:26
Paraprotein level			
IgG (mean ± SD)	60.2 ± 31.5	20.4 ± 8.9	25.8 ± 13.6[d]
Range	10.1–130	9.8–40.8	4.4–71
IgM (mean ± SD)	92.5	30.6±30.7	2.7
Range	92.5	10.2–101	2.7
IgA (mean ± SD)	38.5 ± 25.0		11.9 ± 8.7[e]
Range	4.8–77.1	4.0–29.8	
% with BJ proteinuria[f]	66.4%	53.8%	29.8%[g]
% with hypogammaglobulinemia	70%	20%	5%[h]
% with polyclonal gammopathy	5.2%	52.9%	26.6%[i]

[a]p = 0.002 myeloma *vs* LPD; [b]p = 0.006 myeloma *vs* MGUS; [c]p = 0.014 myeloma *vs* MGUS; [d]$p < 0.001$ myeloma *vs* LPD, $p < 0.001$ myeloma *vs* MGUS; [e]p = 0.002 myeloma *vs* MGUS; [f]% with Bence Jones (BJ) protinuria in patients with intact monoclonal protein in serum; [g]$p < 0.001$ myeloma *vs* MGUS; [h]$p < 0.001$ myeloma *vs* LPD, $p < 0.001$ myeloma *vs* MGUS; [i]$p < 0.001$ myeloma *vs* LPD, $p < 0.001$ myeloma *vs* MGUS.

monoclonal protein in five and IgGλ monoclonal protein in three; and Bence Jones proteinuria in two; none of the eight patients had renal insufficiency or hypercalcemia. Bilateral pleural effusions were found in two patients who died of respiratory failure; and pericardiopleural effusion was found in one patient who died of cardiac tamponade.

Other LPD

Fifty-three patients (18.5%) had other LPD, including 12 (4.2%) with Waldenstrom's macroglobulinemia, 31 (10.8%) with non-Hodgkin's lymphoma, nine (3.1%) with chronic lymphocytic leukemia, and one with immunoproliferative small intestinal disease. Five patients with macroglobulinemia had hyperviscosity syndrome and one had cryoglobulinemia. However, unlike patients with myeloma, the mean concentration of serum IgM in patients with hyperviscosity syndrome was not higher than that in patients without hyperviscosity syndrome.

Essential cryoglobulinemia

Six patients had cryoglobulinemia that was not secondary to the presence of multiple myeloma or macroglobulinemia (Table 3). Hepatitis B virus (HBV) carrier state with positive hepatitis B surface antigen (HbsAg) was found in two and chronic hepatitis C virus (HCV) infection with positive serum anti-HCV in two. Three patients with type II cryoglobulinemia had markedly high titers of rheumatoid factor (≥ 1:5,120).

MGUS

MGUS was diagnosed in 84 (29.3%) patients. Fifteen (17%) of these patients were less than 40 years old, 12 (14%) were 41 to 50 years old, 14 (17%) were 51 to 60 years old, 20 (24%) were 61 to 70 years old, 20 (24%) were 71 to 80 years old, and three (4%) patients were more than 80 years old. The main clinical diagnoses were infections (20.2%), malignancies (16.7%), and autoimmune diseases (10.7%). Five patients developed mono- or biclonal gammopathy after organ transplantation. In a 41-year-old female patient with paroxysmal nocturnal hemoglobinuria, the serum monoclonal IgAκ concentration increased from 19.8 g/L initially to 44.6 g/L after 18 months, with a concomitant increase in the percentage of plasma cells in bone marrow aspirates from 3.8% to 13.6%. There was no Bence Jones proteinuria or osteolytic bone lesions, however. She was probably in the early stage of myeloma.

Biclonal gammopathy

Seventeen patients had biclonal gammopathy (Table 2), including nine with MGUS, four with LPD, two with essential cryoglobulinemia, and two with myeloma.

Comparison of patient groups

Table 2 shows the results of comparison of laboratory findings between patients with myeloma, other LPD, and MGUS. Significantly more patients with myeloma had IgA paraprotein compared to patients with other LPD ($p = 0.002$). Significantly more patients with myeloma had light chain disease compared to patients with MGUS ($p = 0.006$). Significantly more patients with MGUS had biclonal gammopathy compared to patients with myeloma ($p = 0.014$). Bence Jones proteinuria was detected in more patients with myeloma than those with MGUS ($p < 0.001$). Hypogammaglobulinemia was present in more patients with myeloma than in those with other LPD ($p < 0.001$) or those with MGUS ($p < 0.001$ *vs* myeloma). However, concomitant polyclonal hypergammaglobulinemia was present in fewer patients with myeloma than in patients with other LPD ($p < 0.001$) or patients with MGUS ($p < 0.001$ *vs* myeloma).

Discussion

The prevalence of monoclonal gammopathy among ethnic Chinese is unknown. For hospital-based patients, the prevalence in our study was similar to a study from the USA [4], but lower than the prevalence in a series from Hong Kong [1]. Among patients with mono-

Table 3. Clinical characteristics of six patients with essential cryoglobulinemia

Patient No.	Age (yr)/sex	Type of cryoglobulinemia	Monoclonal component	RA factor	Associated disease
1	33/F	I	IgGκ	1:20–	–
2	59/M	I	IgGκ	Not done	HBV carrier
3	57/F	II	IgMκ	1:1,280+	HBV carrier
4	57/F	II	IgMκ	1:20,480+	HCV infection
5	60/F	II	IgMκ+IgGλ	1:5,120+	HCV infection
6	24/F	II	IgMκ+IgAλ	Not done	SLE

RA = rheumatoid factor; HBV = hepatits B virus; HCV = hepatitis C virus; SLE = systemic lupus erythematosus.

clonal gammopathy in our study, the incidence of MGUS (29%) was much lower than was found in a tertiary hospital in Hong Kong (60%; $p < 0.001$) [1] or the Mayo Clinic in the USA (56%; $p < 0.001$) [5]. Possible causes for the lower frequency of MGUS in our patients include the fact that serum or urine electrophoretic studies are not routinely ordered for patients in our hospital, which may decrease the chance of detecting MGUS. Electrophoresis at our hospital was performed on cellulose acetate membrane, which may not detect small amounts of monoclonal protein in patients with MGUS [6]. Another possible cause was that patients with POEMS and those with cryoglobulinemia were diagnosed in our study, but not in other series [1, 5], which probably reflects a local disease pattern.

Although the frequency of multiple myeloma among patients with monoclonal gammopathy in our study was higher than previously reported [1, 5], this result was unlikely to be due to a truly higher number of myeloma patients, but a relative under-diagnosis of MGUS. Actually, Taiwan has a much lower age-adjusted incidence of myeloma, 1.1 per 100,000 for men and 0.57 per 100,000 for women [7], compared to 4.7 and 3.2 per 100,000 for American white men and women, respectively, and 10.2 and 6.7 per 100,000 for American black men and women, respectively [8]. However, in the past decade, there has been a progressive increase in the number of myeloma deaths in Taiwan [2]. The cause of this trend is unknown. Since at least 12.5% of our patients were farmers, an occupation suspected of being associated with myeloma [9], this increasing trend may be related to the widespread use of insecticides in Taiwan during the past four decades [10, 11]. The mean and range of age of myeloma patients in our study were similar to those reported previously [1, 12]. The male-to-female ratio of 2:1 was similar to a study from England [12], but different from a study in Hong Kong (1:1.3, $p = 0.010$) [1]. The percentages of IgG, IgA, IgM, IgD, light chain, and biclonal myelomas and the κ:λ ratio were similar to previous findings [1, 5, 12]. As for complications, our myeloma patients developed hyperviscosity syndrome despite a mild elevation in plasma viscosity (mean, 1.94 cP) in comparison to a previous study which showed that hyperviscosity syndrome occurred only when plasma viscosity exceeded 3 cP [13]. In patients with IgG or IgA myeloma, hyperviscosity syndrome tended to occur in those with high concentrations of myeloma proteins. However, for patients with macroglobulinemia, hyperviscosity syndrome was not correlated with serum IgM levels. This might be due to the fact that IgG and IgA are less likely to form aggregates, and we were therefore more able to predict plasma viscosity from myeloma protein levels. However, IgM molecules are prone to form aggregates, and the measurement of IgM concentration is more difficult due to the instability of the pentameric form of IgM [13, 14]. Therefore, plama viscosity cannot be predicted from IgM macroglobulin levels. Similar to previous findings [15], the frequency of renal insufficiency in this study was higher in patients with light chain myeloma than in those with IgG or IgA myeloma. However, unlike previous reports [15], our patients with λ chain myeloma were more prone to develop renal insufficiency than those with κ chain myeloma. Myelomatous pleural effusions occurred in 4.4% of patients, a percentage at least twice that previously reported (1.6%, $p = 0.131$; 0.8%, $p = 0.002$) [16, 17], and probably reflected the high percentage of patients with advanced stages of myeloma.

In previous studies, POEMS, a syndrome more common in Orientals than Western people [18–21], was not identified as a cause of monoclonal gammopathy [1, 5, 12]. The younger mean age, male predominance, the IgG or IgA paraproteins of the λ type, the associated endocrinopathy, Castleman's disease, osteosclerotic bone lesions, and pleural effusions in the patients in this series were similar to previous findings, but the presence of pericardial effusion and Bence Jones proteinuria were rarely reported in previous studies [18–21]. None of our patients with POEMS had renal insufficiency, which was present in 54.5% of patients in a previous report [20].

LPD occurred in 18.5% of our patients with monoclonal gammopathy, which was higher than reported in previous series [1, 5]. However, the incidence of non-Hodgkin's lymphoma in Taiwan (3.0% for males, 2.0% for females) [7], and the percentage of such patients with monoclonal gammopathy (2.4%) [22], are lower than those in other parts of the world [23, 24]. Thus, the higher percentage of LPD in our patients was not due to a higher number of cases. The results shown in Table 2 indicate that the best laboratory index discriminating LPD from myeloma was polyclonal hypergammaglobulinemia.

In previous studies of monoclonal gammopathy, cryoglobulinemia was not diagnosed [1, 5]. The association between cryoglobulinemia and chronic HCV or HBV infection [25, 26] explains the finding of cryoglobulinemia in our series, since Taiwan has a high prevalence of chronic HBV and HCV infection, and cryoglobulinemia was present in 53% of patients with HCV infection locally [27]. The high titer of rheumatoid factor found in our patients with type II cryoglobulinemia and also in previous studies [28] could be a useful laboratory clue to the diagnosis of cryoglobulinemia.

The diseases associated with MGUS in this study were similar to those reported from Hong Kong [1]

and Finland [29], with infections being the leading category, as opposed to no infections in the Mayo Clinic study [5]. The classical laboratory indices used to differentiate MGUS from malignant monoclonal gammopathy include a low monoclonal protein concentration, the absence of Bence Jones proteinuria, and no hypogammaglobulinemia [30]. As shown in Table 2, the best laboratory index for discriminating MGUS from myeloma in this study was the absence of hypogammaglobulinemia. One patient (1.2%) in our study probably progressed to early-stage myeloma, as indicated by the rapidly increasing paraprotein concentration and plasma cell percentage in bone marrow aspirates. Kyle and Rajkumar reported that about 25% of MGUS patients ultimately develop a malignant plasma cell dyscrasia or LPD during long-term follow-up [31].

Biclonal gammopathy, which occurred in 5.9% of patients in our study, was found in 2% to 10.3% of patients with paraproteinemia in previous series [1, 5, 32]. The results of our study and previous studies suggest that biclonal gammopathy has a greater association with MGUS, which was found in 45% to 73% of such patients, while only 4.5% to 11.8% had myeloma [1, 5, 32].

In conclusion, this study had three major findings: the lower frequency of MGUS in patients with monoclonal gammopathy in Taiwanese in this study was probably the effect of patient selection, methods used in electrophoresis, and local disease patterns. The presence of patients with POEMS syndrome and those with cryoglobulinemia, rarely reported in previous series, was because POEMS syndrome is more common in Oriental than in Western countries, and HBV and HCV infection are highly prevalent in Taiwan. And lastly, the very high association of λ chain myeloma with renal failure, and the higher frequency of myelomatous pleural effusions, probably reflected differences in local disease patterns.

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