MONOCLONAL IMMUNOGLOBULIN AND ITS RELATED ABNORMALITIES IN CASES OF PLASMA CELL DYSCRASIA

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ABSTRACT

One hundred and twenty four cases of plasma cell dyscrasia (PCD) were investigated in terms of monoclonal protein and its related abnormalities. Seventy nine cases of myeloma were compared with 45 cases of PCD without osteolytic myeloma.
Low levels of background immunoglobulins and high proportions of marrow plasma cells were seen in myeloma cases. Among myeloma cases, G-myeloma or A-myeloma had high levels of total serum proteins and monoclonal proteins, in contrast to data of D-myeloma or myeloma with Bence Jones protein only.

INTRODUCTION

Plasma cell dyscrasia (PCD) is an inclusive term[1], synonymous with monoclonal gammopathy[2], which refers to a group of related conditions having as a common feature the excessive proliferation of a single clone of immunoglobulin producing cells. This usually results in the overproduction of a single, homogenous monoclonal immunoglobulin or a polypeptide subunit of an immunoglobulin. PCD included various types of disorders such as osteolytic myeloma, macroglobulinemia, heavy chain disease or other than these with distinctive clinical features[1]. In the present paper, we attempted to elucidate, if present, the differences between myeloma and non-myeloma cases, and the differences among different types of myeloma, regarding marrow plasma cells, erthrocyte sedimentation rate, and the levels of total proteins, monoclonal proteins and background immunoglobulins, since these are presumed to be closely related to the functional status of immunoglobulin producing cells.

MATERIALS AND METHODS

Specific antisera against human IgG, IgA and IgM were developed using rabbits in our laboratory. Anti IgD and anti IgE were obtained from Kallestad Co., USA. Electrophoresis and immunoelectrophoresis were carried out as reported previously[3]. Total protein concentrations were determined by a refractometer (PRP-B, Hitachi Co.). Quantitations of immunoglobulins were carried out as reported previously[4]. The levels of immunoglobulins were tentatively expressed as percentages in reference to the pooled normal sera[4]. Among

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cases with PCD collected at the 1st Department of Medicine of Nagoya University from 1965 to 1975 and at the 3rd Department of Medicine of Kobe University from 1973 to 1975, 124 cases were chosen at random and investigated for the present study. They consisted of 79 cases of myeloma (39 of IgG type, 18 of IgA type, 9 of IgD type and 13 with Bence Jones protein only) and of 45 cases of PCD without osteolytic myeloma (39 cases of IgG type, 6 cases of IgA type).

The latter 45 cases consisted of cases with various diseases; connective tissue disease 8 cases, liver disease 7 cases, non-reticular malignancy 5 cases, arteriosclerosis 5 cases, lymphoreticular malignancy 4 cases, peptic ulcer 3 cases, cholecystitis 2 cases, pulmonary tuberculosis 2 cases, healthy persons 3 cases and miscellaneous elusive 6 cases.

RESULTS

As shown in Fig. 1, age at diagnosis disclosed wide ranges of distribution among 6 types of PCD. Mean age of D-myeloma recorded was 41.2 years, much younger than these of other types as we reported separately[6]. One case with D-myeloma was a 27 year-old male, who is the youngest case of IgD myeloma in the literature. One case with IgG-M-protein, was a 15 year-old female, who had a diagnosis of reticulosis of lymphnodes.

As shown in Fig. 2, numbers of plasma cells in bone marrows were much higher in myeloma groups, irrespective of immunoglobulin types, than in non-myeloma groups.

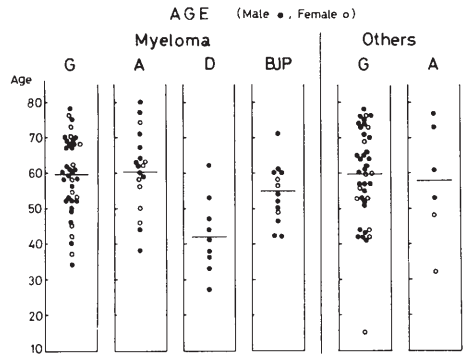


Fig. 1.

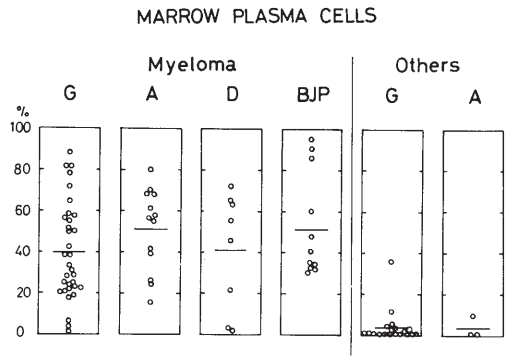
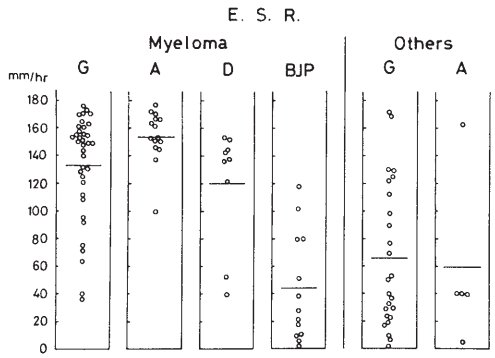


Fig. 2.



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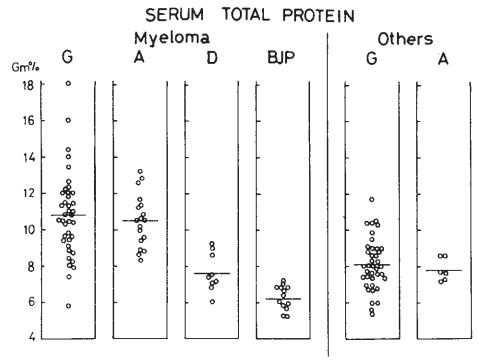

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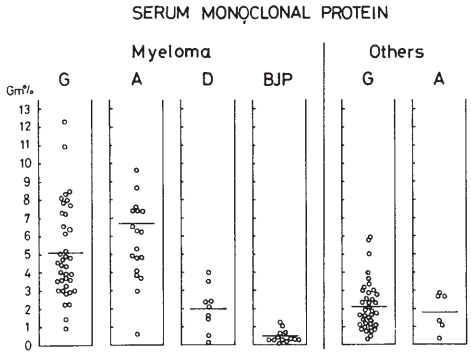

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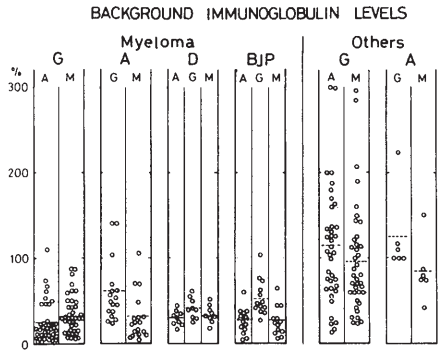

Fig. 6.

Table 1. Mean values and standard deviations

	Myeloma				Others	
	G (39)	A (18)	D (9)	BJP (13)	G (39)	A (6)
Age (yrs)	52 ± 11	61 ± 11	42 ± 10	54 ± 8	60 ± 13	56 ± 13
Marrow plasma cells (%)	39.7 ± 23.4	51.0 ± 19.1	40.8 ± 27.1	53.4 ± 24.6	3.8 ± 8.0	3.8 ± 4.4
ESR (mm/hr)	125 ± 42	154 ± 18	118 ± 43	43 ± 38	64 ± 50	58 ± 55
Total protein (gm/100 ml)	10.8 ± 2.3	10.5 ± 1.4	7.6 ± 1.0	6.3 ± 0.7	8.1 ± 1.4	7.8 ± 0.6
M-protein (gm/100 ml)	5.1 ± 2.5	5.7 ± 2.2	2.0 ± 1.2	0.7 ± 0.3	2.1 ± 1.3	1.8 ± 0.9
IgA (mg/ml) ((%))	56 ± 52 (25 ± 23)		57 ± 8 (25 ± 4)	61 ± 34 (27 ± 15)	256 ± 154 (114 ± 68)	
IgG (mg/ml) ((%))		742 ± 429 (60 ± 35)	548 ± 148 (44 ± 12)	657 ± 250 (53 ± 20)		1554 ± 553 (125 ± 45)
IgM (mg/ml) ((%))	39 ± 25 (34 ± 22)	35 ± 29 (31 ± 26)	34 ± 6 (30 ± 5)	30 ± 18 (27 ± 16)	109 ± 72 (97 ± 63)	95 ± 38 (85 ± 33)

As shown in Fig. 3, erythrocyte sedimentation rate (ESR) revealed wide ranges of distribution. The mean values, however, showed appreciable differences between G-, A-, and D-myeloma (more than 100 mm/hour) and BJP-myeloma or others (less than 70 mm/hour).

As shown in Fig. 4, serum total protein concentrations showed high levels with A- and G-myeloma (mean levels of more than 10.5 gm%), in contrast to low levels with D-myeloma (7.6 gm%), and BJP-myeloma (6.2 g%) and non-myeloma groups.

As shown in Fig. 5, concentrations of serum M-protein measured by cellulose acetate electrophoresis, were somewhat proportional to those of total protein (Fig. 4). G- or A-myeloma showed high levels (mean values of more than 5.1 gm%), whereas the rest of the

groups showed low M-protein levels (mean values of less than 2.1 gm%).

As shown in Fig. 6, background immunoglobulin levels of cases with myeloma were much lower than those of non-myeloma groups.

Table 1 summarized the mean values of data among different types of PCD. Items, which may possibly differentiate myeloma from non-myeloma groups, were low levels of background immunoglobulins and extensive proliferations of plasma cells in marrows. It is noteworthy that one cases (G type of others), with high levels of marrow plasma cells (36%) including cytologically abnormal cells with large nuclei (6%), developed into osteolytic myeloma in 3 years, as reported separately[6]. Among cases with myeloma, BJP-myeloma had low total proteins, low monoclonal protein concentrations and low erythrocyte sedimentation rate.

DISCUSSIONS

PCD is a group of clinical conditions having as common features excessive proliferations of plasma cells and the appearance of monoclonal immunoglobulins. Myeloma is considered to be the most common form of clinically overt PCD and show marrow infiltrations and bone destruction by neoplastic plasma cells[1], as implied by the term myeloma (i.e. marrow tumor).

It may be difficult, however, to evaluate the quality of abnormality and the quantitative distributions of immunoglobulin producing cells in patients with PCD. One of the approaches along this line of investigation is to quantitate the concentration of monoclonal immunoglobulins (Fig. 5), or related abnormalities such as marrow plasma cells (Fig. 2), ESR (Fig. 3), total protein (Fig. 4) and background immunoglobulins (Fig. 6), as shown in the present paper.

Thus, the differences between myeloma and non-myeloma regarding items mentioned above were explored. In non-myeloma, low numbers of marrow plasma cells and relatively well presurved background immunoglobulins were noted. Waldenstrom[7] described that patients with low background gamma were quite common in the benign group, and might indicate that these patients had inhibition of other clones in spite of the fact that the M-component was not very large.

Isobe and Osserman[8] published a clinical study of PCD, where in many cases with M-protein associated with carcinoma a marked plasmacytic infiltration was evident in the stroma of these carcinomas or polyps. This proximity of the epithelial and plasmacytic proliferations suggested a functional association, caused in response to the proliferation of the intestinal epithelium, possibly as part of an immunologic reaction to components of the neoplastic tissues. These plasma cells may possibly be responsible for producing monoclonal proteins in cases with almost normal proportions of marrow plasma cells.

Differences between various types of myeloma, G-myeloma and A-myeloma had similar features in many respects. D-myeloma and BJP-myeloma show low levels of total protein and monoclonal immunoglobulins compared to G-myeloma or A-myeloma, although similar data regarding marrow plasma cells and background immunoglobulin levels were seen in the present study, as well as in reported studies[9) - 11]. The relatively low serum monoclonal protein and total protein levels appear to be a direct result of the rapid rate of IgD[12] or BJP catabolism[13], which are faster than that of other immunoglobulins.

Erythrocyte sedimentation rate (E.S.R.) is a simple but still very useful tool in study of

PCD. Although there are various factors for ESR such as levels of albumin, globulin, fibrinogen, red cell counts, serum viscosity and non-protein nitrogens, the present data (Fig. 3) indicated a clinical usefulness of ESR at the time of screening. Low levels of ESR may suggest D-myeloma or BJP-myeloma more likely than A- or G-myeloma. ESR in cases with non-myeloma showed a very wide range. ESR is, in fact, a nonspecific test and may be of clinical use for the evaluation of treatment in each case.

There is increasing evidence that monoclonal protein associated with PCD in man as well as in BALB/c mice may have functional antibody activity[8), 14)]. Defining the antibody activity in the associated M-protein for each case will ultimately provide significant diagnostic clues to the pathogenesis, and hopefully clues to treatment.

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