Younger Age of Presentation and Extraosseous Tumour in IgD Myelomatosis

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Summary: A study of 14 personal patients and 16 others in the literature shows that (1) IgD myelomatosis often presents at a significantly younger age than other forms of myelomatosis, and (2) during life extraosseous tumour can be detected in about two-thirds of these patients.

The IgD form represents 1.5% of myelomatosis and shows an increased incidence of osteolytic lesions, hypercalcaemia, and renal failure, together with heavy Bence Jones proteinuria (90% type L).

Like only Bence Jones myelomatosis, the IgD form seems to behave clinically in a more vicious manner.

Introduction

Since Rowe and Fahey (1965) described the first case of myelomatosis in which the paraprotein was identified as belonging to a new class of immunoglobulin, IgD, clinical data have become available in a total of 30 such cases (see Table I). In the 14 patients known personally it seemed that the age of presentation was younger than in other forms of myelomatosis and that often the IgD tumour could be found growing out of the bones to form palpable masses—for example, around the ribs (see Fig. 1)—or even as deposits within the soft tissues such as the lymph nodes, spleen, liver, or even kidneys (see Fig. 2).

The available data have therefore been collected to see if these or other clinical features occur with greater frequency in IgD than in other classes of myelomatosis.

Methods

The criteria for accepting a diagnosis of myelomatosis, the methods of examining serum and urine, and the results in patients with IgG, IgA, and only Bence Jones myelomatosis are described elsewhere (Hobbs, 1969). The antiserum specific to IgD was the generous gift of Dr. D. Rowe.

In Table I heavy Bence Jones proteinuria infers over 100 mg./100 ml. and usually nearer 1 g./100 ml. Osteolytic lesions refer to the typical punched out radiological appearances of myelomatosis. Hypercalcaemia implies a serum calcium (corrected for the albumin level) above 5.5 mEq/l. Renal failure was assumed to be present with a blood urea above 80 mg./100 ml. Extraosseous tumour applies to palpable masses around bones, clearly enlarged lymph nodes, or other soft-tissue masses. Hepatosplenomegaly or enlarged kidneys were accepted when shown to contain myelomatosis deposit. One patient (Case 29) who had plasma cell leukaemia is classed as having extraosseous tumour. The numbers at the bottom of Table I refer only to data which were clearly + or 0.

Results

Younger Age at Clinical Presentation

Fig. 3 shows a histogram of the age distribution of the first 24 patients with IgD myelomatosis contrasted to scale with the

frequency distribution found in 188 IgG+94 IgA cases (Hobbs, 1969a), and an early bulge is evident for IgD myelomatosis. This was tested by Kolmogorov's statistic, a χ^2 test at the maximum difference of the cumulated frequency distribution. By 50-59 years 66.7% of the 30 patients in Table I had been reached, whereas only 33.5% of the 282 IgG+IgA cases had been cumulated. This difference was highly significant ($P<0.005$).

TABLE I.—Data from 30 Patients with IgD Myelomatosis at the Time of Clinical Presentation

No.	Age	Sex	Light Chain Class	Heavy Bence Jones Proteinuria	Osteolytic Lesions	Hypercalcaemia	Renal Failure	Extraosseous Tumour	Reference
1	57	M	L	+	—	—	—	—	Rowe and Fahey (1965)
2	53	M	L	+	+	—	+	—	Burtin <i>et al.</i> (1966)
3	55	F	L	+	+	—	+	—	
4	65	M	L	+	—	—	—	—	
5	42	F	L	+	+	+	+	+	Axelsson (1966)
6	42	F	L	+	0	+	+	+	
7	43	M	L	+	+	0	0	+	
8	53	M	L	+	+	+	+	0	Hobbs <i>et al.</i> (1966)
9	56	M	L	+	+	0	0	+	
10	44	M	L	+	+	0	0	+	
11	57	M	L	+	+	+	0	0	R. B. Thompson and A. R. Horler* C. L. Cope*
12	62	M	L	+	+	+	+	+	
13	48	M	L	+	0	+	0	+	
14	67	F	L	+	—	—	+	—	G. Blundell* A. W. Walker* P. H. Everall and G. Grant*
15	74	M	L	+	+	0	0	0	
16	67	M	L	+	0	+	+	0	
17	50	M	K	+	+	+	+	0	R. Penny* R. Penny* Rogentine <i>et al.</i> (1966)
18	67	M	L	+	+	+	+	+	
19	45	M	L	—	—	—	0	—	
20	44	F	L	+	0	—	0	—	Ventruto and Quattrin (1966)
21	71	M	?	0	+	0	0	—	
22	58	M	K	+	+	0	+	—	
23	48	M	L	+	+	0	+	+	Zawadzki and Rubini (1967)
24	55	F	L	+	+	—	+	+	
25	73	M	L	+	0	0	—	—	
26	55	M	L	0	+	0	+	0	Masaki <i>et al.</i> (1967)
27	58	F	L	+	0	0	—	0	
28	55	M	K	+	+	—	+	0	
29	69	F	L	+	+	—	0	+	Wiedermann <i>et al.</i> (1967)
30	71	M	L	+	+	—	0	—	
Total	22 M/ 8 F	3K/ 26 L (90%)	25/27 (93%)	20/26 (77%)	9/19 (47%)	12/23 (52%)	12/19 (63%)		

* Referrals to the M.R.C. myeloma trial centre at Hammersmith Hospital.

The mean age for IgD patients at 57.1 years was similar to that for only Bence Jones patients (55.5 years) who also show a highly significant early bulge in frequency distribution with age (Hobbs, 1969).

Extraosseous Tumour

Figs. 1 and 2 show the two main types of extraosseous tumour growth: breaking out of a bone locally or truly within soft tissue. The photographs were kindly made available by Dr. G. Meachim, who carried out the necropsy in Case 10. In this patient Dr. H. T. Swan first drew our attention to extramedullary tumour. Table I shows that extraosseous tumour was detected during life in 63% of IgD patients where data were available.

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Other Features of IgD Myelomatosis

Table II summarizes the major features of IgD contrasted with the three commonest classes which account for IgG 53%, IgA 22%, and only Bence Jones 20% of myelomatosis.

The incidence of IgD myelomatosis was previously found to be 3% of proved myelomatosis (Hobbs *et al.*, 1966), but this was probably an overestimate. To date only seven IgD patients

FIG. 1.—The IgD myeloma has broken out of the rib into the pleural tissues. In this patient (Case 10) both the pleura and outer wall of the chest were involved by numerous similar tumours. In other patients similar break-outs have occurred in the pelvis.

FIG. 2.—Both renal cortices are infiltrated with greyish IgD myeloma, mottled with purplish patches. Similar involvement was seen in the spleen and liver in this patient (Case 10).

FIG. 3.—Histogram of age of presentation of IgD myeloma patients compared to scale with the frequency distribution for IgG and IgA myelomatosis. Note the excess of IgD patients presenting before age 59 years.

have been found among our 456 consecutive cases, Bachmann (1965) reported 2 among 194 patients, and Zawadzki and Edwards (1967) 2 among 170 patients with definite myelomatosis, so that the true incidence is probably 1.5%.

TABLE II.—Clinical Features of Myelomatosis at Presentation According to Immunochemical Class

No. of Cases	Class	Light Chain Type L (%)	Heavy Bence Jones Proteinuria (%)	Mean Age (Years)	Sex Ratio M/F	Osteolytic Lesions (%)	Hypercalcaemia (%)	Renal Failure (%)	Extraosseous* Tumour (%)
30	IgD	90	93	57.1	2.8	77	47	52	63
94+11*	B.J.	34	67	55.5	1.0	78	62	33	>10
188+6*	IgG	33	20	62.1	1.2	55	33	16	3
94+1*	IgA	33	31	63.7	1.1	65	59	17	1

* Known to be detected during life (see Discussion).

The sex ratio 2.8M:1F is to date most unusual compared with other classes (see Table II). The incidence of osteolytic lesions is as high with only Bence Jones myelomatosis and is significantly greater than with IgG myelomatosis, as are also the high incidence of hypercalcaemia and renal failure. The other striking features are that 93% show heavy Bence Jones proteinuria and that the light chain class is type L in 90% as compared with 33% for other classes.

Discussion

This report establishes that presentation at younger ages is a feature of IgD myelomatosis compared with IgA and IgG myelomatosis. In this, together with the higher incidence of osteolytic lesions, hypercalcaemia, and renal failure, IgD myelomatosis is similar to only Bence Jones myelomatosis, as is also apparent from the high incidence of associated heavy Bence Jones proteinuria. The abortive parent of only Bence Jones myelomatosis is not known—that is, which heavy chain class has failed to be formed.

From the frequency of normal cells producing immunoglobulins of the different classes (Hobbs, 1968) it seems probable that the only Bence Jones parenthood includes all classes and probably only a very small fraction is derived from IgD. Evidence that only Bence Jones myelomatosis represents a dedifferentiated and more vicious form of myelomatosis is given elsewhere (Hobbs, 1969) and the present evidence suggests that IgD myelomatosis behaves similarly.

In this light extraosseous tumour growth might be expected. During life this is infrequently detected in other classes of myelomatosis; Edwards and Zawadzki (1967) found only six such patients among 78 with myelomatosis. At necropsy it is known that extraosseous myeloma is found more frequently; Innes and Newall (1961) reported 14 such cases among 45 necropsies, but in their overall series of 188 cases it appears only six were detected during life. Thus the 63% incidence of extraosseous tumour in IgD myelomatosis during life suggests this class differs significantly from the others. As regards only Bence Jones myelomatosis we have not collected adequate data in the 94 patients who have presented with the usual clinical picture of myelomatosis. On the other hand, another 11 only Bence Jones patients have presented as soft-tissue plasmacytoma. Only 1 out of 95 IgA and 6 out of 204 IgG patients have had extramedullary presentations, so that, like IgD, the only Bence Jones cases seem to have a higher incidence of extraosseous tumour.

Finally, while 30 patients with IgD paraprotein have been shown to have myelomatosis, Bachmann (1965) records one such patient in whom no reticuloendothelial malignancy had been detected, though a bone marrow had not been examined. We have seen a man who died at 49 years of age from metastatic

thyroid medullary carcinoma and who had in his serum 400 mg. of IgDL paraprotein. Bone marrow and radiological examination were negative. In co-operation with Mr. Selwyn Taylor and Dr. E. D. Williams we could detect no arteriovenous difference in the plasma level of IgD across the circulation through a large mass of mediastinal carcinoma, some of which was successfully grown in tissue culture by Dr. P. J. L. Holt. Radioactive amino-acids were added, followed by carrier IgDL protein, but radioimmuno-electrophoresis did not show any IgD synthesis by the thyroid medullary carcinoma. It would thus seem that IgD, like other paraproteins, can sometimes have benign significance.

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Hypermagnesaemia in Presence of Magnesium Depletion in Acute-on-chronic Renal Failure

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Summary: A patient with renal failure developed hypermagnesaemia, with confusion, drowsiness, and dysarthria. Nevertheless, the dietary magnesium content was low, and investigation showed actual intracellular depletion of magnesium. The cause of this state is not known, though it is presumably connected with a failure to maintain the normal concentration gradient of magnesium across the cell wall. The clinical state and the serum magnesium level returned to normal after treatment with calcium gluconate.

Introduction

In renal failure hypermagnesaemia often develops in association with oliguric crisis (Hamburger, 1957; Takayasu *et al.*, 1962). Severe reduction of glomerular filtration rate to less than 30 ml./min. (Robinson *et al.*, 1959), increased tissue catabolism and acidosis leading to shift of intracellular magnesium to the extracellular fluid (Nabarro *et al.*, 1952; Martin and Jones, 1961), and the intake of magnesium-containing medication (Smith and Hammarsten, 1958) are responsible factors, jointly or severally. Very high values, in excess of 4 mEq/l., are usually associated with a large intake of magnesium in the oliguric phase (Randall *et al.*, 1964).

The case reported here is one of acute-on-chronic renal failure where the patient developed very high serum magnesium while on a restricted protein diet of low magnesium content. Magnesium-containing drugs were not given. A very interesting feature is the evidence of magnesium depletion while the patient was hypermagnesaemic.

Case Report

A 57-year-old man, a known acromegalic, was admitted to the General Hospital, Singapore, on 4 August 1967. He gave a history of recurrent attacks of fever and chill associated with frequency of micturition, lethargy, and anorexia for one year, and a dull constant pain in the left loin associated with dysuria for three days. There had been no other past illness of note.

On examination, in addition to features of acromegaly (large protruding lower jaw, "main succulente," large tongue, thick coarse skin with multiple lipomata, and hepatomegaly) he was anaemic and sallow. An early diastolic murmur was heard at the left parasternal edge in the fourth and fifth intercostal spaces. There was collapsing pulse. Blood pressure was 130/60 and the left ventricle was enlarged. There was no evidence of congestive heart failure, and no tenderness in the left loin. The kidneys were not palpable. No abnormality was found in the respiratory and neurological systems. Fundi and visual fields were normal.

Serological tests for syphilis were negative. Blood urea was 240 mg./100 ml.; creatinine clearance 1.6 ml./min.; K 5.8 mEq/l.; Mg 2.9 mEq/l. (normal 2.0±0.34 (2 S.D.) mEq/l.); Ca 8.5 mg./100 ml. (normal 9.5±0.8 mg./100 ml.); phosphate 13.7 mg./100 ml. Both serum magnesium and serum calcium were estimated with atomic absorption spectrophotometry (Unicam SP 90). Urine examination showed the presence of numerous pus cells with albumin. Urine culture grew *Escherichia coli*. Glucose tolerance was mildly diabetic—104 mg./100 ml. (zero hour), 106 mg./100 ml. (½ hour), 133 mg./100 ml. (1 hour), 138 mg./100 ml. (1½ hours), and 138 mg./100 ml. (2 hours). X-ray examination of the abdomen showed vesical calculi and a calcified opacity in the left flank. No filling defects in the right renal pelvis were observed on retrograde pyelography, but stones were seen in the upper and lower calices of the left kidney. Chest x-ray examination showed a large heart with left ventricular enlargement and unfolding of aorta. Skull x-ray examination showed the presence of a large pituitary fossa and bony changes of acromegaly. Hand x-ray examination revealed typical acromegalic features—increase in length of fingers, accentua-

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