CLINICAL FEATURES OF MULTIPLE MYELOMA

A Review of the Clinical Manifestations and Laboratory Investigations in 40 Cases

C. P. DANCASTER, B.Sc., M.B., M.R.C.P.E.*

Lately Medical Registrar, Lambeth Hospital, London

O. A. N. HUSSAIN, M.D.

Assistant Pathologist, Lambeth Hospital, London

W. P. U. JACKSON, M.A., M.D., M.R.C.P.

Physician, Groote Schuur Hospital, Cape Town, South Africa

The study of multiple myeloma really began in 1845 when Sir James Watson and Dr. MacIntyre sent specimens of urine from a tradesman of 45 years suffering from fragile bones to Dr. Bence Jones for analysis. In 1848 the latter published his now famous description of the proteinuria in 'Mollities Osseum'.⁵ Dalrymple had already reported the post-mortem findings in the case.¹¹ Twenty-five years later von Rustizsky described the condition 'Multiple Myelom'—multiple tumours of the bone, and in 1889 Kahler first connected the two conditions and described the syndrome of multiple myeloma (still occasionally referred to as Kahler's disease), as consisting of the tetrad, deformation and abnormal fragility of bones with bone pain, cachexia and the presence of Bence Jones proteinuria. This concept of the disease has been expanded and modified, but the aetiology still remains unknown. It was considered to be one of the rarest of tumours arising from bone and in a review of the literature up to 1928, only 425 cases had been described.¹³ It must now be regarded as fairly common. The apparent increased incidence is in part due to the use of needle marrow biopsy and serum protein electrophoresis, and to the greater number of older people.

This series comprises 28 White and 12 non-White subjects—11 of the latter were South African Bantu. The ages of the patients varied between 36 and 75 years. Sixty-six per cent. were over 50 years. There were 22 males and 18 females (see Table 1).

Symptoms and Signs (Fig. 1)

Bone pain was present in 95 per cent. Its

severity varied—usually it was mild, but in some cases it was severe enough to render any movement agonizing. The pain was most frequently felt in the lumbar region, and this was the presenting symptom in 75 per cent. of the cases. Other common sites of pain were the rib cage in 25 per cent. and the upper end of femur and humerus. In spite of the frequency of radiological changes in the skull (50 per cent.) only one patient complained of pains in the head.

Weight loss and lassitude were present in 25 per cent. of the patients—in one case 70 lb. was lost in 6 months.

Anaemia was common. The haemoglobin was below 75 per cent. in two-thirds of cases and usually got worse as the disease progressed. Nine patients had a haemorrhagic tendency. The sites of bleeding were severe epistaxis (4), mild haematemesis (2), subarachnoid haemorrhage (2), haemoptysis (1), haematuria (1) and bleeding per vaginam (1).

*Present address: Groote Schuur Hospital, Cape Town, South Africa

TABLE I

Case	Sex	Age	Globulin G. per 100 ml.	Electro- phoretic peak	Sedi- mentation rate mm./hr. Westergren	Bence-Jones Proteinuria	Blood urea mg. per 100 ml.	Serum calcium mg. per 100 ml.	Serum inorganic phosphorus mg. per 100 ml.	Alkaline phos- phatase King Armstrong Units	Haemo- globin percentage of 13.8 G.
1	F	39	12.2	Y	164	—	60	9	2.5	6	50
2	M	49	5.2	Y	—	—	26	13	2.0	7	100
3	M	45	5.6	Y	64	—	36	9.7	—	9	68
4	M	32	4.2	Y	32	—	45	12.2	3.1	10	82
5	F	75	2.1	Normal	—	+	27	9	5.1	10.5	86
6	M	63	3.8	—	59	—	68	—	—	—	81
7	F	43	1.4	Normal	47	+	51	15.4	2.6	6	62
8	M	72	6.5	$\beta \downarrow \gamma$	—	+	31	7.2	—	7	48
9	F	46	1.4	α_2	—	—	63	12.9	3.8	7	100
10	M	56	2.1	—	40	+	29	10.6	5.6	10	78
11	F	74	6.1	$\beta \downarrow \gamma$	65	—	64	10.1	3.0	2	26
12	M	68	5.8	Y	—	+	60	—	—	6	81
13	M	55	5.0	Y	56	+	—	—	—	—	73
14	M	30	6.4	Y	50	+	62	9.8	—	6	48
15	M	70	5.6	Y	63	—	47	10.5	4.1	10	65
16	F	60	1.5	α_2	75	+	211	10.4	5.5	5	58
17	M	60	6.5	—	140	—	—	—	—	5.6	100
18	F	52	2.3	—	10	—	37	—	—	—	80
19	F	61	6.3	—	140	+	96	9.2	3.7	4.3	64
20	F	62	2.6	—	60	+	150	10.7	2.5	—	43
21	F	50	4.2	—	160	—	143	—	—	—	50
22	F	77	8.2	—	98	+	—	7.9	—	5	36
23	M	38	2.8	—	17	—	38	11.7	2.9	6	100
24	M	48	3.4	—	7	—	—	—	—	5.3	60
25	F	60	8.7	—	145	—	—	13.0	1.7	—	60
26	M	33	3.5	—	116	—	20	8.8	—	4.6	41
27	M	62	6.0	—	132	+	39	13.9	2.8	8.5	75
28	M	61	7.1	—	—	—	—	10.2	4.0	5.1	57
29	M	51	2.1	α_2	16	+	66	17.6	—	11	100
30	M	42	3.4	Y	18	—	33	10.0	3.8	10.3	70
31	F	50	9	—	61	—	55	9.4	—	9.4	70
32	M	45	6.7	—	58	+	144	11.6	6.6	6.4	80
33	M	38	3.4	—	—	—	—	—	—	—	100
34	F	47	7.1	—	125	+	—	9.4	5.8	7.9	85
35	F	69	7.2	—	155	—	122	—	—	—	45
36	F	60	6.7	Y	67	—	—	9.0	4.0	12.5	60
37	F	55	4.6	Y	75	—	105	9.0	2.2	9.9	40
38	M	54	6.6	—	47	—	32	—	—	9.0	75
39	M	54	4.8	Y	100	+	90	—	—	—	75
40	F	60	8.9	—	75	—	18	9.0	—	9.5	50

Weakness of the legs was a symptom of 6 patients (15 per cent.), all of whom had signs of spinal cord compression, and 4 of these had paraplegia.

The frequency of the above symptoms is about the same as that reported in other series.^{3, 6, 13, 15, 23}

In eight patients vomiting was a prominent symptom.

There was evidence of lung involvement in 45 per cent. of the cases, one of whom (case 1) is described below:

A European female aged 39 had 3 previous hospital admissions for pneumonia in the 18 months prior to the diagnosis of multiple myeloma. On each occasion she suffered pleuritic chest pains, with a pyrexia of

103°-104°, and X-ray changes compatible with broncho-pneumonia. The pneumonia was resistant to antibiotics but finally cleared in 3-4 weeks.

Special Investigations (Fig. 2)

Marrow biopsy

The marrow contained an increase in the plasma cell series in 34 of the cases. In 3 cases the sternal marrow was normal, but in all of these myeloma tissue was found in localized masses—a specimen obtained by laminectomy; a tumour of the mandible; and a mass in the neck. Two of these had widespread bony involvement radiologically.

In 3 cases a marrow biopsy was not done but

the diagnosis had been made on other grounds and was confirmed at autopsy in 2.

Serum Globulins and Electrophoresis

Seventy-five per cent. of these cases had a serum globulin level above 3 G per cent.

Electrophoresis was performed in 19 cases: in 14 there was an elevation of total globulins and in all of these there was an excess of gamma globulin.

Electrophoresis was normal in 2 cases and there was a relative excess of α 2 globulin in 3 cases. There were also 2 cases with the M globulin pattern.

Flocculation tests were abnormal in 9 of 22 cases. All these patients had hyperglobulinaemia. There were, however, occasional patients in whom the flocculation tests were normal in the presence of hyperglobulinaemia.

Sedimentation rate (ESR Westergren)

The ESR was above 40 mm/hr. in 28 cases and below 20 mm/hr. in 5 cases.

There is a correlation between high ESR and high serum globulins (Fig. 3). However we found some cases in which the ESR was raised and the globulins normal, as did Snapper.²³

Bence Jones Proteinuria

This was present in 38 per cent. of cases. In some patients the urine was examined once only. It is important to examine the urine on a number of occasions since Bence Jones proteinuria may be sporadic. However, the fact that little over one-third of our cases had Bence Jones protein, emphasises that this test should not be relied upon as a 'screening test' for myelomas.

Bence Jones proteinuria has been said to occur

FIG. 3.—Relation between sedimentation rate and serum globulin.

FIG. 4.—Relation between serum globulin and Bence Jones proteinuria.

more commonly when the serum globulins are normal. We found it present in 66 per cent. of cases where globulins were below 3 G per cent. but in only 29 per cent. of cases where globulins were above 3 G per cent. (see Fig. 4). (The difference between these two percentages is probably significant, $p = .045$). An association between Bence Jones proteinuria and renal insufficiency has been described by Armstrong² and Snapper,²³ *et al.*, who suggest that renal involvement may be due to blockage of renal tubules by protein. The blood urea was raised above 50 mg. per 100 ml. in 17 of 31 cases, but in six of these cases there was no Bence Jones proteinuria.

Serum Calcium and Inorganic Phosphorus

Serum calcium was elevated above 11 mg. per 100 ml. in 9 cases. The serum phosphorus was below 2.5 mg. per 100 ml. in 4 cases, and above 5 mg. per 100 ml. in 5 patients, 3 of whom had uraemia.

Serum alkaline phosphatase was estimated in 31 cases and was normal in all—the highest being 12.5 King-Armstrong Units. It is a useful test in differentiating this disease from other conditions in which there is widespread osseous involvement, when the alkaline phosphatase is usually raised.

Cerebro-spinal Fluid (CSF)

Changes in CSF have been reported in myeloma.^{7, 9, 12, 16, 19} In our series lumbar puncture was performed in only 6 patients—5 because of neurological signs, 1 because of epilepsy. In the latter, the CSF was normal, but in 4 of the 5 patients with neurological involvement—all of whom had collapsed lumbar vertebrae—the protein was raised (see Table 2). In these cases there was no increase in the cellular

TABLE 2

	CSF Protein	Serum globulin
Paraplegia	Normal	4.2
Collapsed T11 with extensor plantar response	600	5.0
Paraplegia	100	5.0
Epilepsy	Normal	5.2
Paraplegia	200	6.0
Paraplegia	190	6.7

content and no evidence of spinal block. There did not appear to be a relation between the level of serum globulin and elevation of protein in the cerebro spinal fluid.

X-ray Changes

There were only 4 patients who did not have spinal involvement radiologically. The incidence of other skeletal disease is shown in Fig. 5.

Prognosis

Follow-up reports are available on 25 of the 40 patients. Twenty-one of these are dead. The interval between admission and death varied between 2 months and 1 year. However, the first symptoms often preceded admission to hospital by 1 year.

Four of the patients are known to be still alive; two of them have been observed for 4 months, one for 1 year. The one patient who has now been followed-up for 5 years is described below:

Solitary Myeloma becoming Multiple later (Case 2)

A European male aged 49 years, first presented 6 years ago with a swelling of his neck. This was excised and proved to be a myeloma in a cervical gland. There was a local recurrence 2

years later which was again excised and followed by deep X-ray therapy. Following this, he remained well for 3 years during which time there was no radiological evidence of myeloma in his skeleton. However, the serum globulin was 5.2 G per cent. with an excess of gamma globulin. The serum calcium was 13 mg. per 100 ml.

One year later, 5 years after being first seen, he was admitted with thrombophlebitis of his legs and disseminated skeletal myelomatosis. Marrow removed from the iliac crest was normal at the same time as his sternal marrow count showed 80 per cent. myeloma cells. This illustrates the need for multiple punctures if there is an initial negative result in the presence of other strong indications of myelomatosis.

There have been frequent reports of solitary myeloma, and although such cases are unusual in that the prognosis is much better, in most instances dissemination occurs later.^{3, 10, 15, 17, 24}

Antibody Formation

These patients are particularly susceptible to intercurrent infections, especially pneumonia. Geschickter and Copeland,¹³ and Bayrd and Heck³ considered that these lung infections could be ascribed solely to the hypostatic pneumonia which may develop in debilitated or elderly bed-ridden patients. However, recent work suggests a diminished ability to form antibodies in myeloma.^{18, 20} We have found that there is a significantly higher serum globulin level in those white patients who develop pneumonia. (A mean of 6.6 G per cent compared with 3.6 G per cent. in those who did not develop pneumonia: $t = 3.9$; $p = .001$.)

As these are abnormal globulins the inability to form antibodies would seem a likely explanation of recurrent lung infections—a 'dysgammaglobulinaemia' in fact.

We have investigated antibody formation in seven myeloma patients with increased gamma globulin. T.A.B. antigen was given at 4-weekly intervals in a dose of $\frac{1}{4}$, $\frac{1}{2}$ and 1 cc. Standard serological investigations showed no agglutinations for *Salmonella typhi* O and H antigens. In addition 5 of these patients received 15 cc. of incompatible blood. In two, the relevant A or B antibody titre went up from 1/1 to 1/8 and 1/16. The others had no rise in titre. These results indicate diminished ability to form antibodies.

One of these patients, a white female aged 64, had a striking history of recurrent infections. In the few years preceding 1953 she had suffered from 5 attacks of pneumonia and pleurisy, the last one with haemoptysis, and 2 superficial

abscesses. In 1954, bone pain, weakness and anaemia appeared, and the X-rays, sternal marrow and serum proteins were characteristic of myelomatosis. In 1957 she was in hospital with similar symptoms and 2 further attacks of pulmonary infection.

Her past history was interesting in that she had had annual pneumonic episodes, with haemoptyses, for many years from the age of 25. No cause for these attacks was found, and in fact, chest X-rays and bronchograms in 1957, between attacks, were completely normal.

Comment: It is characteristic that the pneumonic episodes should precede the features of myelomatosis itself, presumably because the abnormal gamma globulins appear early in the course of the disease. This case, however, makes one wonder whether this abnormality may not precede the myeloma even by several decades—a condition of pre-myelomatosis, in fact.

States of 'Pre-myelomatosis'

We have suggested that single myelomas and dysgammaglobulinaemia with pulmonary infections may precede for some years the development of generalized myelomatosis with skeletal lesions. The next two patients illustrate, we believe, further varieties of 'pre-myelomatosis', and include the conditions of macroglobulinaemia and primary amyloidosis.^{8, 14, 25}

One patient, a coloured male aged 45 years, had 5 hospital admissions over the course of years for pneumonic episodes in different sites. Between attacks he was healthy and bronchograms were normal. His sedimentation rate was 110 mm. per hour (Westergren) even when afebrile and serum globulin was 6 g. per 100 ml., with a distinct peak of the γ globulin fraction on electrophoresis. About half of this γ globulin was shown to have a molecular weight of over 1 million—i.e. it was a macroglobulin.* His skeletal system was normal on X-ray but the sternal marrow was characteristic of myelomatosis.

Myeloma may also present as primary systematized amyloidosis. A coloured male aged 60 years presented with an enlarged irregular tongue, cutaneous papillomata especially remarkable on the eyelid and indurated firm rubbery nodules in the muscles of the back lying on the deep fascia which, on biopsy, were shown to be amyloid in fibro-adipose tissue. His serum proteins, sedimentation rate, and skeletal system were all normal, but his sternal marrow was characteristic of myeloma.

*Our thanks are also due to Dr. A. Poulsen for this estimation.

Comment: We believe that both these patients have myeloma in an early stage of the disease, but it might be argued that, both conditions, macroglobulinaemia and primary amyloidosis, may include plasma cells in the marrow yet not necessarily be examples of myelomatosis nor even progress to this state. A follow up of these patients with later reports is planned. However, it would certainly appear that further investigation of unexplained high sedimentation rates or unexplained pneumonias might lead to myeloma being discovered more often in this early stage.²²

Discussion

Myeloma is often undiagnosed for some time. Because it occurs in older people and lumbar pain is the commonest presenting symptom, it is often initially misdiagnosed as 'sciatica' or neoplastic secondaries. Other common diagnoses on admission to hospital were unexplained uraemia, anaemia and pathological fractures.

Investigations most often employed when myeloma is suspected are examination of urine for Bence Jones protein, estimation of the sedimentation rate and of serum globulin with electrophoresis, X-rays of the skeleton (often only of the lumbar spine) and marrow biopsy. Although these will usually lead to the correct diagnosis, there are occasional patients in whom one or more of these investigations may be normal. As we have shown in this series, patients with normal sedimentation rates often have normal serum globulins. Although those patients with low globulin levels usually have Bence Jones proteinuria, this is not always so (e.g. case 18). Consequently, when the possibility of myeloma exists, all these investigations together with a more widespread skeletal survey should be performed.

The number of myeloma or plasma cells in the individual marrow aspirates varied from 10 per cent. to over 50 per cent., but it is well known that this is entirely fortuitous as a normal marrow may be obtained at one site and sheets of myeloma cells at another. It is this feature that has given rise to the term 'multiple plasmacytoma' as distinct from 'multiple myelomatosis' though we do not believe that these are separate entities, but merely stages in the development from a solitary plasmacytoma to multiple myeloma.

The appearance of cells in the marrow aspirates is a more satisfactory guide, and the findings of the typical large myeloma cell with foamy cytoplasm, the vacuolated Mott cells and characteristic Russell bodies all help to confirm the myelomatous nature of the marrow. It must be admitted, however, that plasma-cytosis from other causes (e.g. carcinoma and chronic infections) may not be easy

to differentiate in the absence of characteristic sheets of cells and other bio-chemical findings.

Skeletal involvement could account for the elevation of serum calcium, but many patients with extensive osseous involvement have normal serum calcium levels. Moreover, one of our cases (case 2) had a serum calcium of 13 mg. per cent., one year prior to any radiological evidence of myeloma. Although it is still possible that the calcium was derived from bones without evidence of bone pathology radiologically, another possible explanation of hypercalcaemia might be increased gastro-intestinal absorption, as has been shown to occur in sarcoidosis.¹

Beare⁴ and McGeown²¹ have reported cases of myeloma being mistaken for hyperparathyroidism. The similarity of radiological appearance together with a raised serum calcium and low inorganic serum phosphorus accounts for the difficulty in diagnosis. Two of our cases (case 2 and 25) had serum phosphorus levels below 2 mg. per cent. with elevated serum calcium. Moreover, the serum phosphorus may be normal or elevated in hyperparathyroidism complicated by uraemia, which makes differential diagnosis even more difficult. However, unnecessary exploratory operations can be avoided if the serum alkaline phosphatase is determined, as this is, apparently, always normal in myeloma.

Summary

The clinical features and special investigations of 40 cases of multiple myeloma are described. With few exceptions the incidence of the various findings correspond with those reported in other series. The commonest presenting symptom was lumbar backache—often diagnosed as a prolapsed disc.

Recurrent pulmonary infections frequently occur, and we have noted that the patients who develop these pneumonic attacks have a higher serum globulin level than those who do not. We have also confirmed the suggestion that these patients have a diminished antibody response, probably because the only gamma globulins they can make are abnormal.

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be severely jaundiced and showed multiple cutaneous petechial haemorrhages, most notably on the flexor surfaces of the limbs. The cause of death was found to be a left-sided sub-arachnoid haemorrhage with multiple small cerebral haemorrhages. There was also severe pulmonary congestion and oedema, a right-sided plural effusion and multiple haemorrhages into all the tissues of the body.

The liver was enlarged, weighed 2,545 gr. and had numerous subcapsular haemorrhages scattered over its surface. On section numerous haemorrhagic areas, both large and small, were seen to be scattered throughout the hepatic parenchyma (Figure 1). No extra-hepatic obstruction of the biliary system could be demonstrated despite a careful search. The gall bladder and bile ducts were normal in appearance, contained no calculi and showed no evidence of inflammation, strictures or neoplasm while there was no enlargement of lymph glands in the porta hepatis. The pancreas contained no neoplastic, inflammatory or fibrotic changes which could have caused obstruction to the common bile ducts.

Histological examination of the liver showed a gross degree of infiltration with myeloma cells and some necrosis of liver cells, together with fatty infiltration of many of the remainder. (Figures 2 and 3.) In addition, there were numerous haemorrhagic areas filled with red blood cells and some polymorphs and lymphocytes were scattered through the liver parenchyma. There was no portal or biliary cirrhosis and the presence of amyloid could not be demonstrated by methyl-violet or congo-red stains.

Discussion

Visceral involvement has been noted, to some extent, in many cases of multiple myeloma, either by evidence of hepatomegaly or splenomegaly as in the series of Snapper *et al.* (1953)¹, who found palpable hepatomegaly in 40 per cent. of their cases and hepatosplenomegaly in a further

23 per cent., or at autopsy by histological evidence of infiltration of these organs with myeloma cells; Churg and Gordon (1942)² found that 73 per cent. of their series of thirty cases had some infiltration of the liver with plasma cells.

However, diffuse visceral infiltration may occur without invasion of the peripheral blood by plasma cells, as in the patient reported by Stark and Amidon (1948)³, where the clinical picture was very similar to that presented here. In their case the man was admitted for investigation of loss of weight and chest pain and was found to be jaundiced, with an enlarged liver; widespread skeletal involvement was found on radiological examination. Sternal marrow biopsy established the presence of myeloma. At autopsy no cause for the obstructive jaundice could be found but the liver was extensively infiltrated with myeloma cells.

It is difficult to understand how infiltration of the liver by plasma cells can give rise to an obstructive jaundice but the probable explanation is that the cellular infiltration disrupts most of the bile canaliculi and those which are not disrupted have their lumen occluded by pressure from plasma cells on the surrounding hepatic cells.

Summary

A case of multiple myeloma which presented clinically as obstructive jaundice is described. A search of the literature has revealed no previous report of a similar case.

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