MEDICAL PRACTICE

*Occasional Review***Spinal-cord compression in myeloma**

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British Medical Journal, 1979, 1, 1541-1544**Summary and conclusions**

Clinical records of 47 patients in whom spinal-cord compression was the presenting feature of plasma-cell myeloma were analysed retrospectively. Patients were referred during 1954-78. Median survival was 30 months and prognosis was best for those in whom the site of cord compression was the thoracic region. Early laminectomy and decompression followed by adequate radiotherapy resulted in complete or good partial response in over a third of patients who presented with complete paraplegia.

Improvements in supportive care and more effective chemotherapy allow spinal-cord compression in myeloma to be treated promptly and vigorously, thus improving duration and quality of survival in a substantial proportion of patients.

Introduction

Neurological complications of myeloma are relatively common,^{1 2} and include those associated with various metabolic disturbances,

hyperviscosity, amyloidosis, peripheral neuropathy, and, occasionally, cranial nerve palsies. Spread to the central nervous system most commonly presents as compression of the spinal cord or cauda equina. Batts,³ in reviewing 40 patients with myeloma, found that in 35% the central nervous system was affected, and half of these patients had paraplegia secondary to spinal-cord compression. An incidence of spinal-cord compression varying from 6-16% is quoted by several authors.^{4 5} In two large reviews of extradural spinal tumours^{1 6} myeloma accounted for 9-10% of cases.

Spinal-cord compression in myeloma may result from various conditions. Intradural myeloma is exceedingly rare.⁷ Extradural compression of the spinal cord may result from vertebral collapse, extradural extension of plasmacytoma from an adjacent vertebra, or extradural compression without local bone disease. The last is uncommon in multiple myeloma, though in Clarke's selected neurosurgical series,⁸ 20% of patients had epidural lesions without radiological evidence of bone disease. Spinal-cord compression usually follows extension from an adjacent vertebral body with associated erosion or collapse.

Patients and methods

Clinical records (and in a few cases necropsy reports) of 47 patients referred to the Christie Hospital and Holt Radium Institute, Manchester, with evidence of spinal-cord compression as the presenting manifestation of myeloma were analysed retrospectively. Twenty patients (who are also considered in a prospective study of chemotherapy in myeloma) were seen during 1974-8. The remaining 27 patients were referred during 1954-73. All except three had evidence of either localised vertebral disease or generalised myeloma. Three had apparently solitary extradural plasmacytomas. This series included patients referred for radiotherapy after laminectomy (33 out of 47) or vertebral biopsy (three out of 47), when plasmacytoma or myeloma had been diagnosed. The remaining 11 patients had evidence of generalised disease radiologically, and the diagnosis of multiple myeloma was based on findings of bone-marrow plasmacytosis, abnormalities of serum protein detected by electrophoresis, and, in

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some cases, the presence of Bence-Jones proteinuria. Patients who developed spinal-cord compression in established multiple myeloma were not included in the study. Those in whom plasmacytomas were diagnosed at laminectomy or vertebral biopsy but who did not have cord compression were also excluded. All patients presented with paraparesis or paraplegia and no case of cauda-equina compression is included. In each case the histological diagnosis was confirmed by review of the material at the time of presentation.

Results

Of the 47 patients, 28 were men and 29 women. The age distribution was much the same as for myeloma in general, with a median of 56 years. Thirty-one patients presented with complete paraplegia and 16 with paraparesis. In four patients paraplegia was of sudden onset; the remainder had premonitory back pain, sensory symptoms, or progressive paraparesis. The median survival of the whole group was 30 months. Age and sex differences were not related to survival. When level of spinal-cord disease was analysed in relation to survival, survival was significantly better in patients presenting with thoracic-cord compression (36 patients) compared with those presenting with lumbar (seven patients) or cervical cord compression (three patients) (fig 1). When duration of symptoms before presentation

FIG 1—Survival in 46 patients with spinal-cord compression as presenting feature of myeloma, according to level of disease. One patient with quadriplegia was omitted.

was analysed, survival was significantly better in patients who had no back pain before the onset of paraplegia or those whose pain was of sudden onset, compared with the group with pain from three weeks' to 'six months' duration (fig 2). Among the 12 patients who had had back pain for over six months (in some cases in excess of two years) were undoubtedly some whose pain was unrelated to their presenting disease. The duration of weakness, radicular pain, or sphincter disturbances before the onset of paraplegia did not correlate with survival. Four patients had paraplegia of sudden onset, and in two of these, vertebral collapse was not evident. Most patients (33 out of 47) had had laminectomy and decompression when referred.

Forty-five of the 47 patients received radiotherapy.

RADIOTHERAPY

The treatments fell into three groups (see table). The three-week course consisted of fractionated radiotherapy, given for five days a

FIG 2—Survival in 47 patients with spinal-cord compression as presenting feature of myeloma, according to duration of symptoms of back pain before diagnosis.

Response at three months in 45 patients after laminectomy and radiotherapy

Treatment regimen (dose)	Response				Total
	Complete*	Good partial	Poor partial	None	
3 weeks (4000 rads)	5	4	2	0	11
8 days (3100 rads)	2	3	6	6	17
<4 days (1600 rads)	1	4	5	7	17

*No patient who achieved a complete response had a relapse in the irradiated area.

week, to a total of 15 or 16 fractions. Nine patients received multiple-field treatment on a MeV linear accelerator, and three were treated by rotation technique on a cobalt machine. The dose range was 3500-4500 rads and the dose chosen was determined by the accepted level for cord tolerance for the length of field, which varied from 6-18 cm. The eight-day courses were given as eight fractions, usually over 10 days. The average dose of 3100 rads is appreciably below the accepted cord tolerance for the fields used and a dose of 3500 would probably have been tolerable. The one-day and four-day regimens were single-field treatments at relatively low dosage given to patients in poor general condition. When results in 25 patients whose only treatment (apart from laminectomy) was radiotherapy were analysed survival was significantly better in those who received a three-week regimen compared with those who received regimens of eight days, four days, and less (fig 3). None of these patients received chemotherapy. When patients were subdivided into those with solitary extradural disease, localised vertebral disease with extradural extension, and those with advanced myeloma equivalent numbers in each of these three categories received three-week and eight-day treatment courses, showing that the difference in survival was not the result of selection on the basis of extent of disease. Nevertheless, in view of the retrospective nature of this analysis, other important factors, such as social factors, may have influenced selection.

Twenty patients received chemotherapy in addition to radiotherapy. This consisted of alkylating agents with prednisone in various schedules. When these patients were considered with the group who received radiotherapy only the difference in survival between those receiving three weeks and eight days of radiotherapy was maintained, but chemotherapy improved survival in other groups (fig 4). The degree of response was graded as follows: complete—able to walk, with no neurological abnormality; good partial—able to walk, but with residual neurological signs; poor partial—con-

FIG 3—Survival in 25 patients whose only treatment was radiotherapy, according to radiation dose and type of regimen.

FIG 4—Survival in 45 patients who received radiotherapy combined with chemotherapy, according to radiation dose and type of regimen.

siderable residual disability, with only minor relief signs or symptoms. The fourth group were those who failed to respond.

Survival was significantly better in patients whose response was complete than in those whose response was partial (fig 5). The degree of response was better in those who received a three-week fractionated course of radiotherapy compared with those who received an eight-day course. Five out of 11 patients in the three-week radiotherapy group achieved complete response compared with only two out of 17 who received an eight-day course of treatment (table). Eleven out of 30 patients who had complete paraplegia at presentation

achieved a complete (four patients) or good partial (seven patients) response to laminectomy plus radiotherapy. In nine out of 22 who had a history of leg weakness, ranging from three weeks to three months, a complete or good partial response was obtained (four and five patients respectively). Survival in those presenting with complete paraplegia and those with paraparesis was comparable. Presence or absence of sphincter disturbance was not reflected in differing survival figures. The presence or absence of plasma paraprotein, type of paraprotein, and the presence or absence of Bence-Jones proteinuria did not influence survival. Local recurrences occurred in one out of 11 patients who received a three-week course of radiotherapy compared with five out of 17 patients who received an eight-day regimen. In view of the better survival in the group who received three-weeks of treatment, these patients were at risk of a local recurrence for longer. Furthermore, no patient who achieved a complete response to laminectomy and radiotherapy had a recurrence in the treated volume.

FIG 5—Survival in 45 patients according to response to treatment at three months.

Discussion

In most patients with multiple myeloma the disease spreads to the axial skeleton, though the spinal cord is seldom affected. The commonest complication affecting the central nervous system is compression of the spinal cord or cauda equina.^{3 8} Since our analysis was retrospective and extended over 24 years, the median survival of 30 months is better than would be expected, possibly because our patients had early stage disease. In some series patients presenting with solitary vertebral myeloma had a lower median age,⁴ which may support the hypothesis that this type of presentation is associated with earlier stage disease. Nevertheless, we found no significant difference in median age for this group compared with those with multiple myeloma. In 40 of our patients in whom disease could be accurately assessed, 12 had localised vertebral plus extradural disease and the characteristics of their survival curve did not differ from that of the entire group.

Solitary plasmacytoma of bone has attracted attention and controversy.^{5 9-12} Diagnosis of this condition is usually based on failure to demonstrate evidence of skeletal change elsewhere than in the primary site, absence of bone-marrow plasmacytosis, histological verification of the tumour, and failure of the lesion to disseminate over a variable period of observation, usually at least three years.¹³ Most cases of solitary plasmacytoma of bone

have progressed eventually to multiple myeloma, sometimes after many years.⁵ In three of our patients local or distant bony disease was not found nor was bone-marrow plasmacytosis, despite the findings at laminectomy of an extradural plasmacytoma. All three had a complete response to treatment and were still alive at 18 years, three and a half years, and two and a half years from initial diagnosis, with no evidence of recurrence or dissemination. These may be examples of soft-tissue plasmacytomas arising in the extradural space and may behave in a manner similar to solitary plasmacytomas elsewhere.^{14 15}

The level of cord disease influenced survival significantly. Better survival among those with thoracic lesions as opposed to those with lumbar and cervical lesions is difficult to explain. The cervical canal is larger and for cord compression to occur the tumour would have to progress further than a similar lesion in the thoracic region. Tumours occurring in the epidural space seem to have a predilection for the thoracic region, partly because of the number of vertebrae as well as the larger volume of the epidural space.⁶ As in Clarke's series,⁸ most (78%) of our patients presented with thoracic-cord lesions, and he suggests that this is an area of the cord with a relative paucity of blood supply and a greater susceptibility to cord compression. Most of our patients had had laminectomy and decompression before referral. Many authors have emphasised the importance of this procedure, even if paraplegia is already established.^{8 16-18}

The true extent of the extradural extension must be known so that the tumour can be fully encompassed in the radiotherapy field, and myelography greatly helps in doing this. Though several studies have shown that the outcome of treatment with radiotherapy alone is comparable to that of laminectomy followed by radiotherapy,¹⁹⁻²¹ we believe that in cases in which initial presenting symptoms are those of spinal-cord compression surgically removing as much tumour as possible is both a diagnostic and therapeutic procedure. Plasmacytomas are generally radiosensitive and the incidence of local recurrence after a dose exceeding 3000 rads (250 KV in 15 fractions over three weeks) is very low.¹⁴ Allowing for relative biological effectiveness, this would be equivalent to a dose of 3800 rads at MeV. The limiting factor when treating these patients is cord tolerance, but fortunately doses of this order can be given. The highly significant difference in survival and recurrence rates according to different radiotherapy schedules is difficult to analyse completely in a retrospective study, but it suggests that adequate radiotherapy should be given (that is, dosage just within the cord tolerance for the field size used whenever possible). This is so even when myeloma is advanced and paraplegia is complete. Improved survival is being achieved in patients with generalised disease using improved chemotherapy regimens.²²

The approach to management of spinal-cord compression in malignant disease is usually pessimistic, especially when complete paraplegia of more than a few days' duration is present. Nevertheless, vigorous treatment may be worth while in spinal-cord compression due to various malignant disorders.^{21 23} The results of our study show that pessimism is not always warranted in spinal-cord compression in myeloma. A combined approach using laminectomy and radiotherapy resulted in an excellent response in over a third of patients presenting with complete paraplegia and in about 40% of patients with a history of weakness as long as three weeks to three months.

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Does iridocyclitis cause temporary blindness?

Iridocyclitis, an inflammation in the anterior segment of the eye of the iris and the ciliary body, can cause both temporary and permanent severe loss of vision. Temporary blindness can occur if the severity of the inflammation is such that the aqueous humour becomes turbid and loaded with inflammatory cells and with exudate. This may coalesce to form a level of sterile pus (hypopyon) in the anterior chamber. In addition, a secondary rise in intraocular pressure may cause corneal oedema. Prompt treatment with local steroids (both topically and by subconjunctival injection), atropine or similar drops to dilate the pupil, and acetazolamide to lower intraocular pressure usually settles the inflammation satisfactorily even in severe cases. Where this is not the case or when treatment has initially been neglected, permanent blindness may ensue from the formation of cataract and of adhesions between the iris and the lens (posterior synechiae), which may block the passage of aqueous through the pupil and lead on to secondary glaucoma by angle closure. In rarer cases inflammatory membranes may cover the pupil in front of the

lens or may form behind the lens as a long-term result of neglected inflammation. This emphasises the great importance of early correct diagnosis and urgent investigation and adequate treatment of this potentially very serious intraocular inflammation.

Is there any evidence that clofibrate can cause malignancy?

"Cause" is perhaps too strong a word. The trial begun in 1965 of clofibrate as a prophylactic against coronary heart disease in over 15 000 healthy middle-aged men has recently been completed.¹ Its undoubted benefit was offset by the finding of an increase in deaths from other medical causes. These included an excess of gastrointestinal neoplasms affecting the liver, biliary tract, and large bowel. The authors suggested that this might be due to an alteration in sterol metabolism rather than to clofibrate itself.

¹ Report of Committee of Principal Investigators, *British Heart Journal*, 1978, **40**, 1069.