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Chemotherapy in the Management of Extramedullary Plasmacytoma

E. Wiltshaw

The Royal Marsden Hospital,
Fulham Road, London, S.W.3. 6JJ

Summary. *The results of chemotherapy in 24 patients with extramedullary plasmacytoma are reported.*

Complete regressions, including disappearance of monoclonal paraprotein and healing of bone lesions, were seen in 12 of 20 (60%) patients with disseminated disease.

Extramedullary plasmacytoma responds better to chemotherapy than myeloma, and treatment should be pursued with vigour until all signs of disease have disappeared.

Sensitivity to single-agent chemotherapy may vary, and if treatment fails with one agent, others should be tried.

Introduction

All plasma cell tumours have in common a distinct histological appearance, and, in most cases, the tumour cells produce a monoclonal immunoglobulin. The tumour may be associated with local or systemic amyloid deposition, and when bone lesions occur, they are always osteolytic. These features may lead to complications such as hypercalcaemia, renal failure, and cardiac failure.

When plasma-cell tumours present with primary bone involvement, the natural history is that of spread to other bones, with a predilection for those bones containing active bone marrow, i.e., the axial skeleton. A recent survey of plasmacytomas arising outside the bones has shown, in contrast, that spread is similar to that of a carcinoma (Wiltshaw, 1976). That is to say, the early spread is to drainage lymph nodes, followed by metastatic spread to bones and soft tissues. The bone lesions are just as likely to be found in areas where active bone marrow is not usually present in adults, such as the peripheral long bones, while diffuse invasion of the bone marrow is unusual and probably a late event. These differences in natural history make it essential to approach the management of extramedullary plasmacytoma (EMP) in a different way from that of solitary myeloma of bone or myelomatosis.

Since the primary lesions commonly arise in the upper air passages (UAP) (about 70%), they are easy to diagnose and cure may follow adequate local treatment (Wiltshaw, 1976; Todd, 1965; Helmus, 1964; Dolin and Dewar, 1956). When disseminated disease is present, the therapist has certain advantages compared with treatment of myelomatosis. The presence of soft tissue tumours allows therapeutic sensitivity to be established quickly. The bone marrow is usually intact and large doses of chemotherapeutic drugs can be given safely, and the frequent absence of large amounts of monoclonal immunoglobulins in the urine means that kidney function is usually normal.

Until now, the rarity of EMP and the lack of understanding of its natural history has prevented any but single case reports of chemotherapeutic benefits. The purpose of the present report is to show for the first time the effectiveness of even single-agent chemotherapy in producing regressions of disseminated EMP, and the possibility that a more aggressive approach might bring about a proportion of cures.

Materials and Methods

Over the last 13 years, a total of 24 patients with EMP have been treated personally with chemotherapy. Investigations and follow-up have been uniform. Before treatment, full clinical examination, including E.N.T. examination, was carried out and bone marrow aspiration, serum, and urine (concentrated × 200) investigations for monoclonal proteins were performed, together with chest X-ray and a total body skeletal survey. Full blood count, ESR, calcium, urea, electrolytes, and liver function studies were performed routinely. More recently, lower limb lymphangiography was done as well. All patients had at least one histologically proved extramedullary primary plasmacytoma and the histological material was reviewed by Dr. I. Hamlin.

Reprint requests should be addressed to: E. Wiltshaw

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Retrospective staging of these cases was as follows:
Stage 1 — Tumour confined to the primary site (single or multiple lesions may be present at that site).
Stage 2 — Lymph nodes draining the primary site were also involved.
Stage 3 — Metastatic spread had occurred.
Stage 3b — Metastatic spread included bone marrow and/or CNS disease.

Of the 24 patients treated, five had stage 1 or 2 disease, while 20 had stage 3 disease (one patient, case 6, was treated for stage 2 disease and was later treated again when dissemination occured).

Treatment over the 13-year period was not entirely uniform, but the majority of patients were given melphalan with or without prednisone. Melphalan courses varied from 4 mg daily over a 3-week period to 25 mg daily for 2 days. Prednisone was given at a dose of 40 mg daily for 7 days, always with melphalan or cyclophosphamide.

Cyclophosphamide was given intravenously at a single dose of 600 mg/m^2, or orally in doses of 100–150 mg daily. CCNU was given in a few cases, 80 mg/m^2 at 6–8-week intervals.

Combination chemotherapy has been of two types:

1. Cyclophosphamide, 600 mg/m^2 on days 1 and 8, together with vincristine, 1.5 mg/m^2 on days 1 and 8, with prednisone, 40 mg daily over 8 days. This regimen is designated COP, and is given at 3–4-week intervals.

2.

Melphalan	6 mg/m^2	daily for 3 days, repeated 4-weekly.
Cyclophosphamide	250 mg/m^2	
Prednisone	40 mg/day	
CCNU	60 mg/m^2	once.

Definitions of response were as follows:
Complete remissions: complete regression of all measurable tumour masses, complete disappearance of measurable paraprotein together with healing of all osteolytic bone lesions.
Partial remission: more than 50% regression of all measurable masses and incomplete reduction in paraprotein. Incomplete healing of bone lesions occurred in some cases but was not a necessary criterion. All remissions lasted 3 months or more.

Results

Chemotherapy for Primary Local Disease (Stage 1 and 2). Five patients were treated for initial local disease. Three had failed to respond to local radiotherapy and melphalan in two cases, and in one, cyclophosphamide also failed to produce complete regression. The tumours were then removed surgically. In one of these cases (no. 6), the mass consisted mainly of amyloid material (Table 1).

Two other patients treated for local disease are of interest. A man of 83 (case no. 7) was given a total of 48 mg of melphalan in 40 days, with complete regression of the nasal and lymph node masses. He remained free of tumour for the rest of his life (37 months) and died of a chest infection. Case 12 is of particular interest, since this patient had a small tumour mass in the nasopharynx, producing bilateral blindness. The only suggestion of tumour elsewhere was the presence of a trace of half-molecule type IgGK (molecular weight about 75,000) in the urine when concentrated × 200. Bone marrow and whole body skeletal X-rays were normal. She was treated with a combination of radiotherapy and melphalan. The sight returned to one eye but there was irreversible damage to the other. The tumour regressed completely and the paraprotein disappeared. There has been no recurrence thus far, 8 years later. The immunoglobulin abnormality in this case has been reported in more detail elsewhere (Hobbs et al., 1969).

Treatment for Disseminated Disease (Stage 3 and 3B). 20 patients were treated for disseminated disease, one of whom (case 6) had already been given chemotherapy for her primary tumour.

Table 1. Chemotherapy for local disease (stages 1 and 2)

Sex/age	Case no.	Tumour sites	Chemotherapy	Response	Comment
F/52	6	Neck node mass	Melphalan	NR	No response to previous radiotherapy. Surgical removal showed mainly amyloid. Disseminated disease appeared 8 years later
M/83	7	Nose and neck nodes	Melphalan	CR	Died 37 months later. No evidence of recurrence. No autopsy
F/21	12	Nose and nasopharynx. Paraprotein	Melphalan with local radiotherapy	CR	Sight restored to one eye, paraprotein disappeared from serum. NED 8 years later
M/40	13	Pharynx, larynx, tonsil	Melphalan	NR	No response to radiotherapy, tumours then excised. NED 6 years later
M/56	15	Epiglottis and neck nodes	Cyclophosphamide 1.5 g × 4	PR	Poor response to previous radiotherapy. Tumour removed. Dissemination 10 months later

CR = Complete remission. PR = Partial remission. NR = No remission. NED = No evidence of disease

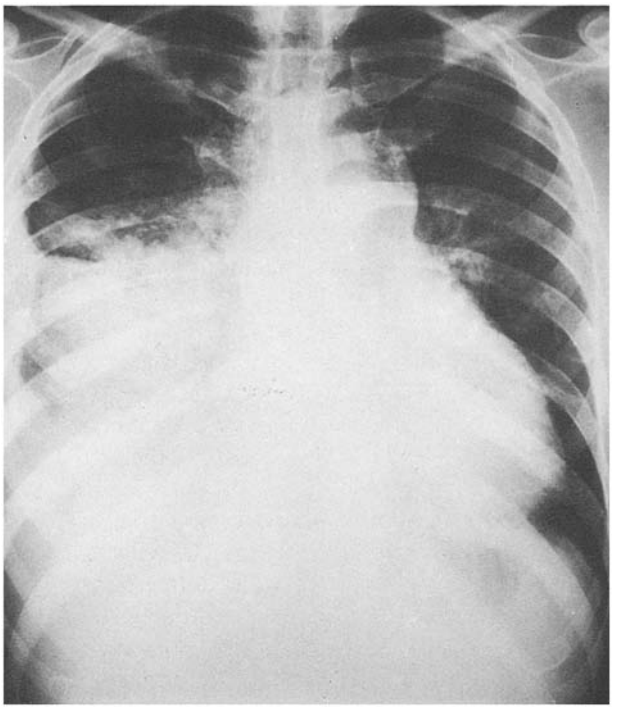

Fig. 1. Chest X-ray of case no. 14 at start of chemotherapy. Pleural effusion contained plasma cells

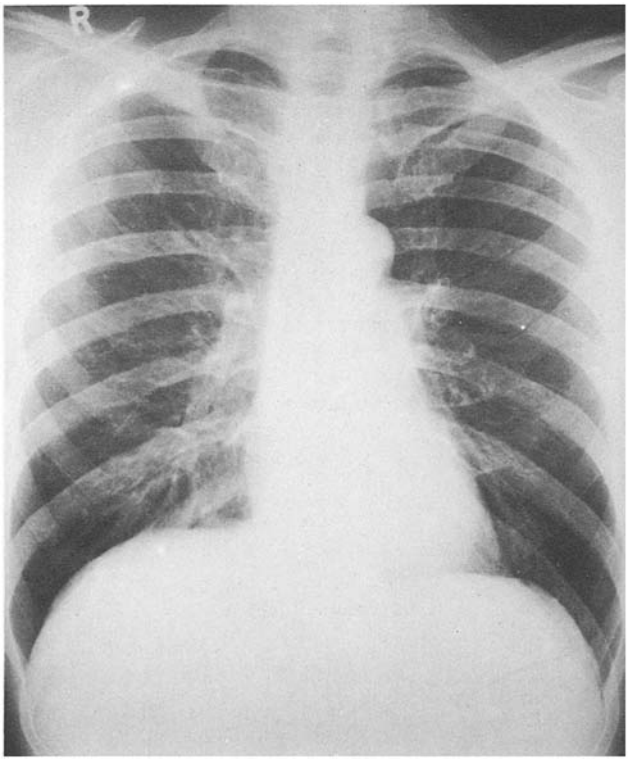

Fig. 2. Chest X-ray of case no. 14, 18 weeks after starting chemotherapy

Response to initial chemotherapy was good in the majority of patients. Complete regressions were achieved in 12 of 20 patients (60%), partial regressions occurred in four of 20 patients (20%) and only four failed to respond to initial treatment. Table 2 shows details of all 20 patients.

Soft tissue masses regressed completely within a month of starting chemotherapy in 12 of 18 patients (67.6%), while two only showed a partial regression and four were unresponsive. Some regressions were very rapid (Figs. 1 and 2).

13 patients had a measurable paraprotein in the serum and/or urine: Bence-Jones protein (BJP) only in six (3 type K; 3 type L) and whole molecules in seven (IgGK 3, IgAK 2, IgGL 2). The paraprotein completely disappeared in nine and was unaffected by therapy in three. In these three cases (no. 9, 10, and 11) there was only a partial response in terms of tumour regression. In one case (no. 6) there was a reduction in BJP, but not to zero.

Five patients had bone marrow involvement, and in two the marrow returned to normal (i.e., from 90 and 40% plasma cells to 4 and 3% respectively in cases 21 and 23).

Bone healing occurred in nine of 13 cases and was only seen in association with complete regression of all soft tissue tumours, falls of paraprotein below measurable level, and return of bone marrow appearance to normal. Examples are shown in Figures 3–6. Radiological appearances of healing were rarely definite until 18 months after complete regression of other lesions.

Three patients developed signs of CNS involvement late in their disease and all had tumour cells in the CSF (cases 14, 16, and 23). In one of them, a brain scan showed a single tumour in the substance of the posterior lobe of the cerebrum. In each case, the CSF contained the same monoclonal paraprotein as that seen in the blood. All three patients received intrathecal methotrexate. In one, there was a reduction in tumour cell number and CNS signs, but after cytosine arabinoside was substituted for methotrexate the tumour cells completely disappeared. In the other two cases, tumour cells disappeared from the CSF with intrathecal methotrexate, and both patients later received cranial irradiation. All three patients have died; autopsy in two of them showed no residual tumour in the brain. In the third case there was clinical evidence of recurrent tumour in the base of the brain. Remissions of CNS disease lasted 9, 8, and 3 months.

The Drug of Choice. For the sake of uniformity most patients were treated initially with melphalan, alone (10 patients) or with the addition of prednisone (6 patients), and complete regression was produced in 10 of 16 (62.5%). Only four patients started with cyclophos-

Table 2. Chemotherapy for disseminated disease

No./sex/age	Primary site	Extent before chemotherapy	Chemotherapy	Response		Survival		Comments
				Type	Length (months)	After chemotherapy (months)	Total (months)	
1. F/72	Disseminated	Tonsils and multiple skin	Mel	CR	8	11	17	Dead. Recurrent EMP
2. M/61	UAP	Subcutaneous nodules	a) Mel	CR	24	–	–	Dead of coronary thrombosis.
		Subcutaneous nodules, lower limb and foot bones	b) Mel	CR	> 3	27	37	No EMP at autopsy
3. M/54	UAP	R. and L. clavicles, skull, R. ilium, bone marrow infiltrated	Mel	PR	36	40	66	Dead. EMP. Local recurrence at primary site
4. F/56	UAP	Temporal soft tissue mass. Multiple lesions in bones, lower limbs. IgGK 29 g/l	Mel → Cyclo	CR	> 156	> 156	> 180	Alive and well
5. M/38	UAP	Tonsils, neck nodes, liver, paraprotein	Chlor + Pred	PR	3	5	13	Dead. Recurrent EMP
6. F/52	UAP	R. and L. ilium, R. and L. femur, skull	a) Mel + Pred	PR	20	36	144	Dead.
	Neck nodes	BJP-K 2 g/l bone marrow infiltrated	b) Cyclo i.v. + Pred	PR	7	–	–	EMP and bone marrow failure
8. M/82	Disseminated	Chest wall mass, L. femur and R. coracoid	Mel	CR	> 7	7	7	No bone healing but no tumour at autopsy. Died of coronary thrombosis
9. F/72	Mediastinal	Femur: local recurrence and bone marrow, BJP type L 9 g/l	Mel	NR	–	4	16	Dead. Advancing disease
10. F/65	Disseminated	Multiple lymph nodes type L., light chains	a) Mel +	NR	–	–	–	
			Pred	NR	–	7	11	Dead EMP
			b) VCR + Cyclo + Asp	NR	–	–	–	
11. M/77	UAP	Primary site and sacrum, d. vert, radius. IgAK 52 g/l	Cyclo	PR	6	8	13	Dead EMP
14. M/52	Testis and abdominal nodes	Other testis, lung, pleural effusion, humerus, radius, tibia, os calcis, clavicle.	a) Cyclo	CR	6	24	35	Dead. EMP
		Recurrence of all lesions and recurrence in CSF	b) Multiple drugs	CR	13	–	–	
			IT MTX	PR	6	17	–	
			IT Ara.C	CR	9	–	–	
16. M/64	Antecubital fossa	Multiple subcutaneous deposits, IgGL and BJP, and bone lesions. Recurrent subcutaneous deposits	a) Mel	CR	13	50	50	Dead. EMP
			b) Cyclo	NR	–	–	–	
			Ara.C Mel + Pred	NR	–	–	–	
			CCNU	CR	–	–	–	

		Recurrent subcutaneous lesions. CNS disease	c) COP	PR	–	–	–	
			MTX	CR	8	–	–	
17. F/72	Nose	IgGL and BJP only	Mel	CR	17	19	27	Dead. EMP
18. M/50	UAP	Multiple lymph nodes	a) Mel + Pred	NR	–	–	–	
			b) Cyclo	CR	2	9	16	Dead. EMP
19. M/47	Disseminated	R. and L. tonsils. Trace of type K BJP and perianal lesions	Mel + Pred	NR	–	> 42	> 43	Alive and well
20. F/52	Breast	Scapula and humerus. Axillary nodes, IgGK 45 g/l	Mel + Pred	CR	> 44	> 44	> 44	(Radiotherapy to scapula). Alive and well
21. M/59	Neck node	Clavicles, skull, humerus, 6th rib. Bone marrow IgAK 31 g/l	Mel + Pred + Cyclo + CCNU	CR	> 28	> 28	> 28	Alive and well
22. M/51	Posterior auricular node	Testes, liver, 6th rib, ulna	Mel + Pred + alt COP	CR	> 28	> 28	> 28	Alive and well
23. M/54	Disseminated	Multiple subcutaneous masses. Mediastinal mass, bone marrow, sternum, rib.	a) COP	CR	16	25	25	Died EMP with leukemia and tumour in CNS
		Bone marrow and blood 1.5 g/l type L BJP	b) COP	CR	3	–	–	
		Deafness, tumour cells in CNS	c) IT MTX	CR	3	–	–	(Radiotherapy to cranium)
24. M/62	Disseminated	Node, chest wall, bones. IgGL 3.3 g/l	a) Mel	CR	14	> 27	> 27	Alive, active tumour present
		Skin	b) Cyclo	NR	–	–	–	
		Skin, spleen	COP	NR	–	–	–	
		Skin, spleen, liver	CCNU	PR	*Continues*	–	–	

UAP = Upper air passages
CR = Complete regression
PR = > 50% regression
NR = No regression
IT = Intrathecal

Mel = Melphalan
Pred = Prednisone
Cyclo = Cyclophosphamide
COP = Cyclo, Pred, and VCR (7 day courses)
VCR = Vincristine

Asp = Asparaginase
MTX = Methotrexate
Ara.C = Cytosine arabinoside
CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea

phamide alone or in combination with other drugs. Three out of these four patients had a complete response. The numbers are too small to draw conclusions, but it is of interest that in the seven patients who went onto other drugs after their first course of chemotherapy it became clear that some tumours were sensitive to one agent and resistant to another (Table 2). For example, in case 18, cyclophosphamide produced a complete remission, while no response was seen to melphalan plus prednisone when given earlier. A similar situation was seen in cases 16, 19, and 24.

Length of Remission. Initial complete remissions have lasted from 6 months to more than 156 months. The median remission is only 15 months, but four of the 12 patients have been in their first complete remission for 18, 28, 44, and 156 months. One other case (no. 8) died of a myocardial infarction while still in remission. Short summaries of two of the best complete remissions are given below.

Case 4. Woman aged 56 years. Presented January 1961 with a tumour filling the nasolabial fold. Biopsy showed a poorly differentiated plasmacytoma. Radiotherapy was given to a dose of 3,600 r, with little regression, and the tumour was then excised. In March 1963 a recurrent mass was excised. At that time, 42 g/l of IgGK was found in her serum. In October 1963, a further 3,600 r was given to the nasal area. In August 1965 a hard mass was noted in the left temporal fossa; skeletal X-rays revealed osteolytic areas in one rib, one femur, both tibiae, fibulae, and patellae. The sternal marrow was normal but she had 29 g/l of IgGK paraprotein in the serum. Treatment with one dose of 25 mg melphalan produced complete regression of the temporal mass. She then had oral therapy with 4 mg daily for 4 weeks. In March 1967 treatment with cyclophosphamide 100 mg daily was substituted for melphalan, and was given continuously until November 1969. By August 1966, the paraprotein had disappeared from the serum, and the IgA and IgM levels had returned to normal values. By January 1967, all skeletal lesions had healed (Figs. 3 and 4). Since then there has been no evidence of any local or metastatic disease, a total of 156 months since the start of chemotherapy.

Case 21. Male, 59 years. In November 1973, the patient had enlarged left neck nodes. Several were excised and showed well-differentiated plasmacytoma. A skeletal survey revealed lesions in both clavicles, the skull, one

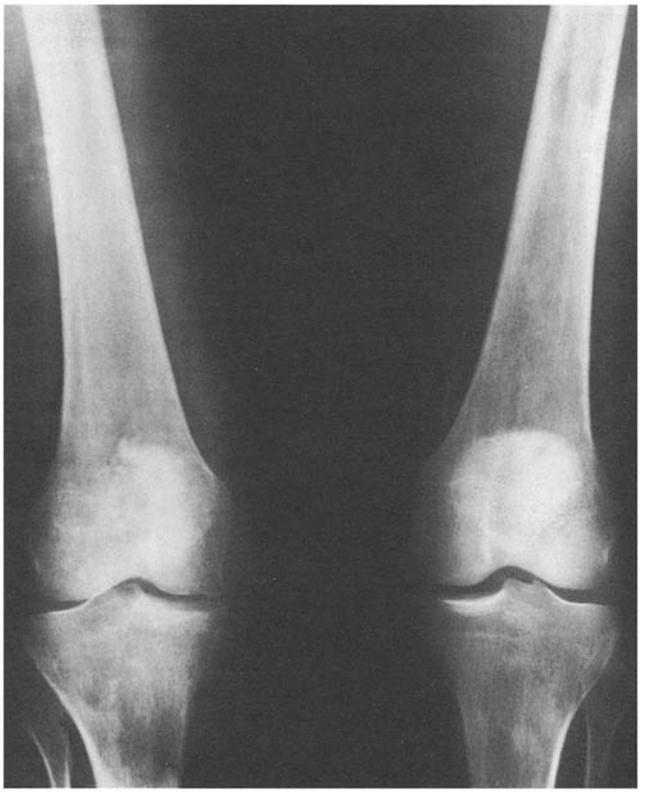

Fig. 3. X-ray of lower femora and knee joint in case 4. Note lesions in shaft of left femur, right patella, and both tibiae

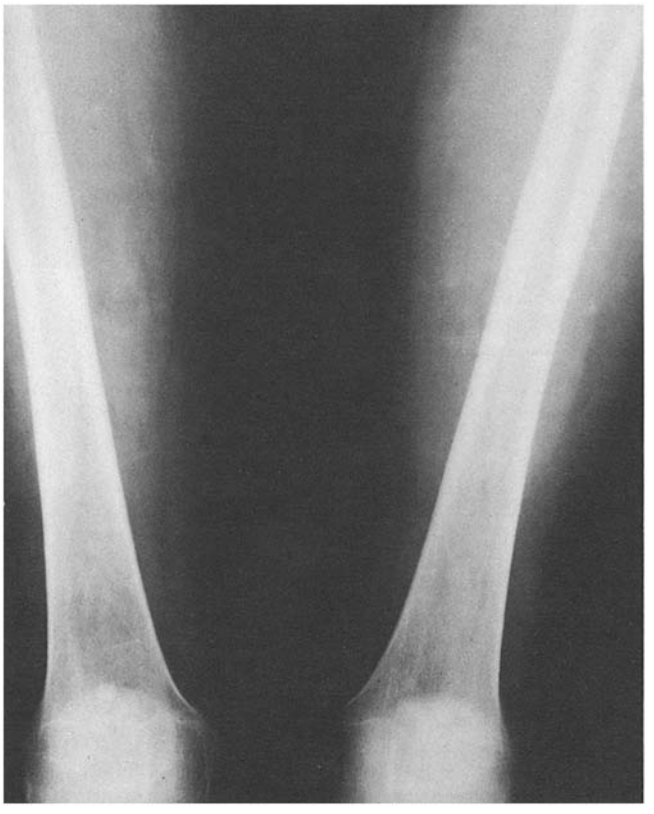

Fig. 4. X-ray of femora and knee joints of case 4, two years after starting chemotherapy. Bone lesions have never recurred

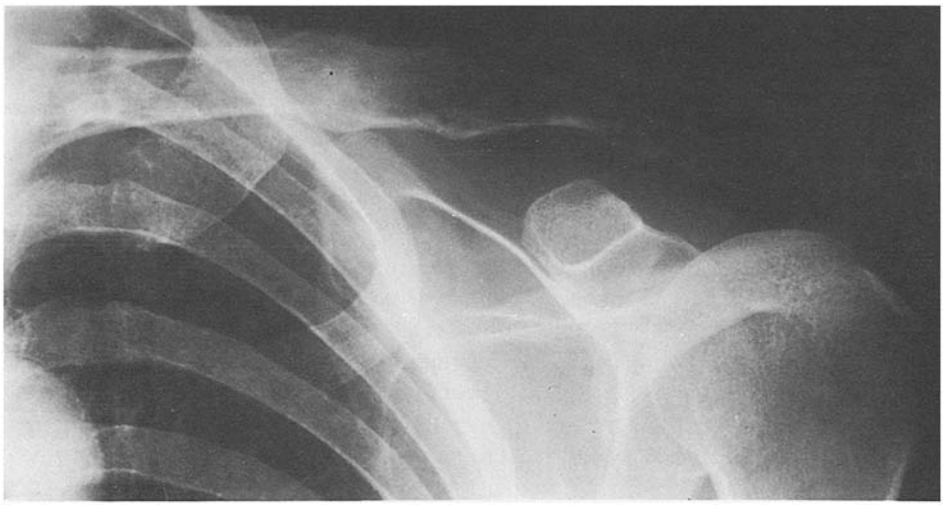

Fig. 5. X-ray of the left clavicle in case no. 16 before chemotherapy

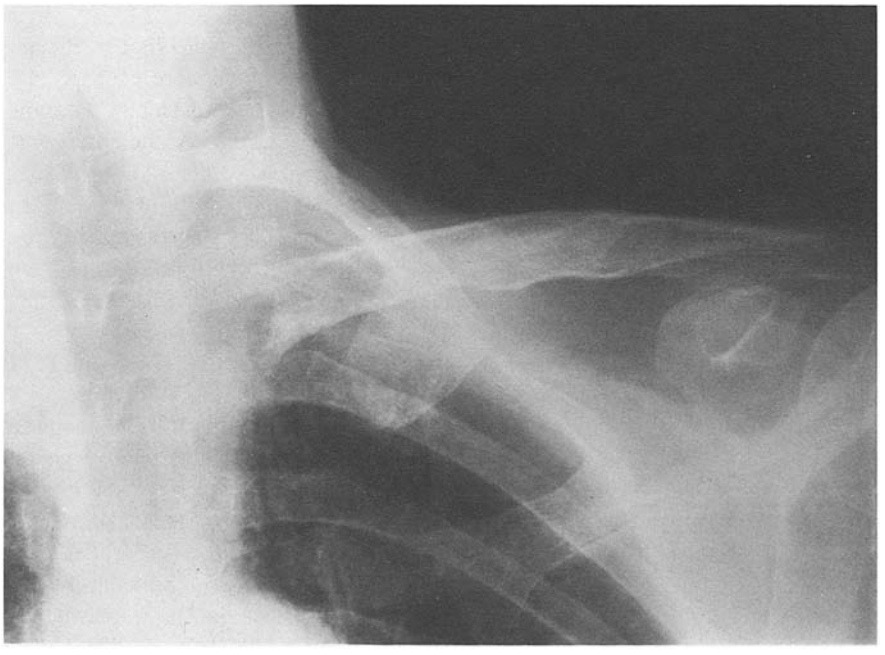

Fig. 6. X-ray of same clavicle as in Figure 5, 11 months after starting chemotherapy. Lesion had not progressed when patient died of disseminated disease 39 months later

rib, and one humerus. Bone marrow aspirate was found to contain 90% plasma cells and serum, 31 g/l of IgAK paraprotein. The lymphogram was normal. Combination chemotherapy was given, with CCNU, melphalan, prednisone and cyclophosphamide in 4-day courses. By March 1974, the IgAK protein had disappeared and the bone marrow was normal. A skeletal survey in November 1975 showed complete healing of all lesions. The patient continues well 28 months after starting treatment. Chemotherapy was stopped after 24 months.

Discussion

There has been no previous study reporting the results of chemotherapy in a series of cases of EMP. The reasons for this are the rarity of the disease and the lack of recognition, particularly by physicians, of the natural history of this entity. Thus only recently, Hewell and Alexanian (1976) reported three cases of 'multiple myeloma' in young people. In case 1, no extramedullary lesion was seen, and perhaps none was sought, but bone

lesions occurred in occiput, femur, knee, and hand. The bone marrow was normal and there was a monoclonal IgA in the serum. The patient was given only radiotherapy, but was alive and well 5 years later. Their case 2 had definite extramedullary lesions in nasopharynx and lymph nodes, with IgGL paraprotein and bone lesions in ribs and skull. The bone marrow was normal. Patient 3 developed diplopia and an occipital mass and received chemotherapy. It is probable that in all these cases the primary tumour was extramedullary – certainly the pattern of lesions without bone marrow invasion is quite atypical of myeloma, as is their young age. Nevertheless there are several reports in the literature, usually of single cases, and in many of these the results of chemotherapy are described as striking; for example, Castleman and Kibbee (1959) reported a man of 70 who had a primary lesion in the upper air passages; he later developed multiple bone deposits and a serum paraprotein. Urethane was given for 8½ years. The patient was well, the bones 'healed', and the paraprotein disappeared. Pomposiello et al. (1964) described a 30-year-old man with a lesion in the upper air passages who was treated with cyclophosphamide, when subcutaneous deposits, bone deposits, and a paraprotein disappeared. The follow-up was only 1 year and it is unlikely that bone healing would have occurred after only 12 months. Other reports include a case with node and lung masses, with complete regression on melphalan (Suissa et al., 1966) and a case with a retropertioneal mass plus a paraprotein, who received urethane. The remission lasted at least 3 years 11 months (Edwards and Zawadski, 1967). The most interesting cases were reported by Martinson and Pulvertaft from Africa. All three of their cases had primary upper air passage lesions and were treated with melphalan or cyclophosphamide. Regressions were complete and lasted more than 2 years (Martinson and Pulvertaft, 1967). These authors noted that where melphalan was ineffective cyclophosphamide could cause regression, and vice versa. I have also noted this feature in my larger series.

The present large series has shown that the striking regressions found in single cases are not unusual when the primary plasmacytoma is extramedullary. Disappearance of paraprotein occurred here in 69% of cases, a much higher proportion than is seen in myeloma (Waldenström, 1970; M.R.C. Myeloma Trial, 1968). Disappearance of paraprotein is of course accompanied by soft tissue regressions, which were complete in 60% of cases. Bone healing is a very rare event in myelomatosis and has been reported only occasionally even in large series of cases treated over long periods of time (Waldenström, 1970). However, in this small number of cases of EMP where one or more osteolytic lesions were present, bone healing was seen on X-ray in 69% of cases. It generally took 2 years for healing to be apparent. Invasion of the bone marrow from an EMP in unusual, but was seen eventually in five patients. The appearance of the marrow returned to normal in two, and these two patients also showed bone healing. Recalcification of bones seems to occur only after a very considerable reduction of tumour mass has been achieved.

The development of CNS tumour in three patients in this series is surprising. Again, it is a very rare event in myeloma, apart from paraplegias due to extradural compression of the cord. All three had tumour cells in the CSF and there was some response to intrathecal chemotherapy. Cranial irradiation and/or continued intrathecal chemotherapy over a long period is recommended in these cases.

These striking improvements of patients with stage 3 plasmacytoma suggest that more aggressive therapy might lead to cures, and it seems likely that cure has been achieved in case 4. For this reason it is a pity that in some of my cases therapy was not continued with vigour after the initial response (cases 2, 23, 24), since with relapse there is often complete resistance to further treatment.

Chemotherapy probably has a part to play in some patients with primary EMP, since experience has shown that some primary lesions are locally rapidly invasive, and in these patients death from the primary tumour occurs within 18 months of diagnosis (Wiltshaw, 1976). Because of this, case 12 received irradiation plus melphalan. The fact that the sight of one eye is still intact and that there has been no recurrence of tumour for 8 years may in part be due to the additional chemotherapy.

Experimental work on plasma cell tumours has used mainly mouse and rat models (Potter, 1973). The tumours produced in these animals resemble EMP in man more closely than they do myelomatosis. In animal tumours responses to chemotherapy have sometimes been curative, and combinations such as melphalan and prednisone were much more effective in the experimental system than they proved to be in human myeloma. The responses reported here are similar to those seen in the animal system.

This study suggests that any patient with a primary extramedullary plasmacytoma should be given chemotherapy in addition to radiotherapy when the tumour appears to be showing a rapid locally invasive character. Furthermore, patients with stage 3 disease should receive chemotherapy until all signs of tumour have disappeared, including the osteolytic lesions, usually for 2 years. In advanced cases CNS involvement may be a serious risk, and this should be looked for at an early stage. If more cases are recorded in the future, then prophylactic therapy for this complication may be necessary.

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