

A patient with a severe remote-effect polyneuropathy and other paraneoplastic features of osteosclerotic myeloma improved dramatically with melphalan and prednisone treatment. Serial electrodiagnostic studies provided an objective means of following the response to therapy and documented the improvement. We believe this represents the first reported patient with multifocal osteosclerotic myeloma and a myelomatous polyneuropathy responding to melphalan and prednisone.

MUSCLE & NERVE 7:137-141 1984

PERIPHERAL NEUROPATHY IN OSTEOSCLEROTIC MYELOMA: CLINICAL AND ELECTRODIAGNOSTIC IMPROVEMENT WITH CHEMOTHERAPY

P. D. DONOFRIO, MD, J. W. ALBERS, MD, PhD,
H. S. GREENBERG, MD, and B. S. MITCHELL, MD

Peripheral neuropathy is detected clinically in only 3%–5% of patients with multiple myeloma.^{2,12} However, approximately half the patients with the osteosclerotic form of plasma cell dyscrasia manifest a severe polyneuropathy, the neuropathy often preceding the detection of osteosclerotic lesions by months to years.^{4,7,9} Improvement in myelomatous neuropathy has been reported in patients with solitary lesions following radiation therapy,^{3,7-10} but rarely in patients with multifocal lesions after chemotherapy.^{5,11} Electrodiagnostic documentation of the clinical improvement has been provided in only two patients with a solitary lesion^{8,9} but not in those few patients with multifocal osteosclerotic lesions receiving chemotherapy. We report a patient with a severe demyelinating sensorimotor polyneuropathy and multifocal osteosclerotic bone lesions in whom melphalan and prednisone therapy resulted in considerable clinical

and electrodiagnostic improvement in the peripheral neuropathy, and associated remote-effects.

CASE REPORT

A forty-two-year-old woman presented with a 3-year history of progressive weakness, gait unsteadiness, and painful extremity dysesthesia. This was accompanied by hirsutism, frequent diarrhea, and a 50-pound weight loss. A prior evaluation disclosed the following: electromyographic evidence of a polyneuropathy; pelvic roentgenograms demonstrating osteosclerotic lesions in the iliac crest, lumbar spine, and sacrum; and bone scan evidence of increased activity in the right sacrum.

On physical examination, the patient was a thin, chronically ill appearing woman who had finger clubbing and increased facial and extremity hair. On assuming the upright position, orthostatic distal cyanosis developed in her upper and lower extremities. Moderate hepatomegaly, hammer toes, and high arches were present. There was marked wasting of the frontalis, temporalis, and sternocleidomastoid muscles, with accompanying muscle atrophy and weakness involving the extremities distally more than proximally. She had slow alternating movements and a mild distal tremor. Her gait was wide-based and steppage in quality. Muscle stretch reflexes were absent. A distal gradient loss to nociceptive, proprioceptive, and vibratory modalities was present.

From the Departments of Neurology (Drs. Donofrio, Albers, and Greenberg) and Internal Medicine (Dr. Mitchell), University of Michigan Medical Center, Ann Arbor, MI.

Presented in part at the 29th Annual Meeting of the American Association of Electromyography and Electrodiagnosis, St. Paul, MN, October 7–10, 1982.

Address reprint requests to Dr. Donofrio, Department of Neurology, B4954, CFOB, University of Michigan Medical Center, Ann Arbor, MI 48109.

Received for publication March 7, 1983; revised manuscript accepted for publication September 19, 1983.

0148-639X/0702/0137 \$04.00/0
©1984 John Wiley & Sons, Inc.



FIGURE 1. Multiple scattered sclerotic bone lesions within the right humerus and clavicle.

Laboratory studies revealed normal routine hematologic and blood chemistry parameters except for elevation of hemoglobin and hematocrit. Roentgenographic bone survey revealed multiple osteosclerotic lesions in the ribs, vertebral bodies, clavicles, humeri, pelvic bones, and proximal femurs ranging from several millimeters to centimeters in size (Fig. 1). Bone scan was normal. Percutaneous bone marrow and liver biopsies were normal. A rectal biopsy showed no evidence of amyloid deposition, while a cervical lymph node biopsy was negative for lymphoma. Multiple protein electrophoretic evaluations of serum and urine were unremarkable. One of numerous serum immunoelectrophoreses disclosed an elevated IgA of 420 mg/dl (normal 24–386), yet a monoclonal protein was never isolated. Cerebrospinal fluid analysis was normal. Fluoroscopy-guided needle biopsy of a right humeral osteosclerotic lesion disclosed an overall increased number of plasma cells within the bone marrow, with several focal areas of dense plasma cell infiltration.

A monthly chemotherapeutic regimen consist-

ing of melphalan (12 mg for 4 days) and prednisone (140 mg for 4 days) resulted in complete resolution of pain, hirsutism, and orthostatic cyanosis after 22 months of treatment. Repeat neurologic examination showed normalization of nociceptive, temperative, and proprioceptive modalities, as well as return of physiologic muscle stretch reflexes. On muscle strength testing, improvement of 1–2 grades in the upper extremities and 0.5–2.5 grades in the lower extremities (MRC scale) was observed; those changes more impressive distally than proximally. Partial clearing of the osteosclerotic lesions in the right humeral head and clavicle after chemotherapy provided a roentgenographic counterpart to the clinical amelioration (Fig. 2). Posttreatment serum immunoelectrophoresis revealed an IgA of 231. The patient is now fully ambulatory and has returned to fulltime employment.

Electrodiagnostic Evaluation. Pre- and posttreatment serial electrodiagnostic testing demonstrated significant improvement in motor and sensory evoked amplitudes, distal latencies, and conduc-



FIGURE 2. Marked resolution of the sclerotic lesions in the right humerus after chemotherapy.

tion velocities (Table 1), paralleling the clinical response. These results are represented on a separate graph (Fig. 3), relating averaged recordable electrodiagnostic responses to the course of the disease expressed as a percentage of the lower limit of normal for age-matched control subjects. No improvement was recorded on serial needle examinations for those parameters reflecting distal axonal degeneration and reinnervation.

DISCUSSION

Approximately 40%–50% of cases of osteosclerotic myeloma reported by Iwashita et al.,⁷ as well as Driedger and Pruzanski,⁴ were associated with polyneuropathy. When contrasted to the clinical presentation of typical multiple myeloma, these patients usually present at a younger age, are not systemically ill, and manifest a lower percentage of abnormalities in serum and urine immunoglobulin analysis, serum calcium, renal function, hematologic parameters, and sedimentation rates. Lymphadenopathy, splenomegaly, and hepatomegaly may be present.^{4,9} In addition, these patients may have hyperpigmentation, excessive perspiration,

peripheral edema, papilledema, digital clubbing, hypertrichosis, and a myriad of associated endocrine abnormalities, including gynecomastia, hypothyroidism, diabetes, impotence, amenorrhea, hirsutism, and elevated serum estrogen or reduced testosterone levels.^{1,6,7,9}

Laboratory abnormalities include radiologic evidence of solitary or multiple osteosclerosis.^{4,9} Bone marrow aspiration or biopsy may be normal, or have a modest increase ($\leq 5\%$) in normal-appearing plasma cells, while fluoroscopically directed needle biopsy or open surgical biopsy of a suspected bone lesion usually reveals bone marrow plasmacytosis.^{8,9} Other abnormalities are anemia, polycythemia, leukocytosis, thrombocytosis, thrombocytopenia, and elevated CSF protein. Results of serum protein electrophoresis and immunoelectrophoresis are quite variable. An M-protein may not be detected in the serum or urine in approximately 25% of patients with osteosclerotic myeloma, yet levels as elevated as 7.4 g/dl have been reported.^{4,8}

Electrodiagnostic studies reveal characteristic abnormalities: low amplitude or absent motor and

Table 1. Electrodiagnostic results.

Motor conduction studies						
Date	5/80	10/80	9/81	11/81	8/81	Normal range
Amplitude (mV)						
Ulnar	3	2	5	5	5.5	(6-16)
Median	4	3	—	8	7	(4-18)
Peroneal	NR	NR	NR	NR	NR	(2-12)
Conduction velocity (m/sec)						
Ulnar	26	24	35	38	39	(49-71)
Median	25	25	—	34	38	(49-71)
Distal latency (msec)						
Ulnar	5.6	5.2	3.4	3.7	3.5	(1.8-3.5)
Median	6.5	5.4	—	4.5	3.8	(2.4-4.4)
Sensory conduction studies						
Amplitude (μ V)						
Ulnar	10	12	12	22	30	(>15)
Median	8	10	—	28	25	(>20)
Sural	NR	1	NR	2	2	(6-47)
Conduction velocity (msec)						
Ulnar	34	36	45	51	54	(53-73)
Median	—	30	—	45	47	(53-73)
Distal latency (msec)						
Ulnar	5.4	5.6	3.8	3.5	3.6	(2.4-3.5)
Median	5.5	5.4	—	3.6	3.6	(2.5-3.7)
Sural	NR	7.2	NR	5.6	4.8	(3.2-4.2)

Treatment initiation 9/80

NR = No response.

(—) = Not done.

sensory evoked responses, prolonged distal latencies, progressive dispersion of motor evoked responses with proximal stimulation, and moderate to marked slowing of conduction velocity. Distal greater than proximal fibrillation potentials and reduced voluntary motor unit potentials with associated changes of chronic denervation are recorded on needle examination.^{8,9} Nerve biopsy

specimens demonstrate combined axonal degeneration and demyelination with remyelination.^{1,8,9,13}

Documented improvement in the peripheral neuropathy of osteosclerotic myeloma after radiation therapy has been reported in numerous cases of solitary osteosclerotic myeloma, but not in cases with multifocal lesions.^{3,7-10} Reitan et al.¹¹ and Driedger and Pruzanski⁵ described patients with multifocal osteosclerotic myeloma whose neuropathy improved after treatment using prednisone and/or cyclophosphamide, although posttreatment electrodiagnostic studies were not described. None of the seven patients with multifocal osteosclerotic myeloma reported by Kelly et al.^{8,9} substantially improved or maintained improvement after chemotherapy. Posttreatment electrodiagnostic studies demonstrated doubling of the evoked amplitude and nerve conduction velocities in two patients with solitary osteosclerotic lesions treated with radiation therapy.^{8,9} In our patient, the marked improvement in nerve conduction velocities and evoked amplitudes reflects repair of the most readily reversible component of the neuropathy, i.e., demyelination.

We believe this represents the first reported case of myelomatous polyneuropathy associated with multifocal osteosclerotic myeloma unequivocally responding to melphalan and prednisone, and having serial electrodiagnostic documentation of the clinical improvement.

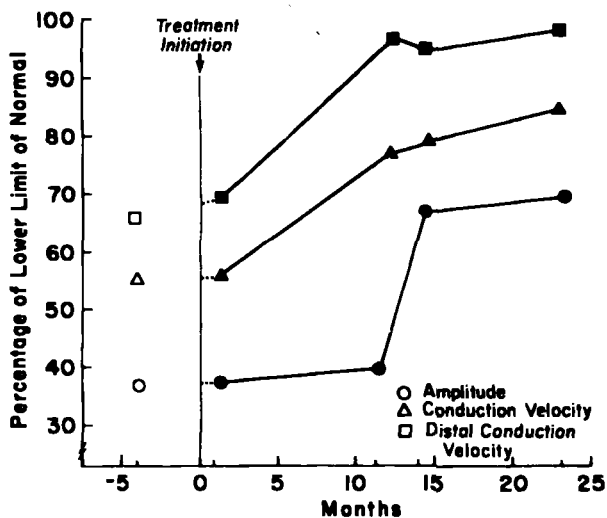


FIGURE 3. Mean sensory and motor evoked response amplitude, conduction velocity, and distal conduction velocity of recordable nerves expressed as percentage of the lower limit of normal, before and after treatment.

REFERENCES

1. Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway, GD, Resnick DL: Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. *Medicine* 59:311-322, 1980.
2. Currie S, Henson RA, Morgan HG, Poole AJ: The incidence of the neo-metastatic neurological syndromes of obscure origin in the reticuloses. *Brain* 93:629-640, 1970.
3. Davis LE, Drachman DB: Myeloma neuropathy: successful treatment of two patients and review of cases. *Arch Neurol* 27:507-511, 1972.
4. Driedger H, Pruzanski W: Plasma cell neoplasia with osteosclerotic lesions. *Arch Intern Med* 139:892-896, 1979.
5. Driedger H, Pruzanski W: Plasma cell neoplasia with peripheral polyneuropathy. *Medicine* 59:301-310, 1980.
6. Imawari M, Akatsuka N, Ishibashi M, Beppu H, Suzuki J, Yoshitoshi Y: Syndrome of plasma cell dyscrasia, polyneuropathy, and endocrine disturbances. *Ann Intern Med* 81:490-493, 1974.
7. Iwashita H, Ohnishi A, Asada M, Yasuhisa K, Kuroiwa Y: Polyneuropathy, skin hyperpigmentation, edema, and hypertrichosis in localized osteosclerotic myeloma. *Neurology (Minneapolis)* 27:675-681, 1977.
8. Kelly JJ, Kyle RA, Miles JM, Dyck PJ: Osteosclerotic myeloma and peripheral neuropathy. *Neurology (NY)* 33:202-210, 1983.
9. Kelly JJ, Kyle RA, Miles JM, O'Brien PC, Dyck PJ: The spectrum of peripheral neuropathy in myeloma. *Neurology (NY)* 31:24-31, 1981.
10. Morley JB, Schwieger AC: The relation between chronic polyneuropathy and osteosclerotic myeloma. *J Neurol Neurosurg Psychiatry* 30:432-442, 1967.
11. Reitan J, Pape E, Fossa SD, Julsrud OJ, Slettnes ON, Solheim OP: Osteosclerotic myeloma with polyneuropathy. *Acta Med Scand* 208:137-144, 1980.
12. Silverstein A, Doniger DE: Neurologic complications of myelomatosis. *Arch Neurol* 9:534-544, 1963.
13. Victor M, Banker BQ, Adams RD: The neuropathy of multiple myeloma. *J Neurol Neurosurg Psychiatry* 21:73-88, 1958.