Multiple myeloma with polyneuropathy and osteosclerotic lesions

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The neuropathy of multiple myeloma is, as Victor, Banker, and Adams (1958) stressed, 'a curious and little known affection of peripheral nerves which is only obscurely related to multiple myeloma, for their disease . . . does not in any way depend upon compression of nervous structures by tumour tissue'. The increasing interest in the relationship between malignant diseases and neuropathy has considerably broadened this field, although the nature of the association is still purely speculative (Brain, 1963). The data available at the present time seem to indicate some relationship between the type of malignancy, its location, and the manner in which the nervous system is affected (Croft and Wilkinson, 1963). The development of a 'toxic metabolic' neuropathy in patients with multiple myeloma is an uncommon complication. However, even more unusual in this disease is the manifestation of osteoblastic rather than osteolytic lesions. It is the purpose of this article to report the clinical and pathological findings of a patient with myelomatosis who exhibited both a polyneuropathy and osteosclerotic lesions, in the hope that it may further the knowledge of these unusual manifestations of malignancy.

CASE REPORT

G.E. (T.G.H. No. 02-91-05), a 44-year-old man, first began having symptoms in December of 1960, 14 months before death. At that time he noted some difficulty in walking due to weakness of the lower limbs. In January 1961, his toes felt numb and by March his sensory complaints had spread as far as his knees. He was admitted to hospital because of the difficulty in walking. On neurological examination, he had some weakness of dorsi and plantar flexion of both feet, loss of tendon reflexes at knees and ankles, and some decrease in light touch and pain sensation in his feet. Investigations included upper gastrointestinal series, barium enema, cholecystogram, myelogram, lumbar puncture, and routine examinations of blood and spinal fluid. The only abnormal findings were a protein level of 100 mg. in the cerebrospinal fluid and the radiological evidence of multiple smoothly demarcated bone lesions in the lumbar spine and pelvis, the nature of which was undetermined.

In June 1961, six months after the onset of his complaints, he was walking with the help of a cane. At the end of that month he was admitted to another hospital, where an attempt to reveal the nature of one of the bone lesions was unsuccessful. The spinal fluid was re-examined and the protein level remained elevated.

By mid-July, he had lost 12 lb. in weight. There was no power in either dorsi or plantar flexion of the feet and ankles and there was evidence of moderate weakness of the quadriceps and hip flexors and extensors. In August, he was on crutches with disagreeable tingling and a burning sensation of moderate severity in the lower limbs.

In September, he developed numbness in both hands and on examination showed definite weakness of fingers and wrists. Some early wasting of the dorsal interossei was noticed. The supinator jerks were present but elbow, biceps and triceps reflexes could hardly be elicited.

At the time of his admission to the Toronto General Hospital in December 1961 he had lost a further 13 lb. in weight, was bedridden, complained of some shortness of breath and had slight difficulty swallowing. On direct questioning, he denied bone pains. On examination, no abnormality of his mental status was found. His speech was normal. The visual acuity was 20/30 and 20/40. The fields were full. The right fundus showed a small, probably old, haemorrhage just beside the disc. The remnants of the cranial nerves were normal. The power of the neck muscles was slightly diminished. Both upper and lower limbs showed complete loss of power distally and moderate weakness proximally. The weakness and wasting was symmetrical. The truncal musculature was weak. No tendon reflexes could be elicited. A symmetrical glove and stocking sensory loss was found. Vibration was lost from the level of the second thoracic downward. Position sense was absent in fingers and toes. Palpation of the peripheral nerves failed to reveal any abnormality. His blood pressure was 130/75 mm. Hg. The pulse was regular. The liver, kidneys, and spleen were not palpable. No pain could be induced by pressure over the bony surfaces and no other abnormality was found on physical examination of the skeletal system.

Investigations included: haemoglobin 13·9 g. %, the sedimentation rate was 14 mm. in one hour (Westergren); white blood cells 8,000 c. mm. (lymphocytes 12%, monocytes 6%, polymorphs 81% eosinophils 1%); platelets 306,000 c. mm., two hour p.c. blood sugar.
96 mg.%, B.U.N. 14 mg.%, acid phosphatase 3-9 K-A units, alkaline phosphatase 10-9 K-A units, serum calcium 9-3 mg.%, phosphorus 4-6 mg.%, bromosulphalein 5% retention in 45 minutes, L.E. cells negative, no cryoglobulins, bleeding time 3 minutes, clotting time 9 minutes, uroporphyrins negative. Urine excretion test for lead gave less than 0-2 mg. in 24 hours. Investigations for arsenic were negative. Congo red 48-8% absorption. Total serum protein 63 g.%. Electrophoretic fractionation gave: albumin 53%, \( \alpha_1 \) globulin 6%, \( \alpha_2 \) globulin 11%, \( \beta \) globulin 9%, \( \gamma \) globulin 3%, abnormal discrete component in the gamma region 18%, the corresponding normal values being 52-70%, 3-6%, 6-11%, 8-14%, 10-22%, and 0. The Sia test for macroglobulinaemia was negative. Cerebrospinal fluid protein was 275 mg.% with 4 lymphocytes. Colloidal gold 00001221000. V.D.R.L. not reactive. Electrophoresis of cerebrospinal fluid gave: albumin 61%, \( \alpha_1 \) globulin 39%, \( \alpha_2 \) globulin 6%, \( \beta \) globulin 10%, \( \gamma \) globulin 3%, and an abnormal discrete component in the gamma region 12%. Urine analysis was normal with negative Bence-Jones heat test. Paper electrophoresis of the urine after concentration, however, revealed a discrete abnormal protein in the gamma position, characteristic of Bence-Jones protein.

A radiological skeletal survey showed multiple well-defined sclerotic lesions of bone with an irregular radiolucent centre. They ranged in size from a few millimetres up, with the average size of approximately 1 to 1.5 cm. in diameter.

Solitary lesions of this nature were seen in the mid shaft of the right femur, the neck of the scapula, and in the upper left humerus. Multiple lesions were present throughout the ribs (Fig. 1), the thoracic and lumbar vertebral bodies (Fig. 2), and also in the pelvis.

A bone marrow aspiration showed only a few clumps of normal-looking plasma cells. A right sixth rib biopsy revealed a dense white lesion (Fig. 3), and histological examination areas of osteosclerosis, in the centre of which was a mass of plasma cells which varied in degree of differentiation (Fig. 4).

Electromyography of the right deltoid and right biceps showed a reduced pattern on maximum contraction. The occurrence of diphasic denervation potentials and bizarre polyphasic potentials was indicative of a neurogenic lesion. In addition, there was some enlargement of the motor units from the right biceps and a few spontaneous fasciculations were recorded. A marked enlargement of the motor unit, indicative of an anterior horn cell disease, was not a feature. Attempts to stimulate both right median and ulnar nerves with a supramaximal stimulus did not induce a potential in any of the distal hand muscles.

A muscle biopsy showed large groups of small fibres, indicating that the atrophy was secondary to a nerve lesion.

A biopsy was obtained from the right sural nerve. A marked reduction in the number of myelin sheaths and axis cylinders was found (Fig. 5). A few lipid-containing macrophages were seen with Scharlach R. Special stains for amyloid were negative in the nerve tissue and adjacent blood vessel walls.

The diagnosis of a polyneuropathy associated with
multiple myeloma was made and the patient was treated with cyclophosphamide (Procytox), 100 mg. o.d., beginning on 15 February. The neuropathy continued to progress and by the first week of March, he had become dysphagic and dysarthric. On 13 March he developed aspiration pneumonia, to die on 15 March.

**FIG. 3.** Cross section of the rib biopsy showing the osteosclerotic lesion with its central nidus.

**FIG. 4.** Neoplastic proliferation of plasma cells. Haematoxylin and eosin × 455.

**FIG. 5.** Lateral peroneal nerve showing almost complete demyelination. Weigert's myelin stain × 430.

**POST-MORTEM EXAMINATION (A:128/62)** The body was that of a poorly nourished white male, measuring 5.5 ft. 2 in. in length and weighing 81 lb. Extensive bilateral purulent bronchopneumonia was present. Multiple focal sclerotic lesions were found in the vertebrae and ribs, which were whitish grey and had the consistency of bone. The central nidus of these lesions was composed of highly cellular neoplastic tissue. Many of the tumour cells were rather immature in appearance, but those which showed definite differentiation were all quite characteristic of plasma cells. The numerous transitional forms indicated that the mature plasma cells were a product of the neoplastic proliferation. Two unusual features were present in this myelomatosus lesion; one, a marked increase in reticulin framework in the area of abnormal proliferation; and the other, a striking deposition of dense new bone which filled the inter trabecular spaces in the immediate vicinity of the myeloma tissue (Fig. 6).

The kidneys and spleen were normal and there were no other findings worthy of mention in the general necropsy examination.

**Nervous system** The brain and its coverings were normal. The thoracic and lumbosacral portions of the spinal cord were carefully examined but no abnormalities were seen on the external surface of the dura or within the subdural space.

Peripheral nerves and spinal cord were stained with...
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FIG. 6. Bone lesion showing obliteration of intertrabecular spaces by osteoplastic process. Haematoxylin and eosin × 90.

FIG. 7. Transverse section of second cervical cord segment, showing demyelination of the dorsal columns. Heidenhain's myelin stain × 67.

FIG. 8. Anterior horn cells of the second lumbar segment showing swelling, loss of Nissl substance, and nuclear eccentricity. Cresyl violet stain × 300.

haematoxylin and eosin, cresyl violet, Mallory's connective tissue stain, Scharlach R, phosphotungstic acid haematoxylin, and Weigert's and Heidenhain's methods for myelin sheaths. The histological examination of serial sections taken at different levels of the spinal cord showed ascending demyelination and gliosis affecting the dorsal columns, mainly the fasciculus gracilis (Fig. 7). A moderate degree of loss of myelin was seen in posterior and anterior roots.

Many anterior horn cells showed axonal reaction (Fig. 8). A prominent feature in the peripheral nerves was an increase in Schwann cell nuclei and connective tissue. All nerves examined showed almost complete demyelination and contained occasional lipid-laden macrophages. The walls of the blood vessels were thickened.

Marked neurogenic atrophy was present in the upper and lower limb muscles that were examined.

DISCUSSION

The salient clinical feature of this patient was a widespread polyneuropathy associated with multifocal myelomatous lesions as in the cases reported by Victor et al. (1958). The patient presented with symmetrical weakness and atrophy, areflexia, and a glove-stocking sensory loss in upper and lower limbs.

At necropsy, no evidence of compression of neural structures by myeloma was present. The striking
pathological finding was the severe degeneration of peripheral nerves.

Certain clinical and pathological findings deserve particular emphasis. The polyneuropathy began 14 months before death and was at all times the dominant clinical feature and the cause of death. The rapid and generalized spread of the disease resulted in almost complete demyelination of the nerves of the limbs, the trunk, and cranial. There was evidence of spinal cord and cranial nerves. Amyloid deposits were not found.

Other causes of a sensori-motor polyneuropathy in this patient were looked for carefully. As the renal function and structure were normal, a uraemic polyneuropathy was excluded. Although ultra-centrifugation of the serum was done, there is no reason to suspect macroglobulinaemia. The Sia test was negative. The paper electrophoreses of the serum, cerebrospinal fluid, and urine all revealed an abnormal protein component migrating in the serum position and typical of multiple myeloma. Finally, no known neurotoxic drugs were given to the patient. We are not aware of any reports of cyclophosphamide (Procytox) affecting the nervous system, and, in any case, the drug was given only terminally.

A most interesting finding was the sclerotic bone lesions. Carson, Ackerman, and Maltby (1955) state 'the lesion of myeloma is a purely osteolytic one, so that radiographic evidence of new bone formation or periosteal reaction would suggest that the process is other than myeloma'. Radiological evidence of a bone lesion was found in 80% of the 83 proven cases of multiple myeloma described by Bayrd and Heck (1947). The most characteristic is a circumscribed, purely destructive lesion of varying size and resembling a punched-out cavity radiologically. We have, however, been able to find references to 20 cases of multiple myeloma with osteosclerotic lesions (Rypins, 1933; Kraf, D'Angio, and Smelin, 1949; Kohler and Laur, 1950; Galgano, 1955; Lewin and Stein, 1958; Engels, Smith, and Krantz, 1960; Porter, 1961; Tuboku-Metzger, 1961; Yentis, 1961). In three of these 20 cases, a coexistent polyneuropathy was described. The first was case 1 of Victor et al. (1958), who state: 'The radiological examination of the lumbar spine and pelvis revealed an extensive area of bone formation'. The second, that of Odelberg-Johnson (1959), showed sclerotic changes in vertebral and pelvic bones on radiological and at post-mortem examination. He, too, described a typical picture of a polyradicular neuritis occurring 10 months before death. Finally, a patient mentioned by Brain (1964), with a four-month history of numbness of the feet and weakness of the legs, presented a picture of a polyneuropathy associated with papilloedema, and radiographs revealed osteoelastic lesions of vertebrae and other bones. The diagnosis of multiple myeloma was confirmed at necropsy.

Puzzled by the coexistence of these two rare findings, we have re-examined the reported cases of peripheral neuropathy and myeloma (Victor et al. 1958; Silverstein and Doniger, 1963). The radiological findings were described in only 15, and of these, all showed osteoelastic lesions except the three patients noted above.

One may conclude that the association of peripheral neuropathy and bone-forming lesions is a rare finding and could possibly be only coincidental. One cannot but question, however, the possibility that some unknown pathogenic link is responsible for the coexistence of these two rare conditions.

**SUMMARY**

The clinical and pathological findings in a patient with osteoclastic multiple myeloma and polyneuropathy are reported. The literature is reviewed and the possible implications of the coexistence of these rare conditions are discussed.

**REFERENCES**