

Osteosclerotic Myeloma with Peripheral Neuropathy

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SUMMARY

A case of solitary osteosclerotic myeloma with peripheral neuropathy and unusual radiological features is presented. The association of myeloma and clinical peripheral neuropathy is unusual, but occurs more commonly with osteosclerotic lesions. The radiological appearance of a lytic focus involving contiguous vertebrae with a surrounding rim of sclerosis is extremely uncommon, but the diagnosis of myeloma should, in future, be suspected in these circumstances. The literature is briefly reviewed.

S. Afr. Med. J., 48, 1246 (1974).

Since the early reports of the last century little attention was paid to the association of malignancy and peripheral neuropathy, until the relationship of peripheral neuropathy to malignant disease, more particularly carcinoma of the bronchus, was firmly established. The association of multiple myeloma and sensory peripheral neuropathy is now well recognised, and Davis and Drachman,¹ in reviewing the literature, found a total of 44 acceptable cases and added 2 more of their own.

The majority of cases with myelomatous peripheral neuropathy have had sclerotic bone lesions, rather than the typical lytic deposits so characteristic of myeloma. It is the purpose of this article to report a further similar case, and to draw attention to the unusual radiological manifestations of contiguous vertebral involvement and the discrete sclerotic margin presenting a 'ring' or 'doughnut' appearance.

CASE REPORT

A 64-year-old Cape Coloured male was admitted in September 1972 with symptoms of prostatic enlargement of 2 years' duration. Because of the presence of a sensory

peripheral neuropathy in the lower limbs, he was referred to the Neurology Service where he gave a history of 2 years' pain in his right hypochondrium, radiating into his bladder and down his legs. The pain subsequently moved towards the midline, and involved the lower thoracic region of his back for 18 months before admission. For one year he had noticed progressive weakness of his legs, his walking being reduced to a shuffle with frequent falls. In addition, he complained of burning paraesthesiae of his soles. He had spent his whole life in a sheep-farming district, and worked as a carpenter. There was no history of heavy alcohol consumption and no known contact with any toxic substance.

Examination

There were no general stigmata of disease, blood pressure was 185/85 mmHg, pulse 80/min, regular, and all peripheral pulses were present and equal. The chest revealed signs of moderate chronic obstructive airways disease, and in the abdomen a soft liver was palpable 2 cm below the right costal margin. Higher mental functions were normal, with intact cranial nerves and normal optic fundi. In the upper limbs, power and tone were normal. Light touch and pain sensations were decreased on the dorsal surfaces of both hands, with normal posterior column function. Reflexes were bilaterally absent and tests of cerebellar function were poorly performed with a mild intention tremor. Abdominal reflexes were absent, and from the T7 level, light touch, pain, and vibration sense were markedly diminished. In the lower limbs, tone was probably normal, but power was graded as 4/5 in all muscle groups. Reflexes were absent and plantar responses were equivocal, with marked withdrawal. Joint position sense was normal throughout. Heel-knee testing and tibial tapping were poorly performed. Gait was wide-based and unstable, and Romberg's test was negative.

Investigations

Most investigations were within normal limits. The erythrocyte sedimentation rate was 14 mm (Westergren) in the first hour. A midstream urine specimen was normal, but urine electrophoresis showed a small quantity of albumin. The total serum protein was 7.7 g/100 ml, of which 5.3 g/100 ml was globulin. Immuno-electrophoresis showed IgG 2.620 mg/100 ml, IgA 320 mg/100 ml, IgM 220 mg/100 ml. Cerebrospinal fluid was clear and colourless, with protein 500 mg/100 ml, globulin + + +, glucose normal, and 1 lymphocyte/mm³.

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Date received: 18 January 1974.

Posterior iliac crest bone marrow aspiration with a Klima needle showed slight erythroid hyperplasia only, with a myeloid-erythroid ratio of 1,5:1. Marrow trephine at the same site using a modified Vim-Silverman needle showed a fairly cellular marrow in which all cell types were present with a large number of haemosiderin-laden macrophages. Plasma cells were not increased in number nor did they appear abnormal.

X-ray films of the chest, cervical and lumbar spines were normal. Radiographs of the thoracic spine with tomography revealed destruction of the bodies of T5 and T6 and the upper margin of T7, with a well-defined corticated margin to the lytic focus which caused some expansion. The T5-6 disc space had disappeared while the T6-7 space was narrowed (Figs 1-3). The skeletal survey was otherwise normal. Myelography revealed an almost complete extradural block between the upper border of T7 and the lower border of T5.



Fig. 1. Anteroposterior tomogram at 5,5 cm demonstrating the sclerotic margin of the destructive lesion of T6 body which crosses the disc space to involve the adjacent T5 and T7 bodies.

Motor nerve conduction studies were carried out based on the principal of Hodes, Larrabee and German, using concentric needle electrodes coupled to a Medelec MS 5 electromyograph. Supramaximal stimuli using square wave pulses of 100 or 200 μ sec duration were used to measure motor nerve velocities only. The right peroneal velocity

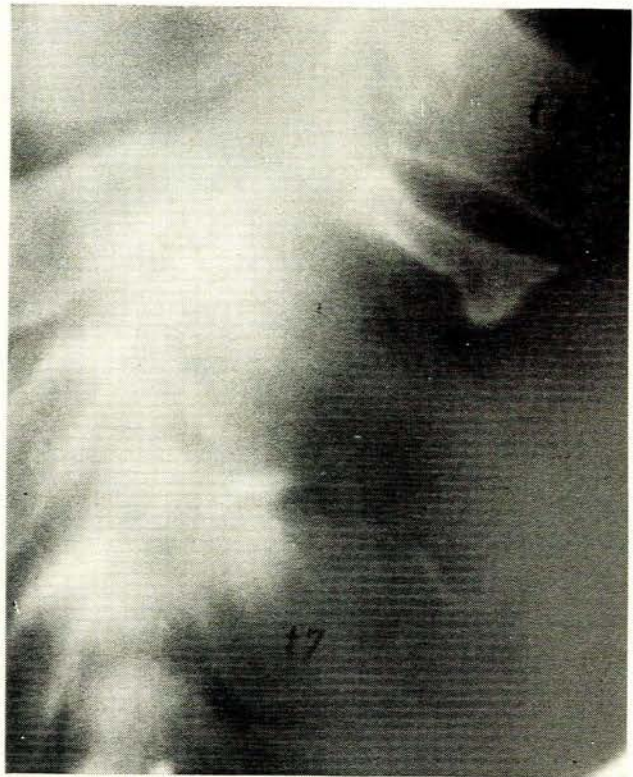


Fig. 2. Lateral tomogram at 15,5 cm demonstrating the corticated margin of the lesion of T5 to T7. No paraspinal lesion is seen. The pedicles of T6 are both destroyed.

was 18 m/sec with latencies of 27,6 msec and 7,7 msec from the knee and ankle respectively. The left peroneal velocity was 19 m/sec with latencies of 26,1 msec and 7,2 msec from the knee and ankle respectively. The right median nerve conduction velocity was 23 m/sec with latencies from elbow and wrist of 17,0 msec and 5,9 msec respectively. (The lower limit of normal nerve conduction velocity for this laboratory is 42 m/sec for the peroneal and 45 m/sec for the median nerves.) Electromyography showed the presence of spontaneous denervation activity in both extensor digitorum brevis muscles, but could not be demonstrated in the abductor pollicis brevis. On volition, discrete motor unit activity was present in both extensor digitorum brevis muscles, while the abductor pollicis brevis produced a full interference pattern. However, during isometric contraction of the abductor pollicis brevis fall-out of motor units was observed, and the patient was unable to maintain the contraction for 2 minutes.

The patient was subjected to open biopsy of the thoracic vertebral lesion and the histology revealed sheets of plasma cells and large plasmacytoid cells. Areas of necrosis and haemosiderin deposition were also present. Thereafter he was treated with 4 500 rads of deep X-ray therapy and two 8-day courses of combination chemotherapy, separated by a rest period of 5 weeks, employing vincristine (1 mg intravenously on days 1 and 8), melphalan (0,2 mg/kg orally on days 1-4), prednisone (1,5 mg/kg orally on days 1-7), and procarbazine (4 mg/kg orally

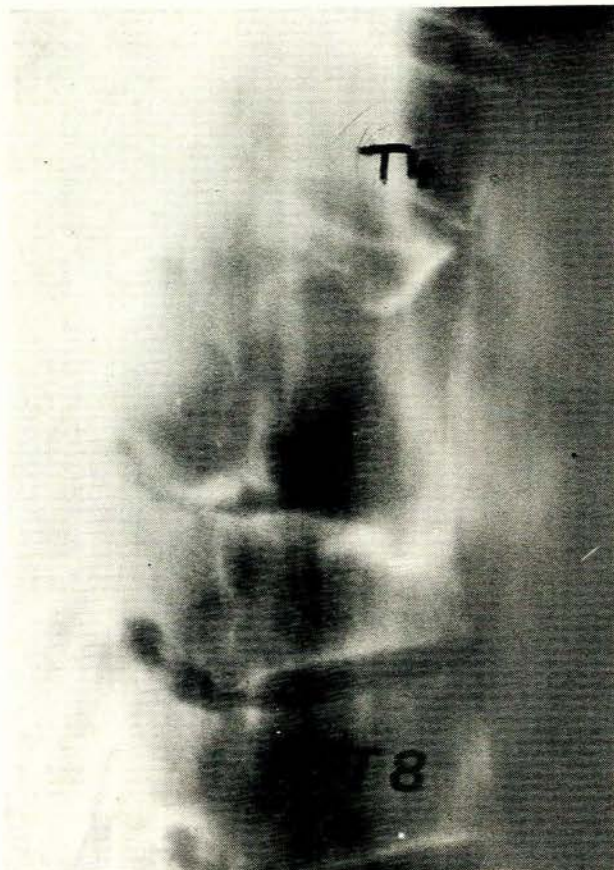


Fig. 3. Lateral tomogram at 16 cm, with similar results as in Fig. 2.

on days 2-6). Unfortunately at this point he refused further treatment, took his own discharge and has been lost to follow-up.

DISCUSSION

Comments on the Radiology

In a review of 45 solitary myelomas of bone, Paul and Pohle² felt the absence of sclerosis to be the rule and a differentiating point from secondary carcinoma. They found only 5 cases with recalcification, but none with new bone formation. As late as 1958 it was stated that an osteosclerotic reaction was incompatible with a diagnosis of myeloma or plasmacytoma, and Murray and Haddad³ endorsed this view, believing that myeloma does not invoke a marginal sclerotic reaction. Indeed, osteosclerotic lesions with myeloma are uncommon and we have been able to find only 39 satisfactorily documented cases of new bone formation in myeloma or plasmacytoma unassociated with radiotherapy, chemotherapy or healing of a pathological fracture.

The radiological appearances of the new bone formation may vary from sclerosis so dense as to be called

'ivory vertebra', to nothing more than bone spiculation. The appearance of ring sclerosis is the least common, and we have found only 6 previous cases.^{2,4-8}

Galgano⁹ states that it is rare for myelomatous vertebral involvement to be contiguous, and still more rare for extension across the disc space to occur, a view endorsed by other authors. In a review of myelomatosis, Yentis¹⁰ made no mention of deposits crossing disc spaces nor of ring sclerosis. However, Heiser and Schwartzman¹¹ reported 2 cases of extension across the disc space, and in the review of Paul and Pohle² myeloma involved one or more contiguous vertebrae in 6 of their 45 cases (13%). In some of their cases in which the vertebral body was primarily involved, follow-up studies showed later extension to adjacent bodies. They concluded that the ability of a destructive neoplastic lesion to cross cartilage and involve contiguous bone is more in keeping with a diagnosis of myeloma than metastatic carcinoma.

Differential Diagnosis

Tuberculosis in the healing phase results in increased bone density, and although the sclerosis is usually more uniform, it may result in an appearance not dissimilar to a ring lesion. Characteristically the discs are obliterated, but as healing progresses, spontaneous bony fusion occurs, leading to the classical appearances of a Pott's spine. In spinal tuberculosis a paravertebral abscess is an extremely common finding, but this cannot be used as a differential feature as it also occurs in myeloma, as was noted in several instances in Paul and Pohle's review, and by McKissock *et al.*¹² in 23% of their series of 22 cases.

A rare manifestation known as osteitis tuberculosa cystica produces multiple lytic deposits throughout the skeleton, and two of the deposits in one reported case showed surrounding sclerosis.

Hydatid cyst was strongly considered, since this disease is endemic in this country and the patient had lived all his life in a sheep-farming community. Spinal hydatid disease, however, is extremely uncommon. Murray and Haddad³ state that 1-2% of hydatids involve bone and 20% of these are situated in the spine, a figure corroborated by other authors. The lesion is usually lytic with a smooth margin, but may have a thin rim of sclerosis. The disc is characteristically spared unless secondary infection supervenes. It is said that myelography in hydatid disease commonly shows a block well below the destroyed vertebral body because of daughter cysts, but in our experience this has not been the case.

Metastatic disease was seriously considered, but the surrounding sclerotic rim proved difficult to explain, especially since the patient had had neither radio- nor chemotherapy. In this context, the report of Cole¹³ is of interest. He found, about one month after hypophysectomy in the treatment of carcinoma of the breast, a gradual filling-in of the lytic lesion leading to normal or even sclerotic bone. However, in some cases ring sclerosis occurs around the lytic lesion and it has been postulated that this is either healing commencing at the junction of malignant and normal tissue, or it is an

attempt by the body to seal off the malignant tissue. It is most attractive to postulate that the ring lesion seen in myeloma occurs on the latter basis.

Other conditions are so rare that they were not seriously considered. Benign osteoblastoma (osteogenic fibroma or giant osteoid osteoma) occurs more commonly in the long bones, but involvement of the posterior neural arches has been recorded showing sclerotic margins on the inner border of a well-circumscribed lytic lesion. However, the sclerosis was not well developed and the process affected the neural arch rather than the vertebral body. Chronic pyogenic osteitis results in bony destruction, intervertebral disc collapse, and subsequent ankylosis. The lesion is homogeneous and ring sclerosis does not develop. Osteoid osteoma is most unusual in the spine and is seen radiologically as a small translucent area with a heavily sclerotic margin. It may contain a small sclerotic nidus in the centre. Hand-Schüller-Christian disease may also present as a lytic area with a corticated margin.

Comments on the Cerebrospinal Fluid (CSF)

The elevation of the CSF protein observed in our patient may have arisen from the myelomatous neuropathy. This has been well documented.^{7,14} Indeed, elevated CSF protein may occur in myeloma without neurological complications. CSF protein is invariably raised in the Guillain-Barré neuropathy, and the high figure seen in myelomatous neuropathy may well be analogous. Unfortunately, as a block in the circulation of the spinal fluid also existed in our patient, we are unable to comment meaningfully on the protein elevation.

Comments on the Neuropathy

Malignant proliferation of plasma cells may affect the nervous system in a number of different ways. Myelomatous paraplegia, due either to extradural deposits or to vertebral collapse, is well recognised, and median neuritis due to amyloid in the carpal tunnel has been described. Peripheral neuropathy is now well recognised as a complication both of multiple myeloma and the less common solitary myeloma or plasmacytoma. Electrophysiological studies¹⁵ demonstrated that a generalised impairment of nerve conduction was present in 9 out of 23 subjects (39%) with multiple myeloma. Only 3 of these had clinical evidence of peripheral neuropathy.

Victor *et al.*¹⁴ describe the neuropathy as being a symmetrical, atrophic, areflexic, sensorimotor affection of the legs, and in 2 of their 5 cases the arms and trunk were affected as well. They comment particularly on the striking lack of parallelism between the symptoms of neuropathy and those of myeloma. In 2 patients the picture was purely of a severe, ultimately fatal polyneuropathy and the usual symptoms of myeloma were lacking. In 3 cases the symptoms of neuropathy antedated the discovery of the myeloma. These authors also drew attention to 1 patient in whom both osteoblastic and osteolytic features were present. In a recent series⁷ it

was noted that peripheral neuropathy antedated the detection of myeloma in 76% of cases, and 55% had osteosclerotic defects, although, generally, osteolytic lesions are far more common in multiple myeloma than osteosclerotic lesions. Our patient had marked osteosclerosis and the symptoms of neuropathy antedated the discovery of the plasmacytoma by about one year.

The primary pathological lesion has clearly been shown to be axonal degeneration and segmental demyelination,^{5,7,14} but the underlying pathogenesis is far from being understood. Although it has been stated that myelomatous tissue never extends in to the nervous system, more recent work describes 3 cases in which local infiltrations of the peripheral nerves by plasma cells led to demyelination of the adjacent nerve fibre. Neither infiltration nor compression of the nerve would, however, explain the typical symmetrical picture of the neuropathy.

Peripheral neuropathy secondary to amyloid, either of the small vessels or of the nerve trunks and perineural connective tissue, is well described and a case of peripheral neuropathy due to accumulation of amyloid in the vasa nervorum of a patient with amyloidosis has been documented. It is of interest that 61% of myeloma patients without evidence of neuropathy have demyelination in peripheral nerve biopsies performed similar to those seen in manifest cases, but amyloid has not been incriminated aetiologically. More recently, Davies-Jones and Esiri¹⁶ found amyloid in all peripheral nerves studied, and in the dorsal root ganglia and nerve roots amyloid deposits were found lying interstitially and in the walls of the vasa nervorum. There was widespread demyelination with a lesser degree of axonal degeneration and the muscle showed evidence of denervation atrophy.

In the pathogenesis of the demyelination it is unclear whether immunological mechanisms are involved or whether the tumour cells themselves elaborate a neurotrophic toxin that can damage nerves distant from the tumour. This latter view is supported by Davis and Drachman,⁷ who report 2 patients who improved promptly after radiotherapy to the myeloma site.

It has long been postulated that Bence-Jones protein may produce the toxic phenomena, and heavy or light chains could injure peripheral nerves, since the excessive production of light chains in experimental myeloma in mice is associated with a peripheral neuropathy. It has been suggested that abnormal serum proteins alter plasma viscosity in the vasa nervorum, encouraging intravascular clotting, or that they may lead to disordered parenchymatous protein metabolism perhaps affecting the peripheral nerve. The protein abnormalities are frequent, however, and the neuropathy which may occur without the presence of abnormal proteins is rare. Immunological mechanisms have been suggested since plasma cells are known to produce immunoglobulins, occasionally with specific antibody properties. In experimental myeloma there emerges a malignant clone of cells, a situation which probably pertains to man, and it has been found that the malignant plasma cell immunoglobulin production conforms to the same pattern as the benign parent population, sometimes resulting in great amounts of free antibody without any antigen. It is possible that this antibody is

directed against peripheral nerves with resultant demyelination. Antibodies to central nervous tissue and dorsal nerve root ganglia have been demonstrated, but not to peripheral nerves, in 4 cases of carcinomatous sensory neuropathy. Antibodies have not been detected in the mixed polyneuropathies, either carcinomatous or myelomatous. At present the evidence for an immunological basis is circumstantial and must await further clarification.

CONCLUSIONS

Osteosclerotic reactions occur uncommonly in myeloma, but when they do the lesions in the spine may involve more than one contiguous vertebra crossing the disc space. This unusual radiological appearance is more likely to be due to myeloma than to any other single condition. The paravertebral shadow commonly seen in tuberculosis may also occur in myeloma and lead to diagnostic difficulty.

In any middle-aged or elderly patient presenting with a polyneuropathy of uncertain origin, myeloma should

be considered in the differential diagnosis. The neuropathy may regress after adequate treatment of the myeloma. The pathogenesis of the neuropathy is obscure, but it is more common with osteosclerotic than with osteolytic lesions.

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