PERIPHERAL NEURITIS IN MYELOMATOSIS

BY

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[WITH SPECIAL PLATE]

In myelomatosis there is a high incidence of neurological lesions. Neurological abnormalities were reported by Geschickter and Copeland (1928) in 40% of 425 cases, by Batts (1939) in 35% of 40 cases, by Adams *et al.* (1949) in 35% of 61 cases, and by Snapper *et al.* (1953) in 40% of 97 cases. The commonest type of lesion is direct compression of nervous tissue or its blood supply by a pathological fracture or tumour mass (Davison and Balser, 1937; Clarke, 1954). Occasionally vascular thromboses or haemorrhages due to gross abnormality of serum globulin occur (Wintrobe and Buell, 1953; Marshall and Malone, 1954). Rarely the meninges, and with them cranial or peripheral nerves, are infiltrated by direct spread from tumour tissue (Sparling *et al.*, 1947). Extramedullary deposits of myeloma, which have been found in most organs, have not been reported in nervous tissue.

Peripheral neuritis, distinct from these mechanical or vascular lesions, also occurs in myelomatosis. Senator (1899) reported a case with bulbar palsy for which no anatomical cause was found. Scheinker (1938) described the case of a man of 39 with a solitary myeloma of the sternum who had a painful progressive peripheral neuritis. This patient also developed two large patches of thickened, deeply pigmented skin on the anterior chest wall. Scheinker postulated a specific "toxic" metabolite of myelomatous tissue which affected skin and peripheral nerves, and he suggested that in many cases the pain of myelomatosis is due to a "toxic disease" of the nerves. Davison and Balser (1937) reported a case of multiple myelomatosis in a woman of 49 who had a painful peripheral neuritis mainly affecting the arms. There was an iron-deficiency anaemia (haemoglobin 50%), and they attributed the neuropathy to the "severe secondary anaemia" or to "unknown toxic factors." Kurnick and Yohalem (1948) described extensive painful peripheral neuritis in two cases of multiple myelomatosis, and regarded the neuropathy as comparable with that which occurs in "some metabolic diseases such as diabetes and pernicious anaemia." Snapper *et al.* (1953) mention four cases with "glove and stocking" type of peripheral neuritis, and also several cases showing "striking atrophy of the interosseous muscles and the musculature of the arms without other evidence of neurological involvement." One of Brewer's (1948) cases had "some loss of feeling in the hands and feet."

The purpose of this paper is to report two further cases of myelomatosis with peripheral neuritis and other striking features.

Case 1

In May, 1953, a married man aged 54, who worked as a lorry driver, developed sudden pain and limitation of movement in the right shoulder without preceding trauma. These symptoms subsided in a few weeks, but mild intermittent pain persisted. About the end of 1953 a painless swelling

appeared in the region of the right acromion process and slowly increased in size. During that year his wife was concerned about a darkening of his skin and noted a "shininess" of his finger-nails.

In February, 1955, he first experienced a sensation of coldness and prickling in both feet with pain on walking. Thereafter weakness of the ankles and increasing numbness of the lower legs developed. Pain in the feet occurred even at rest, and there was oedema of the ankles in the evening. During the first half of 1955 he lost 17 lb. (7.7 kg.) in weight. On July 28 he was admitted to the Bristol Royal Infirmary. He complained of rapid increase in weakness, numbness, pain, and hyperaesthesia of the legs, now extending to the knees, and also the recent development of paraesthesiae and weakness of the hands. He had a good appetite and took a normal mixed diet with very little alcohol. There were no gastro-intestinal symptoms. The only previous complaints of note were a carpal tunnel syndrome of the left hand, which was completely relieved in May, 1948, by division of the flexor retinaculum, and an identical syndrome of the right hand early in 1953, which was only partially relieved by operation in March of that year.

The salient findings were as follows. General wasting; diffuse skin pigmentation of a dark grey-brown colour, most marked distally on the limbs, on the neck, and in the axillae; moderate clubbing of fingers and toes; increased opacity and pallor of the proximal three-quarters of all the finger-nails with loss of normal lunulae (Special Plate, Fig. 1); hyperhidrosis of palms and soles; soft oedema of legs. There was a painless, soft, fluctuant swelling over the right acromion process, over which the skin was hot, red, and shiny. In the right supraclavicular fossa were several enlarged, rubbery, discrete lymph nodes, and there was one smaller similar node in the left supraclavicular fossa. There was a severe peripheral neuritis with marked wasting and weakness of all the small muscles in both hands and of the finger flexors and anterior tibial muscles. Foot-drop was complete. In the upper limbs the only sensory change was loss of vibration sense in the hands, but in the lower limbs there was impairment of all sensation below the ankle-joints with extreme hyperaesthesia of the soles and calves. Deep reflexes could just be elicited in the arms, but were absent in the legs. The gait was "stepping" with sensory ataxia.

After his admission the peripheral neuritis progressed rapidly. Spontaneous pain and hyperaesthesiae were severe. Both sensory loss and weakness increased in severity, and extended proximally so that after three weeks he was unable to stand unsupported and had difficulty in shaving. Radiographs of the right shoulder were reported on as follows: "There is a multiloculated lesion involving the outer two-thirds of the spine of the right scapula and extending into the acromion process. It shows expansion of the bone and sclerosis at the margins of the translucent areas. There is a pathological fracture in the region of the base of the acromion process." (Plate, Fig. 2.) Radiographs of the rest of the skeleton revealed small, well-defined translucencies with sclerotic margins in the right ischium and left ilium. The chest was normal. There was no abnormality of the blood count, serum calcium or phosphorus, blood urea, fractional test meal, or five-day fat balance, and there was no proteinuria at any time. The E.S.R. was 11 mm. in one hour (Wintrobe). The serum proteins were 6.3 g. per 100 ml. (albumin 4.2 g., globulin 2.1 g.) with a normal electrophoretic pattern. In the cerebrospinal fluid there was increased protein, 264 mg. per 100 ml. on July 9 and 400 mg. per 100 ml. on September 10. The sternal marrow was normal, but that from the iliac crest contained 7% plasma cells.

A lymph node from the right supraclavicular fossa and a solid soft-tissue tumour arising from the right scapular spine were removed for histological examination. The tumour was a plasma cell myeloma, and in the node there was complete replacement of normal lymphatic tissue by myeloma cells.

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Intensive parenteral vitamin therapy had no effect. At the end of September, 5 millicuries of radioactive phosphorus was given followed by radiotherapy, 500 r $\times$ 2 to each supraclavicular fossa and 300 r $\times$ 5 to the right scapula. During radiotherapy the neuropathy continued to extend, but the pain and hyperaesthesiae of the extremities were a little improved. Within a few weeks of his discharge from hospital on October 5, however, spontaneous pain recurred.

On December 14, 1955, he was readmitted. Pain in the limbs was now very severe, consisting of a constant painful tingling, with frequent exacerbations which occurred spontaneously or in response to minor external stimuli. There was no change in the physical signs apart from slight progression of the neuropathy. Blood count, E.S.R., and levels of serum calcium and phosphorus, plasma proteins, and blood urea were unchanged and there was no Bence Jones proteinuria. Hepatic function tests showed no abnormality. The C.S.F. protein was 150 mg. per 100 ml. with only slight increase in globulin. Radiographs showed the scapular fracture to be united and consolidated with some new bone formation. There were two small osteolytic lesions in the ribs and an increase in size of the pelvic lesions. Biopsy of skin, muscle, and sensory cutaneous (sural) nerve from the calf showed no significant abnormality.

The patient was given a course of injections, by slow intravenous drip, of 2-hydroxystilbamidine di-esethionate, totalling 2.8 g., in three weeks. The pain in the limbs was dramatically and completely relieved, improvement beginning within 48 hours of the first dose. Coincident with the relief of pain there was a considerable improvement in his general well-being but no significant change in the neurological signs. At the time of writing he is still free from pain and claims to be much better, but there is no objective improvement.

Case 2

A widow of 67 lost over 2 stones (12.7 kg.) in weight in the early months of 1954, but she felt well until May, when she began to have a sensation of coldness and tingling in both hands. Shortly afterwards painful paraesthesiae, hyperaesthesiae, and numbness of the feet with sensory ataxia developed. Towards the end of 1954 she became aware of dusky discoloration of the hands and feet and she had paraesthesiae of the lips, while her hands and feet became weak and more painful and her gait more ataxic. Oedema of the ankles also developed. Her diet was normal, she had no gastro-intestinal symptoms, and never took alcohol. When first seen in December, 1954, there was pigmentation of the limbs. All modalities of sensation were impaired peripherally in the limbs and all the deep reflexes were absent, but there was no demonstrable weakness. Radiography of the chest revealed a well-circumscribed soft-tissue shadow anteriorly in the upper mediastinum, and bone destruction of the lower two-thirds of the sternum with new bone formation on the anterior surface. The appearances were thought to indicate an osteogenic sarcoma of the sternum with a secondary lesion in the mediastinum.

She was admitted to the Bristol Royal Infirmary on February 24, 1955. She had been given intensive therapy with aneurin hydrochloride during the previous eight weeks, but there was no change in her neurological state apart from the development of weakness of the small muscles of the hands. The pigmentation of the skin, a dusky greyish-brown, was more marked and was most prominent distally on the limbs. There was oedema of the ankles. Apart from a slight prominence of the sternum at the level of the third costal cartilage there was no clinical evidence of the sternal or mediastinal tumour. The sternum was not tender. The relevant investigations were as follows. Blood count normal; E.S.R. (Wintrobe) 6 mm.; blood Wassermann reaction negative; fractional test meal normal; serum proteins 7.4 g. per 100 ml. (albumin 3.9 g., globulin 3.5 g.). There was a trace of protein in the urine but no Bence Jones proteinuria. The C.S.F. protein was 80 mg. per 100 ml. Radiographs showed no change in the mediastinal or sternal lesions and no abnormality in the rest of the skeleton. A

pyruvate tolerance test gave normal results. Biopsy specimens from the sternal tumour showed it to be a highly cellular plasma-cell myeloma.

In April, 1955, the patient was treated with radiotherapy, 2,500 r $\times$ 10 to the sternum, and vitamin therapy was continued. There was no change in her symptoms or signs until six months after radiotherapy, when her symptoms began to improve, although no change in the objective signs took place. At the same time enlarged discrete rubbery glands became palpable in the axillae and the lateral chest wall, the serum proteins were abnormal (albumin 3.5 g., globulin 4.0 g. per 100 ml.), and there was increasing albuminuria with casts in the urine. From this time she refused further treatment and all investigations except blood examination.

In February, 1956, she was almost symptom-free and her general condition was maintained, but there was no objective change in the neuropathy or the pigmentation.

Review of Earlier Cases

Prompted by the unusual features of these cases, the records of 14 other consecutive cases of myelomatosis admitted to the Bristol Royal Infirmary between 1950 and 1955 were reviewed. Two of these had features suggesting peripheral neuritis. One patient, a woman of 62, had complained of tingling of the fingers, numbness below the knees, and painful feet for one year before admission. The other, a man of 58, was found to have "particularly noticeable" wasting of the small muscles of both hands, although no reflex or sensory abnormality was noted. There is a close resemblance between the latter case and those mentioned by Snapper *et al.* (1953). Skin pigmentation and clubbing were not found in any of these patients.

Comment

The initial radiological appearances were not characteristic of myelomatosis in either Case 1 or Case 2, and a diagnosis was reached only after biopsy. The high incidence of atypical radiological findings has been stressed in recent reviews of this disease (Bayrd and Heck, 1947, and others), and the diagnostic difficulties encountered have been well reviewed by Heiser and Schwartzman (1952).

In both cases there was lymph-node involvement. This occurrence in myelomatosis, though infrequently mentioned in the literature, is not rare. Churg and Gordon (1950) found such involvement in 18 of 28 consecutive necropsies, and in five of these cases superficial lymph nodes were affected.

Pigmentation was striking in both cases. It was a uniform greyish-brown most marked on the extremities and neck and in the axillae. It is interesting that in Scheinker's case with peripheral neuritis there were localized patches of thickened, deeply pigmented skin. The only other writers to comment on pigmentation in myelomatosis are Adams *et al.* (1949), who describe a "peculiar dusky sallow" coloration associated with the pallor of anaemic cases, but pigmentation is noted without comment in a number of case reports (Geschickter and Copeland, 1928: Case 3; Stewart and Parkes Weber, 1938: Case 3). This pigmentation is probably akin to that seen in malignant disease, which in spite of advances in our understanding of abnormal pigmentation is still unexplained (Lerner, 1955).

Mendlovitz (1942) in his exhaustive review of finger-clubbing did not mention myelomatosis as a cause, but Snapper *et al.* (1953) noted the presence of clubbing of the fingers in a few cases in their large series. In Case 1 clubbing developed before the onset of symptoms. There was no accompanying pulmonary, mediastinal, hepatic, or intestinal disease. The curious "white nails" seen in this case were also reported in myelomatosis by Snapper *et al.*, and have been described by Terry (1954) as occurring in hepatic and other diseases, including malignant states.

Discussion

From the scanty references in the literature and the present two cases there can be no doubt that peripheral neuritis occurs in association with myelomatosis. The finding of two

suggestive cases in a retrospective survey of 14 others may indicate that the occurrence is not very uncommon. There is nothing distinctive about the nature of the neuropathy. In the present cases, as in most of those previously reported, spontaneous painful paraesthesiae and cutaneous and muscular hyperaesthesiae were prominent features. But in Case 1 the condition was predominantly motor, while in Case 2 it was almost entirely sensory. In Case 1 it advanced steadily, whereas Case 2 improved spontaneously even though the myelomatosis was progressing. In neither case was there any response to treatment with vitamins or radiotherapy, nor in Case 1 with radioactive phosphorus.

The pain of the peripheral neuritis in Case 1 was dramatically relieved by stilbamidine. A similar effect is recorded in two cases by Kurnick and Yohalem (1948). This lends some support to Scheinker's suggestion that the pain of myelomatosis may be neurogenic, for stilbamidine frequently relieves the pain, which is the commonest symptom of this disease.

Both cases showed an increase of protein in the C.S.F. In the cases with peripheral neuritis reported by others the C.S.F. protein has been recorded as normal in two (Davison and Balser, 1937; Kurnick and Yohalem, 1948) and raised (200 mg. per 100 ml.) in one (Scheinker, 1938). In myelomatosis, however, an elevated C.S.F. protein, unrelated to neurological or vertebral involvement, is not an uncommon finding (Degenhardt and Sheehan, 1949) and is probably often a general manifestation of the disease (Madonick and Solomon, 1953).

Little is known of the pathological changes. Scheinker (1938) described an unusual proliferation of connective tissue in the peripheral nerves of his case, and a similar proliferation in the affected areas of skin. Davison and Balser (1937) found degeneration of anterior horn cells and patchy demyelination and axon degeneration in peripheral nerves. The biopsy specimen in Case 1 revealed no abnormality of skin or sensory nerve.

Abnormal protein metabolism was considered as a possible cause of this neuropathy, since amyloidosis of the "primary" type is a not uncommon complication of myelomatosis (Lichtenstein and Jaffe, 1947; Kolff and Dhont, 1948) and "primary" amyloidosis can cause peripheral neuritis (Navasquez and Treble, 1938; Kernohan and Woltman, 1942). In neither case, however, was there any clinical evidence of amyloidosis, and in Case 1 biopsy revealed no amyloid in skin, muscle, peripheral nerve, or their blood vessels. The Congo-red absorption test was not carried out, as it is not applicable to this pathological type of amyloidosis (Snapper *et al.*, 1953).

It is tempting to relate this neuropathy to that occurring in bronchogenic carcinoma (Lennox and Prichard, 1950; Henson *et al.*, 1954). Such "carcinomatous neuropathies" have shown very similar features and they often run a course unrelated to the course of the underlying disease, a peculiarity observed in Case 2. But the only apparent common factor in the two diseases is that both are neoplastic. It is true that both Bence Jones proteinuria and plasmocytosis have been reported in bronchogenic carcinoma (Hughes, 1954), but such occurrences are very rare and appear to bear no relation to carcinomatous neuropathy.

Although no explanation can be offered to account for the neuropathy nor for the pigmentation and clubbing in these patients, it is hoped that this account of such an unusual association may lead to the recognition and study of further cases.

Summary

The types of neurological involvement in myelomatosis are briefly surveyed and the literature concerning peripheral neuritis in myelomatosis is reviewed. Two cases are described in which myelomatosis (proved by biopsy) was associated with peripheral neuritis and diffuse pigmentation of the skin. One case had in addition clubbing of the fingers and toes and increased opacity of the finger-nails.

A retrospective survey of 14 other cases of myelomatosis revealed two cases with features of peripheral neuritis. It is suggested that this complication of myelomatosis may not be rare.

The clinical and pathological features of this type of peripheral neuritis are considered, but no distinctive characteristics can be ascribed to it. Similarities to reported cases of peripheral neuropathy complicating bronchial carcinoma are pointed out.

The pigmentation and "white nails" are regarded as being features of the underlying malignant disease, although the mechanism of their production is unknown.

The dramatic relief of neuritic pain by treatment with stilbamidine in one case supports the theory that the pain of myelomatosis is neurogenic.

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"Francis Galton once showed that, in the British peerage, wealth in women was correlated with infertility. An heiress by definition comes of an infertile family, for otherwise there would be many to share her wealth, and many noble families have become extinct through the love of heiresses whose riches were matched by their infertility. We may now put forward another rule, that not only wealth but also nubility in women is likely to be associated with infecundity. Attractive girls will usually marry, and the fecund will have large families while the less fecund will do their best and will certainly leave some descendants in future generations. Unattractive but highly fecund girls will be less likely to marry; but those that do will have plenty of children so that, as a group, the unattractive but fecund will also leave descendants. However, the group that is both unattractive and infecund will be at a double disadvantage and so will tend to be under-represented in future generations. Consequently, in each generation, owing to the elimination of this last group, we would expect to find that the mean fertility of nubile and attractive mothers should be below that of the less attractive."—C. B. GOODHART, *Nature*, September 15, 1956.

T. NICOL, R. S. SNELL, AND D. L. J. BILBEY: EFFECT OF CORTISONE

FIG. 1.—Section of spleen of control male guinea-pig given one subcutaneous injection of trypan blue daily for six days and killed the following day. Shows a moderate number of dye-bearing cells in sinuses of red pulp and in reticulum. Dye appears black in photomicrograph. (Stained weak eosin. $\times 200$.)

FIG. 2.—Section of spleen of male guinea-pig given 10 mg. cortisone acetate intramuscularly daily for seven days plus one subcutaneous injection of trypan blue daily during last six days before being killed. Compared with control animal (Fig. 1) the number of dye-bearing cells in sinuses and reticulum has become reduced, indicating reduced phagocytic activity. Dye appears black in photomicrograph. (Stained weak eosin. $\times 200$.)

FIG. 3.—Section of spleen of male guinea-pig given 10 mg. cortisone acetate intramuscularly daily for 14 days plus one subcutaneous injection of trypan blue daily during last six days before being killed. Shows complete absence of dye granules, indicating gross depression of phagocytic activity of reticulo-endothelial cells. (Stained weak eosin. $\times 200$.)

FIG. 4.—Section of medulla of lymph node of control male guinea-pig given one subcutaneous injection of trypan blue daily for six days and killed the following day. Shows numerous phagocytic cells in sinuses of medulla. Large amount of dye present in cells, indicating normal phagocytic activity. Dye appears black in photomicrograph. (Stained weak eosin. $\times 200$.)

FIG. 5.—Section of medulla of lymph node of male guinea-pig given 10 mg. cortisone acetate intramuscularly daily for 14 days plus one subcutaneous injection of trypan blue daily during last six days before being killed. Shows complete absence of dye granules, indicating gross depression of phagocytic activity of reticulo-endothelial cells. Lymphoid tissue shows marked degree of atrophy. (Stained weak eosin. $\times 200$.)

FIG. 6.—Section of medulla of lymph node of male guinea-pig given 10 mg. cortisone acetate intramuscularly daily for 21 days plus one subcutaneous injection of trypan blue daily during last six days before being killed. Shows moderate number of dye-bearing cells, especially on walls of lymph sinuses, indicating that phagocytic activity of reticulo-endothelial cells has started to recover. Dye appears black in photomicrograph. (Stained weak eosin. $\times 200$.)

R. S. CROW: PERIPHERAL NEURITIS IN MYELOMATOSIS

FIG. 1.—Case 1: The hands, showing pigmentation, "white nails," and clubbing. Left-hand nails are tobacco-stained.

FIG. 2.—Case 1: Myeloma of scapula with pathological fracture.