Motor neuron disease associated with carcinoma

A report of 2 cases

M. C. D. GRITZMAN, V. U. FRITZ, S. PERKINS, C. L. KAPLAN

Summary

Paraneoplastic complications are obscure and difficult to understand. The association of motor neuron disease and carcinoma may sometimes be more than coincidental, and 2 cases are described. One patient had motor neuron disease, limbic encephalitis (a recognized paraneoplastic disorder) and carcinoma of the oesophagus; the other had motor neuron disease and adenocarcinoma of the rectum. In the elderly male with motor neuron disease simple screening tests to exclude lymphoma and carcinoma of the lung, bowel and genito-urinary tract are advocated.

The relationship of motor neuron disease to neoplasia is controversial. If motor neuron disease can be shown to be a non-metastatic manifestation of carcinoma in the elderly patient, this may be of prognostic and therapeutic value.

In this paper 2 elderly patients with motor neuron disease and carcinoma of the gastro-intestinal tract are reported on. One tumour was a well-differentiated adenocarcinoma and the other a poorly differentiated squamous carcinoma.

Case reports

Case 1

A 71-year-old White man presented in March 1981 with a 3-day history of inability to eat or swallow, right loin pain and haematuria. Other symptoms were swelling of the feet for 3 weeks and weight loss over a period of 2 years. His past medical history included a stroke 18 months before admission, a pulmonary embolus in January 1980 and motor neuron disease diagnosed in June 1980, at which time he had complained of difficulty in speaking, swallowing and chewing for 18 months and weakness of the right hand for 4 months; examination had revealed wasting of the temporalis muscle, upper motor neuron weakness of the right facial nerve, difficulty in closure of the jaw, drooling from the mouth, a spastic tongue, a positive jaw jerk, pout and glabellar tap and bilateral palm-chin reflexes. Fasciculations were present in both upper limbs, the right more than the left, there was bilateral wasting of the small muscles of the hands, and upper limb reflexes were very brisk. The legs were normal. Sensation and cerebellar function were normal. Features of upper and lower motor neuron disease, especially fasciculation, suggested a diagnosis of amyotrophic lateral sclerosis. Electromyography confirmed the diagnosis by demonstrating a neurogenic disturbance, fasciculations and giant potentials and mild slowing of motor nerve conduction. No features of myopathy were present. Levels of muscle enzymes, including creatine kinase, aldolase and lactate dehydrogenase, were normal. There was no family history of motor neuron disease.

The patient's condition deteriorated progressively over the following 9 months; he lost 50 kg in weight and complained of leg weakness for 2 months before admission in March 1981.

Examination in March 1981 revealed extreme cachexia; the patient was unable to talk, eat, or swallow and was drooling from the mouth. He had bilateral oedema extending up to the thighs. On clinical examination the respiratory and cardiac systems appeared normal. Abdominal examination revealed a 7 cm tender, firm nodular hepatomegaly with a loud bruit. He now had bilateral upper motor neuron facial palsies, and the previously spastic tongue showed fasciculations and flaccidity. Pout and jaw jerk were brisk and glabellar tap and palm-chin reflexes present. Weakness was now marked in the upper and lower limbs, increased tone, bilateral ankle clonus and brisk reflexes completed the picture of a severe upper and lower motor neuron abnormality now involving the whole body. Sensation and cerebellar function remained normal. Laboratory investigations showed a raised ESR, raised urea, creatinine, bilirubin (mostly direct) and liver enzyme values, a reversed albumin/globulin ratio, a normal creatine kinase level and a slightly raised aldolase level. Alpha-fetoprotein was not present in the serum. A liver isotope scan showed metastatic tumour deposits. A diagnosis of malignant disease - the site of the primary tumour unknown - with multiple liver metastases and associated with motor neuron disease was made. In view of the patient's condition aggressive investigations were not carried out, and he died shortly afterwards. His illness had lasted approximately 27 months.

Autopsy revealed a 4 cm ulcerating tumour involving the entire thickness of the distal third of the oesophagus with metastases to the liver, lungs and lymph nodes. Microscopy showed an infiltrating, poorly differentiated squamous carcinoma (Fig. 1) and confirmed the metastases to lungs, lymph nodes and liver. Neuropathological examination revealed no evidence of metastatic disease. There was severe neuronal loss with degenerative but no inflammatory changes in the anterior horns of the cervical and lumbar spinal cord and the hypoglossal nuclei (Figs 2 and 3). The posterior nerve root fibers were normal and the anterior nerve roots showed loss of myelin and axons. Limbic encephalitis was also present (Fig. 4). Examination of voluntary muscle showed angular, atrophic fibres consistent with a neurogenic process (Fig. 5).
**Case 2**

A 74-year-old White man noted pain in the right shoulder and weakness of the right arm in July 1981. Over 4 months the arm became progressively weaker and then paralysed. By November the left arm had also become weak and he had difficulty with speech and swallowing. A myelogram performed in October was normal. He also complained of constipation, black stools and some weight loss, which started at the same time as the right arm weakness. There was no other history of significance.

On examination in October 1981 the patient was a thin elderly man who spoke with a slurring dysarthria and had some difficulty in swallowing. There was fasciculation and wasting of the tongue, but no pout or jaw jerk was elicited. The right arm was paralysed, while the left arm showed marked deltoid and triceps weakness. Gait was normal. Fasciculations were seen over both shoulder girdles and the triceps, biceps, right quadriceps and the left gastrocnemius muscles. Generalized wasting, especially of the shoulder muscles and small muscles of the hands, was noted. All reflexes were very brisk and clonus was noted over the right ankle. Sensation and cerebellar function were normal. Slight pallor was noted, but otherwise the general examination was negative. Rectal examination, proctoscopy and sigmoidoscopy revealed a fungating friable mass on the left wall of the rectum 5 cm from the anal verge.

The results of laboratory investigations, including renal and liver function tests, thyroid tests and estimation of the creatine kinase, aldolase and lactic dehydrogenase values, were all within normal limits. The chest radiograph was normal, but the cervical spine radiograph revealed osteophytes at C3-C4. Cervical myelography was negative and the cerebrospinal fluid normal. A liver scan was negative. Electromyography demonstrated a neurogenic pattern in the right deltoid muscle with fasciculations, polyphasic potentials and giant motor units. There was mild slowing of motor nerve conduction.

Barium enema examination demonstrated a small area of irregularity in the lower part of the rectum on the left wall.
On 26 October an abdominoperineal resection of the tumour was carried out; the tumour was totally removed and the patient was left with a colostomy. The pathologist reported an infiltrating well-differentiated adenocarcinoma of the rectum (Fig. 6).

In the month following the operation the patient noted progressive weakening of the arms. His gait remained normal. He developed symptoms of prostatism, and transurethral prostatic resection revealed benign prostatic hyperplasia with no malignant features. The patient was diagnosed as having motor neuron disease with associated rectal adenocarcinoma and benign prostatic hypertrophy.

**Discussion**

Motor neuron disease occurs in all parts of the world, with a prevalence of 4 or 5 per 100 000 population. Males are affected approximately 1.6 times as often as females, and the incidence reaches its peak at 50-60 years of age. The search for genetic, metabolic and environmental causes of motor neuron disease has so far yielded nothing conclusive, and as regards its etiology or pathogenesis no single concept has been widely accepted.

The association of motor neuron disease with carcinoma remains the subject of considerable controversy and may be coincidental, as malignant disease is common. Other forms of neumopathy such as polymyositis, peripheral neuropathy and myelopathy may complicate carcinoma. Since these conditions are difficult to distinguish from motor neuron disease in the early phases, the latter diagnosis must be verified by clinical, electromyographic and neuropathological methods. Both our patients showed clinical and electromyographic features indistinguishable from those of motor neuron disease, and our first patient had neuropathological features of muscle denervation and severe neuronal loss. The possibility that the coexistence of motor neuron disease and carcinoma may be more than mere coincidence has been suggested by a number of authors.

Remission of the neurological disease has followed removal of the carcinoma in 3 patients with bronchogenic carcinoma and with a renal cell carcinoma. Our first patient died from his carcinoma, but the second showed slight neurological deterioration despite removal of an adenocarcinoma of the rectum. Failure of remission may be due to remnants of neoplasm or to permanent degenerative changes in the motor neurons. Continued deterioration following cancer surgery may therefore not exclude a direct 'cause-effect' relationship.

Table I presents data (ages and sex of patients and types of neoplasm) recorded by other authors who have described the association of motor neuron disease with carcinoma. Thirty-two cases have been described, 6 in females and 26 in males; the ages of the patients ranged from 35 to 78 years. All the females and 21 of the males were over 50 years of age. Thirteen patients had carcinoma of the lung, 5 gastro-intestinal carcinoma (2 colon, 2 stomach, 1 ileum) and 4 breast carcinoma; 4 cancers fell into the leukaemia/lymphoma group, and 3 involved the male urogenital tract or kidney. The remaining 4 patients had an astrocytoma, a thymoma, a basal cell carcinoma and a tumorlet. Our 2 elderly male patients had gastro-intestinal tract carcinoma (1 oesophagus, 1 rectum).

In elderly patients, especially males, with motor neuron disease certain major carcinomas can easily be excluded. A rectal examination for prostatic enlargement in males and breast examination in females, urinalysis and examination of the stool for occult blood, chest radiography and a full blood count with measurement of the ESR are routine tests in most patients. Barium meal and barium enema examination and intravenous pyelography may be performed if strong suspicion results from any of the previous tests. This simple screening programme would have detected the cancer in our 2 patients and 28 of the 32 described in the literature.

The tumour may precede the neurological symptoms, they may occur together or the tumour may only be detected much later. Twelve of the patients in Table 1 had had neurological symptoms from 3 months to 5 years before carcinoma was diagnosed, and in 12 cases both diseases were detected on initial presentation. In our first case motor neuron disease preceded detection of the tumour by 27 months. In the second case the two diseases presented simultaneously. Prognosis may be affected if the tumour is found and completely excised, as in the 4 patients...
who experienced remission after operation. However, in many patients the carcinoma may be the cause of death and hence prognosis is often associated with the carcinoma and not the motor neuron disease; this was probably the case in our patient.

Neuropathological features in these patients may be unusual. Norris et al. stressed inflammatory reaction as a feature distinguishing this disorder from idiopathic amyotrophic lateral sclerosis and favoring a possible viral cause for the carcinomatous myoneuropathy. However, no inflammatory reaction or microglial activity was present in our patient, possibly because of chronicity. Brain et al. noted that the histological features in two patients who came to autopsy were not those of classic motor neuron disease; no abnormality was seen in the cerebral cortex, white matter, basal ganglia, brainstem or cerebellum. Lesions were present in the spinal cord, peripheral nerves and muscles. Similar features were seen at autopsy in case 1. There was fibre loss in the anterior roots and neuronal loss in the hypoglossal nuclei (Figs 3 and 4). The only other significant abnormality was the presence of limbic encephalitis, which is recognized as a paraneoplastic disorder. This suggests that our patient had developed non-metastatic neurological disease and supports the possibility that his motor neuron disease was not merely coincidental.

We are grateful to Mr Shaun Huey for technical assistance, Mr Mel Anderson for the photography, and Mrs Molly Long, who typed the manuscript.

### REFERENCES


### TABLE I. PREVIOUSLY REPORTED CASES OF CARCINOMA AND MOTOR NEURON DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Type of tumour</th>
<th>Age range (yrs)</th>
<th>M</th>
<th>F</th>
<th>Presenting features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain et al.</td>
<td>11</td>
<td>Carcinoma lung</td>
<td>30-50</td>
<td>7</td>
<td>4</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>Norris and Engel</td>
<td>15</td>
<td>Carcinoma lung</td>
<td>30-50</td>
<td>13</td>
<td>2</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>Buchanan and Malamud</td>
<td>1</td>
<td>Renal cell carcinoma</td>
<td>50-70</td>
<td>64</td>
<td>4</td>
<td>Features of both</td>
</tr>
<tr>
<td>Mitchell and Olczak</td>
<td>1</td>
<td>Carcinoma lung</td>
<td>70</td>
<td>1</td>
<td></td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Peacock et al.</td>
<td>1</td>
<td>Carcinoma lung</td>
<td>50-70</td>
<td>2</td>
<td></td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>Croft and Wilkinson</td>
<td>2</td>
<td>Carcinoma lung</td>
<td>50-70</td>
<td>7</td>
<td></td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Stephens et al.</td>
<td>1</td>
<td>Carcinoma lung</td>
<td>67</td>
<td>1</td>
<td></td>
<td>Carcinoma</td>
</tr>
</tbody>
</table>