Nerve and muscle microvasculitis in peripheral neuropathy: a remote effect of cancer?

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SUMMARY In a series of 50 cases in which nerve and/or muscle microvasculitis was seen on biopsy, seven were associated with malignancy. In two cases, the cancer was found after the discovery of microvasculitis. All patients exhibited sensory-motor neuropathy, which was often painful and asymmetrical, with a progressive course. ESR and CSF protein levels were always elevated. Motor conduction velocity was slightly reduced in three cases, unmeasurable in one case, and normal in three. Cancers involved were adenocarcinoma in five cases (three prostate and two lung), Hodgkin’s disease in one and immunoblastic lymphadenopathy in one. A thorough search for cancer should be performed when microvasculitis is seen in nerve or muscle biopsy specimens, especially when ESR and CSF protein levels are elevated.

Reports of nerve and/or muscle vasculitis in peripheral neuropathy associated with cancer are scarce. 1–5 Seven cases of nerve and/or muscle microvasculitis shown by biopsy were studied in patients with cancer. These observations came from a series of 50 cases of microvasculitis, selected from among 1076 biopsy specimens at the Laboratoire de Neuropathologie Charles Foix in La Salpêtrière Hospital during a 5-year period (1977–1982). The clinical files of all 50 cases were reviewed in 1983, and the aetiology of the microvasculitis was assessed in each case after a post-biopsy follow-up of one to five years. 6

Patients and methods

Patients

Case 1: A 54-year-old woman who smoked cigarettes, previously in good health, presented with a very painful sensory motor multiple mononeuropathy of a few weeks duration, involving both lower limbs, that was more pronounced on the left side. Polyarthralgia and weight loss were associated. Erythema nodosum of lower limbs was noted on admission.

A skin biopsy specimen showed microvasculitis of the dermis. Routine tests revealed hypereosinophilia (800/mm³) and hyponatraemia, related to an inappropriate secretion of antidiuretic hormone. Fiberoptic bronchoscopy showed lung adenocarcinoma, which was subsequently excised. Adjuvant chemotherapy included prednisone, vindesin and cisplatinum. The motor signs improved over 9 months, and then the neuropathy relapsed. The patient was lost to follow up 11 months after the onset of the neuropathy. Biopsy was performed 1.5 months after the beginning of the neuropathy and 2 months before the discovery of the malignancy.

Case 2: A 65-year-old man who smoked cigarettes, previously in good health, was operated on for lung adenocarcinoma. One month later, he developed lower limb pain, then weakness of all four limbs, with diffuse wasting and absent tendon reflexes. There was decreased sensation of all modalities in distal lower limbs. Symptoms and signs worsened until death due to acute pulmonary failure, 3 months after the onset of the neuropathy. Biopsy was performed 2 months after the beginning of the neuropathy and 3 months after the discovery of the malignancy.

Case 3: A 78-year-old man, with no previous pertinent medical history, presented with progressive symmetrical pain, numbness and weakness of the lower limbs of one year’s duration. On examination, there was weakness of distal muscles of four limbs, absence of deep tendon reflexes and decreased position sense of the lower limbs. In addition, there was dysphagia, loss of weight, and generalised pruritis. Routine tests disclosed marked eosinophilia (1100/mm³). Electrophysiological studies revealed a Lambert-Eaton syndrome. Thorough search for cancer,
the beginning of the neuropathy, and 11 months after the
discovery of the malignancy.

Case 5: A 78-year-old alcoholic man had been treated for 1
year for prostate adenocarcinoma by diethylstilboestrol, 3
mg daily. He developed distal tingling followed by diffuse
progressive weakness of all four limbs. The patient was bed-
ridden 3 months later. Examination showed absence of ten-
don reflexes and decreased sensation of all modalities in the
distal upper and lower limbs. The patient died suddenly two
weeks later. There was no post-mortem study. Biopsy was
performed 3 months after the beginning of the neuropathy,
and 13 months after the discovery of the malignancy.

Case 6: A 59-year-old man had a history of non insulin-
dependent diabetes mellitus. Hodgkin's disease, type 3, stage
III Bb) was diagnosed. Before any treatment, one month
after the clinical onset of the disease, bilateral foot drop and
weakness of the left quadriceps appeared. Treatment
included radiotherapy and chemotherapy (vincristine, mel-
phalan, procarbazine and prednisone). Two months later,
there was diffuse weakness of four limbs, with wasting and
absent tendon reflexes. There was decreased sensation of all
modalities in the distal four limbs. There was progressive
regression of neurological signs and symptoms after treat-
ment. Examination was normal 18 months after the onset of
the neuropathy. Biopsy was performed 2 months after the
discovery of Hodgkin's disease and one month after the
onset of the neuropathy.

Case 7: Immunoblastic lymphadenopathy was diagnosed in
a 72-year-old man with no pertinent medical history. Treat-
ment included vincristine, cyclophosphamide, procarbazine
and prednisone for 10 months. Two years later, bilateral
proximal weakness of the lower limbs appeared, more pro-
nounced on the left side, with bilateral pain in the anterior
aspect of the thigh. Myelus Hodgkin was normal. No abnormal
cells were found in the CSF. The weakness spontaneously
resolved in 2 months. Four months later, bilateral foot drop
with pain in both lower limbs appeared over a period of 2
weeks. On examination, there was marked symmetrical
weakness of lower limbs and distal weakness of upper limbs.
A new lymph node biopsy confirmed the diagnosis of immu-
noblastic lymphadenopathy. Corticoid therapy was fol-
lowed by transient improvement of the neuropathy. The
patient died one month later, from septicemia with men-
ingitis and disseminated intravascular coagulation. Post-
mortem examination did not disclose any malignant
infiltration in lymph nodes, liver, spleen, brain, spinal cord
and peripheral nerves (lumbar plexus, brachial plexus and
derone nerves). Numerous pictures of microvasculitis were
found in peripheral nerves. No encephalitis was seen.

Methods

Open nerve and muscle biopsies (superficial peroneal nerve
and peroneus brevis) were performed for diagnostic pur-
puses in our laboratory. A part of the specimen was fixed in
formalin, embedded in paraffin, and cut in semi-serisal sec-
tions (5 to 7 levels). These were stained with haematoxylin-
usin, PAS, MASSON's trichrome and, sometimes May-
Grünewald-Giemsa stain. Cases were selected on the basis of
presence of microvasculitis, that is inflammatory cell
infiltration surrounding and invading vessel walls, with
involvement of small-sized vessels and sparing of arteries

Fig (a) Nerve biopsy. Infiltration of small epineural vessels
by a few mononuclear cells. Case no 3. (prostate
adenocarcinoma). (Haematoxylin and eosin x 310.)

Fig (b) Muscle biopsy. Focal involvement of a small
epimyisal artery wall by a mononuclear infiltrate. Case no 4.
(prostate adenocarcinoma). (Haematoxylin and eosin
x 125.)

including chest radiography, fiberoptic bronchoscopy, bone
marrow aspiration, intravenous pyelography, radioactive
bone scan, acid phosphatase and abdominal CT scan was
negative. Treatment by guanethidine was ineffective. The
patient was then discharged. Twenty-nine months after the
beginning of the neuropathy, prostate carcinoma was dis-
covered. The patient was then lost to follow up. Biopsy was
performed 14 months after the beginning of the neuropathy
and 29 months before the discovery of the malignancy.

Case 4: A 73-year-old man had been treated for 5 months for
prostate adenocarcinoma by radiotherapy and diethyl-
stillboestrol, 2 mg daily, when he developed proximal pain
and weakness of lower limbs with loss of weight, becoming
bedridden 6 months later. Examination showed diffuse wast-
ing, weakness of lower limbs and left ulnar paresis. Deep
tendon reflexes were absent in lower limbs. There was
decreased sensation of all modalities in the lower extremities
and in the left ulnar territory. Bone radiographs, radioactive
bone scan and myelography were normal. The patient then
was lost to follow up. Biopsy was performed 7 months after

Vincent, Dubas, Hauw, Godeau, Lhermitte, Buge, Castaigne
Table 1  Nerve and muscle microvasculitis in cancer. General data

<table>
<thead>
<tr>
<th>Patient (case) No</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Site of microvasculitis</th>
<th>Type of malignant disease</th>
<th>Interval between symptoms of malignant disease and discovery of neuropathy (months)</th>
<th>Interval between symptoms of neuropathy and discovery of malignant disease (months)</th>
<th>Associated disorders</th>
</tr>
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<tbody>
<tr>
<td>1 (8257)</td>
<td>F</td>
<td>54</td>
<td>Muscle</td>
<td>Lung adenocarcinoma</td>
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<td>Inappropriate secretion of antidiuretic hormone</td>
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<td>2 (6834)</td>
<td>M</td>
<td>65</td>
<td>Muscle + nerve</td>
<td>Lung adenocarcinoma</td>
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<td>29</td>
<td>Lambert-Eaton syndrome</td>
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<td>3 (6470)</td>
<td>M</td>
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<td>Prostate adenocarcinoma</td>
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<td></td>
<td>Diabetes mellitus</td>
</tr>
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<td>4 (7486)</td>
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<td>73</td>
<td>Muscle</td>
<td>Prostate adenocarcinoma</td>
<td>8</td>
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<td>Diabetes mellitus</td>
</tr>
<tr>
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<td>78</td>
<td>Muscle</td>
<td>Prostate adenocarcinoma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6 (6982)</td>
<td>M</td>
<td>59</td>
<td>Muscle + nerve</td>
<td>Hodgkin's disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (7020)</td>
<td>M</td>
<td>72</td>
<td>Nerve</td>
<td>Immunoblastic lymphadenopathy</td>
<td>23</td>
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Table 2  Nerve and muscle microvasculitis in cancer. Laboratory data

<table>
<thead>
<tr>
<th>Case No</th>
<th>Erythrocyte sedimentation rate (mm)</th>
<th>Cerebrospinal fluid analyses</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Cells per mm³</td>
</tr>
<tr>
<td>1</td>
<td>58</td>
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<tr>
<td>2</td>
<td>38</td>
<td>0·4</td>
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<tr>
<td>3</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
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<td>0·8</td>
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<tr>
<td>7</td>
<td>40</td>
<td>0·8</td>
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</tbody>
</table>

larger than 70 μm in diameter. In muscle samples, only perimysial microvasculitis was considered. In addition, all patients had cancer proven by biopsy, as detailed in table 1. No other cause of microvasculitis was present (collagen disease, infection or drug).

Results

Microvasculitis The changes were observed in both nerve and muscle biopsies in four cases, in muscle alone in two cases, and in nerve alone in one case (table 1). Although it was sometimes difficult to assess in different sections whether different vessels were involved, there were always two or more sites of vasculitis in nerve and muscle samples. In most cases it consisted of pure mononuclear cell infiltration. In two cases (nos 3 and 6), a few polymorphonuclear cells were seen in the largely predominant mononuclear cell infiltrate. No leucocytoclasis or fibrinoid necrosis were observed. No malignant cells were seen. In the muscle biopsy specimens, denervation atrophy was observed in every case. In addition, the presence of necrotic and basophilic fibres was noted in cases 4 and 6. Nerve biopsies exhibited non-specific changes indicative of axonal degeneration in all cases except for case 7. In no case was the diagnosis of polymyositis made.

Patient profile The patients most frequently exhibited a progressive (cases 2, 3, 4, 5), asymmetrical (cases 1, 3, 4, 6), painful (cases 1, 2, 3, 4) neuropathy of the sensorimotor type. A major proximal motor deficit was seen in cases 2, 4 and 7. Conspicuous improvement with subsequent relapse was seen either spontaneously (case 7) or after chemotherapy (cases 1 and 6). Bulbar palsy was present in two patients (cases 3 and 5). With the exception of one case in which erythema nodosum was observed (1), there were no signs of systemic vasculitis. No signs or symptoms of central nervous system involvement were noted. CSF and erythrocyte sedimentation rate (ESR) data are given in table 2. CSF protein levels and ESR were always elevated. Electrophysiological data are given in table 3. Motor conduction velocities were normal or slightly reduced. Sensory nerve action
We thank Drs P Bouche, HP Cathala and J Scherrer for the nerve conduction velocity studies, Dr E Schuller for CSF analysis, Dr H Baron and M Smith for the English translation and Mrs Bethermin, Freytag, Fenoy and Mr P Miele for technical help.

**Discussion**

Cancer-related microvasculitis has often been suggested, mainly involving the skin. A few reports have suggested that the presence of microvasculitis in peripheral neuropathies could be a remote effect of cancer. In our series, there was one case of Hodgkin's disease and one of immunoblastic lymphadenopathy. Other associated conditions were adenocarcinomas: two involving the lung, and three the prostate. No prostate carcinoma has yet been reported in peripheral neuropathy with microvasculitis, though the association of this site of malignancy and neuropathy have already been mentioned in the literature. In one of our cases (case 3), a Lambert-Eaton syndrome was associated with microvasculitis and prostatic carcinoma. This association has been only rarely noted. Although no post-mortem study was performed, the 29-month interval between the discovery of the peripheral neuropathy and that of the cancer rendered the coexistence of another malignant disease unlikely. In conclusion, a thorough search for cancer should be performed when microvasculitis is seen in nerve or muscle biopsy, especially when ESR and CSF protein levels are elevated.

*Table 3 Electrophysiological investigations*

<table>
<thead>
<tr>
<th>Case No</th>
<th>MCV (m/s)/DL (ms)</th>
<th>SCV (m/s)/Ampl (μV)</th>
</tr>
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<tr>
<td>1</td>
<td>R: 58-4</td>
<td>R: 60</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>R: 43-6/4-1</td>
</tr>
<tr>
<td>3</td>
<td>R: 44-2/5</td>
<td>R: 48/3-2</td>
</tr>
<tr>
<td>4</td>
<td>R: 46-6/5-7</td>
<td>L: 41/6/3-5</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>Non-measurable</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>R: 45-7/3-8</td>
<td>L: 39-4/3-5</td>
</tr>
</tbody>
</table>


References