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. Polyarthritis 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,

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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 bedridden 3 months later. Examination showed absence of tendon 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 III B1 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, melphalan, 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 treatment. 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. Treatment included vincristine, cyclophosphamide, procarbazine and prednisone for 10 months. Two years later, bilateral proximal weakness of the lower limbs appeared, more pronounced on the left side, with bilateral pain in the anterior aspect of the thigh. Myelogram 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 immunoblastic lymphadenopathy. Corticoid therapy was followed by transient improvement of the neuropathy. The patient died one month later, from septicemia with meningitis 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 peroneal 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 purposes in our laboratory. A part of the specimen was fixed in formalin, embedded in paraffin, and cut in semi-seral sections (5 to 7 levels). These were stained with haematoxylin-eosin, PAS, MAISON's trichrome and, sometimes May-Grünwald-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.
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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>
</thead>
<tbody>
<tr>
<td>1 (8257) F</td>
<td>54</td>
<td>Muscle</td>
<td>Lung adenocarcinoma</td>
<td></td>
<td>3</td>
<td></td>
<td>Inappropriate secretion of antidiuretic hormone</td>
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<tr>
<td>2 (6834) M</td>
<td>65</td>
<td>Muscle + nerve</td>
<td>Lung adenocarcinoma</td>
<td></td>
<td>1</td>
<td>29</td>
<td>Lambert-Eaton syndrome</td>
</tr>
<tr>
<td>3 (6470) M</td>
<td>78</td>
<td>Muscle + nerve</td>
<td>Prostate adenocarcinoma</td>
<td></td>
<td>5</td>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>4 (7486) M</td>
<td>73</td>
<td>Muscle</td>
<td>Prostate adenocarcinoma</td>
<td></td>
<td>8</td>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>5 (7234) M</td>
<td>78</td>
<td>Muscle</td>
<td>Prostate adenocarcinoma</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (6982) M</td>
<td>59</td>
<td>Muscle + nerve</td>
<td>Hodgkin's disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (7020) M</td>
<td>72</td>
<td>Nerve</td>
<td>Immunoblastic lymphadenopathy</td>
<td></td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
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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>
<th>Percentage of gamma-globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cells per mm$^3$</td>
<td>Protein g/l</td>
</tr>
<tr>
<td>1</td>
<td>58</td>
<td>4.2</td>
<td>1.55</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>0.4</td>
<td>1.21</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>0.2</td>
<td>0.74</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>0.2</td>
<td>0.81</td>
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<td>5</td>
<td>68</td>
<td>0.2</td>
<td>0.47</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>0.8</td>
<td>0.64</td>
</tr>
</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 leucocytoclasia 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
potentials were altered in three cases. Lambert-Eaton syndrome was present in case 3.

**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.

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**References**

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