Malignancy and Sensory Neuropathy of Unexplained Cause

A Prospective Study of 51 Patients

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Objective: To investigate the frequency of cancer developing in patients with peripheral sensory neuropathy of unexplained cause.

Design: Prospective study.

Setting: A neurologic unit in a general hospital.

Methods: Following the diagnosis of neuropathy, we searched for occult malignancy. This search was repeated together with neurologic evaluations every 6 months thereafter. Patient recruitment began January 1, 1988, and ended December 31, 1995. The end point of the study was December 31, 1996.

Results: In the study period, we observed 363 patients with peripheral sensory neuropathy. Of these, 53 patients without any identified cause of neuropathy were invited to participate in the study. Of the 53, 2 patients refused. Thus, we examined and followed up 51 patients, 42 men and 9 women, with a mean age of 64.5 years (range, 19-80 years). The range between the onset of neurologic symptoms and the diagnosis of neuropathy was 2 to 72 months (mean, 13.9 months). The follow-up period ranged from 14 to 94 months (mean, 27.4 months) after the onset of the neuropathy. The cancer was in the liver in 4 patients (all had a primary hepatoma), the bladder in 3, the lymph nodes in 3 (all with non–Hodgkin lymphoma), the prostate gland in 2, the lungs in 2 (small cell lung cancer in both), the breast in 1, the pancreas in 1, the sublingual gland in 1, and the bone in 1 (a metastatic sarcoma).

Conclusions: More than one third of the patients with peripheral sensory neuropathy of unexplained cause developed cancer without any predominating type of malignancy.

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Patients (17.6%) had an MGUS: 5 had the IgG isotype, and 2 had the IgM isotype. The remaining 2 patients had the IgA isotype. The relationship has been established between those gammopathies and neuropathies.14

The aims of the study and what was involved were clearly explained to both the patients and their relatives. Written consent was obtained.

Patients included in the study underwent cerebrospinal fluid examination; morphologic examination of the sural nerve15; search for circulating immunoglobulins against neural antigens,16-18 called anti-Hu, anti-Yo, and anti-Ri antibodies, detected with previously described methods19; and a protocol of investigation for tumor detection, including determination of the humoral markers for neoplasms (carcinoembryonic antigen, α-fetoprotein, Ca 19-9, tissue polypeptide antigen, Ca 15-3 in women and prostate-specific antigen in men), search for occult blood in stool specimens, chest radiography, total body computed tomographic scanning, echography of the abdomen, pelvis, and thyroid gland, endoscopic examination of the esophagus and stomach, urologic or gynecological examinations, and rectal examination by a surgeon. The medical treatment was based on symptoms.

The patients were invited to return every 6 months for a checkup that included an electrophysiologic study and a search for cancer. This involved an accurate medical examination, routine blood examinations, investigation for occult blood in stool specimens, echography of the abdomen, pelvis, and thyroid, urologic or gynecological examination, and chest radiography. If found, any malignancy was histologically confirmed.

The inclusion of patients in the study ended December 31, 1995. The end point of the follow-up was December 31, 1996.

The mean follow-up of the patients at the end point was 51.4 months (range, 14-94 months); during that time, the symptoms and signs tended to stabilize or progress slowly. Mild to moderate muscle atrophy developed in 14 patients (27.5%), 8 of whom had a mild reduction in the distal muscle strength. The results of the electrophysiologic studies revealed that 11 patients (21.6%) had a slight reduction in the motor conduction velocity in the peroneal and tibial nerves (never below 10% of the lower limit of normal).

Cancer was diagnosed in 18 patients (35.3%) after a mean interval of 27.9 months (range, 3-72 months) after the onset of symptoms of neuropathy.
The patients, 16 men and 2 women, had a mean age of 66.2 years when the clinical diagnosis of neuropathy was made.

Malignancy was discovered in the following: liver in 4 patients (all had a primary hepatoma); lymphatic glands in 3 (all had non–Hodgkin lymphoma); the bladder in 3; the lungs in 2 (both had small cell lung cancer); the prostate gland in 2; the breast in 1; a sublingual gland in 1; the pancreas in 1; and bone in 1 (metastatic sarcoma).

Three patients with MGUS developed primary hepatoma (IgM MGUS), non–Hodgkin lymphoma (IgA MGUS), and metastatic sarcoma (IgG MGUS).

The Table shows the characteristics of the 51 patients.

The patient with anti-Hu antibodies was diagnosed as having small cell lung cancer 9 months after the diagnosis of neuropathy and 16 months after the onset of neurologic symptoms.

No paraneoplastic autoantibodies were found in the serum samples of the other patient who developed the same neoplasm, neither when neuropathy was diagnosed nor when the test was repeated after the detection of the cancer.

After cancer treatment, 4 patients showed neurologic improvement. They included the patient with small cell lung cancer but without anti-Hu antibodies, the patient with sublingual gland tumor, 1 patient with primary hepatoma, and 1 patient with bladder cancer.

All of them improved dramatically within a few weeks of treatment with the exception of the patient with bladder cancer, who improved slowly and did not complain of pain or a burning or aching sensation. This patient had a nearly complete recovery of the vibratory sensation after 12 months of tumor eradication.

Of the 4 patients, 3 were alive at the end point (follow-up of tumor at 58, 34, and 22 months), and none complained of neurologic relapses. The fourth patient, who had the small cell lung cancer, was healthy for 6 months after the treatment of the tumor, but her condition declined rapidly because of multiple cerebral metastases.

Of the other patients, 3 survived long enough to be periodically examined. These 3 patients included the patient with breast cancer, 1 patient with non–Hodgkin lymphoma, and 1 patient with bladder cancer. All 3 patients experienced a slow progression of the neurologic disease, but none lost the ability to walk.

The other patients died a few months after the diagnosis of cancer, including the patient with anti-Hu antibodies.

### Comment

Malignancy was discovered in more than one third of our patients approximately 2 years ± months after the onset of symptoms of sensory neuropathy.

The high tumor rate in our patients with peripheral sensory neuropathies of an unexplained cause was not subject to bias for 3 reasons. First, our department is not a specialty neuromuscular clinic, and it is located in a general hospital. Second, all but 2 of the patients came from the surrounding area of Bergamo. Third, follow-up examinations were conducted in all but 2 of the initially examined 53 patients. Compared with the most recent studies, our tumor rate is higher. In their study of 42 patients, Windebank et al found malignancy in only 2 patients who died of metastatic cancer 11 and 19 years after the onset of neuropathy, whereas in their study of 75 patients with neuropathy of an uncertain cause, Notermans et al found no tumor in 20 patients with sensory neuropathy.

However, these studies were somewhat different. The study by Windebank et al was retrospective and used less restrictive inclusion criteria than our study used. We carried out a prospective study and did not include patients with previous febrile illness, Sjögren disease, vasculitis, or chronic viral hepatitis as they did. Furthermore, due to the design of the study it is possible that those authors did not include patients who had developed a malignancy within 1 or 2 years of the diagnosis of neuropathy. The follow-up in the study by Notermans et al was shorter than our follow-up, being limited to 6 months after the clinic diagnosis of neuropathy.

Therefore, we suggest that it is reasonable to suspect malignancy in patients with peripheral sensory neuropathy without any identified cause and also any associated disease, and those patients should be
observed for an appropriately long time. However, from a practical point of view the results of our study were disappointing.

For several reasons, the discovery of an occult neoplasm was not easy at diagnosis of neuropathy despite our detailed and extensive search. First, it could be that since the time from neuropathy diagnosis to neoplasm discovery is so long, usually longer than a year, the size of the malignancy was below the baseline sensitivity of the investigation methods. A second reason is that cancer had no predominant localization. For example, lung cancer, which is historically the most frequent neoplasm associated with sensory neuropathy,20 was found in only 2 patients. In addition, there was no apparent common embryonic origin of the neoplasms that we discovered.

A third reason is that none of the information resulting from the investigations, such as clinical examinations, electrophysiologic examinations, cerebrospinal fluid analysis, or sural nerve biopsy, could reveal the development of a neoplasm, which is the commonly reported experience.21

The finding of anti-Hu antibodies16 can draw clinical attention to the lungs,22 but results that are negative for anti-Hu antibodies do not rule out small cell lung cancer.23

The main outcomes of our study are to highlight the need to look for cancer in patients with a peripheral sensory neuropathy of unexplained cause and to note that a malignancy can be below the common sites primarily involved in the pathogenesis of paraneoplastic neuropathies. However, the results of our study reveal that the chances of anticipating a diagnosis of an associated malignant neoplasm are low. Furthermore, our data are from a relatively small population and cannot be compared with those from community studies, preventing the translation of our experience into a survey for tumor types. Therefore, there is a need for further data to design an appropriate clinical strategy for patients with peripheral sensory neuropathy of unexplained cause.

Since the manuscript was accepted for publication, another patient from our study developed a high-grade malignant neoplasm. In April 1997, this 76-year-old patient was diagnosed as having a highly undifferentiated adenocarcinoma of the prostate gland, 56 months after the onset of symptoms and 47 months after the diagnosis of neuropathy.

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REFERENCES