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## Case 16-2004

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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## Case 16-2004: A 76-Year-Old Woman with Numbness and Pain in the Feet and Legs

Anthony A. Amato, M.D., and Anne Louise Oaklander, M.D., Ph.D.

### PRESENTATION OF CASE

A 76-year-old woman was referred to the Pain Center of this hospital because of pain and numbness in her feet and legs. Six years earlier, intermittent numbness had developed in the toes of her right foot; the numbness slowly spread to both feet and then to the lower legs. The pain was worse at night and awakened her with a burning sensation that involved both legs nearly up to the knees and extended at times to the hips. She rated her pain as 6 on a scale of 1 to 10, with 10 indicating the most intense pain. Additional symptoms that she reported included “pins and needles” and aching in the legs and feet. She had had no difficulty walking and no change in bladder or bowel function, although she had experienced a decrease in sensation in the perineal area. She had had some episodes of facial flushing and sweating, as well as brief light-headedness on occasion (without syncope). Her only other symptoms were dry mouth and constipation.

Thirteen years earlier, a thoracic meningioma found during an evaluation of midthoracic back pain and anorexia had been removed; both symptoms resolved after the operation. Four years earlier, a laminectomy to decompress stenosis of the lumbar spine was performed because of the onset of low back pain; the back pain improved, but the numbness and burning in the patient’s feet continued to worsen.

One year before her evaluation at this hospital, gadolinium-enhanced magnetic resonance imaging (MRI) of the thoracic region disclosed postoperative changes from the T7 level to the T10 level, with no evidence of any abnormal masses. A central syrinx, 1 to 2 mm in diameter, extended over a length of 2 cm at the T9 level. MRI of the lumbar spine eight months later revealed mild disk bulges, without disk herniation, a mass, or nerve-root impingement. There was evidence of a prior partial laminectomy at the L4 and L5 levels. An MRI examination of the cervical spine revealed mild spondylosis at multiple levels; there was thickening of the ligamentum flavum, which caused mild spinal stenosis but no deformity of the spinal cord.

An electromyographic examination and nerve-conduction studies of the arms and legs that had been performed one year previously were normal, as were the results of motor and sensory conduction studies performed four months before the patient’s evaluation at this hospital. Another electromyographic examination revealed minimal abnormalities in the intrinsic foot muscles, which raised the possibility of the presence of a very early stage of axonal polyneuropathy. Somatosensory evoked potentials of the me-

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dian nerves were normal, and those of the tibial nerves showed latencies at or near the upper limits of normal.

Laboratory tests performed at other facilities before the patient came to this hospital had revealed a normal erythrocyte sedimentation rate, normal results of serum immunoelectrophoresis, and normal levels of glucose (as determined by several tests of fasting blood glucose and two-hour glucose-tolerance tests), thyrotropin, glycosylated hemoglobin, and vitamin B<sub>12</sub>. Tests for anti-ganglioside GM<sub>1</sub>, anti-MAG, and anti-Hu antibodies, and also for serum autoantibodies associated with Sjögren's syndrome, were negative. A radiograph of the chest showed no abnormalities.

Localized cancer of the left breast had been treated three years before with radical mastectomy and axillary lymph-node dissection, followed by radiation therapy. The patient was married with two adult children; she was a retired office worker. She did not use tobacco or alcohol. Two sisters had had diabetes mellitus, several maternal relatives had had colon cancer, and paternal relatives had had cardiovascular disease. The patient's medications included gabapentin (1200 mg per day), acetaminophen with codeine (four to six tablets daily), amitriptyline (75 mg nightly), extended-release morphine sulfate (30 mg daily), as well as hydrochlorothiazide, irbesartan, rabeprazole, vitamin B complex, and docusate sodium. In the past, she had tried topiramate, topical capsaicin, transdermal fentanyl, and intravenously administered immunoglobulin as treatment for her symptoms, but they had not been effective.

On examination at the Pain Center of this hospital, the patient's vital signs were normal. She weighed 80 kg (176 lb). She appeared well. Examination of the heart, lungs, and abdomen revealed no abnormalities. There was mild ankle edema. Two surgical scars were present on the back, and the low back was tender on palpation. There was good lumbar flexion and extension and no pain on performance of straight-leg raising. The results of a neurologic examination showed normal mental status and cranial-nerve function. A motor examination showed normal tone, bulk, and strength throughout. Sensory examination showed marked diminution of the patient's perception of vibration at the toes and ankles; the diminution was less evident at the knees. Sense of joint position was mildly impaired at the toes; sensation of cold was reduced at the feet; perception of pinprick was reduced below

the knees and in the fingers but was intact over the dorsum of the hand and forearm. There was an area of allodynia (pain from light touch) and markedly decreased sensation on the left lateral calf and foot. The tendon reflexes were ++ at the biceps and triceps, and + at the knees and ankles. Plantar reflexes were absent. She could walk on her toes or heels, but not in tandem. She was extremely unsteady on performance of Romberg's test.

A diagnostic procedure was performed.

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#### DIFFERENTIAL DIAGNOSIS

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*Dr. Anthony A. Amato:* There are three goals when evaluating a patient with a neurologic illness: localize the site of the lesion, identify the cause, and offer appropriate treatment. A detailed history and neurologic examination can usually localize the site of the lesion, if not identify the exact cause. Electrodiagnostic testing and laboratory testing should be used as an extension of and not as a substitute for taking a good history and neurologic examination. The answers to several questions (Table 1) can narrow the differential diagnosis.

This 76-year-old woman had slowly progressive numbness, paresthesias, and pain, which began in the feet and ascended to the knees. There was no weakness, gait instability, poor coordination, radicular pain, bowel or bladder incontinence, urinary retention, or syncope. Dry mouth and constipation could be caused by amitriptyline, codeine, or morphine. Neurologic examination showed reduced perception of pinprick from the knees down and in the fingers, as well as diminished temperature perception in the feet. Her awareness of vibratory sensation in the toes and ankles was markedly decreased. Proprioception was decreased in the toes, and the patient had a positive response (unsteady gait with eyes closed) to Romberg's test. She had normal muscle tone, muscle strength, and muscle-stretch reflexes, and plantar responses were absent.

The symptoms as described are those of a painful sensory neuropathy<sup>1</sup> caused by damage to the A- $\delta$  (small myelinated) and polymodal nociceptive C (unmyelinated) nerve fibers. Dull, burning, poorly localizable pain (protopathic pain) is thought to be conveyed by polymodal nociceptive C fibers. Sharp, lancinating, prickly pain (epicritic pain) is probably mediated through A- $\delta$  fibers. The patient's reduced sensitivity to pinprick and temperature sensation in the legs suggests neuropathy affecting the small-diameter nerve fibers.

Reduced vibratory perception limited to the toes may be seen in patients with small-fiber neuropathies, but the marked impairment and diminished proprioception reported in this patient, together with the positive Romberg's test and normal muscle-stretch reflexes, suggest that these abnormalities are the result of damage to the posterior spinal cord columns, rather than superimposed damage to the large, myelinated peripheral-nerve fibers. There was probably trauma to the posterior columns from the thoracic meningioma that was excised 13 years ago. The normal serum levels of vitamin B<sub>12</sub> tend to rule out a diagnosis of a cyanocobalamin deficiency.

The current findings do not suggest a recurrence of lumbar spinal stenosis, which usually produces low back and radicular pain, non-length-dependent aching pain, fatigue, and weakness in the legs that is exacerbated by upright posture and walking (neurogenic claudication) and relieved by lying down. I have seen patients whose symptoms did not improve after lumbosacral laminectomy, because they actually had painful sensory neuropathy rather than spinal stenosis.

I suspect the pain and numbness in this patient's legs are caused by a small-fiber neuropathy.<sup>1-3</sup> Electrodiagnostic testing is essential. Nerve-conduction studies can be used to assess the function of large-diameter myelinated peripheral nerves.<sup>1</sup> The studies are useful in determining whether there is sensory, motor, or sensory and motor involvement and whether the disease process primarily affects the axons or the overlying myelin sheaths. Decreased amplitudes of sensory and compound muscle action potentials are usually associated with axonopathies; prolonged distal latencies, F-wave latencies, and slow conduction velocities imply an abnormality of myelination. The results of standard nerve-conduction studies are normal in patients with pure small-fiber neuropathies. In this patient, the results of these studies were normal, suggesting a small-fiber neuropathy. In the majority of cases of small-fiber neuropathy, we cannot identify the cause.<sup>2,3</sup>

#### CAUSES OF SMALL-FIBER NEUROPATHIES

The causes of chronic, painful sensory neuropathies include diabetes mellitus, impaired glucose tolerance, primary and familial amyloidosis, Sjögren's syndrome or sicca complex, vasculitis, human immunodeficiency virus (HIV) infection, toxic neuropathy due to drugs or other toxins, and rare heredi-

**Table 1. Questions to be Addressed in Evaluating Patients with a Neurologic Illness.**

Was the onset of symptoms acute (e.g., over days to weeks), subacute (e.g., over a couple of months), or chronic (e.g., over several months or years)?
What is the course of the illness (e.g., monophasic, relapsing–remitting, or progressive)?
What was the pattern of involvement (e.g., symmetric or asymmetric) at onset, and what is it at present?
What are the associated symptoms and signs (e.g., motor, sensory, or autonomic nervous system involvement)?
What associated medical conditions are present, including medication use and history of toxic exposures?
Is this a hereditary or acquired disorder?

tary neuropathies.<sup>2,3</sup> However, these neuropathies are usually associated with large-fiber sensory involvement and occasionally motor involvement. There are only a few laboratory tests that are helpful in evaluating patients with a small-fiber neuropathy. They include an assessment of the levels of fasting blood sugar and glycosylated hemoglobin, an oral glucose-tolerance test, serum and urine protein electrophoresis and immunoelectrophoresis, screening for antinuclear antibodies and Sjögren antibodies (anti-Ro and anti-La or SSA and SSB), and a measurement of the erythrocyte sedimentation rate. These tests were all negative or normal in this patient.

Additional studies were ordered that in my opinion were not necessary and that just added to the cost. There is no role for tests for so-called antinerve antibodies (e.g., anti-GM<sub>1</sub> ganglioside, anti-MAG, or antisulfatide antibodies) in patients with painful sensory neuropathy.<sup>4</sup> Anti-GM<sub>1</sub> antibodies are associated with multifocal motor neuropathy and the Guillain-Barré syndrome, neither of which is a consideration here. Anti-MAG antibodies are found primarily in demyelinating polyneuropathy and IgM monoclonal gammopathy; they are not associated with painful small-fiber neuropathies. Antisulfatide antibodies have very low sensitivity and poor specificity for the diagnosis of small-fiber neuropathies.

The most common cause of small-fiber neuropathy is diabetes mellitus. Our patient had normal fasting blood glucose and glycosylated hemoglobin levels. Recent studies suggest that the oral glucose-tolerance test should be performed even if fasting blood glucose and glycosylated hemoglobin levels are normal in patients who have idiopathic polyneuropathy, particularly if it is painful.<sup>5-7</sup> Impaired glucose tolerance (two-hour glucose level, 140 to 200 mg per deciliter) has been reported in up

to 36 percent of patients with painful sensory neuropathy and diabetes mellitus (two-hour glucose level of more than 200 mg per deciliter or fasting blood glucose level of more than 126 mg per deciliter) in up to 39 percent (Table 2). Although the risk of having both previously undetected diabetes mellitus and impaired glucose tolerance is increased in patients with sensory neuropathy, a causal relationship has not as yet been established.<sup>8</sup> The patient under discussion had normal results on two glucose-tolerance tests, which seems to rule out a diagnosis of either impaired glucose tolerance or diabetes mellitus.

Peripheral neuropathy occurs in 15 to 30 percent of patients with primary amyloidosis and is the initial manifestation of the disease in 17 percent of cases.<sup>9</sup> Small nerve fibers are preferentially affected. Eventually, symmetric weakness and large-fiber sensory loss develop, as does autonomic involvement. The results of nerve-conduction studies and electromyography are typically abnormal. Approximately 90 percent of patients with primary amyloidosis have a monoclonal protein detected in the serum or urine. The relatively benign nature of this patient's neuropathy, the lack of systemic involvement, and the absence of a monoclonal gammopathy make a diagnosis of primary or familial amyloidosis unlikely.

Sjögren's syndrome and sicca complex may be associated with an axonal sensory or sensorimotor polyneuropathy.<sup>10</sup> Although small nerve fibers are often involved, prolonged isolated small-fiber neuropathy is unusual with either of these disorders. In the case under discussion, the autoantibodies that are associated with Sjögren's syndrome were absent, making this diagnosis unlikely.

Could this patient have a paraneoplastic neuropathy? This syndrome is most common in patients with small-cell lung carcinoma, but it can also oc-

cur in patients with breast cancer. Neuropathic pain may be present, but the predominant manifestations are unsteady gait and poor coordination; the primary autoimmune attack is directed against the sensory ganglia, and many patients with a paraneoplastic neuropathy have limbic encephalitis.<sup>11</sup> Muscle-stretch reflexes are reduced, as are amplitudes of sensory-nerve action potentials. Antibodies directed against the Hu antigen are often present in the serum or cerebrospinal fluid. The absence of ataxia, the normal muscle-stretch reflexes, the normal results of the nerve-conduction studies, and the absence of anti-Hu antibody make paraneoplastic neuropathy unlikely.

Vasculitis involving the peripheral nervous system typically is manifested with multiple mononeuropathies that can overlap and give a picture of a generalized symmetric polyneuropathy. The neuropathy is painful and usually associated with sensory and motor deficits. Nerve-conduction studies demonstrate multifocal or generalized axon loss that affects motor and sensory nerves, and electromyography reveals denervation. A few cases of vascular inflammation associated with small-fiber neuropathy have been reported,<sup>12</sup> but fibrinoid necrosis of vessel walls and clinically significant improvement with immunosuppressive agents have not been demonstrated. It would be unusual for vasculitis of this duration to be evident only as a small-fiber neuropathy.

#### IDIOPATHIC SMALL-FIBER NEUROPATHY

The majority of small-fiber neuropathies remain idiopathic despite extensive evaluation. Most patients present with symptoms when they are between the ages of 45 and 70 years.<sup>13</sup> Approximately 80 percent of patients report burning pain in the feet. Sharp, lancinating pain, numbness, or paresthesias occur in half the patients. The hands often become affected over time. Symptoms restricted to the upper limbs and cranial-nerve involvement are exceptional. Reduced sensitivity to pinprick or temperature sensation is almost always present. Vibratory perception in the toes is reduced in more than 40 percent of patients, but this sensation is usually normal in the ankles. Less than 15 percent of patients have impaired proprioception. Autonomic impairment (dry eyes or mouth, facial flushing, abnormal sweating, impotence, incontinence, constipation, or diarrhea) is often seen.<sup>14</sup> The results of examinations of motor reflexes and deep-tendon reflexes are usually normal.

**Table 2. Glucose Tolerance in Patients with Small-Fiber Neuropathy.**

Reference	Patients <i>no.</i>	Mean Age (Range) <i>yr</i>	Abnormal	Impaired	Diabetes Mellitus
			Glucose Metabolism	Glucose Tolerance	
			<i>no.</i>	<i>(%)</i>	
Singleton et al., 2001 <sup>5</sup>	33*	64 (44–92)	20 (61)	7 (21)	13 (39)
Novella et al., 2001 <sup>6</sup>	28*	64 (41–82)	18 (64)	10 (36)	8 (29)
Sumner et al., 2003 <sup>7</sup>	73	61 (44–91)	41 (56)	26 (36)	15 (21)

\*The number cited includes only patients with painful sensory neuropathy.



What tests could confirm the diagnosis of small-fiber neuropathy? Quantitative sensory testing of the thresholds of heat, pain, and cold perception is used to assess small-fiber function.<sup>15</sup> Abnormal results of quantitative sensory testing have been reported in 60 to 85 percent of patients with predominantly painful sensory neuropathy.<sup>3,16</sup> However, such testing depends on the attention and cooperation of the patients; moreover, it cannot differentiate between simulated sensory loss and sensory neuropathy, and has relatively low sensitivity and specificity.<sup>17</sup> Another test may be useful. Since the peripheral autonomic nervous system is often affected in small-fiber neuropathies, the function of sweat glands innervated by small nerve fibers can be impaired.<sup>18</sup> The quantitative sudomotor axon reflex test (QSART) is thus highly specific and relatively sensitive for small-fiber damage, with 59 to 80 percent of patients with neuropathies having abnormal results.<sup>14,16</sup>

Quantitation of intraepidermal nerve-fiber density as measured in skin-biopsy specimens identifies an additional 10 percent of patients with small-fiber neuropathies beyond the percentage identified with QSART.<sup>1</sup> Reduced intraepidermal nerve-fiber density is present in 50 to 88 percent of patients with sensory neuropathy.<sup>3,19</sup> A sural-nerve biopsy can be performed, but I would recommend against it in cases such as that under discussion. Nerve biopsies are invasive, associated with permanent sensory loss in the area supplied by the nerve, and frequently complicated by increased neuropathic pain. Finally, they can confirm the presence of small-fiber neuropathy but do not identify the cause.

In summary, I believe the patient has a painful small-fiber neuropathy that is probably idiopathic. The quantitative sudomotor axon reflex test or a skin biopsy could be performed to confirm the diagnosis but neither is likely to help us further delineate the cause.

*Dr. Nancy Lee Harris (Pathology):* Dr. Lawrence Hayward followed this patient before and after her evaluation at Massachusetts General Hospital. Would you give us your impressions?

*Dr. Lawrence J. Hayward (Neurology, University of Massachusetts Medical Center, Worcester):* I first saw this patient two years ago for disabling pain. She had already had much of the workup done, including the antibody panels. Before the electrodiagnostic studies, my initial clinical impression was that she had a progressive, mixed sensory neuropathy. However, the normal results of the nerve-con-

duction studies indicated that this was a predominantly small-fiber neuropathy, perhaps with a myelopathic component to explain the loss of vibratory perception. The patient was severely debilitated by pain and had some additional autonomic symptoms, so we considered further diagnostic procedures.

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#### CLINICAL DIAGNOSIS

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Idiopathic small-fiber neuropathy.

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#### DR. ANTHONY A. AMATO'S DIAGNOSIS

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Idiopathic small-fiber neuropathy.

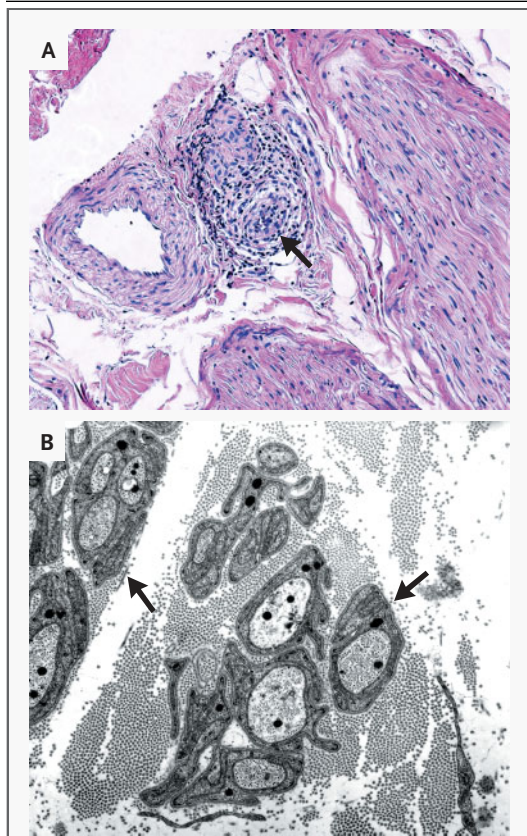
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#### PATHOLOGICAL DISCUSSION

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*Dr. Anne Louise Oaklander:* A left-sided sural-nerve biopsy was performed at the referring institution. The overall density and appearance of myelinated fibers in the specimen were normal. A few perineurial blood vessels had focal perivascular mononuclear-cell infiltrates that extended through the vessel wall (Fig. 1A). There was no vasculitis, fibrinoid necrosis, or amyloid deposition. Electron-microscopical examination showed normal axons, myelin, and Schwann cells, with a few onion-bulb profiles. Empty, apposed Schwann-cell processes consistent with degeneration of unmyelinated axons were numerous (Fig. 1B). Neither morphometric analysis nor teased-fiber preparations were performed.

On initial evaluation at this hospital, two punch-biopsy specimens were taken from the skin of the patient's right lower leg, 10 cm above the lateral malleolus. Scattered perivascular mononuclear infiltrates were present on routine histologic examination (Fig. 2A). There was no evidence of amyloid. Staining with a monoclonal antibody to the panaxonal marker anti-protein gene product 9.5 (anti-PGP 9.5 antibody) revealed axonal swellings in some fibers that are consistent with early degeneration (Fig. 2B).<sup>20</sup> Morphometric analysis revealed 358 neurites per square millimeter of epidermis, which is 42 percent greater than normal for someone the patient's age (median, 205). Eleven months later, additional skin-biopsy specimens were obtained 2 cm proximal to the previous biopsy site. The axonal morphology was again abnormal, and there was a 61 percent reduction in axonal density, to 189 neurites per square millimeter, 32 percent



**Figure 1. Specimen from a Sural-Nerve Biopsy.**

The nerve is morphologically normal on light microscopy (Panel A). There is a focal perivascular lymphocytic infiltrate, and in one small perineurial vessel (arrow) the infiltrate extends through the wall (hematoxylin and eosin,  $\times 125$ ). There is no necrosis or other evidence of vasculitis or intraneural inflammation. An electron micrograph (Panel B) shows empty Schwann-cell processes (arrows) that are consistent with the loss of small, unmyelinated fibers ( $\times 8000$ ). (Photographs courtesy of Drs. Lawrence Hayward and Thomas Smith, University of Massachusetts Medical School, Worcester.)

below normal for her age (Fig. 2C). In summary, specimens from both the sural-nerve and skin biopsies revealed predominantly small-fiber sensory neuropathy and perivascular lymphocytic infiltrates of unclear significance, with no evidence of amyloid deposition or vasculitis.

A sural-nerve biopsy is the traditional method for pathological evaluation of peripheral neuropathy. It permits comprehensive evaluation of all cell types, as well as detailed morphometric analysis of the densities of different-sized axons and of myeli-

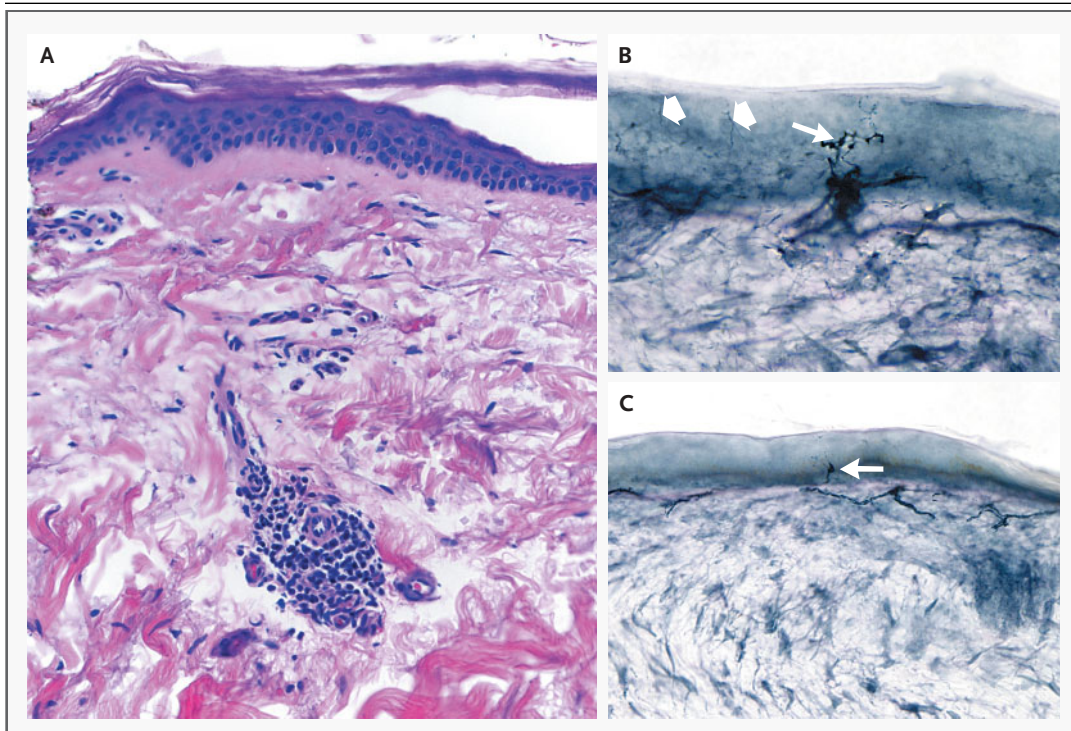
nation. The sural nerve is purely sensory and can be removed without producing weakness; however, most patients experience distal sensory loss or dysfunction.<sup>21</sup> The procedure requires anesthesia and surgery and is thus expensive. It cannot be repeated to monitor the progression of disease or the effects of treatment.

These drawbacks spurred development of a less invasive alternative: punch biopsies of the skin, with the specimens immunolabeled to reveal nerve endings. Anti-PGP 9.5 antibody labels ubiquitin hydrolase, a lysosomal enzyme<sup>22</sup> that is present in all neurons.<sup>23</sup> Localization has been verified by electron microscopy,<sup>24</sup> and the methods have been validated for the study of small-fiber sensory neuropathies (due to diabetes, HIV, or unknown causes).<sup>25</sup> The epidermis contains the terminals of unmyelinated C and A- $\delta$  nociceptive axons that terminate individually and that can be quantitated. Even in patients with normal neurite density, abnormal branching patterns and axonal swellings suggest early small-fiber neuropathies.<sup>20</sup> The nociceptive axons best studied with the use of skin-biopsy specimens are precisely those not captured by electromyographic and nerve-conduction studies, so these two methods of analyzing peripheral nerves are complementary.<sup>19</sup> As in this patient, skin biopsies can be repeated to follow the progression of the disease.

#### DISCUSSION OF MANAGEMENT

The best management of painful neuropathies consists of treating the underlying causes, but these are identified in only a minority of cases. Neurosurgical decompression is not often helpful, and alternative medical treatments are largely ineffective.<sup>26</sup> Thus, symptomatic pain relief is often the only option. Four classes of medication have documented efficacy against painful neuropathy: tricyclic antidepressant agents, antiepileptic agents, topical local anesthetic agents, and opioid agents. If these fail, immunosuppression may be appropriate in selected patients. Many other treatments are prescribed without evidence of efficacy. There are no clinical trials specifically of treatment for idiopathic painful neuropathy, so conclusions are extrapolated from therapeutic trials involving neuropathy associated with diabetes or HIV.

Tricyclic antidepressants are a useful initial step and were prescribed for this patient.<sup>27</sup> Potentiation of noradrenergic neurotransmission appears to be their major effect, but they have other actions, in-



**Figure 2. Specimens from Skin-Punch Biopsies.**

A specimen obtained at the time of the patient's first evaluation at this hospital (Panel A) shows a focal perivascular lymphocytic infiltrate (hematoxylin and eosin,  $\times 125$ ). A section immunolabeled against protein gene product 9.5 to reveal neural processes or axons (thick arrows) (Panel B) shows an epidermal neurite with axonal swellings, which are abnormal (thin arrow). The density of nerve fibers is greater than normal (immunoperoxidase,  $\times 500$ ). A specimen obtained 11 months later (Panel C) shows marked reduction in neurite density and axonal swelling (arrow) in a remaining neurite ( $\times 300$ ).

cluding sodium-channel blockade. Desipramine, nortriptyline, and amitriptyline are agents in this class, are all available in generic form, and have documented efficacy.<sup>28</sup> Selective serotonin-reuptake inhibitors are not effective in diabetic neuropathy; two newer antidepressants, venlafaxine and bupropion, have been reported to be effective, but there has been only one study of each to date.<sup>29,30</sup>

Gabapentin, an anticonvulsant agent, is now perhaps the most commonly prescribed medication for painful neuropathies.<sup>31</sup> Its efficacy is comparable to that of tricyclic antidepressants, but it has fewer side effects. This patient obtained some relief from gabapentin. Other anticonvulsants, including carbamazepine, oxcarbazepine, and lamotrigine, may be effective.<sup>32-34</sup>

Topical local anesthetics, including lidocaine patches, appear to be efficacious and are without systemic effects.<sup>35</sup> Topical capsaicin, which is available without prescription, produces degeneration

of nociceptive axon terminals.<sup>36</sup> It is poorly tolerated because it causes a burning sensation, and it is relatively ineffective, as it was in this patient.<sup>27</sup>

Opioid agents have been shown to be reasonably efficacious and safe.<sup>37</sup> The risk of addiction is low when there is a clear indication for use and when the patient has no history of substance abuse. Most patients are best treated with long-lasting forms taken at regular intervals. If the pain worsens at night, as is characteristic of neuropathy, bedtime-only use is an option. Methadone is a good option because of its low cost; its activity at the *N*-methyl-D-aspartate receptor may potentiate its analgesic effect.<sup>37</sup> Initial adverse effects of opioids, such as nausea and drowsiness, usually improve rapidly after initiation, but constipation may persist and require long-term treatment. This patient reported only moderate relief from sustained-release morphine, at a dose of 30 mg four times daily, and requested an increase in the dose.



My recommendation was to consider switching from amitriptyline to either nortriptyline or desipramine, because they have equal efficacy without additional side effects, and to continue morphine and gabapentin at the same dosage. Topical lidocaine patches should be considered.

*Dr. Harris:* How does the loss of nociceptive fibers produce pain?

*Dr. Oaklander:* There is an assumption that the mechanisms of neuropathic pain are similar to the mechanisms of inflammatory pain, namely an increase in electrical activity of the subgroup of neurons that is nociceptive. In fact, the loss of nociceptive fibers is one of the major pathologic hallmarks of neuropathic pain conditions, such as postherpetic neuralgia. There are other situations in which the reduction of normal sensory input results in increased central activity and sensory perception; these include tinnitus after hearing loss and phantom pain after the amputation of a limb.

*Dr. Harris:* Dr. Hayward, can you give us follow-up on this patient?

*Dr. Hayward:* Because she was obese and had a family history of diabetes, the patient was advised to follow a diet, and she has lost 20 pounds over the past year. The numbness has slowly begun to involve her hands and forearms, but her strength has been preserved. She has had fewer side effects after switching from amitriptyline to nortriptyline, and she is trying a topical lidocaine patch. We are considering a trial of tramadol, a mixed opioid and monoaminergic agent.<sup>38</sup> Serial glucose-tolerance

testing, performed because of the family history of diabetes, recently showed a fasting blood glucose level of 97 mg per deciliter and a two-hour post-challenge glucose level of 216 mg per deciliter, suggesting a new diagnosis of diabetes.

*Dr. Amato:* Although we cannot be sure in this case that an abnormality of glucose metabolism that became evident seven years after the onset of symptoms is the cause of her neuropathy, one has to be open to the possibility. In patients with small-fiber neuropathy in whom diabetes mellitus or impaired glucose tolerance is detected, the duration of neuropathic symptoms before the diagnosis ranges from 3 to 240 months (median, 54).<sup>5-7</sup> These data suggest that one can have diabetic neuropathy in the absence of long-standing diabetes. Although we do not know the natural history of impaired glucose tolerance or the effect of improved glycemic control on the neuropathy, rigorous glycemic control reduces the incidence of neuropathy in patients with known diabetes mellitus.<sup>39</sup> Even if this patient's neuropathy is unrelated to the newly diagnosed diabetes, improved glycemic control may prevent or slow further deterioration resulting from superimposed diabetic neuropathy.

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#### ANATOMICAL DIAGNOSIS

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#### Small-fiber neuropathy.

Presented at the Neurology Grand Rounds, Massachusetts General Hospital, May 1, 2003.

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