Case Description

A 61-year-old man with poorly controlled type 2 diabetes mellitus presented to our clinic with a 5-month history of right foot drop and severe excruciating pain in the right leg that progressed to the right and left buttocks and left leg, resulting in left foot drop. Prior to the visit, a neurologist had diagnosed him with diabetic amyotrophy and GM1 antibody-mediated autoimmune neuropathy. Magnetic resonance imaging (MRI) of the brain was unremarkable. Nerve conduction studies showed absent sural, ulnar, and radial potentials with a right peroneal motor nerve conduction velocity of 19.6 m per second and a right posterior tibial conduction velocity of 32.9 m per second. The patient could walk a few steps using a cane but mainly used a wheelchair. He complained of numbness and burning sensations in the feet and legs. Pain control was inadequate using duloxetine (Cymbalta, Lilly) 60 mg per day, pregabalin (Lyrica, Pfizer) 75 mg in the morning and 150 mg in the afternoon and evening, gabapentin 300 mg as needed, tramadol 50 mg 3 times daily, and hydrocodone/acetaminophen 7.5/750 mg as needed.

An examination revealed quadriceps/foot wasting, thigh adduction, and leg extension weaknesses, and a total loss of ankle dorsiflexion and great toe extension bilaterally. Knee and Achilles reflexes were absent. A sensory exam showed a bilateral decrease in soft touch perception to 30 cm as measured from the great
toes, prickling pain reduction to 34 cm, absent vibration sense in the great toes using a 128 Hz tuning fork, and absent 1- and 10-g monofilament sensation and joint proprioception in the great toes.

A biochemical work-up found normal results for B<sub>12</sub>, serum protein and immunoelectrophoresis, motor and sensory antibody profile (including GM1 antibodies), urine 24-hour heavy metal profile for arsenic, mercury, and lead, and rapid plasma reagin. In-house NINA Assay to test the patient’s serum toxicity to our N1E-115 neuroblastoma cell line in vitro<sup>1,2</sup> (compared with the serum toxicity of pooled human serum) over 4 days of growth revealed the patient’s serum to be highly toxic to the nerve cells, resulting in complete apoptosis of the nerve cells by day 2 (see Table).

**Diagnosis and Treatment**

We diagnosed the patient with chronic inflammatory demyelinating polyneuropathy (CIDP), which is a progressive, symmetrical immune-mediated peripheral neuropathy resulting in weakness of the proximal and distal muscles.<sup>3</sup> This condition also may be associated with aching pain in the affected muscles.<sup>4</sup> First-line treatment for CIDP is IV immunoglobulin (IVIG),<sup>5</sup> so we began with a course of Gamunex (Talecris) 1 g/kg per day 2 days per week for 3 consecutive weeks (a total of 6 treatments).

After the first round of IVIG therapy, the patient discontinued use of the wheelchair and could occasionally walk short distances without a cane. Small gains in thigh muscle strength were noted. However, the treatments made the patient very weak and he needed 24-hour assistance with activities of daily living for 3 weeks after finishing IVIG treatment. The follow-up NINA Assay demonstrated no change in toxicity, with all neuroblastoma cells apoptosed by day 2. The treatment provided a short-term, mild improvement in pain, where the patient rarely needed either hydrocodone/APAP or tramadol. His leg pain returned 1.5 months after finishing the treatments, and he resumed his regular pain medicine regimen.

We ordered a second course of IVIG treatment. Once again, the patient experienced profound weakness and required 24-hour assistance at home. He then developed metabolic acidosis, with the serum lactic acid level reaching 7.1 mmol/L (normal, 0.5-2.2 mmol/L). This returned to normal after rehydration at the emergency department. He was able to discontinue hydrocodone/tramadol, but the gabapentin was increased to 600 mg 4 times daily. The patient could ambulate for longer distances without a cane, but had little energy to do so. Movement of the right great toe was observed (previously absent) and he returned to functional activities 1 month after treatment. Repeat NINA Assay showed only moderate toxicity with neuroblastoma cells surviving all the way to day 4, although in a markedly reduced number compared with the pooled human serum (see Table).

Four months after the second IVIG treatment, the patient once again developed leg pain and began using a cane. He began taking hydrocodone/tramadol once more. Repeat NINA Assay was highly toxic with 100% neuroblastoma apoptosis by day 4. He tolerated 4 of 6 IVIG treatments in the third course of therapy, having stopped due to weakness requiring hospitalization and uncontrolled blood glucose levels in excess of 550 mg/dL. His blood sugars improved after discharge but were still poorly controlled with nightly insulin glargine. Despite all this, the peripheral neuropathy was improving. Notwithstanding the improvement in neuropathy, the patient developed abdominal pain in both upper quadrants. He was found to have cholelithiasis and a laparoscopic cholecystectomy was performed. The surgery resolved the right-sided colicky pain but a residual band of pain developed in the left lateral abdominal region in the T9/T10 distribution along with a roll of fat protrusion (see Figure). This was consistent with a

**Table. NINA Assay Results**

<table>
<thead>
<tr>
<th>Total Number of Cells</th>
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<th>0 Day</th>
<th>1 Day</th>
<th>2 Days</th>
<th>3 Days</th>
<th>4 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Assay</strong> - Highly toxic (100% apoptosis of neural cells in culture by day 2 in patient serum)</td>
<td></td>
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<tr>
<td>Pooled Human Serum</td>
<td>3/25/09</td>
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<td>96,250</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient</td>
<td></td>
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</table>

<p>| Status post 2 IVIG courses at 1 g/kg/day twice weekly for 3 consecutive weeks – Moderately toxic (best IVIG response) | | | | | | |</p>
<table>
<thead>
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<th>Total Number of Cells</th>
<th>Date</th>
<th>0 Day</th>
<th>1 Day</th>
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<th>3 Days</th>
<th>4 Days</th>
</tr>
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<tbody>
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<td>61,250</td>
<td>91,250</td>
<td>130,000</td>
</tr>
<tr>
<td>Azathioprine 50 mg/day</td>
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</tbody>
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<p>| Azathioprine 50 mg/day – Moderately toxic (comparable to best IVIG response) | | | | | | |</p>
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<tbody>
<tr>
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<td>112,500</td>
<td>64,000</td>
<td>60,000</td>
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mononeuropathy, because entrapment at the thoracic spine was ruled out by MRI. His NINA Assay returned to being highly toxic, with all neuroblastoma cells undergoing apoptosis by day 3.

We considered another course of IVIG but had doubts about the patient’s ability to further tolerate this treatment. Corticosteroids also are first-line therapy for CIDP, with expected responses comparable with IVIG. However, the patient’s hemoglobin A1c at 8.9% (normal, 4.8%-5.9%) indicated poor glycemic control and chronic steroid use surely would have exacerbated that. The European Federation of Neurological Societies Task Force 2010 revised guidelines on management of CIDP support the above considerations and also add plasmapheresis if IVIG and corticosteroids are ineffective. A fourth option in those guidelines was adding an immunosuppressant. Data was limited and inconclusive about the immune-modulator azathioprine’s potential use in CIDP, but it is a potentially attractive option given its activity against immune responses, availability in oral form, favorable side-effect profile, and low cost. After the patient’s complete blood count (CBC) proved to be normal, a trial of azathioprine 50 mg per day was started.

Discussion

We have previously reported the discrepancy between cerebellar ataxia and peripheral nerve root responses to IVIG. This patient’s CIDP had a notable response to IVIG yet he still developed the mononeuropathy while under treatment. There was precedence in our initial treatment with IVIG and subsequent use of an immune-modulating agent for autoimmune-mediated neuropathy. In that patient, we used IVIG and then etanercept (Enbrel, Amgen/Pfizer) to successfully mitigate the effects of an acetylcholine receptor antibody-induced autonomic neuropathy. It was clear that the disparity in IVIG responses between the CIDP and mononeuropathy suggested mechanistic differences.

Seven months into treatment, the patient no longer has leg pain and there is no biochemical evidence of CBC abnormalities or transaminase elevation. He has regained 50% of strength in the ankle dorsiflexors and great toe extensors. The knee and ankle reflexes are still absent. His only pain medication now is gabapentin 300 mg twice daily. Functionally, the patient is able to walk more than several blocks at a time, needs a cane only for stability (not support), and is able to sail on his boat nearly every weekend. His current NINA Assay demonstrates moderate toxicity (see Table) with the neuroblastoma cells present in reduced numbers to day 4 when compared with pooled human serum—similar to his best response after the second round of IVIG. Additionally, the pain from the mononeuropathy at T9/T10 is almost completely resolved. Because the mononeuropathy may be autoimmune-related, it is reasonable to question whether azathioprine may have had a beneficial effect on shortening its course and severity.

References

Case Description

The patient was a 21-year-old college psychology major from Ohio. Following our interview with the patient, our general impression was that he could best be described as an “immature frat boy.” The patient had a diagnosis of graft-versus-host disease (GVHD), a frequent complication following allogeneic bone marrow or stem cell transplantation for acute myeloid leukemia. The patient had received his transplant at an outside cancer center.

GVHD following allogeneic bone marrow transplants mainly affects the skin like scleroderma, but also can affect the liver and gastrointestinal (GI) tract. Acute GVHD occurs 60 to 100 days after transplantation as a response by the donor marrow or cells to the foreign environment. GVHD can be chronic, with recurrence common years after the transplant procedure. The most frequent skin symptoms of GVHD are red rash, itching, and darkening of the skin. Pain resulting from GVHD often takes the form of severe abdominal pain occurring later in the course of the disease. Cracked and irritated skin occurring around the rectum as a result of chronic diarrhea also is quite painful.¹

Treatment for GVHD involves long-term immunosuppressive therapy, often in the form of corticosteroids, cyclosporine, or tacrolimus. Treatment is effective in approximately 50% to 60% of GVHD cases.² The mean duration of immunosuppressive therapy, discontinued as a result of symptom resolution or death, has been shown to be about 23 months.³

This patient arrived at our clinic complaining of “total body pain.” He admitted to heavy alcohol use, as well as to using tobacco and marijuana. The patient further told of sharing prescription pain medications at fraternity parties, but denied the use of any IV drugs. He had discontinued his immunosuppressive therapy, and had been on a regimen of 2 to 3 tablets of oxycodone/acetaminophen daily and benzodiazepines.

The patient’s GVHD gradually responded to instituting an immunosuppressant regimen. A course of steroids was added, and he was further treated with muscle relaxants, lymphedema therapy, and physical therapy.

The patient continued to report a high degree of incidental pain, which was responsive to increasing levels of opioids. He was followed by psychiatry for reported...
Discussion

Suspicions involving this patient’s misuse of pain medications proved to be accurate and initially underestimated, and urine drug testing (UDT) and a range of risk management strategies would have been justified, particularly at the start of therapy with a patient who lived at a great distance from the center. Indeed, misuse of opioids and illicit drug use occurs in roughly 25% of pain clinic and primary care pain patients. Furthermore, recent research shows that more than 20% of pain patients with no aberrant drug behavior tested positive on UDT for misuse of pain drugs or illicit drug use; thus, it is not an easy task to know who should be monitored by UDT. Physicians must be vigilant throughout the treatment process, as this case shows that even patients who legitimately need pain treatment misuse prescription medications. With more and more people surviving cancer and many becoming chronic pain patients as a result of their disease and treatment, consideration must be given to the adaptation of risk management procedures into cancer pain treatment, matched to the level of risk in each individual patient. Although commonplace in chronic noncancer pain management, these strategies remain controversial in the management of cancer pain.

UDT can have both positive and negative implications in the pain patient. The mere suggestion of UDT can have an adverse effect on the trust relationship between a physician and the patient. Physicians do not always have a complete understanding of UDT and the many factors that can affect results, a fact that can make interpretation difficult. Inaccurate or misinterpreted results can have devastating personal, clinical, and even legal effects on a patient’s life, not the least of which is a potential impact on his or her ability to obtain continued and needed pain treatment. To quote Reisfeld et al., “urine drug testing should be only one component of a comprehensive, compassionate, and ethical plan of care.”

Table. Potential Aberrant Drug-Related Behavior

Please check any of the following items that you discovered during your interactions with the patient. Please note that some of these are directly observable (eg, appears intoxicated), whereas others may require more active listening and/or probing. Use the “Assessment” section below to note additional details.

- Purposeful oversedation
- Negative mood change
- Appears intoxicated
- Increasingly unkempt or impaired
- Involvement in car or other accident
- Requests frequent early renewals
- Increased dose without authorization
- Attempts to obtain prescriptions from other doctors
- Changes route of administration
- Uses pain medication in response to situational stressor
- Insists on certain medications by name
- Contact with street drug culture
- Abuses alcohol or illicit drugs
- Hoard (ie, stockpile) medication
- Arrested by police
- Victim of abuse
- Other: ____________________________

Anxiety, and was treated with clonazepam. During the patient’s care, clinicians began to notice some aberrant drug-related behavior (Table).

The patient relocated to Florida to attend college, and received follow-up treatment at Moffitt Cancer Center, in Tampa. During a visit to the hematology clinic, the patient was noticeably intoxicated. A urine drug screen showed the presence of opiates, benzodiazepines, marijuana, and cocaine. Subsequently, he was admitted to inpatient rehabilitation. Five months later, the patient was off all illicit narcotics and was taking only pregabalin (Lyrica, Pfizer) for the legitimate treatment of his pain.

References