PALLIATIVE CARE
CASE OF THE MONTH

"When pain doesn't go away: palliation of post-herpetic neuralgia"

by

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Case: Mr. T is a 53-year-old man with grade IV gliobastoma multiform diagnosed after a motor vehicle accident and a subsequent witnessed tonic-clonic seizure. He underwent resection of a deep left parieto-occipital tumor with subsequent radiation and chemotherapy. Shortly after completion of his radiation; he developed increased headache and slurred speech and was found to have progressive disease. His medication regimen included dexamethasone which was increased to help with symptomatic control of his worsening headaches and slurred speech. Around this time, he developed shingles along the left T6-T7 dermatomes and was treated appropriately with resolution of the acute infection; however, he continued to have severe pain along the site of the rash. He was started on Gabapentin and incrementally titrated up to 900mg by mouth TID; however, he developed an allergic reaction to this medication consisting of a diffuse drug rash. He was prescribed a Lidoderm patch and 4% Lidocaine cream with no relief. Over a period of several months, he was prescribed hydrocodone and eventually oxycodone again without effective control of his pain. Palliative care was consulted four months after his initial infection for assistance with pain management. On examination, he had a dry scaly rash along the T6-T7 dermatomes consistent with a healing rash secondary to shingles. He described the pain as constant and burning in nature and had significant allodynia. The patient was started on nortryptiline 25mg with little effect despite dose titration to 50mg. He was rotated from oxycodone to hydromorphone for breakthrough pain which caused increased sedation, but no improvement in his pain. He was also evaluated by the interventional pain service regarding an intercostal nerve block. It was felt that his performance status was too low, and there was concern for recurrent shingles.

Discussion: Acute herpes zoster is caused by reactivation of the varicella zoster virus (VZV) which persists for years in the dorsal root ganglia of cranial or spinal nerves after resolution of the original varicella infection. As cellular immunity wanes with either age or a compromised immune system, the virus is transported along peripheral nerves producing an acute neuritis and causing pain known as acute herpetic neuralgia. The thoracic (especially T4 to T6), cervical and trigeminal nerves are most commonly affected (1). Acute herpetic neuralgia is defined as either preceding or accompanying the eruption of the rash and can persist up to one month.

It is likely a combination of the inflammation associated with transfer of viral particles from sensory nerves to skin and subcutaneous tissues and by the damage to peripheral nerve structures thought to be characterized by hemorrhagic inflammation. Acute herpetic neuralgia is often described as sharp or stabbing in nature.

In contrast to acute neuralgia, subacute herpetic neuralgia is classified as pain persisting up to four months from the onset of the rash, while post-herpetic neuralgia (PHN) is defined as pain that persists more than four months from the onset of the rash (2). The cause of pain in subacute and PHN is thought to be related to the dorsal horn neurons' reaction to the acute neuritis and the resultant tissue damage . These changes result in dorsal horn sensitization, promoting spontaneous neuronal firing that is experienced as pain in the absence of ongoing tissue damage. Substance P, serotonin, and norepinephrine are neurotransmitters thought to play a role in the inhibition of pain signals; however, studies have failed to show a difference in the level of these neurotransmitters in patients with PHN (3).It is unlikely that ongoing VZV viral replication is responsible for the pain (4). Clinically, PHN is classically described as "burning" with paroxysmal lancinating pain, and most patients also describe allodynia, defined as pain evoked by normally non-painful stimuli such as light touch or wearing clothes. In addition, there may also be areas of anesthesia or other sensory impairments, including deficits of thermal, tactile, pinprick, and vibration sensation. It has been suggested that spontaneous pain occurs predominately within the area of anesthesia or impaired sensation, while allodynia is most prominent in areas of relatively preserved sensation. Although the risk of acute herpes zoster is increased in immunocompromised patients, including those with an underlying malignancy and those receiving chemotherapy, the risk of PHN has not traditionally thought to be increased in these patients. The major risk factors for PHN are older age, greater acute pain, and greater rash severity**.**

Treatment: The list of potential treatment modalities used for PHN includes tricyclic antidepressants (TCA), selective norepinephrine reuptake inhibitors (SNRI), anticonvulsants, opioids, topical agents such as lidocaine and Capsaicin, intrathecal glucocorticoids, NMDA receptor antagonists, cryotherapy, and surgery. Mild analgesics such as NSAIDs are generally not effective.

"Treatment Continued"

TCAs, which inhibit the reuptake of norepinephrine and serotonin in the central nervous system, are often the first line treatment for PHN. There have only been two small studies looking at the use of TCAs in PHN: one study finding TCAs better than both placebo and benzodiazepines and the other showing nortriptyline to be more efficacious than amitriptyline (mean dose 60mg) with less adverse effects (sedation and dry mouth) (5,6).

The two SNRIs that have been studied in neuropathic pain are venlafaxine and duloxetine. However, neither have been shown to be efficacious in PHN. Both are efficacious in painful diabetic neuropathy, and duloxetine is also used in fibromyalgia and chronic low back pain from osteoarthritis (7).
The two most commonly used anticonvulsants studied in randomized trials for use in PHN are gabapentin and pregabalin.

Two placebo-controlled randomized trials show the most common formulation of gabapentin to be efficacious in PHN at doses between 1800-3600mg daily (8,9). The most common side effects include dizziness and somnolence. Pregabalin, a structural analogue of gabapentin, also is efficacious. The recommended starting dose is 150mg, divided into two to three doses daily, with increase to a total daily dose of 300mg. Pregabalin should be tapered over a week if discontinued (10). Pregabalin is a schedule V drug due to its ability to cause euphoria and its most common side effects include dizziness, somnolence, dry mouth, peripheral edema, and weight gain. Both drugs are renally excreted and need to be dose reduced in renal failure. There are no studies comparing gabapentin and pregabalin; the cost of maximum dose gabapentin is $52 per month compared to $263 per month for the recommended maximum dose of pregabalin.

The use of opioids for PHN in noncancer patients is controversial due to the risk of physical dependence, tolerance, addiction, and overdose. Several trials evaluating the efficacy of opioids in PHN have shown superiority only to placebo or NSAIDs (11,12). Morphine (mean dose of 91mg daily) and methadone (mean dose of 15mg daily) are the two most studied opioids in PHN. Methadone is felt to be more effective for neuropathic pain than other opioids due to its inhibition of norepinephrine and serotonin reuptake (similar to SNRI anti-depressants) and the fact that it binds to the NMDA receptor, a modulator of neuropathic pain. There is limited data, however, to support methadone over other opioids in PHN.

Topical treatments such as lidocaine and capsaicin are beneficial in the treatment of PHN. Capsaicin cream is difficult to use given that it requires multiple daily applications and often causes severe burning and skin irritation (limiting the ability to study it in blinded trials). A high-concentration capsaicin patch (8%) in a single 60-minute application (up to four patches) every three months is beneficial in some patients. Several studies show significant reduction in pain intensity after eight weeks (13). This medication must be administered initially by a healthcare professional and monitored for up to two hours after treatment for severe pain. A topical anesthetic is used prior to application and oral analgesics, such as opioids, are often needed to manage pain post treatment. There are a few small placebo-controlled trials and open-label studies suggesting that topical lidocaine 5% is beneficial in PHN.

Intrathecal glucocorticoid injections may be useful in those with refractory PHN affecting nerves other than the trigeminal nerve. One large trial compared weekly injections of intrathecal methylprednisolone plus lidocaine once per week for four weeks with injections of lidocaine alone or no treatment. More than 90 percent of patients in the methylprednisolone group reported excellent or good pain relief at four weeks and at one and two years compared with 6 and 4 percent in the lidocaine and no treatment groups, respectively. In addition, the areas of allodynia were reduced by more than 70% in the methylprednisolone group and only 25% in the lidocaine group. There were no serious adverse events associated with the injection (14).

Other potentially useful treatments for refractory PHN include botulinum toxin injection, intravenous ketamine, cryotherapy, and surgical interventions. These treatments need better data to support their use and should be considered on a case-by-case basis.

Case Resolution: Given Mr. T's allergic reaction to gabapentin and the lack of efficacy of TCAs, topical anesthetics, and traditional opioids, Mr. T was rotated to Methadone for treatment of his PHN. He tolerated this well and was titrated up to a total daily dose of 30mg with significant improvement in his pain and allodynia.

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