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Neuropathic Pain

Ms. S is a 36-year-old Caucasian female with metastatic invasive ductal breast carcinoma. She is being admitted to home hospice services. Her chief complaint during the admission visit is "burning, piercing" pain radiating from her xiphoid process along the ribs to the subscapular region of her back. She describes the intensity of her pain on average as 6 on a 0–10 scale, with discomfort escalating to 8 with a light touch or with predictable activities and movements. The pain began four months ago when she was diagnosed with acute herpes zoster (AHZ) (i.e., shingles). However, the pain did not abate with the resolution of the AHZ rash. The discomfort is causing difficulty sleeping, interfering with her ability to participate in normal activities of daily living, and leading to progressive withdrawal from her husband and three-year-old son.

Ms. S was diagnosed three years earlier with invasive ductal breast carcinoma and treated with a modified radical mastectomy with lymph node dissection, chemotherapy with doxorubicin and cyclophosphamide, and hormonal therapy with tamoxifen. Ms. S had a two-year, disease-free interval but experienced disease recurrence with metastases to the bone (i.e., L4–5, pelvis, and right femur), ovaries/adrenals, and liver. She underwent palliative radiation therapy to her lumbar spine, pelvis, and right femur for painful bone metastases and palliative chemotherapy with capecitabine.

Following her final round of chemotherapy, Ms. S developed AHZ. A painful vesicular rash erupted along the T 2–4 dermatome, which lasted 14 days. She was treated with acyclovir 800 mg orally (po) five times per day for 10 days. This antiviral treatment was initiated within 48 hours of the rash onset.

Ms. S's current medications include tamoxifen 10 mg po twice daily, dexamethasone 4 mg po twice daily, famotidine 20 mg po twice daily, sustained-release oxycodone HCl 10 mg po every 12 hours, and immediate-release oxycodone 5 mg po for breakthrough pain. She is using between four and six doses of immediate-release oxycodone daily for exacerbations of pain with incomplete relief.

Ms. S is diagnosed with postherpetic neuralgia (PHN) with associated mechanical allodynia and hyperalgesia. The following pain management was instituted.

- Amitriptyline 10 mg po daily at bedtime
- 5% lidocaine patch over the painful region of the chest wall daily in the morning and removed at bedtime
- Sustained-release oxycodone 20 mg po every 12 hours and immediate-release oxycodone 10 mg po for breakthrough pain

The home hospice nurse visited Ms. S three days after initiation of this new regimen. Ms. S rated her pain on average as 3 out of 10 and noted a decrease in the intensity of the painful paroxysms. Over the prior 24 hours, she used two doses of immediate-release oxycodone. Ms. S noticed that she was able to fall asleep faster and sleep eight or nine hours a night. She expressed a new concern that she frequently was experiencing a dry mouth (xerostomia), which was making her uncomfortable.

The hospice nurse educated Ms. S and her family that peak analgesic effect of amitriptyline might not be achieved for one to three weeks and emphasized the importance of daily dosing at bedtime. Additionally, she explained that xerostomia was a normal side effect of amitriptyline. Ms. S was encouraged to take frequent sips of cold liquids, eat ice, and suck on hard candies to stimulate salivation.

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Clinical Problem Solving

Responding to this clinical challenge are Libby Bowers, RN, BSN, CCRN, CHPN, and Linda Gorman, RN, MN, CS, OCN®, CHPN. Bowers is the palliative care services coordinator at Santa Monica–UCLA Medical Center, a Cedars-Sinai Home Hospice case manager, and a UCLA oncology nurse practitioner student. Gorman is a palliative care/hospice clinical nurse specialist with Cedars-Sinai Medical Center and is a member of the board of directors of the Hospice and Palliative Nurses Association.

How is the neuropathic pain Ms. S is experiencing different from nociceptive (visceral and somatic) pain?

L. Gorman: Neuropathic pain results from injury to neural tissues and is sustained by aberrant somatosensory processing in the peripheral or central nervous system. Neuropathic pain presents with unique clinical characteristics differentiating it from nociceptive pain. Burning, stabbing, throbbing, lancinating, shock-like paroxysms, and pain elicited by non-noxious stimuli (allodynia) are common features of neuropathic pain.

In advanced cancer, 40% of patients experience neuropathic pain. Most neuropathic pain exists in combination with nociceptive pain, and nearly one-third of patients experience three or more distinct pain syndromes (Caraceni & Portenoy, 1999). Nociceptive pain involves normal processing within the nervous system of painful stimuli. Visceral pain is a subtype of nociceptive pain that characteristically is poorly localized and described as a deep pulling or stretching resulting from insults to internal organs. Somatic pain is well localized, described as gnawing, intense, and aching, and commonly is worse with weight bearing because of involvement of bone, muscles, or joints. In the case of Ms. S, the pain she experienced relating to her metastatic cancer was managed with opioids and steroids. However, the opioid analgesics and corticosteroids were ineffective in relieving the neuropathic pain of PHN.

What is the role of amitriptyline, lidocaine patches, opioids, and dexamethasone in the management of PHN?

L. Bowers: Amitriptyline, topical lidocaine patches, and dexamethasone are adjuvant analgesics. The primary indication for these drugs in a pain management regimen is their analgesic properties (McCaffery & Portenoy, 1999). Amitriptyline, a tertiary amine tricyclic antidepressant, is considered a first-line adjuvant analgesic in the management of PHN. Tricyclic antidepressants interfere with the reuptake of serotonin and norepinephrine and work synergistically with endogenous opioids to enhance descending modulation of nociceptive impulses. Amitriptyline would

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be of particular benefit for Ms. S because it is well known to have anticholinergic effects that are likely to help both in reducing her neuropathic pain and managing insomnia. Given at bedtime and in a low dose (i.e., subtherapeutic for treating depression), tricyclic antidepressants are efficacious, safe, and the most extensively researched in the management of neuropathic pain.

Topical 5% lidocaine patches are effective for achieving local control of PHN. Lidocaine, an anesthetic agent, is applied directly over the painful area to intact skin. It penetrates beneath the skin to anesthetize painful and damaged nerves. Additionally, the lidocaine patch serves to protect sensitive regions of the skin where allodynia is present. Lidocaine patches are applied in the morning and

Clinical Highlights: Postherpetic Neuralgia

Definition: Postherpetic neuralgia (PHN) is the name given to pain that lingers for months or even years after the rash caused by acute herpes zoster (AHZ) (i.e., shingles) has healed (Sugeng, Yosipovitch, & Leok, 2001). Pain that persists more than four months following the healing of the characteristic zoster rash is classified as PHN (Dworkin & Portenoy, 1996). Some experts consider PHN to be pain persisting from one to six months following healing of acute zoster rash (Beydoun, 2001; Sugeng et al.). Pain associated with PHN is neuropathic in nature and accompanied by mechanical or thermal allodynia (i.e., pain elicited by non-noxious stimuli) and hyperalgesia (i.e., increased pain response to noxious stimuli).

Pathophysiology: After the resolution of varicella zoster virus infection in childhood (i.e., chicken pox), the latent virus resides for decades in the dorsal root ganglia of the cranial or spinal nerves. The virus may be reactivated in later years in individuals with impaired cell-mediated immunity. The virus is transported along peripheral nerves producing an acute neuritis with hemorrhagic inflammation at the cellular level. PHN is a syndrome resulting from alterations in the processing of stimuli within the nervous system (neural plasticity). Two distinct pathologic events give rise to PHN. First, irritable nociception occurs when c-nociceptors in the peripheral nervous system are either damaged or inflamed (both of which occur during an AHZ outbreak), leading to hyperexcitability and spontaneous activity in the peripheral nervous system. Prolonged and enhanced stimulation of the central nervous system (CNS) by the irritable nociceptors in the peripheral nervous system leads to central sensitization (neuroplastic changes in the CNS that maintain neuropathic pain). In the absence of sensory alterations or deafferentation (i.e., deficits in thermal, tactile, pinprick, and vibratory sensation), irritable nociception results in the clinical presentation of allodynia (Fields, Rowbotham, & Baron, 1998).

The second category of neuropathic pain in PHN is phenotypic switching. This characteristically presents as allodynia with sensory alterations or deafferentation. Phenotypic switching occurs when the c-nociceptors are damaged, regressed, or dead. C-nociceptors are replaced with A-fibers (myelinated) that have a lower activation threshold and rapidly conduct noxious and innocuous stimulus to the CNS (Regan & Peng, 2000; Woolf & Mannion, 1999).

Incidence: Herpes zoster occurs in approximately 25% of individuals during their life trajectory, and 15%–40% of those who are affected will develop PHN (Edmunds, Brisson, & Rose, 2001).

Risk factors: Risk factors for AHZ include any factors that impair cell-mediated immunity. Delayed or lack of treatment of acute herpes correlates with a 70% incidence of developing PHN. However, the cardinal risk factor is age; nearly half of patients older than 60 years and 75% of patients older than 70 years will develop PHN following an AHZ episode (Beydoun, 2001). Women have been noted to have a higher incidence of developing PHN (Sugeng et al., 2001). Also, if the intensity of initial zoster pain is severe, the risk for developing PHN increases. The psychosocial factors of living alone, anxiety, and depression positively and independently correlate with development of PHN (Rowbotham & Peterson, 2001).

Clinical findings: Patient descriptions of neuropathic pain often include burning, throbbing, stabbing, numbing, lancinating, or shock-like pain. Allodynia occurs in more than 90% of patients, and deafferentation within the affected dermatome may occur. The contralateral side has normal sensation. Neuropathic pain associated with PHN can be continuous or intermittent and may interfere with activities of daily living, quality of life, and sleep. Chronic, untreated PHN may contribute to psychosocial withdrawal, isolation, and depression.

Differential diagnosis: Herpes simplex virus or coxsackievirus should be considered; a Tzanck diagnostic virology test yields a definitive diagnosis. Other dermatologic conditions, such as contact dermatitis, impetigo, or cellulites, should be ruled out.

Treatment: Opioids, tricyclic antidepressants (e.g., amitriptyline, nortriptyline), anticonvulsants (e.g., gabapentin), corticosteroids, and topical analgesics/anesthetics (Bajwa & Ho, 2001; Kanazi, Johnson, & Dworkin, 2000)

Prevention: Prevention of PHN includes administration of antiviral therapy (e.g., acyclovir, famcyclovir, valacyclovir) within three days of rash onset (Johnson, 2000). Pasqualucci et al. (2000) demonstrated that one or more courses of epidural bupivacaine with intermittent corticosteroids via epidural catheter are effective in reducing the incidence of PHN if administered within the first seven days of AHZ rash and continued daily for seven days. The efficacy of live attenuated varicella vaccination in the elderly to boost cell-mediated immunity currently is being evaluated in clinical trials (Edmunds et al., 2001).

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removed each night (12 hours later). The patch may be cut into smaller sizes, and up to three patches may be applied at one time to achieve pain relief. Other topical anesthetics have included capsaicin cream 0.025%. In my clinical experience, this cream may elicit burning on application and may be poorly tolerated. To achieve a therapeutic effect, it must be reapplied four times a day, and thus, patients may have low compliance or their quality of life may be affected adversely.

In AHZ, an acute neuritis with hemorrhagic inflammation at the cellular level occurs. Dexamethasone, a corticosteroid with potent anti-inflammatory properties, may reduce the somatic pain resulting from Ms. S's painful bone metastases and share a role in modulating the inflammatory response initiated by herpes zoster.

Opioids are a mainstay of cancer pain management; they block the transmission of pain by binding to opioid receptors and preventing the neurotransmitters involved in the propagation of the pain impulse. Oxycodone is a potent opioid analgesic that selectively antagonizes both mu and kappa opioid receptors. In comparison with several other potent opioid analgesics, sustained-release oxycodone has a lower risk of opiate metabolite accumulation. For Ms. S, sustained-release oxycodone was selected as the long-acting agent; twice daily dosing maintains therapeutic levels of analgesia. Supplementation with a rapid-acting opioid is needed to cover breakthrough pain.

What variables influenced the decision to begin a tricyclic antidepressant instead of an anticonvulsant, such as gabapentin, in this particular case?

L. Bowers: Anticonvulsants and tricyclic antidepressants both are considered first-line treatments for neuropathic pain and have demonstrated efficacy and safety. In this clinical situation, amitriptyline was selected because Ms. S concurrently was experiencing problems with insomnia. Amitriptyline has anticholinergic properties that decrease sleep latency and promote sleep quantity. Anticonvulsants also have sedative effects. Gabapentin generally is administered three times daily, and other anticonvulsants, such as clonazepam and oxycarbazepine, are administered twice daily. Amitriptyline is dosed once a day at bedtime. This may lead to enhanced compliance and less interruption of daily routines with medication administration. The cost of amitriptyline is considerably less than gabapentin and many other anticonvulsants.

Tricyclic antidepressants have a higher rate of drug-drug interactions than gabapentin. However, Ms. S was not taking any medications that would potentiate a drug interaction. Tricyclic antidepressants would not be a treatment consideration if Ms. S had a past medical history of cardiovascular problems, such as dysrhythmias or orthostatic hypotension.

What nonpharmacologic interventions can augment the management of PHN?

L. Gorman: Nonpharmacologic interventions can supplement traditional pharmacologic interventions to reduce pain perception. Transcutaneous electrical nerve stimulation (TENS) relies on the gate control theory of pain, which theorizes that selective stimulation of nerve fibers blocks signals carrying the pain impulse to the brain. In some cases of neuropathic pain conditions, TENS has been found to heighten the experience of pain; therefore, individualization of TENS therapy is necessary. Acupuncture and acupressure activate nerve impulses traveling to the spinal cord, triggering the release of chemicals that react with opioid receptors and thereby influencing pain modulation. Application of superficial cooling measures may have an anesthetizing effect and provide temporary reprieve from PHN. Distraction from the presence of pain may be achieved by participation in guided imagery, biofeedback, or music, art, or pet therapy. Management of the emotional stressors facing Ms. S and promoting positive coping mechanisms are other major nonpharmacologic interventions that directly can modify her perception and experience of pain.

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