CLINICAL VIGNETTE

Refractory Pruritus at End of Life: Management of an Often Overlooked Symptom

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Case Presentation

A 66-year-old woman with metastatic ovarian carcinosarcoma, chronic kidney disease due to malignant obstruction, severe rheumatoid arthritis, and hypothyroidism was admitted to the hospital after a mechanical fall from standing. She was found to have cauda equina syndrome secondary to newly identified metastatic epidural masses. During her hospitalization, the palliative care team was consulted for management of progressive, poorly controlled back pain despite use of oxycodone and extended-release morphine, the latter of which was reported to have caused highly distressing pruritus.

After an initial pain assessment, oxycodone and extended-release morphine were discontinued and patient-controlled analgesia with hydromorphone was initiated. As her pain improved on this regimen, pruritus, which persisted despite discontinuation of morphine, became her chief complaint. She reported severe, continuous, generalized pruritus resulting in persistent scratching, even during sleep. Given the multiple potential etiologies, including her progressive metastatic cancer, chronic kidney disease, and history of hypothyroidism, a broad approach to her work-up was necessary.

In eliciting further history, the palliative care team learned that the patient had a similar episode of pruritus approximately six months earlier, which, on chart review, corresponded to the onset of worsening renal function due to obstructive nephropathy. At the time, she had achieved symptomatic relief with a combination of as-needed topical, oral, and intravenous diphenhydramine. She underwent tumor debulking, total abdominal hysterectomy with bilateral salpingo-oophorectomy, and interval placement of bilateral nephrostomy tubes. While her renal function had stabilized, her pruritus had gradually recurred in the four weeks since she underwent nephrostomy tube removal. Altogether, her presentation was most consistent with uremic pruritus.

Despite her prior response, diphenhydramine no longer provided sufficient relief and caused excessive sedation. The palliative care team recommended switching to a less-sedating second-generation antihistamine as well as renally-adjusted gabapentin, which has been shown to have some effectiveness in uremic pruritus.[1] However, this regimen was associated with only mild improvement in her symptoms. The palliative care team then trialed topical agents such as calamine lotion and ice packs, which offered transient relief. Ultimately, the palliative care team recommended topical pramoxine, which resulted in complete resolution of her pruritus, even though her blood urea nitrogen level had nearly doubled. For the remainder of her hospitalization, the patient's pruritus remained well-controlled with topical pramoxine 1% cream applied twice daily as well as oral loratadine 5mg daily, oral gabapentin 200mg nightly, and topical calamine lotion four times daily as needed.

While the patient and her family were initially guarded and unwilling to acknowledge her impending clinical decline, by successfully managing her pain and pruritus, the patient and her family opened up, sharing their hopes, worries, and end of life goals with the palliative care team. These discussions helped empower the patient and her family to participate in shared decision making, culminating in a decision to pursue comfort-focused care in the final days of her life.

Discussion

This multifaceted case demonstrates the importance of a broad differential in the workup of pruritus. An often overlooked yet prevalent symptom, pruritus can be severely distressing and profoundly debilitating.[2,3] Increased stress and anxiety due to unrelieved pruritus can lead to further activation of the autonomic nervous system, thereby lowering the itch threshold and increasing the perceived intensity of itch.[4] The resulting vicious cycle of itch-and-scratch is often associated with a sense of powerlessness, which can be a greater emotional and physical burden to some than pain.[2-4]

Given the significant impact on quality of life as well as the range of etiologies and poorly understood pathophysiology, pruritus requires an individualized approach to guide therapy.[3,5] The 2007 International Forum for the Study of Itch proposed a two-part broad approach to pruritus, which can assist clinicians in avoiding the pitfalls of anchoring bias and prematurely disregarding potential etiologies.[6] The first part classifies conditions by the presence of pruritus on inflamed (group I) and non-inflamed skin (group II), as well as by conditions associated with "severe chronic secondary scratch lesions" (group III).[6] The second part classifies pruritus based upon the category of underlying disease: dermatologic, systemic (i.e. hepatic, renal, hematologic, and metabolic etiologies), neurologic, psychogenic/psychosomatic, mixed, and other or undetermined.[6] In this patient, given multiple potential systemic

etiologies, obtaining a complete, detailed history, understanding the course of her pruritus in the context of her various medical conditions, and identifying alleviating and exacerbating factors was crucial to her work-up and management.[2]

Uremic pruritus impacts 40-90% of patients with end stage renal disease (ESRD) and its pathophysiology is incompletely understood.[7,8] While previously believed to be associated with secondary hyperparathyroidism, currently the predominant hypotheses center on the opioidergic and immunologic systems.[7-9] The opioid hypothesis proposes that imbalances of endogenous mu- and kappa- opioid receptors are at the root of uremic pruritus, with itch signals stemming from mu-opioid receptor agonism and kappa-opioid receptor antagonism.[8,10-12] Pharmacologic studies have further elucidated how the mu- and kappa- receptors interact to control the sensation of itch. An example is itch suppression achieved by kappa-receptor antagonism of mu-receptors.[8,10-12] The immunologic hypothesis proposes that uremic pruritus is due to systemic inflammation from increased pro-inflammatory cytokines and acute phase proteins, which may lead to derangements of T helper cell differentiation and sensitization of peripheral c-fiber itch receptors in a mechanism similar to that of neuropathic pain transmission.[8,9,13] It has been postulated that uremic pruritus is caused by a combination of neurogenic itch, as described above, as well as neuropathic itch (nervous system damage along the afferent pathway).[1] Another potentially contributing factor implicated in uremic pruritus is histamine release from mast cells due to elevated levels of histamine noted in ESRD and the close proximity of dermal mast cells to afferent c-fiber terminals.[7,10]

Many therapeutics aimed at relieving uremic pruritus have been based on these proposed physiologic mechanisms as well as related theories.[3,5] In uremic pruritus, dialysis has long been used to manage symptoms, while more invasive and definitive therapies such as renal transplant and parathyroidectomy have also been used.[7,9] Therapies targeted at the opioid system include kappa-opioid receptor agonists such as nalfurafine (grade I evidence).[2,5] Although the opioid antagonist naltrexone has also been under investigation, evidence for its efficacy has been inconclusive in uremic pruritus and due to the risk of reducing analgesia, it is not recommended in the palliative care setting.[3,5] While many potential immunologic therapies are being explored, such as calcineurin inhibitors (e.g. Tacrolimus), UV-B phototherapy, thalidomide, montelukast, and cromolyn sodium, it is the related anticonvulsant class of neuropathic pain modulators (e.g. gabapentin), which has been proven to have the most efficacy in treating uremic pruritus (grade I evidence).[1,2,5,7-9,13] Histamine's potential role in uremic pruritus has also been targeted with the use of mast cell stabilizers, both sedating (grade III evidence) and non-sedating antihistamines (grade I evidence), and even the use of selective serotonin reuptake inhibitors (SSRIs) (grade II evidence). However, use of SSRIs as a therapy for pruritus has also been related to its efficacy in treating the psychological effect of itching on patients (grade I evidence).[2,7] Finally, therapies targeted at reducing pruritus through neuron depolarization have also proven to be effective, including pramoxine cream (grade II evidence) and eutectic mixtures of lidocaine and prilocaine (grade II evidence).[2,8,10]

In this case, given the patient's history, opioid-targeted therapies were not utilized due to concerns for sedation and worsening pain.[5] Standard immunologic therapies were avoided to prevent interactions with her etanercept for rheumatoid arthritis while gabapentin was employed due to its effects on neuropathic itch transmission as well as based on its mechanism of countering the sensitization of nociceptors, described in both the immunologic hypothesis as well as theories of neuropathic pain transmission.[1,7,9,13] A second-generation antihistamine was used to address possible histamine release by mast cells while reducing the risk of sedation.[2] Finally, pramoxine cream was recommended to reduce the neuronal transmission of the itch sensation after it was determined that calamine lotion alone was insufficient.[2] This multi-faceted approach to her pruritus enabled her to achieve symptomatic relief as she approached the end of her life.

While much of medicine remains based upon the principles of Cartesian dualism, it is critical to appreciate the intertwined nature of the physical and emotional domains, as incomplete consideration of one will mitigate healing of the other.[14] Applying a biopsychosocial approach through active listening, skilled communication, and effective management of the patient's pain and pruritus, the palliative care team was able to build a foundation of trust with the patient and her family.[14] This trust, coupled with helping her achieve symptomatic relief, proved essential in allowing the patient to communicate her end of life wishes.

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