



PALLIATIVE CARE CASE OF THE MONTH

“Restless Leg Syndrome”

by

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Case: The patient is a 71-year-old female with colon cancer with omental and uterine metastases who received an extensive debulking surgery and HIPEC 1.5 months ago, who was admitted to the surgical oncology service for LUQ pain, nausea, vomiting, and a minor dehiscence from a laparoscopic incision. She was found to have leukocytosis and a small amount of gas and fluid within the subcutaneous fat of the recent surgical incision but overall had expected post-surgical changes and no other pathologic findings. Cefepime and metronidazole were started for the surgical site wound and then switched to fidaxomicin after the development of *Clostridium difficile* colitis. Three days into her hospital stay, she developed severe restless legs at night and bilateral paresthesias in her lower extremities. Surgical oncology consulted palliative care for restless leg syndrome.

The patient started having restless leg syndrome a few months prior to admission. Initially, her symptoms had been generally mild and did not require medication management. Over the prior three days, her restless leg symptoms had progressively worsened. At night she experienced an uncontrollable discomfort in her bilateral lower extremities accompanied by the urge to walk around in an effort to relieve her discomfort. Because of her surgeries and frail state, she was unable to get out of bed and thus unable to relieve the sensation, which interfered with sleep and became psychologically distressing to the point of bringing her nearly to tears on interview.

Clinical presentation of restless leg syndrome:

Restless leg syndrome (RLS) often presents with complaints of unpleasant sensations in the legs leading to an uncontrollable urge to move the legs which provides temporary relief of the discomfort. Patients seldom describe these sensations as painful (1). These symptoms are exacerbated by inactivity and occur in the evening or night. In early and moderate RLS, these symptoms tend to wax and wane over time and in many cases spontaneously remit. When severe, these symptoms become persistent every night and/or interfere with sleep.

Pathophysiology of restless leg syndrome:

The pathophysiologic basis of restless legs syndrome remains incompletely understood but has two main hypotheses that stem from observing clinical improvement with the two major classes of treatment. Dopamine agonists alleviate RLS symptoms, while dopamine antagonists exacerbate them, suggesting perturbations of the dopaminergic system. However, biochemical studies of dopamine are conflicting and fail to consistently show dopaminergic deficiencies. The other major class of treatment is iron supplementation. Biochemical studies suggest decreased intracellular iron stores in the CNS in spite of adequate systemic iron availability. Nonetheless, systemic iron supplementation improves symptoms of RLS if blood levels indicate iron deficiency.

Differential diagnosis:

Distinguishing RLS from akathisia is important. Unlike RLS, akathisia is not associated with inactivity or a specific time of day, although this can be challenging to discern in a hospital setting in which patients may be inactive due to nursing orders, and during which dopamine antagonists such as olanzapine are often given at bedtime.

Clinical reasoning tip: Consider the pace of disease progression during clinical reasoning. An abnormally fast tempo of disease progression should raise suspicion for iatrogenic or medication-induced causes.

Management

- 1.) Remove offending meds when possible. Chart review and ask patient specifically about antihistamines (particularly first generation) which may be obtained over the counter and not reflected in the medication history, dopamine antagonists (including those primarily used as anti-emetics), mirtazapine, and tricyclic antidepressants.
- 2.) Iron supplementation if indicated. Iron supplementation (either oral or IV) is generally recommended if fasting serum ferritin level is ≤ 75 ng/mL or if transferrin saturation is $< 20\%$ when the patient has a comorbid acute or chronic inflammatory disorder.
- 3.) Avoid exacerbating factors such as sleep deprivation and behavioral interventions such as moderate regular exercise, abstinence from alcohol or caffeine, or leg massage.
- 4.) Treat symptomatically based on frequency of symptoms. For intermittent symptoms that do NOT warrant daily treatment, options include as needed carbidopa-levodopa, a benzodiazepine or a low-dose opioid (3). The starting dose of carbidopa-levodopa is 12.5mg/50mg or 25 mg/100 mg. For persistent symptoms that warrant daily treatment, both gabapentinoids (pregabalin, gabapentin) and dopamine agonists (pramipexole, ropinirole) are reasonable first line therapies and head-to-head trials have demonstrated similar efficacy (4). However, some advocate for using gabapentinoids first due to the increased risk of augmentation (a paradoxical treatment-related increase in RLS symptoms) with dopamine agonists. Determination of which to pick typically comes down to comorbidities (e.g. diabetic neuropathy) and side effect profile. If the first drug chosen is ineffective or poorly tolerated, then the other class may be effective.
- 5.) Neurostimulation or neuromodulation techniques are an active area of investigation. In a randomized sham-controlled trial in medication-refractory RLS, a new device which delivers peroneal nerve stimulation over the head of the fibula was safe and improved RLS severity scores (5). It is anticipated to be released in the United States in 2024.

Personal details in the case published have been altered to protect patient privacy.

For palliative care consultations please contact the Supportive and Palliative Care programs at PUH/MUH, 412-647-7243, pager # 8511, Shadyside, 412-647-7243, pager # 8513, Perioperative/ Trauma Pain, 412-647-7243, pager # 7246, UPCI Cancer Pain Service, pager 412-644-1724, Magee Women's Hospital, pager 412-647-7243 pager # 8510, VA Palliative Care Program, 412-688-6178, pager # 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore and Children's pager 412-456-1518

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Case Conclusion: Iron studies did not show iron deficiency and thus iron supplementation was not recommended. A comprehensive chart review revealed that the patient had received dopamine antagonists (Reglan and Compazine) for nausea for the past three days. Palliative care recommended switching to ondansetron for nausea and avoiding dopamine antagonists. After 24 hours without dopamine antagonists, her symptoms significantly improved, allowing her to sleep without additional medications.

References:

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