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Case Report

Opioid-Induced Hyperalgesia (OIH): Case Study of a Woman with Metastatic Colon Cancer

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ABSTRACT

Pain is an unpleasant experience and a subjective term that is associated with tissue damage. Cancer patients experience pain for a myriad of reasons, from disease related to treatment causes and unrelated to both of these categories.
Opioids are the mainstay in the treatment of moderate to severe cancer pain. Progressive opioid dose increases can cause opioid-induced hyperalgesia (OIH).
OIH has no definite management, here we present a 47-year-old cancer patient with OIH and her management.

Introduction

Opioids like morphine can paradoxically induced pain, hence instead of an analgesic effect, there is an increase in pain perception. Opioid-induced hyperalgesia seems under-recognized. If OIH is not diagnosed, opioids' dosage can increase, and it can cause more pain, agitation, or sedation. Here, we present a woman with a diagnosis of OIH.

Case Report

A 47-year-old woman with metastatic colon cancer was admitted to Imam Khomeini Hospital's Palliative Care Unit, complaining of uncontrollable lower limb pain despite increasing her opioid dosage, as well as widespread hypersensitivity. Despite applying analgesics, she was in constant pain.

Three months prior to admission spiral abdominal and pelvic CT scan revealed wall thickening in the sigmoid and descending colons, as well as a few (at least 8) regional lymph nodes up to 11 mm and pericolic fat inflammation. The CT scan showed a few para-aortic enlarged LNs up to 23*12mm, as well as urinary stones in the left lower calyx measuring 9mm and 7mm. Extensive colon cancer metastases to the lymph nodes, liver, adrenal glands, and peritoneum diagnosed for her.

Considering her disease state, it was believed that she must do a partial colectomy and cancer would progress as time passed, hence she received FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) plus Bevacizumab regimen. Her pain relief regimen at-home palliative care included fentanyl patch 50 µg every 72 hours and oxycodone 15 mg as needed (which she eventually took every three hours). She refused to use the fentanyl patch since it caused her to have hypersensitive responses. Therefore, she was taking 15 mg of oxycodone every three hours for the pain.

The patient was not cooperative for examination since she was experiencing tingling and burning pain and sensitivity to touch. She rated the pain an 8 out of 10. We think opioids caused her suffering, given her condition as OIH. Her oncologists recommended her to a palliative medicine clinic, where she was hospitalized on the spot.

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First of all, as it can be reviewed in table 1, she was given a combination regimen of

- 7.5-10 mg q4h S/C morphine Amp,
- 1-2.5 mg q4h S/C midazolam Amp,
- 15 mg TDS S/C ketamine Amp
- 1 mg TDS haloperidol Amp,
- 10 mg PRN S/C morphine Amp,
- 1 mg PRN S/C haloperidol Amp.

Because she hadn't defecated in three days, 10 cc TDS Magnesium Hydroxide Syrup was added to her medicines the following day. Her bowel sound was auscultated with significant abdominal distension, and the discomfort was tolerable and she was somniferous. Midazolam was weaned to 1 mg q4h S/C, morphine was tapered to 5-7.5 mg q4h S/C, and 15 mg BD ketamine and 1 mg BD S/C haloperidol were all reduced to 1 mg q4h S/C.

On the third day, an Amp of Zoledronic acid 4 mg was given after her laboratory test revealed hypercalcemia (Corrected calcium: 11.2) in her second-day sample. She complains of burning and tingling discomfort in her groin region, as well as a lack of feces. Ketamine, morphine, and midazolam were discontinued, but 5 mg QID S/C methadone Amp, 10 mg S/C PRN morphine Amp, 1 mg BD S/C haloperidol Amp, and 2 mg midazolam Amp, PRN were added to her medicines. Three instances of stool defecation were recorded the next day. Because the treatment had a significant impact on her pain relief, we decided to discharge her the next day. The patient was given a prescription for 5 mg methadone Amp QID S/C and 10 mg morphine Amp S/C PRN. She was also prescribed 1 mg of clonazepam Tab to assist her manage her tension and anxiety (she was extremely worried about being discharged and experiencing a new episode of pain). To prevent hypocalcemia caused by Zoledronic acid, calcium carbonate with vitamin D Tab was launched.

Table 1- Our approach toward OIH management

Day 1:	Day 2:	Day 3:	Discharge plan:
7.5-10 mg q4h S/C morphine Amp, 1-2.5 mg q4h S/C midazolam Amp, 15 mg TDS S/C ketamine Amp 1 mg TDS S/C haloperidol Amp, 10 mg PRN S/C morphine Amp, 1 mg PRN S/C haloperidol Amp.	10 cc TDS Magnesium Hydroxide Syrup 5-7.5 mg q4h S/C morphine Amp, 1 mg q4h S/C midazolam Amp, 15 mg BD S/C ketamine Amp, 1 mg BD S/C haloperidol Amp.	Zoledronic acid 4 mg Amp, Ketamine, morphine, and midazolam were stopped, 5 mg QID S/C methadone Amp, 10 mg S/C PRN morphine Amp, 1 mg BD S/C haloperidol Amp, 2 mg PRN midazolam Amp.	5 mg QID S/C methadone Amp, 10 mg S/ C PRN morphine Amp, 1 mg clonazepam Tab.

Discussion

Pain is an unpleasant experience and a subjective term that is associated with tissue damage.

Cancer patients experience pain for a myriad of reasons, from disease related to treatment causes and unrelated to both of these categories.

Opioids are the mainstay in the treatment of moderate to severe cancer pain. Progressive opioid dose increases can cause opioid-induced hyperalgesia (OIH), often misdiagnosed as progressing disease-related pain.

Traditionally, OIH descriptions go back to the 19th century; Dr. Albutt defined this paradoxical phenomenon: “at such times, I have certainly felt it a great responsibility to note that pain which I know is evil, is less harmful than morphia, which may be evil. Does morphia tend to encourage the same pain it pretends to relieve?” [1]

Two mechanisms may explain this phenomenon: the first is linked to opioid receptor signaling, and the second is Cross-Talk between Neuronal and Non-Neuronal Cells.

In addition to reducing opioid antinociceptive efficacy, prolonged opioid therapy also activates a pronociceptive system that lowers the nociceptive threshold. It is thought that opioids cause OIH by releasing Adenylate Cyclase, Protein Kinase C, Protein Kinase A, N-methyl-D-aspartate (NMDA), and pronociceptive peptides from non-neuronal cells [2-5].

Several therapy options for OIH have been discussed in publications, ranging from reducing or stopping existing opioid medication to exploring non-opioid treatment.

Different methods have mentioned not just opioid switching, but also the use of an NMDA receptor antagonist [2].

At first, since ketamine antagonizes the NMDA receptor, it may be utilized to treat OIH [3, 6-8]. Ketamine treatment substantially reduced pain intensity in nearly all cancer patients in a randomized controlled trial [9].

Second, NSAIDS may be used as a treatment option. Pain stimulates excitatory neurotransmitters such as substance P and glutamate. After pain stimuli, which activate a variety of intracellular pathways and enzymes, including phospholipase A2, an increased amount of

intracellular calcium is generated [10]. As a result, there is an increase in free arachidonic acid, which leads to the production of prostaglandins, thus NSAIDs and COX inhibitors may help with OIH treatment.

Methadone has the benefit of being both an opioid and an antagonist of the NMDA receptor. Methadone treatment may be a good option [3,11].

Conclusion

The development of tolerance or OIH may occur in patients who receive prolonged opioid treatment. Diagnosis and prompt management of OIH are crucial. Initially, we managed the patient with a combination of ketamine and morphine. We discharged the patient after morphine was switched to methadone and ketamine tapered. Three months later, she died peacefully at home surrounded by her family, as she wished.

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