Case Report

Chronic Cancer Pain: Diagnostic Dilemma and Management Challenges

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Abstract

A 32-year-old female, diagnosed case of neuroendocrine tumor of pancreas, was admitted to the pain and palliative care unit with complaints of diffuse abdominal pain which was severe in intensity with score on numerical rating scale-9/10. Pain was not relieved even after taking tablet morphine immediate release 360 mg every 4 hourly, paracetamol 500 mg 6 hourly, and gabapentin 300 mg 8 hourly. She had undergone distal pancreatectomy with splenectomy and also received multiple lines of chemotherapy. After making a diagnosis of opioid-induced hyperalgesia, opioid rotation from morphine to fentanyl was done. This case report reflects various conditions where strong opioids fail to relieve cancer pain, and a multimodal approach is needed for its management.

Keywords: Fentanyl, Hyperalgesia, opioid rotation, pain

Introduction

Cancer pain management primarily revolves around the use of high-potency opioids such as morphine.[1] However, with increasing use of opioids, the intricacies associated with it can be challenging in clinical practice. Opioid-induced hyperalgesia (OIH) is a less acknowledged entity which can complicate the clinical course of patients receiving opioids by reducing the efficacy of therapy. The occurrence of phenomenon of OIH was observed as early as 1870 by Albutt, when he perceived that a potent analgesic such as morphine could actually result in increase in pain.[2] The condition is further perplexed by causes such as disease progression, tolerance, pseudotolerance, interval injury, opioid withdrawal, and substance use disorder.[3] Several intra- and inter-cellular mechanisms involved in OIH development have been proposed.[4] Diverse treatment options targeting the postulated mechanisms have been tried, opioid rotation being one of them which involves changing from one opioid to another to achieve better analgesia and avoid side effects. Hence, it is indispensable on the part of physicians to distinguish between all the causes since it determines the subsequent treatment plan.

Case Report

A 32-year-old female was admitted in pain and palliative care unit with complaints of diffuse abdominal pain. It was severe in intensity (numerical rating scale-9/10), episodic in nature, radiating to back, and got aggravated after taking meals. She was taking tablet morphine immediate release (IR) 360 mg every 4 hourly, paracetamol 500 mg 6 hourly, and gabapentin 300 mg 8 hourly.

She was a diagnosed case of neuroendocrine tumor of pancreas for which she underwent distal pancreatectomy with splenectomy 8 years back. Then, she received gemcitabine and 5-flourouracil-based chemotherapy after the surgery. In the follow-up period, she developed acute-onset epigastric pain for which she was treated on lines of acute gastritis. When the pain was not relieved, an upper gastrointestinal endoscopy was done, which revealed normal study. Subsequently, abdominal ultrasonography was done that showed multiple lymph nodes in pancreatic bed and along mesenteric vessels. Hence, biopsy was taken from peripancreatic lymph node which showed features of metastatic neuroendocrine carcinoma. In addition, contrast-enhanced computerized tomography (CECT) scan of abdomen and pelvis showed hypodense necrotic lymph

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nodes in mesentery and coeliac axis. ^{68}Ga-DOTANAC positron emission tomography-CT (PET-CT) study revealed the presence of somatostatin receptor (SSTR) expressing metastatic disease in peripancreatic and mesenteric lymph nodes, suggestive of metastatic neuroendocrine tumor. Then, she received 6 cycles of capecitabine- and temozolomide-based chemotherapy and was put on Sandostatin®. At this point of time, she was referred to pain clinic for further management. In the beginning, she had epigastric pain radiating to the back which was controlled with tablet morphine (IR) 10 mg every 4 hourly. However, with recurrence and further progression of disease, despite administration of multiple cycles of chemotherapy, her analgesic requirements increased dramatically. ^{68}Ga-DOTANAC PET-CT was repeated that showed SSTR expressing disease involving peripancreatic, perigastric, paracaval, aortocaval, and mesenteric lymph nodes, which was suggestive of disease progression. Gradually, over a period of 6 months, her opioid requirement increased to tablet morphine (IR) 120 mg every 4 hourly. This increase was acknowledged since sequential PET-CT had shown a progressive disease. In view of her accelerating opioid requirements, CT-guided therapeutic coeliac plexus neurolysis was done, following which the patient's morphine requirement was reduced to half. But, over a period of 3 months, her morphine requirement had increased to 240 mg every 4 hourly. As splanchnic nerve block can be used in upper abdominal malignancy for better pain control and it has opioid-sparing effect too,[5] bilateral percutaneous splanchnic nerve block was performed under fluoroscopy with 0.25% bupivacaine and 20 mg triamcinolone acetonide, but her pain scores remained unchanged. In view of persistent pain, neuraxial morphine was given through single-space combined spinal-epidural route. Intrathecal morphine 0.3 mg was given and a catheter was inserted in T10-T11 intervertebral space. She had temporary pain relief (6–8 h) after administration of intrathecal morphine which was less than the usual expected duration. Epidural infusion of morphine at 2.5 mg/h was started. The patient was monitored and it was observed that there was no pain relief, rather she complained of persistent pain with increased intensity after morphine administration. By this time, she had completed two cycles of 150 m Ci Lu-177 DOTATATE therapy. CECT scan of chest, abdomen, and pelvis was repeated that showed heterogeneously enhancing mass in mesentry, measuring 6.6 cm × 3 cm, encasing superior mesenteric artery and vein. Bowel and major vessels (aorta and inferior vena cava) were free from the mass. Enlarged necrotic nodal mass was seen at the coeliac axis, encasing the main coeliac trunk and common hepatic artery.

Although the disease had progressed further with appearance of new lesions in liver, there was no pain relief despite all efforts. Later, psychiatry consultation indicated the presence of mild anxiety symptoms and sleep disturbances exacerbated by worsening of pain. The patient was counseled, reassured, and prescribed tablet amitriptyline 10 mg and clonazepam 0.25 mg at bed time. Various causes of increased pain even after opioid administration such as clinically worsening pain, tolerance, OIH, pseudotolerance, interval injury, opioid withdrawal, substance use disorder, and opioid administration for nonopioid responsive condition were considered. After ruling out the possible causes, it was found that the features were most consistent with OIH. Hence, opioid rotation with intravenous fentanyl bolus 40 μg followed by infusion at 20 μg/h was started and increased gradually until adequate analgesia was obtained. Simultaneously, the patient was monitored continuously and it was noted that she had adequate pain relief with fentanyl infusion at 40 μg/h. Hence, fentanyl patch of 50 μg/h was applied. The patient was discharged on fentanyl patch 50 μg/h, paracetamol 500 mg 6 hourly, gabapentin 300 mg 8 hourly, clonazepam 0.25 mg, and amitriptyline 10 mg at bed time. Her pain was settled on these medications till the last follow-up.

Discussion

Patients on longstanding opioids for chronic pain may present with lack of analgesic efficacy. There may be many causes that can lead to such clinical situation. It can be due to disease progression, tolerance to opioids, OIH, pseudotolerance, interval injury, opioid withdrawal, substance use disorder, administration of opioid for nonopioid responsive condition,[3] and psychosocial factors in underdeveloped world. Suboptimal management of cancer pain significantly lowers the levels of role functioning, emotional functioning, and ultimately reduces the quality of life.[6] Hence, it is absolutely essential on the part of pain physician to differentiate between different clinical conditions to achieve optimal results.[3] The patient in our case was diagnosed as a case of neuroendocrine tumor of pancreas 8 years back for which she underwent distal pancreatectomy with splenectomy followed by administration of gemcitabine and 5-flourouracil-based chemotherapy. Three years after completion of treatment, she developed epigastric pain which after evaluation was found to be due to metastatic lymph nodes in peripancreatic, mesenteric, and celiac lymph nodes. Over the next 3 years, the disease progressed to involve perigastric, paracaval, aortocaval, and retroperitoneal lymph nodes alongwith an encasement of superior mesenteric vessels. The disease had progressed despite the administration of multiple therapies such as capecitabine-based chemotherapy, Sandostatin®, temozolomide, and 150 m Ci Lu-177 DOTATATE therapy. This clearly indicates the slow progressive nature of the disease. The patient is on regular follow-up and her disease is in stable condition without any signs of progression for the past 2 years. Her recent CT scan showed no new changes as compared to scans done in the past. Since increase in pain intensity was not due to disease progression, we started searching for other causes. Tolerance is a pharmacologic concept characterized by progressive lack of response to a drug because of decrease in efficacy which can be easily overcome by titration of drug dosages. It was excluded in our patient as she had reported an increase in pain on increasing opioid doses. Pseudotolerance was excluded as there was no

movement-related increase in pain. Compliance to opioid medication was good and she was taking it as advised. Furthermore, there were no opioid-associated side effects such as nausea, vomiting, and constipation that could be attributed to poor compliance. Psychiatric evaluation of the patient was done for suspected substance use disorder or withdrawal. She was also taking adjuvant analgesics (acetaminophen, ibuprofen, and gabapentenoids) which excluded the possibility of nonopioid-responsive conditions. After ruling out the possible differential diagnoses, we reached at a diagnosis of OIH in our patient as her pain worsened with increasing opioid dosage. OIH is defined as a state of nociceptive sensitization caused by exposure to opioids and is characterized by a paradoxical response whereby a patient receiving opioids for treatment of pain might actually become more sensitive to certain painful stimuli.[3] It was first reported by Albutt in 1870 and he described it as, "At such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphine, which may be an evil."[2] This type of pain may present as same or different from the original underlying pain. OIH typically produces diffuse pain, less defined in quality, which extends to other areas of distribution from preexisting pain and may be accompanied by other signs of opioid toxicity such as myoclonus, delirium, and seizures. OIH has been described with acute and chronic exposure, at high and low doses with different routes of administration, and with all types of opioids.

Several mechanisms have been proposed that may lead to OIH including activation of neuroexcitatory receptors, long-term potentiation leading to sensitization of peripheral nociceptive C-fibers and neurons in dorsal horn, descending pain facilitation, neuroinflammation, and genetic mechanisms. At the cellular level, neurons and glia play a major role in the development of OIH.[4,7] Sensitization of spinal neurons accompanying OIH is mediated by central glutaminergic system; in particular, the N-methyl-D-aspartate (NMDA) subtype receptor plays a major role in OIH development.[8] Increase in the levels of spinal dynorphins has been observed with continuous infusions of μ-receptor agonists which in turn lead to release of spinal excitatory neuropeptides such as CGRP from primary afferents, supporting the fact that OIH is a pro-nociceptive process facilitated by increased synthesis of excitatory neuropeptides and their release upon peripheral nociceptive stimulation. Increased activity of excitatory peptide neurotransmitter cholecystokinin in rostral ventromedial medulla (on and off cells) activates spinal pathways that upregulate spinal dynorphins and consequently enhance nociceptive inputs at the spinal level, constituting descending facilitation. Jensen *et al*. described genetic influence by the activity of catecholamine breakdown enzyme catechol-O-methyltransferase (COMT).[9] The genetic polymorphism leading to substitution of amino acid valine for methionine decreases the rate of breakdown of dopamine and noradrenaline, resulting in different levels of synaptic dopamine/noradrenaline following neurotransmitter release. The decreased reuptake of neurotransmitters from the primary afferent fibers has been considered as the common mechanism. Mesenchymal stem cells (MSCs) have been attributed to neuronal protection, regeneration, and modulation due to their immunomodulatory and anti-inflammatory properties. In animal studies, MSC transplantation (MSC-TP) by intrathecal and intravenous routes has shown promising results in the prevention and treatment of OIH. Hence, in the future, MSC-TP may be a viable option for treating patients developing OIH.[10]

The treatment of OIH includes rational polypharmacy with nonopioids (paracetamol, nonsteroid anti-inflammatory drugs, e.g., cyclooxygenase-2 inhibitors) and adjuvant medications such as antidepressants and anticonvulsants, preferably in neuropathic pain to minimize opioid dosage,[11] interventional pain management technique to isolate or block pain input from specific nociceptive points in the nervous system,[12] behavioral management,[13] and opioid rotation. Opioid rotation is the process of changing from one opioid to another to obtain a satisfactory clinical balance between analgesia and adverse effects.[14] The major indications for opioid rotation include poorly controlled pain with unacceptable adverse effects due to opioid toxicity, rapid development of tolerance, refractory pain, or difficult pain syndromes.[15] Though initially introduced to reduce adverse effects associated with high opioid dosages for achieving adequate pain relief, now it is commonly being employed for the management of uncontrolled pain itself. Factors such as inter-individual variability in pharmacokinetics, pharmacodynamics, and pharmacogenetics of strong opioids and incomplete cross-tolerance have been implicated as the biological mechanisms for the observed beneficial effect of switching from one opioid to another.[16] The ROTODOL study done by González-Barboteo *et al*. evaluated the effectiveness of opioid rotation in control of cancer pain and found that it was both safe and effective in the management of basal and breakthrough cancer pain.[17] As we had already explored all other treatment options, we decided to proceed with opioid rotation. Methadone, a pure μ-receptor agonist, is a racemic mixture in which d-isomer is an NMDA receptor antagonist that also displays incomplete cross-tolerance properties unique from other μ-receptor agonists and might make it responsible for its role in the treatment of OIH.[18] Since methadone has a relatively long half-life (24-36 h) leading to fewer variations in plasma levels, it can be used for the treatment of pain and OIH. Buprenorphine, being a kappa receptor antagonist, has also been used to treat OIH by counteracting the effect of spinal dynorphin, a known kappa receptor agonist that increases during opioid administration, thus contributing to OIH. Due to nonavailability of methadone in our setting, fentanyl was used. Opioid rotation from morphine to fentanyl may be effective in alleviating morphine-induced delirious symptoms[19] and also provides good analgesic control, thus leading to overall improvement in the quality of life.[20]

Conclusion

Use of opioid medications for the management of chronic pain is like using a double-edged sword. The pain physician should utilize opioids cautiously in these patients, as on one end of the spectrum, they may produce health problems such as endocrinopathies, osteoporosis, neurological or cardiopulmonary effects, and substance use disorder,[21] whereas on the other end of the spectrum is the paradox of OIH.[22] Hence, the failure of opioid therapy in a patient should be evaluated thoroughly and management plans can be tailored accordingly to reach an optimal effect.

Learning points

- The diagnostic dilemma in clinical scenarios where opioids fail to relieve cancer pain and it can only be overcome by proper evaluation and exclusion
- Various causes such as disease progression, tolerance, OIH, pseudotolerance, interval injury, opioid withdrawal, and substance use disorder can be attributed to inadequate pain relief
- Opioid rotation may be helpful in these patients to relieve their sufferings.

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Conflicts of interest

There are no conflicts of interest.

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