Palliative Care Rounds

Delirium with Severe Symptom Expression Related to Hypercalcemia in a Patient with Advanced Cancer: An Interdisciplinary Approach to Treatment

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Abstract
Delirium is considered to be multifactorial, especially in elderly patients and those with advanced cancer, and can cause significant distress. High baseline vulnerability at the end of life, combined with cachexia, hepatic impairment, general comorbidities, and impaired functional status, can make delirium difficult to correct. Nonetheless, approximately 50% of delirium episodes are potentially reversible and reversible causes should be investigated. Hypercalcemia is one of the reversible metabolic causes of delirium in patients with advanced cancer. Here, we present the case of a patient with metastatic small cell prostate carcinoma who presented to our palliative care clinic with uncontrolled symptoms. A thorough evaluation using appropriate assessment tools revealed that he had delirium, and hypercalcemia was found to be the major etiologic factor. An interdisciplinary team approach (including a nutritionist, pharmacist, counselor, social worker, chaplain, and case manager) was provided. With aggressive symptom management and correction of hypercalcemia and other reversible causes of delirium, the delirium was resolved and the symptoms were controlled. This case illustrates the importance of screening for delirium in patients with severe symptom distress and how the interdisciplinary management of reversible causes of delirium, including hypercalcemia, can improve patients’ symptoms and quality of life. J Pain Symptom Manage 2008;36:442–449. © 2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Delirium, symptom distress, hypercalcemia

Introduction
Delirium is a transient and potentially reversible disorder of cognition and attention. In general, its origins are multifactorial, especially in advanced cancer patients and elderly patients. In patients with advanced cancer, delirium causes significant distress and frequently complicates care at the end of life.
It is common during the last hours or days of life as an irreversible or terminal event.\textsuperscript{4,7} It may occur earlier, however, and can be reversed in approximately 50% of episodes.\textsuperscript{5} High baseline vulnerability at the end of life, combined with cachexia, hepatic impairment, general comorbidities, and impaired functional status, can make delirium difficult to correct. It is important to look for reversible causes, including metabolic problems such as hypercalcemia.

Hypercalcemia occurs in up to 30\% of cancer patients; it is more common in patients with advanced disease stages.\textsuperscript{12–17} It is rare in prostate cancer, occurring in less than 2\% of cases.\textsuperscript{18–22} Thus, it would not usually be suspected as a cause of delirium in these patients. We present a case of a prostate cancer patient who developed delirium due to hypercalcemia. A comprehensive patient assessment, which included a thorough medical history, screening tools, and a search for reversible causes, identified the nature of the problem. The main goal of the interdisciplinary treatment strategy was to improve quality of life by addressing the delirium first.

**Case Report**

A 60-year-old white man with neuroendocrine small cell carcinoma of the prostate was referred to our palliative care service by his primary oncologist for evaluation and treatment of generalized pain, episodes of confusion and agitation, and profound fatigue.

Six months earlier, the patient had been diagnosed with neuroendocrine small cell carcinoma of the prostate. Initial chemotherapy with etoposide and cisplatin was complicated by severe pancytopenia, diarrhea, and dehydration. These symptoms were resolved, but the disease had continued to progress, and the patient was treated with docetaxel and carboplatin. He developed metastases to the lumbar spine and brain and local invasion to the bladder. He then received ifosfamide, paclitaxel, and cisplatin, and a total dose of 3,000 cGy of radiation to the brain and thoracolumbar spine. Because of the progression of his disease despite intensive chemotherapy, the patient was no longer considered a candidate for further disease-modifying treatment. Approximately four weeks after his last cycle of chemotherapy, he was referred to the palliative care service for symptom management.

At our institution, the patient presented with severe back pain originating from the lumbar area and radiating to the lower extremities. He also reported that he had felt occasional diffuse abdominal pain for two weeks. A week prior to his visit to our clinic, he had begun experiencing episodes of confusion, with delusional thoughts and periods of visual hallucinations. This was confirmed by the patient’s friend. The patient also reported feeling fatigued and having a poor appetite. In addition, he reported episodes of constipation, with no nausea or vomiting. There was no history of spontaneous bleeding, ecchymosis, or petechiae. Self-rated symptoms were assessed using the Edmonton Symptom Assessment Scale (ESAS) (Fig. 1). The ESAS revealed disinhibited expression of symptoms, which increased our suspicion for the presence of delirium.

On physical examination, the patient was conscious, alert, and cooperative; he was oriented to person and place, but not time. He was found to have dry mucosa. The patient was inattentive, with impairment in immediate and delayed recall of three items and abnormal digit span, as evidenced by the Memorial Delirium Assessment Scale (MDAS), a validated tool to evaluate patients with delirium.\textsuperscript{1–3} The MDAS was 14/30 (normal <7/30). Cardiac features included tachycardia (110 beats per minute at a regular rate); blood pressure of 90/60 mm Hg, with no orthostatic changes; no jugular venous distension; and no murmurs or rubs. Respiratory system features included occasional rhonchi, but no crackles or hypoventilation. An abdominal examination revealed no abnormalities. The patient had no edema in the lower extremities. He had mild decreased strength and reflexes in four extremities and no focal neurologic deficit.

Because of the alteration in psychomotor activity, with periods of agitation and sleepiness, the diagnosis was mixed delirium, and because his delirium was associated with uncontrolled symptoms, the patient was admitted to our inpatient palliative care unit for symptom control. The results of our assessment indicated that delirium was contributing to the presence of severe symptom distress and that possible
reversible causes needed to be investigated and treated promptly.

Laboratory tests showed that the patient had severe anemia (hemoglobin of 7.7 g/dL), leukopenia, and thrombocytopenia. According to a hematologic evaluation, this pancytopenia was considered to be related to infiltration of the bone marrow by the tumor. Laboratory tests also showed renal impairment (blood urea nitrogen of 27 mg/dL [9.7 mmol/L] and creatinine of 1.6 mg/dL [133.3 micromol/L]) and hypercalcemia (corrected calcium of 12.44 mg/dL [3.11 mmol/L]).

In keeping with institutional standard practice, a multidisciplinary team (including a nutritionist, pharmacist, counselor, social worker, chaplain, and case manager) was assembled to manage the case. Environmental strategies were established, which included reorientation, increasing the presence of the caregiver, educating the caregiver about delirium, limiting staff changes, and decreasing the patient’s level of noise stimulation. Emotional support was provided for the patient and his caregiver by our counselor, social worker, and nurses, and spiritual support was provided by our chaplain.

To control agitation and hallucinations related to delirium, 1 mg of haloperidol was given intravenously (IV) every six hours. Hypercalcemia treatment consisted of normal saline (200 mL IV every hour), pamidronate (60 mg IV, once), and calcitonin (4 units/kg subcutaneously every 12 hours) to promote a rapid decrease in the calcium level, and dexamethasone (4 mg IV twice daily) to decrease the risk of tachyphylaxis that is seen with the use of calcitonin.

During the first 48 hours of treatment, the patient’s serum calcium level progressively improved. By the end of the second day, his symptoms were controlled. His MDAS score improved to 0/30, and he had no evidence of hallucinations or agitation. Fig. 1 shows the patient’s self-rated ESAS subscale scores at the time of admission and after treatment. Fig. 2 documents the relationship between the patient’s MDAS score and the correction of reversible causes, including hypercalcemia.

In the inpatient palliative care unit, the patient experienced severe urinary retention, which was treated with placement of a supra-pubic catheter. This was performed without complications. He also received a transfusion of two units of packed red blood cells, with no complications. The patient’s renal function improved (creatinine 1.2 mg/dL [106.1 micromol/L]).
after the prerenal (hypotension and volume depletion) and postrenal causes of impairment were corrected.

There were minimal changes in the patient’s pain medication regimen; his pain was controlled with methadone (5 mg IV every 12 hours) without complications. An aggressive bowel treatment regimen was initiated to relieve constipation: sennosides/docusate, lactulose (30 mL, PO twice daily), and milk and molasses enema.

The patient’s mental status continued to improve over the next seven days. By the second day after his admission to the palliative care unit, he was able to participate in physical and occupational therapy. His pain was well controlled by administration of methadone, with no dose escalation. Furthermore, the patient showed no evidence of visual hallucinations or agitation. The multidisciplinary team continued to provide not only physical but also emotional and spiritual support. On the tenth day after admission, the patient was discharged from our unit to a skilled nursing facility with hospice care; his symptoms were well controlled, and he had no evidence of delirium.

**Discussion**

A fluctuating course of acute-onset reduced sensorium, attention deficit, and cognitive or perceptual disturbances, as described in our patient, are the main features of delirium. In patients with advanced cancer, prospective data suggest a 28%—42% prevalence of delirium on admission to a palliative care unit and rates as high as 88% before death. Most of the time, delirium is considered to be multifactorial, especially in patients with advanced cancer and elderly patients. In our patient, dehydration, advanced disease, and hypercalcemia played important roles in the development of delirium.

Hypercalcemia is not a common finding in patients with prostate cancer, but when it is present, neuroendocrine tumors of the prostate are usually related to its development. Neuroendocrine carcinoma subtypes range from anaplastic small cell carcinomas to more differentiated carcinoid tumors. Patients with neuroendocrine tumors have a variable clinical course, but they typically present with early metastasis and involvement of unusual sites. Neuroendocrine carcinoma has been associated with endocrine paraneoplastic syndromes, such as ectopic corticotropin secretion. Of particular relevance to the current case, in 1992, Smith et al. reported that 11 of 20 published cases of hypercalcemia associated with prostate carcinoma were in patients with neuroendocrine carcinomas.

However, hypercalcemia has not been definitively associated with a specific histologic type.

Fig. 2. Corrected calcium levels and improvement observed in MDAS findings after multidisciplinary treatment, including correction of hypercalcemia. Calcium levels are expressed in mg/dL (multiply the value by 0.25 to express it in mmol/L).
of prostate cancer. In addition, the mechanism by which hypercalcemia develops is unclear, although it seems most likely to be associated with the production of parathyroid hormone-related protein.\textsuperscript{18} The treatment of hypercalcemia in symptomatic patients does not depend on the cause of the condition; in terminally ill patients, the relief of symptomatic distress is the main goal, as in our patient.

Other factors to consider in delirium are the presence of infections; medication side effects, such as those of opioids and psychoactive medications; and withdrawal from substances of abuse, such as alcohol.\textsuperscript{4,5,11} Comorbidities, hypoalbuminemia, prior cognitive impairment, liver and kidney failure, and poor functional status are also predisposing factors for delirium.

**Diagnosis of Delirium**

Delirium is frequently misdiagnosed as depression or dementia.\textsuperscript{11} This confusion might be secondary to unfamiliarity with terminology, fluctuation of symptom intensity, and failure to objectively assess cognition.\textsuperscript{11,27–29} In our patient, the main cause of delirium was hypercalcemia, which can present with neurologic and psychiatric features, including lethargy, delirium, disrupted sleep, nightmares, irritability, depression, hypotonia, hyporeflexia, stupor, and coma. Hypercalcemia also causes gastrointestinal symptoms such as anorexia, vomiting, constipation, peptic ulceration, and acute pancreatitis. Cardiac symptoms, such as arrhythmias, synergism with digoxin, and hypertension, may also be present. The clinical features of hypercalcemia with malignancy also may include signs and symptoms of the underlying cancer. The prognosis can be poor in patients with advanced cancer and delirium due to hypercalcemia, as in our patient.\textsuperscript{14–17}

Delirium impedes communication between patients and family members and caregivers at a time when it is often most desired.\textsuperscript{4,5} It is important to recognize delirium because it can be difficult for patients to reliably report their symptoms; they frequently present with disinhibition of symptom expression,\textsuperscript{4,5,29} an inability to participate in decisions about therapeutic interventions, and an inability to benefit from supportive psychotherapy.\textsuperscript{4}

Another important consideration is that if delirium is not recognized, not only family members but also health care providers can misinterpret agitation as a sign of pain. This can lead to dose escalation of opioids, producing toxicity and complicating the delirium. To facilitate the diagnosis of delirium and impose relatively little burden on patients, instruments with adequate psychometric properties have been created, such as the Mini-Mental State Examination,\textsuperscript{30} the Confusion Assessment Method,\textsuperscript{31} and the MDAS,\textsuperscript{1–3,7} a validated tool used in our palliative care practice. The MDAS was used to diagnose and monitor delirium in our patient.

**Treatment of Delirium**

High baseline vulnerability at the end of life, combined with cachexia, hepatic impairment, general comorbidities, and impaired functional status, can lead to delirium; these factors are difficult to correct. Thus, reversible causes of delirium should be investigated. Delirium is reversible in approximately 50\% of cases.\textsuperscript{7} Such reversible causes can be secondary to dehydration and electrolyte abnormalities such as hypercalcemia, as in our patient. Reversible causes should be identified and treated, and aggressive symptom management, especially for agitation, should be implemented to decrease distress in patients and their family members.

Team work is considered a central component of palliative care and is a key component in helping patients in distress and their family members and caregivers.\textsuperscript{32,33} A team should be actively developed to produce a setting that enables the team to perform well and to create an atmosphere that allows team members to cope with the specific challenges of palliative care. Having an interdisciplinary team in the palliative care setting allows us to interact better with each other and to better understand patients’ and family members’ illness experience. In the interdisciplinary team setting, multiple professionals are joined in a mutual goal and collective spirituality\textsuperscript{34} to relieve patients’ and family members’ suffering; they provide different management skills and perspectives to improve patients’ quality of life. Interdisciplinary teams also provide an environment in which each member can share emotionally and physically draining situations, creating an environment of mutual trust, autonomy, and a good work climate.\textsuperscript{32}

A team can be invaluable when providing continued information and support to family

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\textsuperscript{1} Delgado-Guay et al.
members and caregivers when patients develop delirium or other distressing symptoms. Information is extremely important because it helps the caregivers understand the disease and its treatment, and thus helps decrease their emotional distress.

Another possible cause of delirium, although not present in our patient, is opioid-induced neurotoxicity. If this is suspected, it should be treated with opioid rotation and medication for agitation, usually an antipsychotic. The drug of choice for agitation is haloperidol, although atypical antipsychotics such as risperidone and olanzapine can be considered. In our case, because of the presence of visual hallucinations and restlessness, haloperidol was administered at a scheduled dose.

Once the possible reversible causes of delirium have been identified, treatment should be started to control symptoms and decrease distress. In cases of hypovolemia and renal impairment in the setting of hypercalcemia, the first step in treatment should be the IV administration of normal saline, starting at a volume of 500–1,000 mL during the first hour and continuing at a lower rate until intravascular repletion is achieved and urine output is established. Particular care must be taken in elderly patients and patients with congestive heart failure. The use of loop diuretics should be avoided until euvolemia is achieved to avoid renal hypoperfusion and further kidney damage.

Bisphosphonates play an important role in the treatment of hypercalcemia of malignancy. Their main mechanism of action is blocking osteoclastic bone resorption. They are known to have multiple actions on osteoblasts, including modulating proliferation and differentiation, preventing apoptosis, modulating extracellular matrix protein production, regulating the expression and excretion of interleukin-6, and decreasing angiogenesis. The most commonly used bisphosphonates in the treatment of hypercalcemia are pamidronate and zoledronic acid. Both drugs are poorly absorbed from the gut; thus, in hypercalcemia, they must be administered IV. Pamidronate combines high potency with low toxicity and has become the agent of choice for the treatment of hypercalcemia of malignancy. In studies of pamidronate administered in a 90 mg infusion over four hours, normal calcium levels were achieved after a mean of approximately four days.

To achieve a rapid and sustained reduction in serum calcium concentration, pamidronate can be used in combination with 4–8 units/kg of calcitonin. To decrease the risk of tachyphylaxis, which frequently occurs within 48 hours of calcitonin administration, concomitant glucocorticoids should be used to prolong the effective time of treatment, producing an up regulation of cell-surface calcitonin receptors that increase de novo production of calcitonin receptors in osteoclasts. Our patient received the mentioned regimen and experienced improvement in his calcium level, with no complications. Glucocorticoids play an important role in the treatment of hypercalcemia related to multiple myeloma and hematologic malignancies associated with increased levels of 1,25 (OH)2 D3, which inhibits osteoclastic bone resorption, decreases tumor production of locally active cytokines, and also has direct tumorlytic effects.

Zoledronic acid is the most potent bisphosphonate available. At a dose of 4 mg, it has a response rate, time to calcium normalization, and response duration superior to those seen with pamidronate. However, zoledronic acid should be used cautiously in patients with renal insufficiency, and the dose should be adjusted according to the calculated creatinine clearance.

It is important to evaluate patients’ medications and eliminate any direct sources of calcium, such as thiazide, diuretics, and vitamin D, although it was not a significant problem in our patient. It is also important to evaluate for possible medication interactions, avoiding polypharmacy, particularly any medications with anticholinergic effects and any medications that can lead to delirium, such as chemotherapeutics and antibiotics. Ifosfamide has been associated with neuropsychiatric toxicity, but in our patient, this was not a likely cause of delirium because his last chemotherapy cycle was more than four weeks before the episode of delirium.

In our patient, the combination of IV hydration, bisphosphonate, and calcitonin with dexamethasone to treat hypercalcemia as the main cause of delirium, and the use of haloperidol to treat hallucinations and restlessness, helped to control symptom distress related to
delirium. This, along with the integration of a multidisciplinary team approach, improved the quality of life of our patient.

**Conclusion**

Delirium is multifactorial. It is common in patients with advanced stages of cancer and contributes to significant distress in affected patients, family members and caregivers, and health care providers. It is important to recognize delirium using proper tools and to treat it using an interdisciplinary approach, with specific emphasis on identifying and treating possible reversible causes, such as hypercalcemia and dehydration. The overall goal of delirium treatment is to improve patients’ quality of life.

**References**


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