

Hypercalcemia in Colorectal Cancer

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Abstract

Humoral hypercalcemia of malignancy is common in many cancers but is rarely present in colorectal cancers with only 24 documented cases in the literature. In this report, we present a case of a 67-year-old woman complaining of right sided abdominal pain and diarrhea. Imaging showed an obstructing cecal mass and the pathological diagnosis was poorly differentiated adenocarcinoma. After a hemicolectomy, she developed humoral hypercalcemia of malignancy which was treated with intravenous bisphosphonates. She continued to worsen due to her rapid progression of disease and died less than one month after her initial diagnosis. We reviewed the 24 other documented cases to investigate the prognosis of hypercalcemia in colorectal cancers along with reviewing the clinical presentation and management of humoral hypercalcemia of malignancy.

Résumé

L'hypercalcémie humorale maligne est courante dans de nombreux cas de cancers, mais elle est rare dans les cancers colorectaux; la documentation recense 24 cas seulement. Dans le présent article, nous décrivons le cas d'une femme de 67 ans se plaignant de douleurs abdominales du côté droit et de diarrhée. Un examen d'imagerie indiqua la présence d'une masse caecale obstructive dont le diagnostic pathologique s'est avéré être celui d'un adénocarcinome peu différencié. À la suite d'une hémicolectomie, la patiente a développé une hypercalcémie humorale maligne qui a été traitée à l'aide de bisphosphonates intraveineux. Son état a continué de se détériorer en raison de la progression rapide de la maladie et la patiente est décédée moins d'un mois après le diagnostic initial. Nous passons en revue les 24 cas documentés pour analyser les pronostics d'hypercalcémie dans les cas de cancers colorectaux, tout en examinant le tableau clinique et la prise en charge de l'hypercalcémie humorale maligne.

Hypercalcemia is a common metabolic manifestation of cancer, historically affecting 20–30% of all cancer patients.¹ The mechanisms of malignancy-related hypercalcemia are ectopic hyperparathyroidism, calcitriol secreting lymphomas, local osteolytic hypercalcemia and humoral hypercalcemia of malignancy (HHM).² The two most common causes of hypercalcemia in malignancy are local osteolytic hypercalcemia and HHM, with HHM being the most common. The underlying mechanism of the hypercalcemia is increased osteolytic activity which can be achieved with or without bone metastasis.³ In local osteolytic hypercalcemia, bone metastasis causes local destruction and increased osteolytic activity. In humoral hypercalcemia

of malignancy (HHM), tumours secrete increased levels of a parathyroid hormone related protein (PTHrP) which mimics parathyroid hormone systemically. This results in an increased level of both bone resorption and renal retention of calcium. Cancers associated with HHM include breast cancer, renal cancer, ovarian cancer, endometrial cancer, and lymphoma along with squamous cell cancers of the head and neck, esophagus, lung, and cervix.² HHM associated with colorectal cancers are rare with only 24 documented cases in the literature. In addition to reviewing the literature to characterize the prognosis, we report another case of colorectal cancer with HHM.

Case Description

A 67-year-old woman presented to the emergency room with right sided abdominal pain and diarrhea. She had been well up until 2 weeks prior with no obstructive symptoms, bleeding or weight loss. She had no past medical history, and took no medications. She had no family history of cancer. She was an ex-smoker who drank alcohol minimally. Computed tomography (CT) scan of her abdomen revealed a large cecal mass and multiple lesions in her liver concerning for metastases. A colonoscopy was performed where a mass was seen in the ascending colon. A biopsy showed poorly differentiated non-small cell carcinoma compatible with high grade primary colonic adenocarcinoma. The tumour demonstrated loss of CDX2 and CD20, which is associated with a negative prognosis.⁴ A screen for mismatch repair proteins was negative. The patient was discharged home with plans for outpatient management. 28 days later she developed abdominal pain and returned to hospital and was found to have a large bowel perforation on a subsequent CT scan. The previously noted liver lesions had grown in size and number. Her vitals were stable and she was afebrile. Physical exam revealed tenderness to deep palpation in the right upper and lower quadrant with no rebound tenderness or guarding. Laboratory investigations showed elevated liver enzymes and hypoalbuminemia (29 g/L, normal > 35 g/L). She was stabilized and placed on broad spectrum antibiotics in preparation for a laparoscopic right hemicolectomy which was performed later that week.

Seven days post-operatively she developed delirium and the internal medicine service was consulted. The workup of her delirium involved a CT head, which was negative and she remained on intravenous antibiotics (piperacillin-tazobactam). Her blood and urine cultures showed no growth. Her medications were also reviewed and no offending medications could have caused her delirium outside of narcotic analgesia. Serum calcium was checked and was elevated (2.95 mmol/L, normal < 2.60 mmol/L). Her laboratory data also showed hypophosphatemia (0.6 mmol/L, normal > 0.8 mmol/L), a severe deficiency in 25 hydroxyvitamin D (19 nmol/L, moderate deficiency > 25 nmol/L), and a suppressed parathyroid hormone (PTH) (0.5 pmol/L, normal > 1.5 pmol/L). Renal function was normal. Subsequent testing revealed very high levels of PTH related peptide (PTHrP) (36 pg/mL, high < 30 pg/mL). A bone scan was negative for bony metastases. She was treated with IV pamidronate and 2 days later her calcium normalized. She continued to deteriorate and her liver enzymes increased while her hypoalbuminemia worsened. Treatment began to focus on supportive palliative measures and she died 13 days from her diagnosis of hypercalcemia and 27 days from her diagnosis of colon cancer.

Discussion

Clinical Presentation

The most common symptom of malignancy-associated hypercalcemia is fatigue followed by confusion, anorexia, pain, polydipsia/polyuria, constipation and nausea.⁵ A rapid increase in calcium levels along with higher levels of calcium are associated with neurological symptoms such as confusion which was seen in our patient.⁵ If these symptoms are present in patients with colorectal cancers, hypercalcemia should be considered despite its rare occurrence. Investigations into serum calcium levels should be accompanied by levels of ionized calcium since abnormal albumin levels can cause misinterpretation of results.² Once hypercalcemia is diagnosed, it is important to investigate the mechanism and consider concomitant primary hyperparathyroidism along with other non-malignant mechanisms. The diagnosis of HHM can be confirmed with elevated PTHrP measurements but can also be made on clinical grounds.²

Management

IV bisphosphonates such as pamidronate and zoledronic acid have been well documented to effectively treat malignancy-associated hypercalcemia by blocking the PTHrP mediated osteoclastic bone resorption.^{2,6,5} Calcitonin can be used in the acute setting to rapidly decrease calcium levels, although its use is limited by tachyphylaxis which typically occurs within 48 hours. Intravenous hydration can alleviate associated dehydration and renal dysfunction. IV bisphosphonates are very efficacious with 60–90% of patients having normalized calcium levels within 4–7 days that lasts up to 3 weeks.^{2,7} Zoledronic acid reduces calcium levels faster than pamidronate and is more effective in patients with moderate to severe hypercalcemia.⁸ Bisphosphonates such as zoledronic acid are generally well tolerated but can cause elevations in serum creatinine. Serum creatinine should be monitored before each dose and extra caution should be applied in patients with low creatinine clearance or if other nephrotoxic medications are administered.⁹

Management of the underlying malignancy including surgery and/or systemic therapy which can be effective in the long term control of hypercalcemia.¹⁰ However, patients are often too unwell to receive disease directed therapy, as was the patient in our case.

Prognosis

Malignancy-associated hypercalcemia has a poor prognosis with primary research reporting median survivals ranging from 30 to 90 days.^{2,5,6} It has been suggested that this poor prognosis is due to hypercalcemia being a marker of advanced disease rather than the hypercalcemia directly causing death. This is supported by research showing that the control of hypercalcemia does not influence survival and that the majority of deaths in cases of

malignancy-associated hypercalcemia were due to progressive cancer and its complications.^{5,6} To compare the prognosis between calcium associated malignancy and HHM in colorectal cancers, we reviewed the 24 published cases (Table 1). In the 18 cases that had the prognosis result documented, the median survival after the diagnosis of HHM was 32 days. The similarly poor prognosis is likely due to the same reasons, since colorectal cancers with HHM are associated with poorly differentiated tumours and distant metastasis such as the liver.¹¹ This poor prognosis with HHM in colorectal cancer contrasts significantly to the natural history of disease, where median survival in advanced colon cancer is up to 28 months with modern chemotherapy.¹²

Conclusion

In summary, we present a patient with colorectal cancer associated with HHM that progressed rapidly. While humoral hypercalcemia is rare in colorectal cancers, it is associated with a poor prognosis and should be considered in patients who have symptoms or present with aggressive disease. If appropriate with

treatment goals, IV bisphosphonates should be administered to relieve symptoms.

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Table 1. Prognosis of Documented Cases of Colorectal Cancers with Humoral Hypercalcemia of Malignancy

First author	Year	Primary site	Result after hypercalcemia diagnosis
Castleman ¹³	1963	Colon	Died after 3 weeks
Mozaffarian ¹⁴	1969	Colon	Died after 3 weeks
Omenn ¹⁵	1969	Colon	Died with date unreported
Kubota ¹⁶	1980	Colon	Died in under 1 month
Kubota ¹⁶	1980	Rectum	Died after 1 week
Palvio ¹⁷	1985	Rectum	Died after 2 months
Chevinsky ¹⁸	1987	Colon	Died after 6 days
Berkelhammer ¹⁹	1989	Colon	Died after 2 weeks
March ²⁰	1991	Rectum	Died with date unreported
Gurney ²¹	1993	Colon	Result not reported
Gurney ²¹	1993	Colon	Result not reported
Links ²²	1994	Colon	Died after 7 months
De Souza ²³	1995	Rectum	Died after 3 weeks
Sidler ²⁴	1996	Colon	Died after 6 months
Petrelli ²⁵	1996	Colon	Died with date unreported
Sekine ²⁶	1998	Colon	Result not reported
Lortholary ²⁷	1999	Colon	Died 5 weeks later
Lortholary ²⁷	1999	Rectum	Died 7 weeks later
Thompson ²⁸	2001	Colon	Alive with disease 10 months later
Luh ²⁹	2002	Colon	Died 6 months later
Sakata ¹¹	2005	Colon	Died 3 weeks later
Fujita ³⁰	2005	Colon	Died 4 months later
Cooper ³¹	2006	Rectum	Alive at discharge, date not recorded
Current Case		Colon	Died after 13 days

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