Case Report

Hypercalcemia associated with lymph node metastasis following radical cystectomy for bladder cancer

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Abbreviations & Acronyms
CCa = corrected calcium
CT = computed tomography
HE = hematoxylin and eosin staining
PTH = parathyroid hormone
PTHrP = PTH-related peptide
RANKL = receptor activator of nuclear factor kappa-B ligand
SCC = squamous cell carcinoma
UC = urothelial carcinoma

Introduction: A part of hypercalcemia is a paraneoplastic syndrome. Its association with lymph node metastasis of bladder cancer has been infrequently reported in the literature.

Case presentation: A 75-year-old male presented with gross hematuria and was diagnosed with bladder cancer without metastasis. Following neoadjuvant chemotherapy, radical cystectomy was performed. The surgical margin was negative. The bladder cancer was classified as pT3bN0 and mainly constituted squamous differentiated urothelial carcinoma and sarcomatoid variant. His perioperative serum calcium levels were normal. At 6 months of surgery, computed tomography revealed lymph node enlargement, and additional 2 weeks later, he developed epileptic seizures with a serum corrected calcium level of 18.7 mg/dL. He was diagnosed with hypercalcemia caused by the lymph node metastasis of bladder cancer. Despite receiving several supportive therapies for 22 days, he died.

Conclusion: Hypercalcemia associated with bladder cancer is highly resistant to existing therapy, particularly when caused by cancer metastasis.

Key words: bladder cancer, cystectomy, hypercalcemia, lymph node metastasis, squamous differentiation, urothelial carcinoma.

Keynote message

Hypercalcemia can be caused by advanced bladder cancer but hypercalcemia associated with lymph node metastasis of bladder cancer without bone metastasis or massive tumor is rather rare. Because hypercalcemia associated with bladder cancer is a lethal paraneoplastic syndrome, further accumulation of relevant knowledge and clinical experience is crucial.

Introduction

Hypercalcemia is a paraneoplastic syndrome that can occur in up to 30% of patients with a malignancy.1 Hypercalcemia associated with malignancy is most commonly observed in patients with breast cancer, lung cancer, multiple myeloma, and renal cell carcinoma. Histologically, high-grade UC, SCC, and sarcoma have the potential to cause hypercalcemia.1-3 Hypercalcemia associated with bladder cancer without bone metastasis or massive tumor is rare, and primarily, individual case reports of hypercalcemia have been reported.4,5 Here, we report the case of a patient with hypercalcemia caused by the lymph node metastasis of bladder cancer following radical cystectomy.

Case presentation

A 75-year-old man presented to our hospital with gross hematuria. Cystoscopy and CT revealed bladder cancer originating from the bladder diverticulum, which was classified as cT2-3N0M0 (Fig. 1). At 2 months after neoadjuvant chemotherapy (three cycles of gemcitabine/cisplatin/docetaxel) that did not improve the cancer, radical cystectomy with
ileal conduit and intrapelvic lymph node dissection was performed. Pathological examination revealed bladder cancer, which was classified as pT3bN0. The surgical margin was negative. The bladder cancer mainly comprised squamous differentiated UC (80%), sarcomatoid variant (15%), and UC (5%) (Fig. 2). His perioperative serum calcium levels were normal. At 6 months following the surgery, CT revealed paraaortic lymph node enlargement without bone or visceral metastases, and his serum CCa level was elevated to 12.5 mg/dL (Fig. 3a). Two weeks later, he experienced an epileptic seizure and was transported to the hospital. During admission, his serum CCa level was 18.7 mg/dL and PTH level was normal; thus, the patient was diagnosed with neurological manifestation due to severe hypercalcemia caused by the lymph node metastasis of bladder cancer. Although he required endotracheal intubation for one night, his neurological manifestation improved as serum calcium levels decreased following the administration of loop diuretic, calcitonin, and zoledronic acid (Fig. 4). At 1 week after admission, his serum CCa level decreased to 12.7 mg/dL, and it was nadir; however, his serum calcium level increased again after the treatment, and malignant ascites with pleural effusion rapidly worsened (Fig. 3b). The patient died 22 days after admission.

Verbal informed consent was obtained from the patient family regarding the publication of the case details.

Discussion

Hypercalcemia is a paraneoplastic syndrome and is not rare in clinical practice; however, hypercalcemia associated with bladder cancer without bone metastasis or massive tumor is rare. Few case reports of hypercalcemia caused by cancer recurrence following radical cystectomy are available in the literature, and these cases appear with massive local recurrence, visceral metastasis, or leukemoid reaction. To the best of our knowledge, there is no report of hypercalcemia
caused by the lymph node metastasis of bladder cancer, which was the only detectable metastatic lesion in our case after performing radical cystectomy. A few published reports suggest that hypercalcemia associated with bladder cancer is related to the presence of high-grade UC or SCC component and the bladder cancer of this case comprised squamous differentiated UC.²,³,⁵

Hypercalcemia associated with invasive bladder cancer before treatment may be resolved by radical cystectomy. However, there is no preferred treatment for hypercalcemia associated with the recurrence or metastasis of bladder cancer following cystectomy owing to its rarity.⁶ Radiotherapy or chemotherapy for treating hypercalcemia may be effective, but the possibility remains unknown. Furthermore, it is difficult for patients undergoing treatment or those with hypercalcemia to receive these therapies simultaneously, like in the present case. We could not perform chemotherapy because of his further decreased renal function due to hypercalcemia and poor improvement of the general condition, although it would be an only treatment option for him.

Hypercalcemia is categorized according to the total serum calcium level: mild, 10.5–11.9 mg/dL; moderate, 12.0–13.9 mg/dL; and severe, ≥14.0 mg/dL. Severe hypercalcemia may be lethal, causing neurocognitive symptoms, such as epileptic seizures or coma, acute renal failure, and acute heart failure. Typically, fluid replacement and the use of loop

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**Fig. 3** Thin-sliced CT. Paraaortic lymph node enlargements (white arrows) were revealed at 12 days before the admission (a). Paraaortic lymph node further enlargements (white arrows), ascites, and pleural effusion were revealed at 9 days after the admission (b). Bone metastasis or local recurrence were not revealed by both CT.

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**Fig. 4** Clinical course and treatment of hypercalcemia. The changes in serum CCa levels or serum creatinine (Cr) were shown by green line or orange line, respectively. The results of CT were shown in Figure 3. I.V., intravenous; P.O., per os.
diuretic, glucocorticoid, calcitonin, zoledronic acid, and denosumab are recommended as hypercalcemia treatment. Additionally, hemodialysis may be considered for severe hypercalcemia. PTHrP, which is structurally similar to PTH, is considered a humoral factor for hypercalcemia and one of the main mechanisms underlying hypercalcemia associated with malignancy without bone metastasis. Indeed, we affirmed the existence of PTHrP in cancer cell cytoplasm of squamous differentiated UC in the present case, although his serum PTHrP level was not measured. PTHrP can enhance the renal tubular reabsorption of calcium while simultaneously increasing urinary phosphorus excretion and the RANKL secretion due to the stimulation of osteoblasts. Binding of RANKL to the receptor activator for nuclear factor-κB on an osteoclast causes osteoclastogenesis and bone resorption, and it increases the serum calcium level. Several drugs that can inhibit these mechanisms are used for treating hypercalcemia. Calcitonin downregulates osteoclast activity and promotes bone calcification, and glucocorticoids support these effects of calcitonin. Zoledronic acid, which is a bisphosphonate, reduces osteoclastic bone resorption due to the induction of osteoclast apoptosis and the inhibition of osteoblast activation. Denosumab, which is a human monoclonal antibody against RANKL, substantially reduces osteoclast activity and bone resorption. Although these treatments can produce short-term effects, the condition of most patients deteriorates unless bladder cancer is completely treated. Actually, our present case rapidly worsened according to re-elevation of serum calcium and reduced renal function after a short lull. According to the case reports in the literature, most patients with hypercalcemia associated with bladder cancer died within few months (Table S1).  

In conclusion, we reported the case of hypercalcemia caused by the lymph node metastasis of bladder cancer after radical cystectomy. Because there is no standard treatment for hypercalcemia caused by bladder cancer metastasis following cystectomy and because it is a lethal disease, further knowledge and clinical experience regarding hypercalcemia caused by bladder cancer are crucial.

Conflict of interest

The authors declare no conflict of interest.

References

1. Goldner W. Cancer-related hypercalcemia. J. Oncol. Pract. 2016; 12: 426–32.
2. Jagtap SV, Sarda SD, Demde RB, Huddedar AD, Jagtap SS. Primary squamous cell carcinoma of urinary bladder—a rare histological variant. J. Clin. Diagn. Res. 2015; 9: ED03–4.
3. Beltran H, Robinson BD, Tagawa ST. Primary squamous cell carcinoma of the urinary bladder presenting as peritoneal carcinomatosis. Adv. Urol. 2010; 2010: 179250.
4. Yoshida T, Suzumiya J, Katakami H et al. Hypercalcemia caused by PTHrP associated with lung metastasis from urinary bladder carcinoma: an autopsied case. Intern. Med. 1994; 33: 673–6.
5. Hirakawa K, Miyabe N, Kawakura K. Bladder carcinoma associated with hypercalcemia: report of 3 cases. Hinyokika Kiyo 1988; 34: 162–7.
6. Michel F, Gattegno B, Meyrier A et al. Paraneoplastic hypercalcemia associated with bladder carcinoma: report of 2 cases. J. Urol. 1984; 131: 753–5.
7. Matsuoka S, Miura Y, Kachi T et al. Humoral hypercalcemia of malignancy associated with parathyroid hormone-related protein producing transitional cell carcinoma of the ureter. Intern. Med. 1994; 33: 107–9.
8. Donovan PJ, Achong N, Griffin K, Galligan J, Pretorius CJ, McLeod DS. PTHrP-mediated hypercalcemia: causes and survival in 138 patients. J. Clin. Endocrinol. Metab. 2015; 100: 2024–9.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Reported cases in recent literature who presented with hypercalcemia associated with bladder cancer without bone metastasis.