CASE REPORT

Hungry bone syndrome secondary to prostate cancer successfully treated with radium therapy

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Accepted 17 June 2018

SUMMARY

A 50-year-old man with a history of prostate cancer with extensive bone metastasis and hypocalcaemia presented with muscle aches and cramps. Physical exam was significant for Chvostek's and Trousseau's sign. Laboratory assessment was consistent with profound hypocalcaemia. This was believed to be due to hungry bone syndrome secondary to advanced prostate cancer. He was treated with intravenous calcium, vitamin D and calcitriol. He also received three doses of radium²²³ therapy. After therapy, hypocalcaemic episodes resolved. Follow-up after 2.5 years showed continued resolution of hypocalcaemia.

BACKGROUND

Hungry bone syndrome (HBS) is due to excessive calcium and phosphorous sequestration in the bone, manifesting as hypocalcaemia and hypophosphataemia. It is most commonly seen as a postoperative complication of parathyroidectomy.¹ Prostate cancer is one of the most common cancers in men. It has a propensity to spread to the bone, forming osteoblastic metastasis. Advanced prostate cancer with osseous metastasis is a rare cause of HBS.^{1 2}

We present a case of HBS secondary to prostate cancer with extensive bone metastasis successfully treated with radium²²³ therapy resulting in the resolution of hypocalcaemia.

CASE PRESENTATION

A 50-year-old male patient with a history of prostate cancer and hypocalcaemia was admitted to the hospital for muscle aches and cramps. Physical examination showed a positive Chvostek's and Trousseau's sign. Laboratory assessment showed a profound hypocalcaemia of 4.7 (8.5–10.2 ng/dL). He was given 4 g of calcium gluconate and started on a calcium gluconate infusion.

He had initially presented to urology about 9 months earlier for evaluation of suspected prostate cancer. He had an 18-month history of back pain. Prostate-specific antigen (PSA) was found to be high at 928 (0–4 ng/dL). Bilateral orchiectomy was planned but cancelled as the patient was severely hypocalcaemic. He was treated with calcium carbonate 1500 mg three times a day and ergocalciferol 50 000 units weekly for 12 weeks. Subsequently he was started on lupron, prednisone, bicalutamide and ketoconazole.

INVESTIGATIONS

Laboratory assessment done for the evaluation of hypocalcaemia showed low vitamin D, elevated

1,25-dihydroxycholecalciferol and parathyroid hormone (PTH) (table 1).

Bone scan revealed diffuse skeletal uptake through the axial and appendicular skeleton consistent with extensive osseous metastasis and absent uptake in the kidneys (superscan pattern) (figure 1). MRI of the spine showed metastasis of the cervical, thoracic and lumbar spines.

TREATMENT

During this admission hypocalcaemia was persistent, necessitating the administration of multiple doses of intravenous calcium and use of ergocalciferol (50 000 units twice weekly) and calcitriol (1 µg twice daily). It was believed that hypocalcaemia was due to sequestration of calcium in the bone by osteoblastic metastasis. Since there was a history of hypocalcaemia and no profound change in the calcium status after administering denosumab, this was not believed to be denosumab-induced hypocalcaemia.

He received three cycles of radium²²³ dichloride therapy over a period of 2 months for the treatment of his metastatic prostate cancer.

OUTCOME AND FOLLOW-UP

Hypocalcaemic episodes resolved after radium²²³ therapy (figure 1). Bone scan was repeated 18 months later; however, it did not show any significant changes (figure 2). Follow-up at 2.5 years showed no recurrence of hypocalcaemia, and he was on calcium carbonate 600 mg daily but off vitamin D analogues.

DISCUSSION

We searched PubMed using the following keywords: hypocalcemia, prostate cancer. We restricted our search to publications in 'English' and involving 'Human subjects'. Abstracts of meetings and unpublished results were not included in our study. The last search was done on 27 December 2017. The initial

Table 1 Laboratory assessment on admission

Serum calcium (8.6–10.2 mg/dL)	4.7
Plasma albumin (3.5–5.5 g/dL)	3.8
25(OH) cholecalciferol	17
Parathyroid hormone (15–65 pg/mL)	117.3
1,25(OH) cholecalciferol (18–64 pg/mL)	175
24-hour urinary calcium (mg/24 hours)	<0.8
Phosphorous (2.7–4.5 mg/dL)	2.5
eGFR (estimated glomerular filtration rate) (>60 mL/min/1.73 m ²)	>60
Sodium (135–145 mEq/L)	138
Potassium (3.5–5.5 mEq/L)	4.1

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To cite: Garla VV, Salim S, Kovvuru KR, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225039

Calcium trend before and after Radium²²³ therapy

Figure 1 Serum calcium trend before and after radium²²³ therapy.

search resulted in 87 articles, and of these only 11 reported hypocalcaemia secondary to osseous metastasis from prostate cancer and thus were included (table 2).

Lethargy was the presenting symptom in 3 of the 11 cases, and back pain in 2 of the 11 cases. Four of the 11 patients died within 4 months, and long-term follow-up was unknown in all other patients. Eucalcaemia was achieved only in one patient at discharge (12 weeks).

HBS is characterised by hypocalcaemia and hypophosphataemia. It was first described in 1950 by Albright and Reifstein in a post-parathyroidectomy patient.³ It is typically seen after parathyroidectomy done either for primary hyperparathyroidism or secondary hyperparathyroidism or parathyroid carcinoma.⁴ Hypocalcaemia in the setting of prostate cancer is most commonly due to the use of bisphosphonates or Receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors. However, rarely, it can be seen in

metastatic prostate carcinoma secondary to calcium and phosphorous sequestration by osteoblastic bone metastasis (table 2).^{5–15}

Various theories have been put forth to explain the pathogenesis of osteoblastic metastasis seen in prostate cancer (figure 3). Metastatic prostate cancer cells produce various osteoblast-stimulating substances like platelet-derived growth factor, transforming growth factor- β (TGF- β), fibroblast growth factor and bone morphogenetic protein, which result in increased bone formation. In addition PSA can activate TGF- β and insulin-like growth factors by releasing them from their inhibitory binding proteins.¹⁶ Parathyroid-related peptide (PTHrp) has several physiological functions, including transfer of calcium through the placenta and inhibiting osteoclastic resorption. PSA also inactivates PTHrp by cleaving their amino terminal, and this can result in the destruction of the bone matrix and potentially increase tumour invasiveness.¹⁷

Hypocalcaemia can present as muscle spasms, tetany, seizures, lethargy paraesthesias and cardiac arrhythmias. The development of symptoms depends on the rapidity of the fall and the chronicity. As mentioned in the literature review, lethargy can be a presenting symptom and potentially can be falsely attributed to either the use of narcotics or renal failure in patients with advanced prostate cancer. Hypocalcaemia in malignancy could also be due to hypoparathyroidism, renal insufficiency, vitamin D deficiency, and prior administration of bisphosphonates or denosumab. A careful evaluation for the above factors needs to be done before ascribing the hypocalcaemia to be due to osteoblastic metastasis.

Treatment of HBS is to normalise the calcium levels using calcium and vitamin D supplementation. Intravenous calcium is recommended for patients with symptoms and long QTc interval on ECG. Calcium gluconate is the preferred intravenous formulation as calcium chloride can cause tissue necrosis on extravasation. Oral supplementation with either calcium carbonate or citrate is recommended for mild hypocalcaemia. Concomitant vitamin D deficiency and hypomagnesaemia need to be treated as well.

About 80%–90% of patients with prostate cancer respond to androgen deprivation therapy, while the remaining 10%–20% are

Figure 2 Bone scan before and after radium²²³ therapy.

Table 2 Literature review

Study number	Authors	Presenting symptoms	Treatment	Outcome
1	Smallridge <i>et al</i> ⁵	Asymptomatic.	DES. Bilateral orchidectomy. TURP. ERT. Cyclophosphamide. 5-FU.	Radiological progression of metastatic disease.
2	Szentirmai <i>et al</i> ⁶	Lethargy.	None.	Died in 2 weeks.
3	Tandon and Rizvi ⁷	Unknown.	Goserelin. Leuprolide.	Hypocalcaemic on discharge.
4	Fokkema <i>et al</i> ⁸	Lethargy.	Leuprorelin. Bicalutamide.	Died in 4 months.
5	Rizzo <i>et al</i> ⁹	Lethargy.	ADT.	Died in 2 months.
6	Pusulari <i>et al</i> ¹⁰	Back pain and fatigue.	None.	Unknown.
7	Yener <i>et al</i> ¹¹	Tetany and anorexia.	TURP. Goserelin. Bicalutamide.	Eucalcaemic after 12 weeks.
8	Riveros <i>et al</i> ¹²	Bone pain.	ADT. Docetaxel. Mitoxantrone. Abiraterone. Zoledronic acid.	Died in 3 weeks.
9	Lim <i>et al</i> ¹³	Seizures.	Calcitriol.	Unknown.
10	Kabadi ¹⁵	Back pain.	Prostate resection. Bilateral orchidectomy. DES. ERT.	Calcium and phosphorous normalised.
11	Kukreja <i>et al</i> ¹⁴	Not mentioned.	Calcium and magnesium supplementation.	Unknown.

5-FU, 5-fluorouracil; ADT, androgen deprivation therapy; DES, diethylstilbestrol; ERT, external radiotherapy; TURP, transurethral resection of prostate.

Figure 3 Pathogenesis of osteoblastic metastasis. BMP, bone morphogenetic protein; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IGF-BP, insulin derived growth factor binding protein; PDGF, platelet derived growth factor; PSA, prostate-specific antigen; PTHrP, parathyroid-related peptide; TGF- β , transforming growth factor- β .

labelled as having castration-resistant prostate cancer (CRPC).¹⁸ Radium²²³ is a radiopharmaceutical primarily used in the treatment of CRPC. It is an alpha-emitting radiopharmaceutical which forms complexes with hydroxyapatite in bone metastasis. This, combined with its high-intensity energy release and short range, makes it ideal to be used in the treatment of metastatic prostate cancer.¹⁹ Radium²²³ therapy has been proven to increase quality of life,

survival and symptomatic skeletal-related events (SRE) in patients with CRPC and symptomatic bone metastasis.²⁰

To our knowledge this is the first case of HBS secondary to prostate cancer treated with radium²²³ therapy which has resulted in the resolution of hypocalcaemia. Further research is needed to evaluate whether this may be an alternate to bisphosphonates in patients with extensive bone metastasis to prevent SRE.

Learning points

- Hypocalcaemia secondary to hungry bone syndrome (HBS) is a rare complication of prostate cancer with osseous metastasis.
- Physicians need to have a high index of suspicion as the presentation of hypocalcaemia in the terminal stages of cancer may be non-specific but life-threatening.
- Although no specific guidelines exist for the management of HBS, the treatment consists of replenishing the calcium deficit using calcium (oral and intravenous) and vitamin D analogues.
- Bisphosphonates and Receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors, which are used to prevent symptomatic skeletal-related events in prostate cancer with bone metastasis, can aggravate hypocalcaemia; therefore, calcium needs to be frequently monitored and supplemented as needed.
- To our knowledge this is the first case where radium²²³ dichloride has been used and has prevented further severe hypocalcaemic episodes, and more research is needed in this direction to evaluate if this is a viable therapy for HBS secondary to metastatic prostate cancer.

Contributors VVG was involved in writing the case description. SS and KRK were involved in writing the discussion section. AS is the senior author involved in editing the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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