Case Reports

Ref: Ro J Med Pract. 2021;16(4)
DOI: 10.37897/RJMP.2021.4.24

Not just weight loss

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Abstract

Renal cancer (RC) – associated increased calcium is rather frequent among cases of kidney neoplasia; it may be the first sign of presentation that allows the detection of the malignancy; typically representing a poor prognostic factor. Weight loss is part of the panel underlying hypercalcemia-related signs, but also of the malignancy-associated phenotype. We aim to introduce a male case who was admitted for a clinical picture (including weight loss) correlated with alarming high calcium levels; the biochemistry anomaly was actually a paraneoplastic syndrome due to RC. When admitted as emergency, the assays revealed hypercalcemia of 16.9 mg/dl (normal levels between 8.4 and 10.2 mg/dl) with low PTH (Parathormone) and high CrossLaps as bone turnover marker of resorption. Intravenous contrast computed tomography showed a large left retroperitoneal tumor (involving the kidney and adrenal gland) with iodophil pattern, and post-contrast heterogeneous structure of 8.06/11.09 cm (axial), 10.58/12.16 cm (coronal - reconstruction), 9.12/10.59 cm (sagittal - reconstruction), also associating a mixt structure and micro-calcifications as well as hypodense areas. Whole body scintigrame did not show metastasis. The calcium levels were controlled under subcutaneous denosumab 60 mg in addition to IV fluids replacement; then the patient was referred to nephrectomy; post-operative confirmation confirmed a clear cell renal cell carcinoma (T4N1Mx). A normalization of calcium and PTH levels was found immediately after surgery. Unintentional weight loss might become a valuable tool in order to assess a routine biochemistry panel that will detect hypercalcemia. Low PTH represents the next step in order to further look for a tumor. Symptomatic control of hypercalcemia in addition to targeted approach of originating tumor are essential to improve the outcome.

Keywords: weight loss, hypercalcemia, malignancy-related hypercalcemia, calcium, parathormone, tumor, parathyroid gland, kidney cancer

Introduction

Calcium metabolism and kidney status are linked through renal complications of primary hyperparathyroidism (like kidney stones etc.), renal hyperparathyroidism that is associated with long standing renal failure, as well as malignancy-related hypercalcemia accompanying a renal cancer (1,2). At the point when hypercalcemia becomes symptomatic, the renal tumor might be already diagnosed or not (3,4). Among the cases of cancer-related hypercalcemia, this is a rare cause opposite to other cancers originating from breast...
or lungs or even some particular types of neuroendocrine neoplasia (5,6,7). Weight loss is part of the panel underling hypercalcemia-related signs, but also of malignancy-related clinical picture (8).

We aim to introduce a male case who was admitted for a clinical picture (including weight loss) correlated with alarming high calcium levels; the biochemistry anomaly was actually a paraneoplastic syndrome due to a renal cancer. The patient’s consent is signed.

**CASE PRESENTATION**

**Admission**

This is a 63-year old male who is admitted for weight loss (14 kg/6 months), high blood pressure controlled under adequate medication with a 1-year history of mild hypercalcemia complicated as acute type (requiring admission as emergency).

**Assessments as emergency**

When admitted as emergency, the assays showed hypercalcemia with low PTH (parathormone) and high CrossLaps as bone turnover marker of resorption (Table 1).

**TABLE 1. Hypercalcemia on a 63-year old patient who is admitted for massive, unintentional weight loss within the last few months**

| Parameter                        | Value | Normal       | Units |
|----------------------------------|-------|--------------|-------|
| Total serum calcium              | 16.9  | 8.4-10.2     | mg/dl |
| Serum phosphors                  | 2.4   | 2.3-4.7      | mg/dl |
| 25OHD (25-hydroxyvitamin D)      | 17    | >30          | ng/ml |
| PTH (parathormone)               | 1.2   | 16-65        | pg/ml |
| CrossLaps (bone resorption marker)| 1.48 | 0.33-0.782   | ng/ml |
| Osteocalcin (bone formation marker)| 47  | 15-46        | ng/ml |
| 1,25 (OH)D2                      | 96    | 18-79        | ng/ml |
| Alkaline phosphatase             | 173   | 8-105        | U/l   |

**Imaging assays**

Abdominal ultrasound showed a left kidney tumor at superior pole, with inhomogeneous structure, associating necrosis and calcifications (of 10.34 by 10.69 by 9.11 cm as largest diameters) (Figure 1).

IV (intravenous) contrast CT (computed tomography) showed a large left retroperitoneal tumor (involving the kidney and adrenal gland) with iodophil pattern, and post-contrast heterogeneous structure of 8.06/11.09 cm (axial), 10.58/12.16 cm (coronal - reconstruction), 9.12/10.59 cm (sagittal - reconstruction), also associating a mixt structure (liquid/solid) and micro-califications as well as hypodense areas (Figure 2A,B,C).
Whole body bone scintigrame showed no distance metastasis, but a renal stasis at left upper kidney level (Figure 3).

**FIGURE 3.** Negative whole body scintigram for bone metastases

**Follow-up**

The calcium levels were controlled under subcutaneous denosumab 60 mg in addition to IV fluids replacement; then he was referred to nephrectomy; post-operatory confirmation showed a clear cell renal cell carcinoma (T4N1Mx). A normalization of calcium and PTH levels was found immediately after surgery (Figure 4). Lifelong follow-up is essential according to a multidisciplinary team.

**DISCUSSIONS**

Renal cancer-associated increased calcium is actually frequent among cases of kidney cancer; it may be the first sign of presentation that allows the detection of the malignancy; typically representing a poor prognostic factor (9,10). Multiple mechanisms are involved in this condition: humoral subtype due to the production of PTHrP (parathormone related peptide), one third of cases associate bone metastasis (which may also cause pain, fragility fractures, spinal cord compression depending on site) and even anomalies of vitamin D metabolism (11,12). PTH is typically suppressed (unless an ectopic production of PTH is the underlying cause, not extra PTHrP), while PTHrP might become a useful tool to differentiate humoral mechanism (with high PTHrP) from osteolytic metastases (with low PTHrP) (13,14). However, PTHrP assessment in daily practice is not routinely feasible (15,16). Non PTHrP-related molecules that cause increased calcium levels are also interleukins as, for instance, IL-6, IL-1 as well as TNF-α, transforming growth factors alpha & beta (17,18). PTHrP uses PTH receptor type 1 of PTH which explains calcium anomalies; but it does not stimulate the production of active form of vitamin D as PTH while PTHrP shares an inhibitor feedback with PTH (19). Symptomatic control of hypercalcemia in addition to targeted approach of originating tumor are essential to a good outcome (20).
CONCLUSIONS

Unintentional weight loss might become a valuable tool in order to assess a routine biochemistry panel that will detect hypercalcemia. Low PTH represents the next logical step in order to further look for a tumor, for instance, a kidney cancer.

REFERENCES

1. Islam AK. Advances in the diagnosis and the management of primary hyperparathyroidism. *Ther Adv Chronic Dis.* 2021 Jun;11:12:20406223211015965.
2. Palumbo VD, Palumbo VD, Damiano G, Messina M, Fazzotta S, Lo Monte G, Lo Monte AI. Tertiary hyperparathyroidism: a review. *Clin Ter.* 2021 May 5;172(3):241-246.
3. Dandurand K, Ali DS, Khan AA. Primary Hyperparathyroidism: A Narrative Review of Diagnosis and Medical Management. *J Clin Med.* 2021 Apr 9;10(8):1604.
4. Oberger Marques JV, Moreira CA. Primary hyperparathyroidism. *Best Pract Res Clin Rheumatol.* 2020 Jun;34(3):101514.
5. Efthymiou C, Spyroatos D, Kontakiotis T. Endocrine paraneoplastic syndromes in lung cancer. *Hormones* (Athens). 2018 Sep;17(3):351-358.
6. Sandru F, Carsote M, Valea A, Albu SE, Petca RC, Dumitrascu MC. Somatostatinoma: Beyond neurofibromatosis type 1 (Review). *Exp Ther Med.* 2020;20(4):3383-3388.
7. Carsote M, Paun S, Neamtu MC, Avramescu ET, Iosif C, Terzea D, Constantinoiu S, Daniciulescu Miulesc R, Neamtu OM, Poiana C. The immunohistochemistry aspects in two cases of neurofibromatosis-associated abdominal tumors, Rom Journal Morphol Embryol. 2012;53(2):401-405.
8. Gaafar OU, Zimmers TA. Nutrition challenges of cancer cachexia. *J Pen Enteral Nutr.* 2021 Nov;45(S2):16-25.
9. Sternlicht H, Glezerman IG. Hypercalcemia of malignancy and new treatment options. *Ther Clin Risk Manag.* 2015 Dec 4;11:1779-88.
10. Karki S, Galiveeti S, Leung V. Hypercalcemia and Renal Mass: A Diagnostically Challenging Case. *Cureus.* 2021 Jul 29;13(7):e16718.
11. Gomes Linda S, Kulak CA, Costa TM, Vasconcelos EC, Carvalho Md, Borba VZ. Association of primary hyperparathyroidism and humoral hypercalcemia of malignancy in a patient with clear cell renal carcinoma. *Arch Endocrinol Metab.* 2015 Feb;59(1):84-8.
12. Goltzman D. Pathophysiology of Hypercalcemia. *Endocrinol Metab Clin North Am.* 2021 Dec;50(4):591-607.
13. Motlaghzadeh Y, Bilezikian JP, Sellmeyer DE. Rare Causes of Hypercalcemia: 2021 Update. *J Clin Endocrinol Metab.* 2021 Oct 21;106(11):3113-3128.
14. Edwards CM, Johnson RW. From Good to Bad: The Opposing Effects of PTHrP on Tumor Growth, Dormancy, and Metastasis Throughout Cancer Progression. *Front Oncol.* 2021 Mar 22;11:644303.
15. Gurram PR, Castillo NE, Esquer Garrigos Z, Vijayvargiya P, Abu Saleh OM. A Dimorphic Diagnosis of a Pleomorphic Disease: An Unusual Cause of Hypercalcemia. *Am J Med.* 2020 Nov;133(11):e659-e662.
16. Lai NK, Martinez D. Physiological roles of parathyroid hormone-related protein. *Acta Biomed.* 2019 Dec 23;90(4):510-516.
17. Asonitis N, Angelouisi A, Zafeiris C, Lambrou GI, Donias I, Kassi E. Diagnosis, Pathophysiology and Management of Hypercalcemia in Malignancy: A Review of the Literature. *Horm Metab Res.* 2019 Dec;51(12):770-778.
18. Zhang R, Li J, Assaker G, Camirand A, Sabri S, Karaplis AC, Kremer R. Parathyroid Hormone-Related Protein (PTHrP): An Emerging Target in Cancer Progression and Metastasis. *Adv Exp Med Biol.* 2019;1164:161-178.
19. Goltzman D. Nonparathyroid Hypercalcemia. *Front Horm Res.* 2019;51:77-90.
20. Sheehan M, Tanimu S, Tanimu Y, Engel J, Onilío A. Cinacalcet for the Treatment of Humoral Hypercalcemia of Malignancy: An Introductory Case Report with a Pathophysiologic and Therapeutic Review. *Case Rep Oncol.* 2020 Mar 25;13(1):321-329.