Journal of Clinical and Translational Endocrinology: Case Reports 29 (2023) 100151

Contents lists available at ScienceDirect

Journal of Clinical and Translational Endocrinology: Case Reports

journal homepage: www.elsevier.com/locate/jctecasereports.com

Metastatic parathyroid carcinoma: A tale of refractory hypercalcemia

Johns T. Johnson [a], Arun George [b], Junita Rachel John [c], Nishok David [d], Ashish Singh [e], Deepak Abraham [f], Birla Roy Gnanamuthu [d], Nihal Thomas [a,*]

[a] Department of Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India
[b] Department of General Pathology, Christian Medical College, Vellore, Tamil Nadu, India
[c] Department of Nuclear Medicine, Christian Medical College, Vellore, Tamil Nadu, India
[d] Department of Cardiothoracic Surgery, Christian Medical College, Vellore, Tamil Nadu, India
[e] Department of Medical Oncology, Christian Medical College, Vellore, Tamil Nadu, India
[f] Department of Endocrine Surgery, Christian Medical College, Vellore, Tamil Nadu, India

ARTICLE INFO

Keywords:
Refractory hypercalcemia
Parathyroid carcinoma
Denosumab
Scintigraphy
Hyperparathyroidism

ABSTRACT

Background/objective: Parathyroid carcinoma is a rare entity presenting as parathyroid hormone (PTH) dependent hypercalcemia. Our objective was to report a case of metastatic parathyroid carcinoma in a middle-aged woman, who presented with refractory hypercalcemia and the strategies we used to induce remission.
Case report: A 47 year old lady with a past history of a left superior parathyroid adenoma excision, presented with recurrent PTH dependent hypercalcemia. An ultrasonography of the neck and parathyroid scintigraphy were normal. Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scan picked up metabolically active lesions in the lingular segment of the left lung and another lesion in the diaphragmatic pleura of the left hemithorax. Following metastectomy of the lung nodules, she developed symptomatic hypocalcemia with a reduction of serum PTH levels. The histopathology and immunoprofile were consistent with metastatic carcinoma. The PTH levels started rising 2 months after the surgery, with calcium levels remaining stable on cinacalcet, denosumab and cabozantinib.
Discussion: Parathyroid carcinoma is a rare endocrine malignancy with typically indolent, yet progressive course. There is no consensus on the treatment and follow-up of parathyroid carcinoma, owing to its rarity. The greatest likelihood of cure is achieved if complete resection of all malignant tissue is successful at the time of initial surgery. Surgical reduction of the tumor mass may also render the patient's hypercalcemia more amenable to medical treatment with hydration, potent intravenous bisphosphonates, denosumab and cinacalcet.
Conclusion: Surgical debulking of the metastatic lesions, followed by medical management of hypercalcemia offers promising results in the management of metastatic parathyroid carcinoma.

1. Introduction

Parathyroid carcinoma (PTC) is an uncommon clinical entity presenting as PTH-dependent hypercalcemia. It may occur in the context of a genetic syndrome or sporadically. In patients with sporadic primary hyperparathyroidism (PHPT), the prevalence of PTC is reported to be less than 1% [1]. Given the considerable overlap in the clinical and pathological features between benign parathyroid disease and PTC, diagnosis and management are often challenging [3]. This case discussion highlights the presentation of metastatic PTC in a middle-aged woman, who presented with refractory hypercalcemia and the strategies that were used to induce remission of the disease.

2. Case report

A 47-year-old homemaker presented to our center for the evaluation of refractory hypercalcemia. She was initially evaluated elsewhere in 2013 with a history of generalized body aches, difficulty in walking, and fragility fracture of her left humerus and was found to have elevated serum calcium (15mg/dl) with elevated PTH (4000pg/ml) and alkaline phosphatase (746 U/L). Imaging studies were suggestive of a left

* Corresponding author. Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India.
E-mail addresses: johnstj321@gmail.com (J.T. Johnson), arungeo5@gmail.com (A. George), junitajohn@yahoo.co.in (J.R. John), nishok.david@gmail.com (N. David), todrashish@gmail.com (A. Singh), abrahamdt@gmail.com (D. Abraham), roygnanamuthu@yahoo.co.in (B.R. Gnanamuthu), nihal_thomas@yahoo.com (N. Thomas).

https://doi.org/10.1016/j.jecr.2023.100151
Received 28 April 2023; Received in revised form 18 July 2023; Accepted 8 August 2023
Available online 9 August 2023

Abbreviations

GATA 3	GATA binding protein 3
PAX 8	Paired box gene 8
RANK	Receptor activator of nuclear factor kappa beta
TTF 1	Thyroid Transcription Factor 1
ER	Estrogen Receptor
PR	Progesterone Receptor

superior parathyroid adenoma (no reports available) and she underwent a focused left superior parathyroidectomy in November 2013, at the same center. Postoperatively she developed symptomatic hypocalcemia, requiring active vitamin D and oral calcium supplements, which were continued till 2015 (the histopathology reports and postoperative PTH reports were not available for our scrutiny).

She was asymptomatic till 2019 when she again started having diffuse body aches. On evaluation at her hometown, she was found to have a recurrence of PTH dependent (PTH: 1261pg/ml) hypercalcemia (albumin corrected serum calcium: 11.6mg/dl). Ultrasound of the neck, parathyroid scintigraphy, and 4D CT were negative for a parathyroid adenoma. The FDG PET-CT picked up a metabolically active lesion in the upper lobe of the left lung. FNAC from the lesion and wedge resection of the lesion (done elsewhere) were reported as inconclusive. She continued to have persistent body aches with hypercalcemia and received 3 doses of injection zoledronic acid at her hometown between March 2021 and October 2021. In view of persistent hypercalcemia, she was started on cinacalcet and was then referred to our center for further evaluation and management.

On examination, she was found to have bilateral proximal myopathy in the lower limbs. Examination of the neck and systemic examination was unremarkable. Investigations were suggestive of PTH-dependent hypercalcemia with high bone turnover (Table 1). Serum prolactin (10.9ng/ml) and gastrin levels were normal.

Ultrasound of the neck and parathyroid scintigraphy done at our center were normal. The FDG PET CT showed metabolically active rounded lesion in the lingular segment of the left lung, in contact with the parietal pleura (Fig. 1) and another broad based lesion in the diaphragmatic pleura of the left hemi-thorax.

After multidisciplinary discussions involving experts from endocrine surgery, cardiothoracic surgery, nuclear medicine, and endocrinology, a left postero-lateral thoracotomy was done in November 2021. Intraoperatively a 3cm nodule in the lingular segment, another 3cm nodule on the diaphragmatic surface (corresponding to the metabolically active lesions in the FDG PET CT), and multiple other punctate nodules on the parietal pleura overlying the aorta were detected. Metastectomy of the nodules at the lingula, diaphragm, and parietal pleura was done. On postoperative day 3, she developed symptomatic hypocalcemia (Serum calcium 7.68mg/dl) and the serum PTH decreased to 136.5pg/ml. She was started on oral calcium supplements. Histopathological examination of the metastatic nodules revealed a solid neoplasm composed of uniform polygonal cells with moderately pleomorphic nuclei, finely granular chromatin, and moderate amounts of pale eosinophilic to clear cytoplasm (Fig. 2). The immunoprofile (Fig. 3) was suggestive of a neoplasm of parathyroid origin, with the cells staining positive for GATA3, chromogranin, synaptophysin (patchy), CK7 (patchy), and PAX-8 (patchy weak); while being negative for CK20, TTF1, p40, ER and PR.

She was discharged on oral calcium supplements. Subsequent follow-up after 3 months showed a rising PTH (1133pg/ml) with recurrence of hypercalcemia (12.68mg/dl). In view of the metastatic nature of the disease, a medical oncology opinion was taken and she was initiated on cabozantinib 20mg once daily. Hypercalcemia was managed with 3 monthly denosumab and daily oral cinacalcet (30mg/day). At the last follow-up in January 2023, she was clinically asymptomatic with a stable current serum calcium of 9.15mg/dl.

Table 1
Biochemical parameters.

Parameter	Normal	Observed value
Albumin corrected calcium(mg/dl)	8.3–10.4	14.4
Serum phosphate (mg/dl)	2.5–4.6	2.4
25-hydroxy vitamin D (ng/ml)	23.7	>30
Parathyroid hormone (pg/ml)	18.4–80.1	1348
Alkaline phosphatase (U/L)	40–125	305
P1NP[a] (ng/ml)	15.1–58.3	1020
CTX[b] (pg/ml)	137–573	>6000

[a] Procollagen 1 Intact N-Terminal Pro-peptide.
[b] C-telopeptide of type 1 Collagen.

3. Discussion

With a prevalence of less than 1% among patients with sporadic primary hyperparathyroidism (PHPT), parathyroid carcinoma is a rare endocrine disorder [1]. The exact pathogenesis of PTC remains unclear. It may either occur sporadically or in the context of a genetic endocrine syndrome [Multiple Endocrine Neoplasia type 1 and type 2A, familial isolated hyperparathyroidism, and hyperparathyroidism/jaw tumor syndrome [2]]. PTC poses a diagnostic challenge, given the absence of specific characteristics that allow the distinction of malignant from benign parathyroid disease during the initial presentation [3]. The diagnosis of PTC is often made only when local recurrence and/or metastases occur. The common sites of metastases include the lung (40%), cervical nodes (30%), and liver (10%) [4]. Rarely, distant metastases to bone, pericardium, pleura, and pancreas can also occur. In most instances, the markedly elevated serum PTH levels and hypercalcemia cause the clinical manifestations of parathyroid malignancy, rather than the local infiltration and distant metastases.

The course of PTC is typically indolent but usually progressive. There is no consensus on the management of PTC, given its rarity. The greatest likelihood of curing PTC is achieved by the complete resection of all the malignant tissue at the time of initial surgery. The management of recurrent or metastatic parathyroid carcinoma is also primarily surgical. Even though the resection of the malignant parathyroid tissue or metastatic foci is rarely curative, their removal may produce varying periods of normocalcemia ranging from many months to years [3]. Debulking the tumor mass through surgery may also render the patient's hypercalcemia more amenable to medical treatment. In situations like a widely metastatic parathyroid carcinoma, where the surgical options are exhausted, medical management of hypercalcemia forms the cornerstone of treatment. Management options include hydration, potent intravenous bisphosphonates [5], RANK-ligand inhibitor (denosumab) [6], and calcimimetics (cinacalcet) [7]. Chemotherapy and radiotherapy are of limited use, while there is a paucity of data on the efficacy of targeted molecular therapy in the management of metastatic PTC [8]. Most patients with recurrent and/or metastatic PTC ultimately succumb to the effects of hypercalcemia rather than to distant metastases or direct tumor invasion [9].

4. Conclusion

Parathyroid carcinoma is a rare clinical entity presenting as parathyroid hormone-dependent hypercalcemia. The course of parathyroid carcinoma is typically indolent but progressive. Due to the rarity, there is no general consensus on its treatment and follow-up. Surgical debulking of the metastatic lesions, followed by medical management of hypercalcemia offers promising results in the management of metastatic parathyroid carcinoma.

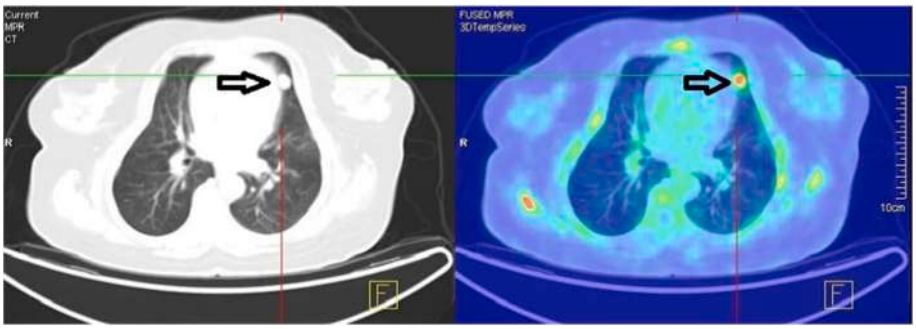

Fig. 1. FDG PET-CT showing metabolically active left lingular nodule.

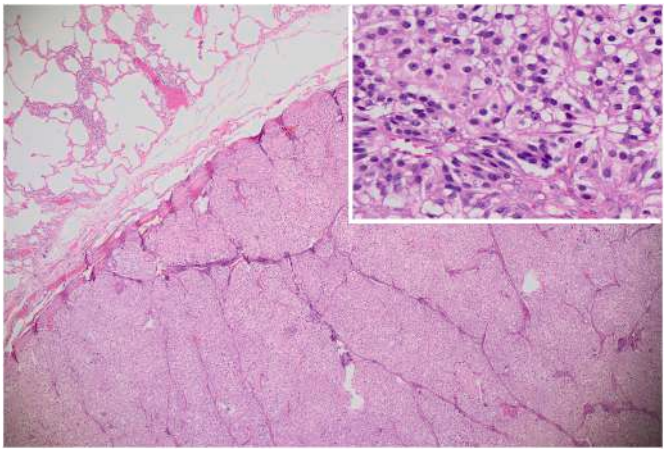

Fig. 2. Lung parenchyma (on the upper left) infiltrated by a circumscribed tumor arranged as nests, separated by delicate fibrovascular septae.(H&E, 100X) [Inset shows uniform
polygonal cells with moderately pleomorphic nuclei (H&E, 400X)].

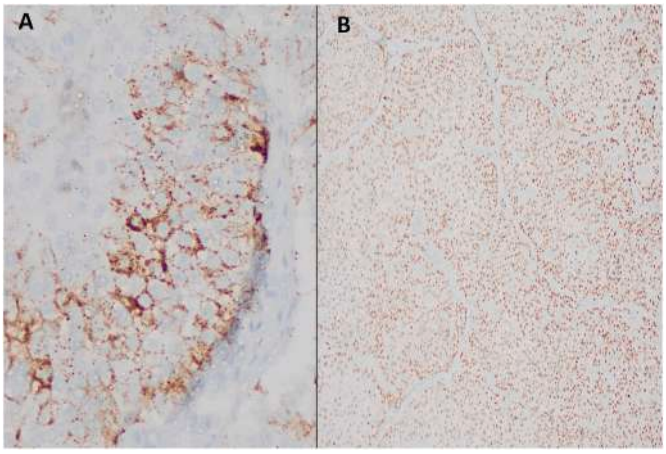

Fig. 3. Immunoreactivity for A) chromogranin A and B) GATA 3.

Sources of support

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Patient consent was obtained prior to writing up of this article.

References

[1] Givi B, Shah JP. Parathyroid carcinoma. Clin Oncol 2010 Aug 1;22(6):498–507.
[2] Marcocci C, Cetani F, Rubin MR, Silverberg SJ, Pinchera A, Bilezikian JP. Parathyroid carcinoma. J Bone Miner Res 2008 Dec;23(12):1869–80.
[3] Selvan B, Mazhuvanchary Jacob P, Seshadri M, Thomas N, Paul T, Abraham D, et al. High index of clinical suspicion with optimal surgical techniques and adjuvant radiotherapy is critical to reduce locoregional disease progression in parathyroid carcinoma. Am J Clin Oncol 2012 Jan 19:36.
[4] Shane E. Clinical review 122: parathyroid carcinoma. J Clin Endocrinol Metab 2001 Feb;86(2):485–93.
[5] Bowyer SE, White AM, Ransom DT, Davidson JA. Resistant hypercalcaemia in metastatic parathyroid carcinoma. Med J Aust 2013;198(10):559–61.
[6] Karuppiah D, Thanabalasingham G, Shine B, Wang LM, Sadler GP, Karavitaki N, et al. Refractory hypercalcaemia secondary to parathyroid carcinoma: response to high-dose denosumab. Eur J Endocrinol 2014 Jul;171(1). K1-5.
[7] Silverberg SJ, Rubin MR, Faiman C, Peacock M, Shoback DM, Smallridge RC, et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. J Clin Endocrinol Metabol 2007 Oct 1;92(10):3803–8.
[8] Angelousi A, Dimitriadis GK, Zografos G, Nölting S, Kaltsas G, Grossman A. Molecular targeted therapies in adrenal, pituitary and parathyroid malignancies. Endocr Relat Cancer 2017 Jun 1;24(6):R239–59.
[9] Ferraro V, Sgaramella LI, Di Meo G, Prete FP, Logoluso F, Minerva F, et al. Current concepts in parathyroid carcinoma: a single Centre experience. BMC Endocr Disord 2019 May 29;19(Suppl 1):46.