Case Report

Parathyroid Carcinoma and Persistent Hypercalcemia: A Case Report and Review of Therapeutic Options

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Abstract

Parathyroid carcinomas are very uncommon, accounting for 0.1% to 5% of all causes of primary hyperparathyroidism. Parathyroid–jaw tumor syndrome, with a mutation in *HRPT2* that encodes parafibromin, is the most common genetic association. Unique features include aggressive clinical course and a lack of preoperative definitive diagnostic criteria. The authors report a case of a 33-year-old male with bilateral nephrocalcinosis, a left-sided neck mass, high calcium, very high parathormone level and a history of parathyroid adenectomy. Computed tomography and 99m-technetium methoxyisobutylisonitrile scan revealed a localized tumor in the left inferior parathyroid region. The patient underwent radical surgery, and histopathology revealed characteristic features of parathyroid carcinoma. Preoperative identification with clinical clues is very important to plan a more radical surgical approach, as both radiotherapy and chemotherapy are ineffective. Recurrence is common and mostly occurs within 2–3 years after surgery. Patient's age, histology and tumor DNA aneuploidy are predictors of survival. Hypercalcemia is controlled with calcimimetics, bisphosphonates and denosumab in inoperable cases. Furthermore, biologic therapy with parafibromin and telomerase inhibitors is under development.

Keywords: Nephrocalcinosis, parathyroid carcinoma, parathyroid–jaw tumour syndrome, primary hyperparathyroidism

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INTRODUCTION

Parathyroid carcinoma is an uncommon cause of primary hyperparathyroidism, accounting for 0.1% to 5% of all cases.[1] It is often under- or overdiagnosed because a lack of universal diagnostic criteria.[2] Many patients have a genetic predisposition to this tumor and have a more aggressive clinical course.[3] Clinical clues include presence of renal or bone disease; severe hypercalcemia (>14 mg/dl); very high intact parathormone (iPTH) level (more than five times the upper normal limit); the presence of lymph node and/or distant metastasis.[1] Radical surgery remains the treatment of choice; chemotherapy and radiotherapy have very limited role.[4,5]

Access this article online	
Quick Response Code:	Website: www.sjmms.net
	DOI: 10.4103/sjmms.sjmms_104_16

CASE REPORT

A 33-year-old male presented with bilateral dull-aching flank pain for 3 years. It was not associated with fever and urinary symptoms, and was not radiating from loin to groin. There was no history of passage of stones in the urine. He had a history of left inferior parathyroidectomy 3 years ago for the management of hypercalcemia. Previous reports suggested complete tumor removal (intraoperative iPTH after 15 min of tumor removal: 7.1 pg/ml). However, the patient was lost to follow-up, until presenting to us again

How to cite this article: Pramanik S, Ray S, Bhattacharjee R, Chowdhury S. Parathyroid carcinoma and persistent hypercalcemia: A case report and review of therapeutic options. Saudi J Med Med Sci 2018;6:115-8.

with recurrence after 3 years, and the biopsy report was not available. He did not have any history of jaw, pituitary or pancreatic tumors. There was no similar family history. On examination, vital signs and higher functions were normal. There was a small nodule measuring 2 × 2 cm in the left lower neck. The abdominal examination revealed no mass or organomegaly. Systemic examination was unremarkable.

Routine biochemistry including urea, creatinine, sodium, potassium and liver function tests were normal. Serum calcium was 13.7 mg/dl (albumin 4.2 g/dl), phosphorus 2.3 mg/dl and serum iPTH 1779 pg/ml, consistent with biochemical diagnosis of primary hyperparathyroidism. Computed tomography (CT) scan of the abdomen showed bilateral nephrocalcinosis [Figure 1]. CT scan of the neck revealed re-growth of the tumor (4.2 cm × 2.9 cm × 1.1 cm) in the previously operated left inferior parathyroid gland region, but the lymph nodes were not enlarged [Figure 2a]. 99m-technetium (^{99m}Tc) methoxyisobutylisonitrile scan with 20 mCi radiotracer at 3 h revealed a small fairly round-shaped area, with a mildly increased uptake of radiotracer below the lower pole of the left lobe of the thyroid [Figure 2b]. Further, there was no abnormal uptake elsewhere in the body. Based on the presentation and regrowth of the tumor, the possibility of parathyroid carcinoma was considered.

A radical operative procedure was planned, and the patient underwent left hemithyroidectomy with modified neck dissection. Histopathology revealed cellular atypia, pleomorphism of nuclei, prominent nucleoli, abundant eosinophilic cytoplasm [Figure 3a] and unequivocal capsular invasion [Figure 3b], further suggesting parathyroid carcinoma. The margins were free from the disease. At the time of reporting this case, the patient was planned for follow-up with regular ultrasound and serum calcium level monitoring. Genetic test for hyperparathyroidism–jaw tumor syndrome could not be performed owing to cost constraints.

DISCUSSION

Although parathyroid adenoma is a common cause of primary hyperparathyroidism, parathyroid carcinoma is rarely encountered in day-to-day practice.[1] It may occur sporadically[6] or in conjunction with familial hyperparathyroidism, hyperparathyroidism–jaw tumor syndrome or multiple endocrine neoplasia type 1 or 2A [Table 1].[7-11] Almost 40% of the patients present with a palpable neck mass; metabolic complications such as hypercalcemic crisis, bone or renal abnormalities are more common.[12] At the time of initial presentation, in

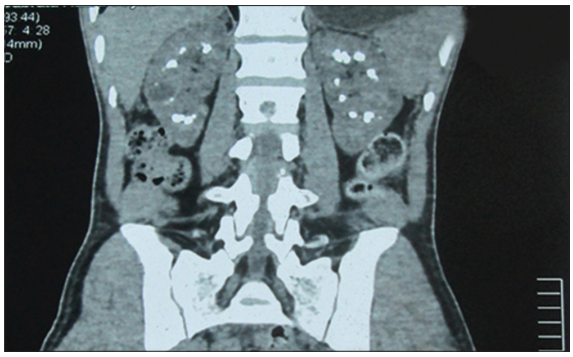

Figure 1: Computed tomography scan of abdomen (coronal section) showing bilateral nephrocalcinosis

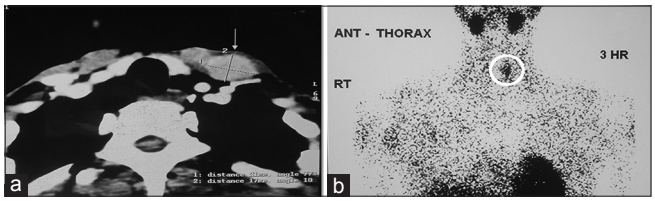

Figure 2: (a) Computed tomography scan showing a mass in the left lower part of the neck (white arrow); (b) Increased radiotracer uptake in 99m-technetium methoxyisobutylisonitrile scan at 3 h

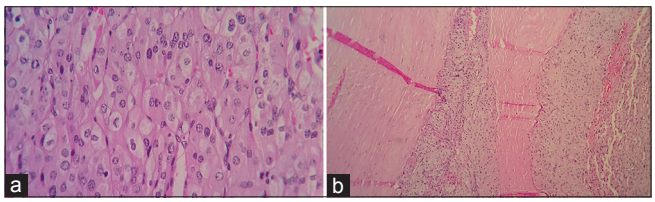

Figure 3: (a) Cellular atypia, pleomorphism of nuclei, prominent nucleoli, abundant eosinophilic cytoplasm (H and E, ×400); (b) Unequivocal capsular invasion (H and E, ×100)

15%–20% of the patients, the disease is found to have spread to regional lymph nodes. Distant metastasis is also common, mostly to lungs and bones.[6] Severe hypercalcemia (>14 mg/dl), very high iPTH (five times above the normal range) and palpable neck lymph node on presentation should raise suspicion.[1] No diagnostic criteria exist, but capsular invasion, angioinvasion, nuclear atypia, fibrosis, pleomorphic cells in a trabecular growth pattern and numerous mitotic figures on histology are characteristics, and the presence of locoregional spread or distant metastasis to lungs or bones confirms the diagnosis.[12,13] Surgical *en bloc* resection is the treatment of choice, as neither chemotherapy nor radiotherapy is effective. Clinical awareness is essential, as this leads to a more radical surgical approach. Almost 50% of the patients have recurrences or persistent disease, and the disease mostly recurs 2–3 years after the initial surgery,[1,12] as was with our case. Most recurrences are locoregional and functioning, and thus regular ultrasound monitoring and serum calcium, phosphate and albumin

Table 1: Genetic syndromes associated with parathyroid carcinoma

Syndrome	Gene involved	Components	Comments	References
HPTJT	HRPT2 (inactivating mutation) that encodes parafibromin	Ossifying fibromas of the jaw, cystic and neoplastic renal lesions, uterine tumors and parathyroid neoplasia	Autosomal dominant Most common mutation in patients with parathyroid carcinoma 15% of patients with this mutation have parathyroid carcinoma	[7,8]
Retinoblastoma, p53 mutation	RB1, p53 (inactivating mutation)		Increased chances of second malignancy	[9,10]
Multiple endocrine neoplasia 1	Menin	Pituitary tumor, pancreatic tumor and parathyroid adenoma	Only one small study found this mutation in 3 of 23 cases	[11]

HPTJT – Hyperparathyroidism-jaw tumor syndrome

measurements are necessary. However, nonfunctioning metastasis to bones, lungs and liver rarely occurs.[14] This disease has an overall mortality rate ranging from 51% to 78% at 10 years. Patient's age, characteristic of the histology and tumor DNA aneuploidy are predictors of survival, but tumor size or lymph node status at presentation are not.[15] The cause of death is usually from metabolic complications such as renal failure and rarely from the tumor burden. In cases of surgically inoperable parathyroid carcinoma, protocol-based chemotherapy or external beam radiation should be considered.[4,5] For the management of hypercalcemic crisis, intravenous bisphosphonates, calcimimetics or denosumab may be used, but they do not have any effect on tumor burden.[16,17] Novel therapy with biologic agents (e.g., gene products of parafibromin, telomerase inhibitors such as azidothymidine and immune therapy) has shown effectiveness in *in vitro* studies and may prove to be clinically useful in the future.[18]

CONCLUSION

In parathyroid carcinoma, recurrence is common. Presence of characteristic cellular features, capsular invasion and angioinvasion are diagnostic. *En bloc* resection is the treatment of choice, as neither chemotherapy nor radiotherapy is effective.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Acknowledgment

The authors would like to thank Dr. Pradip Mukhopadhyay, Department of Endocrinology, Institute of Post Graduate Medical Education and Research, Kolkata, for critical review of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

None to declare

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