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

Subhodip Pramanik, Sayantan Ray, Rana Bhattacharjee, Subhankar Chowdhury
Department of Endocrinology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India

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 of 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.\[4\] Radical surgery remains the treatment of choice; chemotherapy and radiotherapy have very limited role.\[5\]

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.
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 (99mTc) 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. It may occur sporadically or in conjunction with familial hyperparathyroidism, hyperparathyroidism–jaw tumor syndrome or multiple endocrine neoplasia type 1 or 2A [Table 1].

Almost 40% of the patients present with a palpable neck mass; metabolic complications such as hypercalcemic crisis, bone or renal abnormalities are more common. At the time of initial presentation, in 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. Severe hypercalcemia (>14 mg/dl), very high iPTH (five times above the normal range) and palpable neck lymph node on presentation should raise suspicion. 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. 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 as was with our case. Most recurrences are locoregional and functioning, and thus regular ultrasound monitoring and serum calcium, phosphate and albumin
measurements are necessary. However, nonfunctioning metastasis to bones, lungs and liver rarely occurs. 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. 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. For the management of hypercalcemic crisis, intravenous bisphosphonates, calcimimetics or denosumab may be used, but they do not have any effect on tumor burden. 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.

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

REFERENCES

1. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: An update and review. World J Surg 1991;15:738-44.
2. McKeown PP, McGarity WC, Sewell CW. Carcinoma of the parathyroid gland: Is it overdiagnosed? A report of three cases. Am J Surg Pathol 1984;147:292-8.
3. Favia G, Lumachi F, Polistina F, D’Amico DF. Parathyroid carcinoma: Sixteen new cases and suggestions for correct management. World J Surg 1998;22:1225-30.
4. Shane E. Parathyroid carcinoma. Curr Ther Endocrinol Metab 1994;5:522-5.
5. Chow E, Tsang RW, Brierley JD, Filice S. Parathyroid carcinoma – The Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys 1998;41:569-72.
6. Kebebew E. Parathyroid carcinoma. Curr Treat Options Oncol 2001;2:347-54.
7. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 2000;22:676-80.
8. Sharretts JM, Simonds WF. Clinical and molecular genetics of parathyroid neoplasms. Best Pract Res Clin Endocrinol Metab 2010;24:491-502.
9. Crys VL, Thor A, Xu HJ, Hu SX, Wierman ME, Vickery AJ Jr., et al. Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. N Engl J Med 1994;330:757-61.
10. Crys VL, Rubio MP, Thor AD, Louis DN, Arnold A. p53 abnormalities in human parathyroid carcinoma. J Clin Endocrinol Metab 1994;78:1320-4.
11. Haven CJ, van Puijenbroek M, Tan MH, Teh BT, Fleuren GJ, van Wezel T, et al. Identification of MEN1 and HRPT2 somatic mutations in paraffin-embedded (sporadic) parathyroid carcinomas. Clin Endocrinol (Oxf) 2007;67:370-6.
12. Kebebew E, Clark OH. Parathyroid adenoma, hyperplasia, and carcinoma: Localization, technical details of primary neck exploration, and treatment of hypercalcemic crisis. Surg Oncol Clin N Am 1998;7:721-48.
13. Schantz A, Castelen B. Parathyroid carcinoma. A study of 70 cases. Cancer 1973;31:600-5.
14. Kebebew E, Arici C, Duh QY, Clark OH. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. Arch Surg 2001;136:878-85.
15. Sandelin K, Auer G, Bondeson L, Grimelius L, Farnebo LO. Prognostic factors in parathyroid cancer: A review of 95 cases. World J Surg 1992;16:724-31.
16. Collins MT, Skarulis MC, Bilezikian JP, Silverberg SJ, Spiegel AM, Marx SJ. Treatment of hypercalcemia secondary to parathyroid carcinoma with a novel calcimimetic agent. J Clin Endocrinol Metab 1998;83:1083-8.
17. Vellaki P, Lange K, Elaraj D, Kopp PA, El Muayed M. Denosumab for management of parathyroid carcinoma-mediated hypercalcemia. J Clin Endocrinol Metab 2014;99:387-90.
18. Owen RP, Silver CE, Pellitteri PK, Shaha AR, Devaney KO, Werner JA, et al. Parathyroid carcinoma: A review. Head Neck 2011;33:429-36.