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Controversies in the management of parathyroid carcinoma: A case series and review of the literature

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HIGHLIGHTS

- Management of parathyroid carcinoma is controversial due to its rarity and lack of large-scale series.
- Postoperative diagnosis is the most frequent scenario and requires a decision on possible surgical re-exploration.
- An aggressive approach is indicated in case of unclear surgical margins and local or distant recurrence.

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ABSTRACT

Parathyroid carcinoma is a rare malignancy representing less than 1% of primary hyperparathyroidism cases. Its management is controversial due to lack of large-scale, multicentric studies. We report 8 new cases of parathyroid carcinoma and review the literature. Preoperative diagnosis of carcinoma was possible in 2 (25%) cases. Unclear surgical margins were present in 5 (62.5%) patients; 4 of them underwent subsequent re-exploration and ipsilateral hemithyroidectomy, in one case associated to central lymph node dissection. Recurrent disease is reported in 2 (25%) patients. Considering the high incidence of local recurrence in case of unclear surgical margins, a re-exploration with ipsilateral hemithyroidectomy is indicated in these patients. A neck dissection should be performed only in case of clinically involved lymph nodes, avoiding prophylactic lymphectomy. An aggressive approach is indicated in case of local or distant recurrence to reduce hypercalcemia.

1. Introduction

Parathyroid carcinoma is a rare disease, accounting for less than 0.1% of all malignancies and 1–2% of all cases of primary hyperparathyroidism [1–3]. Due to its rarity in literature there is a lack of large-scale, multicentric series, thus natural course of parathyroid carcinoma is still unclear, and there is not universal consensus regarding management and follow-up. In this study we report our experience of 8 cases of parathyroid carcinoma who underwent surgery at our institution and we review the literature.

2. Material and methods

We retrospectively reviewed 319 patients who underwent parathyroidectomy for primary hyperparathyroidism at our department (Surgical Sciences, University of Cagliari, Italy) between 2001 and 2014. Only patients with histopathological diagnosis of parathyroid carcinoma were included in the study. We extracted data from patients' medical records on demographic data, clinical history, preoperative assessment including blood tests and localizing studies, surgical procedure, postoperative course and complications, histology and follow up.

3. Results

Patients' data are reported in Table 1. We included in our study 8 patients with parathyroid carcinoma, which represent 2.5% of all cases of primary hyperthyroidism; 7 of them were female and 1 was male. Mean age was 61.5 ± 6.3 years (range 55–73).

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Table 1
Demographic and biochemical data, management, pathological findings and follow-up in 8 patients with parathyroid carcinoma.

ID	Sex, age	Year of diagnosis	Preoperative PTH (pg/ml)	Preoperative calcemia (mg/dl)	Surgical procedure	Pathological features	Re-exploration	Follow-up
1	F, 57	2003	122	12.4	Left superior PTX	Chief cells carcinoma, clear margins	No	Disease free
2	M, 59	2005	1498	15.6	Mediastinic PTX, prophylactic CLND	Chief cells carcinoma, angioinvasive, unclear surgical margins	No	Local recurrence and lung metastasis 6 years after surgery
3	F, 55	2006	400	9.7	Right inferior PTX, total thyroidectomy	Oxyphil cells carcinoma, capsular invasion, clear margins	No	Disease-free
4	F, 62	2007	187	9.2	Right inferior PTX	Chief cells carcinoma, angioinvasive, unclear margins	Right hemithyroidectomy, therapeutic CLND	Disease-free
5	F, 67	2010	135	11.9	Right inferior PTX	Chief cells carcinoma, unclear margins	Right hemithyroidectomy	Disease-free
6	F, 53	2013	158	12.1	Right inferior PTX	Chief cells carcinoma, unclear margins	Right hemithyroidectomy	Disease-free
7	F, 73	2013	182	10.8	Left superior PTX	Chief cells carcinoma, capsular invasion, unclear margins	Left hemithyroidectomy	Disease-free
8	F, 66	2014	1693	13.4	Right inferior PTX, right lobectomy	Chief cells carcinoma, clear margins	Retroesophageal PTX[a]	Severe hypercalcemia and hyperparathyroidism with negative imaging studies one year after surgery

PTH: parathyroid hormone; PTX: Parathyroidectomy; CLND: central lymph node dissection.
[a] Postoperative hypercalcemia and hyperparathyroidism.

Preoperative calcemia and PTH were, respectively, 11.9 ± 2.1 mg/dl (range 9.2–15.6) and 547 ± 655 pg/ml (range 122–1693). Calcemia was in normal range in 2 cases, while PTH was over the upper limit in all the patients. None of the patients was affected by MEN syndrome, while one had a coexisting multinodular goiter.

All the patients but 2 were symptomatic: a history of nephrolithiasis was present in 5 cases, osteoporosis in 4 (in two cases with previous pathological bone fractures), asthenia in 3, main depressive syndrome in 3, peptic ulcer disease in 2. One patient was admitted at our department with hypercalcemic crisis which required fluid resuscitation and medical therapy with bisphosphonates before surgical procedure.

Both preoperative ultrasound (US) and MIBI scan were performed in 6 cases: in 2 cases they correctly localized the site of the tumor. In one case they wrongly identified an ectopic mediastinic lesion as orthotopic left-sided. In another case they both recognized a single right parathyroid lesion, but the disease was multi glandular. In one case US was negative and MIBI identified two pathological parathyroid, with only one being really a tumor. Finally, in one case US was negative and MIBI rightly positive. In 2 cases only preoperative US was performed, with one true-positive and one false-negative result. Overall, US was helpful in 3 out of 8 cases (37.5%) and MIBI in 3 out of 6 (50%).

Preoperative suspicion of parathyroid carcinoma arose in 2 cases due to severe hypercalcemia and hyperparathyroidism. The first patient had an ectopic mediastinic parathyroid, and surgical procedure consisted in a wide excision of the neoplasm with surrounding tissues including central compartment lymph nodes. The second underwent a right parathyroidectomy with ipsilateral hemithyroidectomy. In the other six patients a simple parathyroidectomy was performed, in one case associated to a total thyroidectomy for multinodular goiter, and diagnosis of parathyroid carcinoma was made postoperatively.

Intraoperative PTH assay was performed in all the cases to confirm removal of all hyperfunctioning parathyroid tissue. We consider a positive result when post-excision PTH value decreases at least 50% than basal value and returns in range values (15–65 pg/ml). We had 7 true-positive results. In one case post-excision PTH didn't decrease satisfactorily and, despite prolonged exploration, no other pathological glands were found; postoperative calcemia and PTH were high, thus a MIBI scan was performed, revealing a hyperfunctioning retroesophageal parathyroid gland. The patient underwent a re-exploration with excision of the suspected gland, with pathological features of hyperplasia.

A transient hypoparathyroidism with hypocalcemia was present in 4 patients in the immediate postoperative period and was treated with oral administration of calcium. No recurrent nerve injuries were observed.

Pathological examination revealed a chief cells parathyroid carcinoma in 7 cases and an oxyphil cells carcinoma in one case. Vascular invasion was present in 2 cases and extracapsular infiltration in 6. Lymph nodes removed in a patient who underwent prophylactic central neck dissection were negative. Surgical margins were unclear in 5 patients: in 4 of them a re-exploration with ipsilateral hemithyroidectomy was performed, in one case associated to central neck dissection, being the lymph nodes clinically involved.

None of the patients received adjuvant radio or chemotherapy.

At present all patients are alive and 6 are disease free. One patient presented hyperparathyroidism and hypercalcemia 6 years after surgery; US was negative but MIBI scan revealed an area of increased uptake in central compartment. The patient underwent re-exploration, which was very difficult due to dense scar tissue, and no pathological lesions were found; another exploration was performed but resulted still negative. Currently the patient has mild hypercalcemia treated with calcimimetic agents (cinacalcet); a recent PET-CT scan revealed a lung hypermetabolic area compatible with distant metastasis. Another patient with concomitant parathyroid carcinoma and hyperplasia presented biochemical signs of recurrence one year after initial surgery. US and MIBI scan were performed but were both negative; a PET-CT scan was also negative. At present the patient has severe hypercalcemia (>16 mg/dl) poorly responsive to medical therapy, and is hardly symptomatic with severe bone pain, asthenia and recurrent nephrolithiasis.