Case series of diagnosis and surgery challenges in parathyroid carcinoma

Diani Kartini *, Ahmad Kurnia, Erwin Danil Yulian, Sonar Soni Panigoro, I. Gusti Ngurah Gunawan Wibisana, Jessica Wardana
Division of Oncology Surgery, Department of Surgery, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

ARTICLE INFO

Keywords: Case series En bloc resection Ipsilateral parathyroidectomy Hyperparathyroidism Parathyroid carcinoma Parathyroidectomy

ABSTRACT

Introduction: Parathyroid carcinoma (PC) is a rare malignancy that accounts for 1 % of cases of hyperparathyroidism. Data regarding PC in Indonesia are scarce, which poses challenges to diagnosis and treatment. This study aims to describe a series of PC cases from a tertiary health care center over 12 years. Presentation of cases: Retrospective data of six patients with hyperparathyroidism diagnosed with PC between 2008 and 2020 were reviewed. Clinical presentation, diagnosis, management, and short-term outcomes of PC were analyzed. All six PC patients were diagnosed postoperatively. Four of the patients presented with symptomatic hypercalcemia, and two presented with neck swelling. Elevated serum parathyroid hormone was observed in five patients. Only two patients had imaging results corresponding to PC characteristics. Ipsilateral parathyroidectomies were performed on 5 patients where invasion and metastasis are not evident. Frozen section samples suggested PC, and two suggested parathyroid adenoma. Further histopathologic examination confirmed a diagnosis of PC in all patients. No metastasis to the adjacent lymph nodes or distant target organs was found during surgery.

Discussion: Preoperative diagnosis of PC remains challenging. Suspicion of PC is appropriate in the presence of severe hypercalcemia, elevated parathyroid hormone level, and a mass observed either during imaging or intraoperatively.

Conclusion: Ipsilateral parathyroidectomy seems to be feasible compared to total resection in order to preserve function and structure. Incomplete excision may lead to an increased risk of recurrence, emphasizing the importance of routinely following up on PC cases.

1. Introduction

Parathyroid carcinoma (PC) is one of the rarest endocrine malignancy [1]. PC is clinically difficult to distinguish from benign causes of primary hyperparathyroidism (PHPT). Reports have recognized PC cases in multiple endocrine neoplasia 1 (MEN1), an autosomal dominant syndrome affecting endocrine tumors. 90 % of MEN1 patients found presented with hyperparathyroidism [2]. Primary hyperparathyroidism is usually characterized by hypercalcemia, which occurs due to excessive autonomous secretion of parathyroid hormone (PTH) and is three to four times more likely to be found in women aged 50 to 65 years [3,4].

PC is indicated by a mass with signs of malignancy observed by imaging or a tender mass with uneven margins found intraoperatively. Findings of serum calcium levels higher than 14 mg/dL and PTH levels 10 times or more than the upper limit of normal indicate malignancy [5]. The absolute prerequisite for PC consists of lymph node metastasis, local invasion, and distant metastases [6,7]. Histopathologic examination remains the gold standard and the only method to establish the diagnosis of PC [8].

Complete surgical resection of thyroid and parathyroid glands (en bloc resection) with microscopically negative margins is the gold standard for PC treatment [1]. Less radical resection may lead to a higher risk of recurrence [9]. Radiation therapy and chemotherapy have not been proven beneficial in PC management [1,10,11]. Data regarding PC profiles in Indonesia are still limited. This case series aims to describe the clinical manifestations, diagnosis, management, and outcome of PC over 12 years from a single institution.

Abbreviations: 4D-CT, 4-dimensional computed tomography; MRI, magnetic resonance imaging; PA, parathyroid adenoma; PC, parathyroid carcinoma; PTH, parathyroid hormone; US, ultrasound.

* Corresponding author at: Division of Oncology Surgery, Department of Surgery, Faculty of Medicine Universitas Indonesia, Indonesia. E-mail address: diani.kartini@ui.ac.id (D. Kartini).

https://doi.org/10.1016/j.ijscr.2022.107390
Received 18 May 2022; Received in revised form 3 July 2022; Accepted 4 July 2022
Available online 9 July 2022
2210-2612/© 2022 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
2. Presentation of cases

This was a single retrospective study and case series of all patients with hyperparathyroidism treated in the Surgical Oncology Clinic of Cipto Mangunkusumo General Hospital, Jakarta, between January 1, 2008, and December 31, 2020. Medical records of patients diagnosed with PC postoperatively by histopathologic examination were reviewed. We obtained written informed consent from all patients. This case series

| Sex  | Age | Clinical symptoms                                                                 | Calcium level (mg/dL) [N: 8.4–10.2] | PTH level (pg/mL) [N: 15–65] | Preoperative imaging                                                                 | Frozen section                                                                 | Treatment                      |
|------|-----|---------------------------------------------------------------------------------|-------------------------------------|-----------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|
| Male | 46  | Painless lump on upper mouth palate, history of routine hemodialysis due to chronic renal failure | 8.5 N/A                            | 2898 2607 –                  | US: Hypoechoic lesion at posterior left thyroid, possible parathyroid origin. dd/PA | Parathyroid mass was histologically appropriate for parathyroid hyperplasia (left inferior lobe) and carcinoma (right lobe) | Ipsilateral parathyroidectomy |
| Male | 28  | Lump on the left thigh for 4 months                                             | 16.6 6.8                            | 1872 – 8.51                  | US: Solid tumor likely to be malignant, possibly originating from the right parathyroid lobe. Lymphadenopathy was observed at the submandibular and superior right neck MRI: No focal lesion or enhancement observed in the right thyroid bed. Bilateral neck lymphadenopathy was not found Sestamibi: Mass on left parathyroid lobe suggestive of adenoma; no remaining mass on right thyroid and parathyroid lobe was observed | Malignant tumor supporting PC diagnosis | Ipsilateral parathyroidectomy |
| Female | 26 | Neck lump, complaints of bone fracture                                          | 13.4 8.9                            | – – 202.7                    | US: Morphology of bilateral thyroid lobes was within normal limits; no mass was found in both parathyroid lobes. No lymphadenopathy was observed MRI: Left neck mass suggestive of a parathyroid tumor with intrathoracic extension. No tumor infiltration into the thyroid gland, trachea, or vascular structures of the neck was observed. No lymphadenopathy of the neck was observed | Benign parathyroid lesion, suggestive of hyperplasia | Ipsilateral parathyroidectomy |
| Female | 31 | Coccygeal stiffness for 7 months                                               | 12.9 9.3                            | 1327 – 34.91                 | US: Left supraclavicular lesion was found, suggestive of lymphadenopathy. Bilateral thyroid lobes were within normal limits MRI: No lesion or lymph node enlargement was observed at the neck. Thyroid and parathyroid glands were within normal limits, and no enlargement of the parathyroid gland was observed Sestamibi: Imaging suggestive of PA at the inferior lobe was observed | Frozen section indicative of PA; lymph node metastasis was not found in preparation | Ipsilateral parathyroidectomy |
| Female | 24 | Recurring nausea and vomiting in the last 1 year                                | 14.2 7.8                            | 82.51 – –                    | US: Left thyroid struma was observed, and a hypoechoic mass of the posterior thyroid lobe suggestive of PA was also observed MRI: Left parathyroid mass with a measurement of $\pm 3.05 \times 2.61 \times 2.47 \text{cm}$ | Histologically appropriate for PC | Ipsilateral parathyroidectomy |
| Female | 52 | Lump on left side of the neck for 10 months                                    | 16.7 13.8                           | 1593 – 124 –                 | –                                                                                | Histologically appropriate for PC | En bloc resection |

Abbreviations: 4D-CT, 4-dimensional computed tomography; dd, differential diagnosis; MRI, magnetic resonance imaging; PA, parathyroid adenoma; PC, parathyroid carcinoma; PTH, parathyroid hormone; US, ultrasound.
has been reported in line with the PROCESS Guideline [12].

Six patients were identified, with a median age of 29.5 years (28–52 years), four were female and two were male. Skeletal involvements were found in 50% of cases, while renal and gastrointestinal involvements were each present in 16.7% of cases. Neck swelling was observed in two patients, and four patients had hypercalcemic symptoms, consisting of gastrointestinal complaints, bone pain, and reduced urine volume. Hypercalcemia was biochemically evident in three patients, although all patients had symptoms of hypercalcemia: bone fracture, joint stiffness, and painless lumps. One patient with a history of routine hemodialysis had no signs of adhesions or invasion of surrounding tissue, including thyroid tissue, was seen during surgery. The histopathologic results of all patients during surgery, and four of six samples exhibited suspicious of malignancy in its immediate-read frozen section. In most of our patients, and four patients had hyperparathyroidism identified at follow-up [4]. Surgery is rarely curative in cases with distant metastases, although palliative debulking of the tumor mass may aid in controlling hypercalcemia [11]. In the largest cohort evaluating the overall survival of PC patients, no significant difference was found between en bloc resection and local resection [14]. Radical en bloc resection is controversial, because it leads to significant morbidities, such as muscular dysfunction and laryngeal nerve palsies [14,15]. Locoregional surgeries, including ipsilateral parathyroidectomy, were found useful in certain situations, such as local disease control, when a less aggressive approach was opted for. However, more studies reported that patients with ipsilateral parathyroidectomy were found to undergo en bloc resection to achieve disease control and eliminate residual disease [15–18]. Therefore, en bloc resection was still deemed preferable to avoid reoperations and achieve remission.

Neither radiotherapy nor chemotherapy was done in this study because PC is considered radioresistant. Although a few small retrospective studies have found a lower recurrence rate with adjuvant radiotherapy [7,9], Successful chemotherapy has been reported, but data on the efficacy of adjuvant chemotherapy are still lacking [5]. Long-term outpatient management is commonly required in which patients are treated with calcimimetic therapy with or without bisphosphonate therapy to aid in decreasing calcium levels and associated symptoms [9]. Morbidity and mortality of PC patients are largely due to sequelae of hypercalcemia and end-organ damage [5].

Our study strengths are the inclusivity of all PC patients over years and comparison of clinical evaluations made to decide the method of surgery opted. We also showed that ipsilateral parathyroidectomy could be considered in some cases compared to en bloc resection. The study limitations include the absence of follow-up due to nonattendance during COVID-19 pandemic, which prevents observation of recurrence of the disease and performance of re-exploration for those receiving only ipsilateral parathyroidectomy. Follow-up should be lifelong, with measurement of calcium and PTH levels every 6 months [10].

The prognosis of PC is dependent on complete resection at initial surgery, although a prognostic classification system developed by Talat and Schulte may be used to determine patient survival [19]. To date, there is no consensus or guidelines for PC due to the rarity of the disease. Studies usually consisting of case reports and case series have too few cases to represent the general population. Further studies involving a large number of patients are warranted to establish a general guideline for PC.

4. Conclusion

Parathyroid carcinoma is a rare disease which often mimics its benign counterparts posing a challenge for diagnosing PC preoperatively. Suspicion of PC is appropriate in the presence of severe hypercalcemia (>14 mg/dL), high level of PTH (3 to 10 times the upper limit of normal), and a large mass, observed either during imaging or intraoperatively. The best chance for a cure is complete surgical resection, which can be achieved by en bloc resection. However, whether to perform this extensive surgical procedure or local resection by ipsilateral parathyroidectomy is a difficult decision determined by patients' condition and tumor adherence. Incomplete excision may lead to an increased risk of recurrence, thus emphasizing the importance of close follow-up of PC cases that could last for a lifetime.

Provenance and peer review

Not commissioned, externally peer-reviewed.
Ethical approval

The study was exempted from ethical approval in our institution, Faculty of Medicine Universitas Indonesia because it is a retrospective study with data taken solely from medical records.

Funding

None.

Guarantor

Diani Kartini, as the guarantor, hold full responsibility for the work and conduct to the study and hold the decision to publish.

Research registration number

-

CRediT authorship contribution statement

Diani Kartini: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Review and editing, Supervision.

Ahmad Kurnia: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Review and editing.

Erwin Danil Yulian: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Review and editing.

Sonar Soni Panigoro: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Review and editing.

I Gusti Ngurah Gunawan Wibisana: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Review and editing.

Jessica Dewati Wardana: Resources, Writing – Original draft, Writing – Review & editing.

Declaration of competing interest

The authors declare they have no conflicts or financial ties to disclose.

Acknowledgments

The author would like to thank the staff of the Oncology Department of Cipto Mangunkusumo General Hospitals for their assistance in the surgeries of the patients and the staff of the Radiology Department of Cipto Mangunkusumo General Hospitals for their assistance during the examinations of patients. We also thank Dr. Zoya Marie Adya for her contribution in data analysis, writing, and finalization of this case series.