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Hypercalcaemic Crisis Secondary to Parathyroid Carcinoma Presenting with Pathological Fractures: A Case Report

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Introduction: Hypercalcaemia Crisis is a rare and serious complication of primary hyperparathyroidism. Parathyroid carcinoma is one of the causes of primary hyperparathyroidism that is very rare with an incidence of 0,005% of all malignancy cases.

Case Presentation: We report the case of 46-year-old Man with hypercalcaemia crisis due to parathyroid carcinoma. He presented with right upper arm and left thigh fractures after falling while riding a motorcycle. Because a pathological fracture is suspected, further diagnostic examination is carried out. His serum calcium and parathyroid hormone levels were at 15,3 mg/dL and 4.063 pg/mL, respectively. An ultrasonography of his neck showed a nodul in the left lobe of thyroid gland (TIRADS 4) while the parathyroid gland was not visualized and abdominal ultrasonography showed bilateral nephrolithiasis. A total Thyroidectomy and total parathyroidectomy were performed. Histology revealed a parathyroid carcinoma with an intranodular parathyroid in the left lobe thyroid. Postoperatively, the patient has a significant decrease in serum calcium and PTH levels.

Conclusion: In patient with parathyroid carcinoma, the best treatment modality is surgery. In our patient, surgical intervention in the form of total parathyroidectomy proved successfully reduce serum calcium and PTH levels. Early diagnosis and surgery before arising the complications of the hypercalcaemia crisis, nephrolithiasis, or pathological fractures could reduce morbidity and mortality in patient with parathyroid carcinoma.

Keywords: parathyroid carcinoma, primary hyperparathyroidism, parathyroidectomy, case report

I. INTRODUCTION

Parathyroid carcinoma is a rare malignancy occurring in 0.5–4% of patients with primary hyperparathyroidism. Parathyroid carcinoma was first described by de Quervain in 1904 as a nonfunctional metastatic carcinoma. Since then, fewer than 1,000 cases have been reported in the literature. The incidence of parathyroid carcinoma is 0.005% of all malignancies according to the National Cancer Database from 1985 to 1995.[1] Because of the rarity of parathyroid carcinoma, data on its clinical and pathological characteristics remain limited. Parathyroid carcinoma is generally associated with higher calcium and parathyroid hormone (PTH) levels compared with primary hyperparathyroidism caused by benign adenoma, and tends to be symptomatic.[2]

Parathyroid carcinoma is usually indolent but progressively growing. The main morbidity of parathyroid carcinoma is caused by complications of hypercalcaemia, such as neuropsychiatric symptoms, cardiac arrhythmia, renal failure, and pathological fractures. Benign and malignant parathyroid lesions are difficult to distinguish, even with histopathological examination. In most patients, preoperative staging is difficult to establish.[3] Therefore, intraoperative findings play a critical role, as the surgeon must differentiate between adenoma and parathyroid carcinoma.

Surgical management of patients with primary hyperparathyroidism has advanced significantly over the past two decades. Improvements in preoperative and intraoperative imaging modalities, including rapid PTH assay, have enhanced the development of minimally invasive surgical techniques in developed countries. Definitive therapy for parathyroid carcinoma is surgery, with en-bloc resection of the tumor together with adjacent critical structures as the recommended treatment of choice.[2] This is evidenced by the decrease in PTH secretion and serum calcium levels after surgery. We report a rare case of parathyroid carcinoma at Dr Soetomo General Hospital, Surabaya, presenting with pathological fracture due to primary hyperparathyroidism.

II. CASE PRESENTATION

A 46-year-old man was referred from Jombang Regional General Hospital to the Emergency Department of Dr Soetomo General Hospital, Surabaya, after 7 days of treatment following a fall while riding a motorcycle. Before admission, the patient had frequently complained of pain and weakness in his right hand and left leg for the previous 2 months. He also frequently complained of nausea and easy fatigue. The patient had never complained of a neck mass. He had no history of hypertension, diabetes mellitus, or other diseases. There was no family history of similar complaints.

On physical examination, the patient appeared weak with GCS E4V5M6. His body weight was 52 kg, height 167 cm, with a body mass index (BMI) of 18.65 (adequate body weight). Vital signs were: blood pressure 120/70 mmHg, pulse 89 beats/minute, respiratory rate 18 breaths/minute, temperature 36.3°C, and oxygen saturation 98% without supplemental oxygen. In the neck region, a firm-soft left thyroid mass measuring 2 cm x 2 cm was palpable, with a smooth surface, indistinct borders, moving with swallowing, and no tenderness.

On radiological examination, neck ultrasonography showed a solid nodule in the left lobe of the thyroid gland (moderately suspicious left thyroid lobe, TIRADS 4) measuring 1.57 x 2.1 x 2.66 cm with macrocalcification. The right thyroid lobe was of normal size with no abnormalities, and a non-suspicious subcentimeter lymph node was noted in the right submandibular region. The parathyroid gland was not visualized, as shown in Table 1. Pelvic AP/lateral radiographs showed multiple lytic lesions in the pelvis, right humerus radiographs showed a complete fracture of the middle third of the right humerus, and left femur radiographs showed a complete fracture of the proximal third of the left femur.

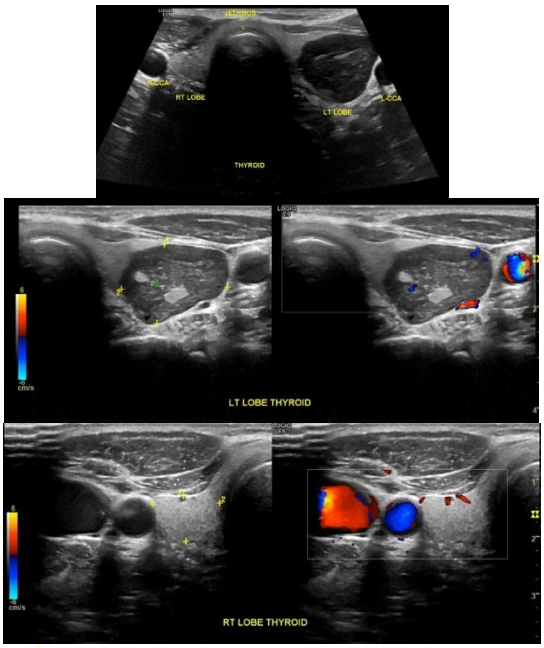

Figure 1. Neck ultrasonography showing the right and left thyroid lobes. The parathyroid gland was not visualized

Preoperative laboratory results showed a phosphate level of 3.1 mg/dL and blood calcium of 15.3 mg/dL, with postoperative results shown in Table 1.

Table 1. Laboratory findings sorted by time

Parameter	Preoperative	Postoperative Day 1	Postoperative Day 7
Hb/L/PLT	9.9/26.9/302	8.7/24.7/232	12.3/17.9/256
Na/K/Cl	140/3.6/101	135/4.4/105	141/4.0/102
BUN/SCr	54/2.56	48/2.1	18/1.2
Alb	3.4	3.1	3.5
RBG	89	102	119
FT4	1.86	0.73	1.76
TSH	5.26	1.652	4.12
Phosphate	3.1	4.1	5.7
Calcium	15.3	8.2	6.2
PTH	4,063 pg/mL	121 pg/mL	65 pg/mL

The patient underwent FNAB of the left thyroid lobe, which showed nodular colloid goiter with atypical cells. The patient received crystalloid fluid therapy with 0.9% NaCl 2 liters over the first hour, followed by 0.9% NaCl maintenance fluid targeting urine output of 3,600 mL per day, along with KCl infusion of 40 mEq in 1,000 mL 0.9% NaCl.

The patient underwent total thyroidectomy with total parathyroidectomy. Intraoperative evaluation revealed a firm, hard left lower parathyroid mass measuring 4x3x2 cm; the left thyroid lobe measured 2 cm x 2 cm x 2 cm and was adherent to the left lower parathyroid gland. The right thyroid lobe measured 2x1x1 cm, with the right superior and inferior parathyroid glands beneath it, each measuring 0.5 cm in diameter.

Histopathological examination of the left lower parathyroid tissue showed features of parathyroid carcinoma. The left thyroid lobe showed normal thyroid tissue with features of invasive parathyroid carcinoma (satellite nodule) accompanied by calcification. The right thyroid lobe showed normal thyroid tissue with no evidence of tumor cell infiltration.

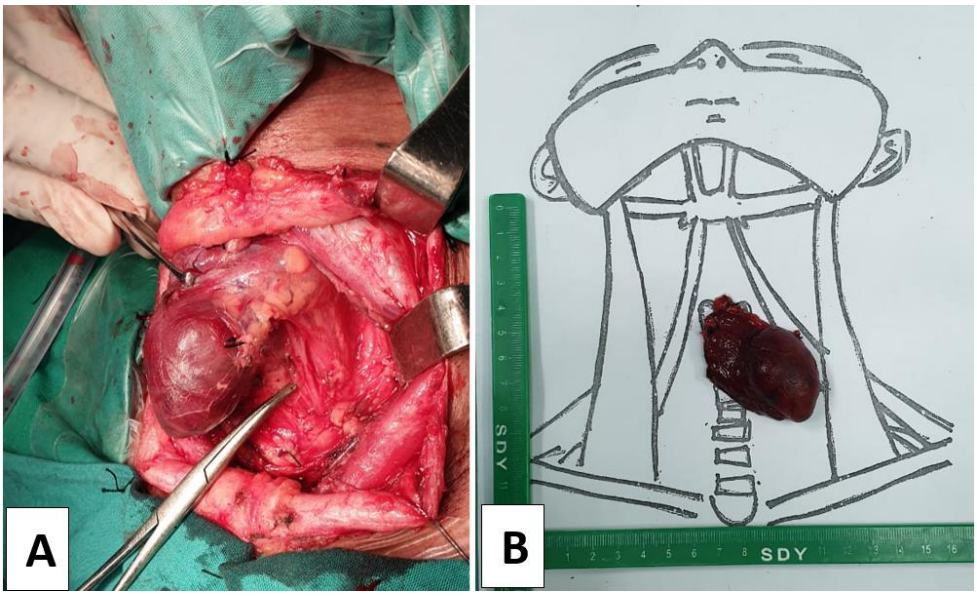

Figure 2. A. The left thyroid lobe adherent to the left superior parathyroid gland, difficult to separate.
B. Left thyroid lobe and left parathyroid gland after resection

Postoperatively, the patient was fully conscious and did not require supplemental oxygen. Laboratory results on postoperative day 1 showed a decrease in calcium to 8.2 mg/dL, and to 6.1 mg/dL on postoperative day 7 (normal range 8.5–10.1 mg/dL). The patient experienced hypocalcaemia following total thyroidectomy and parathyroidectomy. During hospitalization, intravenous calcium gluconate and oral calcium tablets were administered. Serial blood calcium measurements continued to show levels below the normal threshold (normal range 8.5–10.1 mg/dL).

At discharge, the patient was educated to take calcitriol and follow a high-calcium diet to prevent complications from postoperative hypocalcaemia. At 3 months postoperatively, the patient's condition was stable but he remained on a high-calcium diet due to persistently low blood calcium levels.

III. Discussion

Parathyroid carcinoma is a malignancy with an incidence of 0.1%–5% among patients with primary hyperparathyroidism.[4] Primary hyperparathyroidism is defined as a condition of elevated serum calcium with non-suppressed (elevated) parathyroid hormone levels.[5] Primary hyperparathyroidism (PHPT) was first recognized in the early 1900s, with patients showing significant clinical manifestations as described by Fuller Albright et al. using the mnemonic "Stone, Bone, Groans." The prevalence of primary hyperparathyroidism in the United States is 23 cases per 10,000 women and 8 cases per 10,000 men, while the incidence is 66 new cases per 100,000 women annually and 25 new cases per 100,000 men annually.[5] Parathyroid carcinoma occurs equally in men and women, whereas parathyroid adenoma occurs predominantly in women with a ratio of 3–4:1. The mean age is the fourth decade of life, while for benign adenoma the mean age is 30 years.[6] In the patient treated at our institution, the patient was a 46-year-old man.

In developed countries, 85% of patients with primary hyperparathyroidism are asymptomatic, and only 20% present with symptoms. Symptoms commonly found in patients with primary hyperparathyroidism arise from complications in either the kidney (urolithiasis) or bone (fracture, osteitis fibrosa cystica, bone pain) or from symptoms of hypercalcaemia. In developing countries, the majority of patients present with complication-related symptoms.[5]

To date, the primary cause of parathyroid carcinoma remains unknown. However, several studies suggest an association between gene mutations and the development of cancer cells. One study also discussed a syndrome known as "Hereditary Hyperparathyroidism-Jaw Tumour Syndrome." In this syndrome, patients experience primary hyperparathyroidism and fibro-osseous lesions of the maxilla and mandible. Nearly 15% of patients may progress to parathyroid carcinoma. The responsible gene is known as HRPT2, with its core protein called parafibromin. A history of neck irradiation and end-stage renal disease has also been associated with an increased incidence of parathyroid carcinoma.[7]

Obara et al. stated the clinical criteria for suspicion of parathyroid carcinoma as (1) age under 55 years; (2) hypercalcaemia and hyperparathormonemia (more than 10 times the upper limit of normal); (3) severe

symptoms affecting bone (fibrocystic osteitis in 40–60% of cases) and kidney (nephrocalcinosis, nephrolithiasis in 30–60% of cases); (4) recurrent laryngeal nerve palsy due to tumor invasion; (5) palpable mass.[8]

The clinical presentation of parathyroid carcinoma is usually related to symptoms caused by elevated PTH levels and hypercalcaemia rather than mass effects from local infiltration or distant metastasis. This is because nearly 90% of parathyroid carcinoma cases are functional. Manifestations of hyperparathyroidism on bone include osteitis fibrosa cystica, absence of lamina dura, diffuse osteopenia, osteoporosis, bone pain, or pathological fracture, occurring in nearly 22–91% of patients with parathyroid carcinoma at diagnosis. Renal complications such as nephrolithiasis, nephrocalcinosis, decreased GFR, or renal colic are found in 32–60% of patients with parathyroid carcinoma. Renal involvement alone is not specific for malignancy. Concurrent bone and renal disease is seen in 40% to 50% of patients and is uncommon in benign primary hyperparathyroidism.[2]

Our patient presented clinically with a pathological fracture accompanied by complaints of weakness, nausea, weight loss, and polyuria. All these clinical signs are highly nonspecific and often lead to delayed diagnosis; even when clinical signs of hypercalcaemia are evident, the diagnosis of parathyroid carcinoma may still be missed.

A palpable neck mass is found in 30–76% of patients with parathyroid carcinoma. Clinical findings can help differentiate between benign and malignant disease, and indeed fewer than 5% of patients with benign disease present with a palpable neck mass. Data from the American National Cancer Database reported a median tumor size of 3.3 cm in 286 cases of parathyroid carcinoma.[9] In our patient, physical examination of the neck region revealed a palpable soft left thyroid mass measuring 2 cm x 2 cm, moving with swallowing, without tenderness. On physical examination, it was difficult to distinguish whether the mass originated from the thyroid or parathyroid gland, as both glands overlapped and were adherent to the trachea.

In establishing the diagnosis of parathyroid carcinoma, serum PTH and serum calcium levels play an important role. A PTH level higher than 300 pg/mL (3–10 times above the upper limit of normal) is an indicator of potential parathyroid malignancy. In addition, elevated alkaline phosphatase and serum beta-hCG levels are often found. In our patient, blood calcium was 15.3 mg/dL, phosphate 3.1, alkaline phosphatase 491, and PTH 4,063 pg/mL.

Preoperative radiological examination is very helpful, particularly in determining tumor location; however, evaluating primary parathyroid tumors to differentiate benign from malignant disease remains difficult. A hypoechoic mass on ultrasound with indistinct, irregular borders, accompanied by signs of invasion of surrounding structures, may suggest malignancy, but these characteristics are not always present in parathyroid carcinoma. In this case, neck ultrasonography showed a solid nodule in the left thyroid lobe, while the parathyroid gland was not well visualized.[10]

Sestamibi scan is useful in demonstrating abnormal parathyroid tissue; however, this diagnostic modality is not available in some hospitals in developing countries. Contrast-enhanced CT scan can provide detailed imaging of lesion location and involvement of surrounding tissue.[7]

In cases where a neck mass is present, FNA examination is not recommended. This is because it is difficult to distinguish benign from malignant cases cytologically. In addition, this examination carries a risk of tumor cell seeding.[11–12] Histologically, it is quite difficult to differentiate parathyroid carcinoma from adenoma or hyperplasia. However, the Schantz and Castleman criteria can help distinguish parathyroid carcinoma from adenoma. Cytologically, parathyroid carcinoma shows atypical mitoses, pleomorphic and enlarged nuclei. Typical features of parathyroid carcinoma also include a thick, dense fibrous capsule dividing the gland. These criteria include capsular invasion, vascular invasion, or local invasion into surrounding soft tissue, lymph nodes, or even distant metastasis.[8] However, McKeown and Bondeson et al. reported finding mitotic activity and trabecular pattern in benign lesions. Therefore, several studies have developed alternative methods such as immunohistochemistry and DNA analysis.[7]

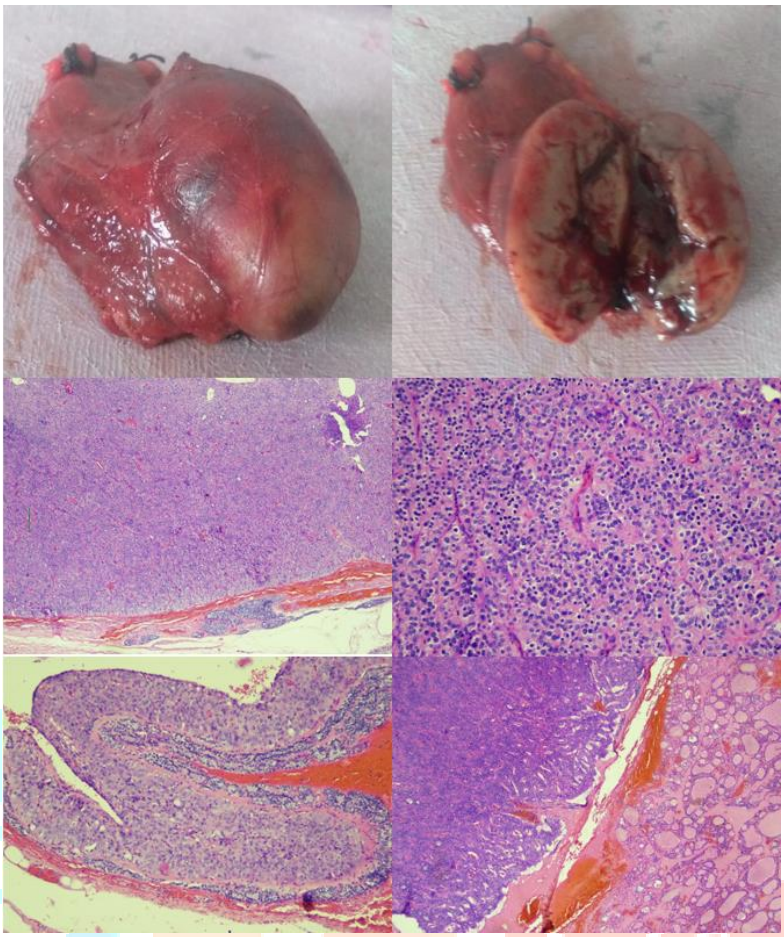

Figure 3. Macroscopic and microscopic findings of parathyroid carcinoma.

An important modality in the management of parathyroid carcinoma is surgery. Most researchers recommend en-bloc resection with ipsilateral thyroid lobectomy and removal of all enlarged or abnormal lymph nodes. Aggressive resection can reduce local recurrence and distant metastasis. However, caution must be exercised to prevent tumor capsule rupture, which could cause seeding at the operative site. If the recurrent laryngeal nerve is involved and non-functional, it should be resected. Central neck modified functional radical neck resection and ipsilateral dissection are often performed only if lymph node enlargement is found on frozen section examination.[11] Due to the rarity of cases and infrequent preoperative diagnosis, prospective data on surgical management of parathyroid carcinoma remain limited. Although en-bloc resection is recommended and supported as reducing recurrence when performed at the initial surgery, in practice this procedure is only performed in 12% of all cases. In this case, we performed total thyroidectomy and total parathyroidectomy with preservation of the recurrent laryngeal nerve. This was done in consideration of tumor invasion into the left thyroid lobe. Therefore, to prevent recurrence, parathyroidectomy was also performed on the contralateral side. Radiotherapy and chemotherapy modalities are generally ineffective in cases of parathyroid carcinoma.[14–15]

The diagnosis of parathyroid carcinoma is often established intraoperatively. The tumor is usually firm in consistency, sometimes lobulated, and infiltrates surrounding tissue such as the ipsilateral thyroid lobe, strap muscles, recurrent laryngeal nerve, esophagus, and trachea. Frozen section examination is not sufficiently helpful in differentiating benign from malignant disease, and excisional biopsy is not recommended due to the risk of intraoperative tumor seeding, which may lead to parathyromatosis. In nearly 25% of cases, surgeons fail to recognize the presence of parathyroid carcinoma.[16] Although very rare, 3 cases of parathyroid carcinoma involving more than 1 parathyroid gland lobe have been reported.[17] Therefore, exploration of all four parathyroid glands is important to avoid repeat surgery.

The goal of surgery is not only oncological but also to control endocrine function. In fact, morbidity and mortality in patients with parathyroid carcinoma are generally caused by the functional endocrine aspect (PTH hypersecretion and persistent severe hypercalcaemia) rather than the oncological aspect.[18]

Poor treatment outcomes are generally related to incomplete resection, tumor seeding, and recurrence/persistence of cancer cells. Surgical complications include recurrent laryngeal nerve injury, esophageal and tracheal injury, neck hematoma, and surgical site infection. Metabolic complications that may occur after resection include hypocalcaemia and hypophosphatemia. The perioperative mortality rate is estimated to reach 1.8%.[19]

As shown in the postoperative laboratory results, PTH levels decreased drastically after parathyroidectomy, accompanied by a decrease in blood calcium levels. However, in our patient, refractory hypocalcaemia occurred, in which after surgery calcium levels remained at the minimum threshold, below 8.5 mg/dL.

The prognosis of patients with parathyroid carcinoma cannot be predicted, because once the diagnosis of malignancy is established, recurrence occurs in most cases. The average time to recurrence is approximately 3 years, although longer intervals of up to 20 years have been reported.[16]

Despite all advances in surgical technique and technology, recurrence remains very common in parathyroid carcinoma. Patients undergoing en-bloc tumor resection have lower recurrence rates, with a survival rate of 90% at 5 years and 67% at 10 years. Unfortunately, most patients are not diagnosed at initial surgery and do not undergo total resection. The average recurrence occurs 2–3 years after initial surgery. Therefore, postoperative follow-up is necessary, including clinical examination and monitoring of calcium and PTH levels every 3 months for the first 3 years, every 6 months up to year 5, and annual evaluation for life. Intravenous calcium, oral supplements, and calcitriol are generally required. This aims to maintain blood calcium levels at least within the lower limit of normal.[15]

The patient reported significant improvement in his overall well-being following surgery, with resolution of nausea and fatigue. He expressed satisfaction with the outcome despite requiring long-term calcium and calcitriol supplementation, and emphasized the importance of early medical attention for unexplained bone pain and fractures. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

IV. Conclusion

Parathyroid carcinoma is an extremely rare tumor that poses considerable challenges for clinicians in establishing the diagnosis and management. This is related to delayed diagnosis, by which time the tumor is already palpable, reducing the potential to achieve a tumor-free histological resection margin.

Patients with persistent hypercalcaemia require comprehensive evaluation, including radiological examination (ultrasonography/CT scan/MRI) and laboratory testing (serum calcium and PTH). In patients suspected of having parathyroid carcinoma, exploration of all four parathyroid glands intraoperatively is necessary, along with en-bloc resection accompanied by ipsilateral thyroid lobectomy, to prevent tumor capsule rupture and intraoperative seeding. Surgeons should also consider contralateral parathyroidectomy to prevent recurrence.

Because of the substantial risk of recurrence for up to 20 years, lifelong postoperative follow-up after parathyroidectomy is necessary to prevent recurrence as well as morbidity from hypocalcaemia.

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