

Parathyroid carcinoma: review of a problematic case

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Abstrak

Karsinoma paratiroid merupakan neoplasma yang jarang ditemukan, dengan frekuensi kurang dari 1% dari seluruh kasus hiperparatiroidisme primer. Beberapa gambaran klinis dan biokimiawi dapat mengarahkan pada karsinoma paratiroid namun diagnosis pre dan intraoperatif yang akurat masih sulit ditegakkan. Studi ini melaporkan satu kasus karsinoma paratiroid yang terdiagnosis pasca-operasi. Intraoperatif ditemukan pembesaran kelenjar paratiroid yang telah menginfiltrasi laringeus rekuren dan kelenjar tiroid kanan. Hasil histopatologik menunjukkan nodul tumor yang dipisahkan oleh jaringan ikat tebal, disertai invasi pada kapsul dan jaringan sekitar. Diagnosis akhir karsinoma paratiroid ditegakkan berdasarkan gambaran klinis dan pemeriksaan spesimen. (*Med J Indones. 2012;21:170-4*)

Abstract

Parathyroid carcinoma (PTCA) is a rare neoplasm that accounts for less than 1% of primary hyperparathyroidism cases. Several clinical and biochemical features can directing to PTCA, but accurate pre and intraoperative diagnosis are still difficult. This study presents a case of PTCA that diagnosed postoperatively with a discussion of microscopic feature. The surgical exploration revealed an enlarged parathyroid mass which invade recurrent laryngeal nerve and right thyroid gland. Histologic features showed tumor nodules separated by thick fibrous band with capsular invasion and local infiltration to adjacent tissues. The final diagnosis of PTCA was made based on clinical feature and specimens examination. (*Med J Indones. 2012;21:170-4*)

Keywords: *Diagnosis, invasion, parathyroid carcinoma, primary hyperparathyroidism*

Parathyroid carcinoma (PTCA) is a rare endocrine neoplasm. Among the causes of primary hyperparathyroidism, PTCA cases occur in less than 1% of patients, after adenoma (80-85%) and hyperplasia (10-15%).¹⁻³ Nonfunctional parathyroid carcinoma was first reported by de Quevain in 1904, and later in 1933, Sainton and Millet reported the first functional case. The etiology of PTCA is unknown; however, an increased risk of PTCA has been associated with familial hyperparathyroidism, type 1 multiple endocrine neoplasia syndrome, and radiation on the head and neck.^{4,5}

The clinical manifestations of PTCA are caused primarily by the effects of parathyroid hormone secretion from a functional tumor, rather than by infiltration or metastatic tumor mass. Patients usually present with bone disease, kidney disease, or even a hypercalcaemic crisis.⁶ Although several clinical and biochemical findings can lead to PTCA but it is difficult to establish an accurate pre and intraoperative diagnosis. The diagnosis of PTCA is usually made by a pathologist from the operation specimen, so that some patients must undergo reoperation to avoid recurrence.^{7,8}

While the diagnosis of adenoma is usually straightforward, parathyroid carcinoma still posed a diagnostic problem. Schantz and Castleman in 1973 have considered diagnostic criteria for PTCA, includes thick fibrous bands between the tumor cells, mitotic activity,

and capsular/ vascular invasion.^{1,9,10} But these features, except capsular and vascular invasion, sometimes were also found in benign lesions. Some new classification have been considered to establish diagnosis and predict the aggressiveness of the tumor cells, including the examination at the molecular level.^{9,11,12}

This study presents a case of parathyroid carcinoma that diagnosed postoperatively with a discussion of microscopic feature.

CASE REPORT

A 52-year-old female patient came to the Cipto Mangunkusumo Hospital, Jakarta, with a chief complaint of pelvic pain since 4 months before admission. Patient had a history of recurrent renal stone and previous surgery of adenomatous goiter. Physical examination obtained deformity in her right hand and palpable neck mass with diameter of 3 cm (Figure 1). Magnetic resonance imaging (MRI) of the neck region showed there is an enlargement of a bleeding thyroid gland. The suspicion that the tissue may be a parathyroid lesion failed to be confirmed by Sestamibi examination that give negative results, but serum calcium increased at level of 14.8 mg/dL, and parathyroid hormone levels reached 1455 pg/mL. Plain abdominal x-ray showed right renal stone and bladder stone. Other x-ray examination also found fracture of distal radius bone. The other findings were within normal limit.



Figure 1. Patient with neck mass



Figure 2. Gross feature of the tumor

The patient was referred to the department of surgery with a diagnosis of primary hyperparathyroidism due to suspected parathyroid adenoma, and decided to do exploratory surgery of the thyroid and parathyroid. Tumor mass was found measuring 6x3x3 cm, which infiltrated right recurrent laryngeal nerve and right thyroid gland. The frozen section yielded benign parathyroid lesion. The operator performed an en bloc resection with preservation of the recurrent laryngeal nerve. Recurrent laryngeal nerve is not taken in consideration to avoid postoperative hoarseness and the absence of a definite diagnosis of malignancy, intraoperatively.

Macroscopic examination showed tissue measuring 7x4x1.5 cm, brown, firm, attached to the thyroid gland (Figure 2). The tissue contained small amount of fat. Histopathologic findings showed neoplasm with a thick fibrous band separates the tumor cells in nodular patterns. The tumor composed of cells with mild pleomorphic, hyperchromatic, and partly vesicular nuclei with nucleoli. Cytoplasm is generally clear (Figure 3). Two atypical mitosis figures were found in 50 high power field (hpf). Capsular invasion was found but there is no vascular invasion. The tumor has invaded adjacent tissue such as the fat tissue and thyroid gland (Figure 4 and 5).

To ensure the tumor origin and reason of academic interest, we have made chromogranin and thyroglobulin

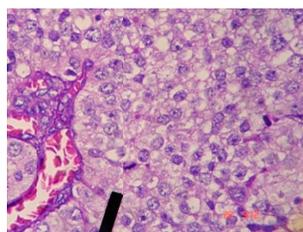


Figure 3. Tumor cells with prominent nucleoli and mitotic figure

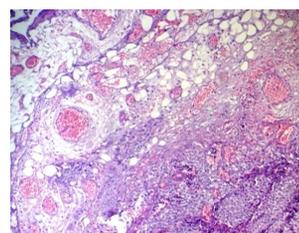


Figure 4. Tumors invades the fat tissue

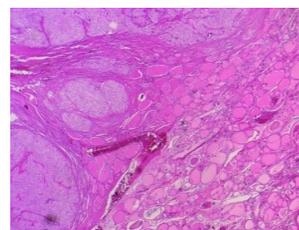


Figure 5. Infiltration of tumor cells to thyroid gland

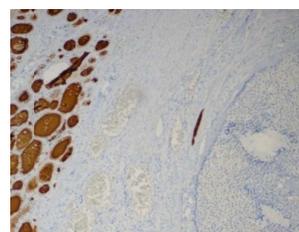


Figure 6. Thyroglobulin stained the thyroid gland but not the tumors

immunohistochemistry staining. Tumor areas gave negative result on the thyroglobulin staining but showed positivity while stained by chromogranin (Figure 6).

DISCUSSION

Parathyroid carcinoma usually occurred in fifth decade, a decade earlier than adenomas, with the ratio of affected women to men is 1:1.^{1,13} It is in accordance with patient characteristics in this case, however, there seems to be a late diagnosis that patient know the illness at 52 years old.

Morbidity in PTCA usually caused by the effects of parathyroid hormone secretion and severe hypercalcaemia, not because of the tumor mass.¹⁴ Such as in this case, the patient did not initially aware of a lump in the neck. The combination of bone and kidney disease, which is a major complaint of this patient, was a strong predictor of the occurrence of parathyroid malignancy, because the majority of PTCAs are functional. Kidney involvement (nephrolithiasis, nephrocalcinosis, and impaired renal function) were reported in 80% of patients with PTCA, whereas bone involvement, such as fractures and bone pain was found in 90% of patients.^{1,10} A palpable mass in the neck on physical examination adds to the suspicion of the diagnosis of malignancy. In contrast to adenomas, a

palpable tumor mass was found in nearly half of patients with PTCA.⁷ Diagnosis of PTCA, without distant metastasis, is difficult to establish preoperatively, but marked hyperparathyroidism, such as those suffered by this patient may be one tool of diagnosis. Level of blood calcium and parathyroid hormone increased in all parathyroid lesions including hyperplasia, adenomas, and carcinomas. The higher level, the greater likelihood carcinomas.^{13,15}

Preoperative imaging modalities such as computed tomography (CT), MRI and Technetium Tc99 Sestamibi, can help determine the location of the primary tumor as well as knowing the metastasis. Technetium Tc99 Sestamibi is a lipophilic isotope that has a high affinity for abnormal parathyroid tissue. Although unable to distinguish between adenoma and carcinoma, this modality is very effective to determine the location of parathyroid tumors with a sensitivity of 84.4% and specificity 95%.^{3,6,14} In this case, both imaging modalities MRI and Sestamibi could not found any abnormality in the parathyroid. This is contrary to the theories that have been raised so make clinicians hesitate, whether the tumor originated from the parathyroid or thyroid.

Malignant potential of parathyroid tumors sometimes could not be predicted, so the diagnosis of carcinoma is made after histopathological examination or in case of recurrence. Intraoperative recognition, although not easy, helps direct the diagnosis. The surgeon should be alert if found: (a) an enlarged gland with a diameter more than 3 cm, (b) gland with firm or hard consistency and pale, (c) local invasion to adjacent structures such as thyroid, strap muscle, and laryngeal recurrent nerve, and (d) lymph node involvement. If the conditions as mentioned above, the surgeon must performed an en bloc resection, which is removal of the tumor mass and the invaded adjacent tissues, which most often is the ipsilateral thyroid gland (89%), strap muscles (71%), and ipsilateral recurrent laryngeal nerve (26%). However, not all PTCA provides a clear clinical finding, because it must be confirmed by histopathological examination.⁴ In this case, tumor size more than 3 cm, as well as the invasion of the thyroid gland and ipsilateral recurrent laryngeal nerve support the diagnosis of malignant tumors although the frozen section have not enough evidence to suggest malignancy.

False of the frozen section were influenced by many things. The presence of artifacts, less representative sampling and diagnostic criteria which are not fulfilled are several factors that cause positive or false negative results. Examination of frozen section only helps if capsular or vascular invasion were present. The feature of mitosis, pleomorphic nuclei, and fibrotic septa could

not be the only one basic of intraoperative diagnosis.⁸ Tumors that originate from the parathyroid sometimes difficult to distinguish from the thyroid. Hyperplastic parathyroid glands can form structures such as follicles containing eosinophilic colloid material. If the parathyroid tumor cells are dominated by oncocytes, the feature may also resemble hurthle thyroid tumor cells. In addition, the swollen stroma of the thyroid can be similar to fat cells which found in parathyroid.¹⁶

In this case, there is no microscopic evidence that strong enough to establish the diagnosis of parathyroid carcinoma, but the image of the tumor cells which are composed mostly by chief cells, and no structure of follicles, may answer clinician question about the origin of this tumor.

Macroscopic of PTCA usually were grey, solid, and attached to adjacent tissues. Large tumor as in this case causes difficulty in identifying the primary tumor and surrounding tissue. Histopathologic findings met the criteria of Schantz and Castleman for PTCA i.e. the presence of thick fibrous bands that separates the tumor mass in a nodular pattern, mitotic figures and the presence of capsular invasion. Thick connective tissue found in 90% of 70 cases of PTCA studied by Schantz and Castleman, but this feature is not pathognomonic because it can still be found in a large parathyroid adenoma.¹⁰ Because of its slow-growing, mitotic figures are uncommon in many PTCAs, neither in this case. Capsular invasion was found in about 60% of cases while vascular invasion of the lower frequency range between 10-15%. Carcinoma capsule usually was thicker than the adenoma. True capsular invasion should be distinguished from the benign tumor mass which trapped between the connective tissue capsule.^{17,18} In this case, the local tumor mass was found to protrude into the capsule (tongue-like).

Although the Schantz and Castleman criteria had been widely accepted, the prognosis of patients with PTCA could not be predicted from these factors. Bondenson et al in 1993 proposed three criteria that can be used as an indicator of poor prognosis in PTCA i.e. macronucleoli, necrosis, and mitotic activity more than 5 per 50 hpf. Cases that met the criteria are said to be more likely recurrent.^{9,12} In this case, macronucleoli found in vesicular nuclei but there is no extensive area of necrosis and mitotic activity less than 5 per 50 hpf.

Kameyama and Takami tried to simplify the classification of PTCA with dividing this tumor to minimal and extensive invasion, in order to shed light on the clinician regarding the prognosis of PTCA cases.¹² Referring to the recent classification, these cases

presumably belonging to parathyroid carcinoma with extensive invasion, because both macroscopically and microscopically tumor has invaded many surrounding structures.

Because of its rarity, parathyroid carcinoma is often misdiagnosed with parathyroid adenoma which is more common. Clinical manifestations that distinguish parathyroid carcinoma with adenoma include same sex ratio between men and women (different from the adenoma that more common in women), a relatively young age, marked elevated levels of serum calcium and parathyroid hormone, also bone and kidney involvement. Parathyroid carcinoma is usually larger than adenomas (so it palpable on physical examination), and attached to the thyroid gland and soft tissues in the neck.^{10,18}

Another differential diagnosis is parathyromatosis, the implantation of parathyroid tissue in soft tissue. This situation usually following parathyroid adenoma surgery due to incomplete excision or capsule rupture. Microscopically, parathyromatosis are difficult to differentiate with PTCA, but these abnormalities do not cause obvious symptoms of hyperparathyroidism and there was history of parathyroid surgery.¹⁸

Immunohistochemistry examination is useful to improve the accuracy of PTCAs diagnosis.¹⁰ These tumors have positive staining of parathyroid hormone (PTH), chromogranin, and synaptophysin, but negative staining on thyroglobulin, calcitonin, and thyroid transcription factor-1.¹ In this case we performed immunohistochemistry staining of thyroglobulin and chromogranin to confirm origin of the tumor. The tumor cells showed positivity on chromogranin staining, whereas negative for thyroglobulin; ensure that these tumors originate from the parathyroid.

Proliferative markers such as Ki-67, cyclin D1 and p27 indicate abnormal expression in PTCA but the values are overlapping with adenomas so that are rarely used as additional tests to distinguish carcinoma with parathyroid adenoma.^{3,10} Research on genetic disorders give new insights into the pathogenesis of PTCA. The role of HRPT2, a tumor suppressor gene that encodes a parafibromin protein, was first demonstrated by Howell et al in 2003. In subsequent studies, Shattuck et al found a mutation of this gene in 10 of 15 patients with PTCA but not in adenoma.¹⁸ Khanafshar and Zante observed, in problematic cases, a combination of parafibromin and galectin-3 is the most useful. Loss of expression parafibromin has a high specificity, and on the other side, galectin-3 positivity is very sensitive for detecting PTCA.¹⁹ In

this case, molecular examination is not done because of the limited availability of reagents.

Surgery is the only effective therapy in PTCA management. If the intraoperative findings suspicious for malignancy then the surgeon must perform en bloc resection, because the situation will become difficult if a diagnosis of parathyroid carcinoma made postoperatively through histopathological examination. In such circumstances, patient must undergo re-exploration of the neck to remove the tissue structure adjacent to the tumor mass. Although no large-scale clinical trials studying the effects of other additional therapies, but some references mention parathyroid carcinomas are less responsive to chemotherapy and radiation.^{2,6} The en bloc resection which done in this patient is appropriate, but we afraid there were still residual tumor attached on the nerve.

Parathyroid carcinoma has a tendency to recur but appropriate surgical approach can reduce these risks. Local recurrence rate in patients who underwent en bloc resection was 8%, with a survival rate of 89%. It is contrary to local recurrence in patients undergoing simple parathyroidectomy i.e. 51% with a survival rate of 53%.^{1,20}

In addition, so far there was no staging criterias for parathyroid carcinoma. TNM staging system that commonly used in malignant tumors could not be applied for two reasons. First, PTCA rare metastasis to lymph nodes, and the second, tumor size does not play a role in determining prognosis.⁵

Patient in these case report did not undergo follow-up at our hospital, so that post-operative conditions can not be known clearly.

In conclusion, parathyroid carcinoma is an endocrine malignancy which requires interdisciplinary evaluation and management. We hope the greater understanding of the pathogenesis of parathyroid cancer, including the molecular pathology, will lead to the improvement of its management.

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