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Water-clear Cell Carcinoma of Parathyroid Gland with Primary Hyperparathyroidism: First Case Report with Review of the Literature

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Abstract

Parathyroid tumor of water-clear cell type is extremely rare and all cases that have been reported to date are adenoma. These tumors are composed of cells with foamy cytoplasm containing abundant glycogen. Here we report a case of water-clear cell carcinoma of the parathyroid gland in a 74-year-old Japanese woman who presented with mildly increased serum calcium (10.9 mg/dl, reference range 7.8-10.6 mg/dl) and intact parathyroid hormone (137.0 pg/ml, reference range 4.0-65.0 pg/dl). Both ultrasound examination and ^{99m}Tc-MIBI subtraction scintigraphy revealed a small tumor mass in the posterior aspect of the left side of thyroid gland. The patient was clinically diagnosed as parathyroid adenoma with primary hyperparathyroidism and underwent surgical resection. The excised tumor measured 1.5 x 1.2 x 0.6 cm and weighed 1.0 gram. Histologically, the tumor was composed of water-clear cells, exhibiting vascular invasion. These findings led to the diagnosis of water-clear cell carcinoma of the parathyroid gland although cellular atypia and mitotic activity were unremarkable. Three-year follow-up after surgery showed neither distant metastases nor recurrence of the hyperparathyroidism. To the best of our knowledge, the present case is the first case of water-clear cell carcinoma of the parathyroid gland. In this report, we also reviewed the reports of water-clear cell tumors and discussed the diagnostic criteria of malignant parathyroid tumors.

Keywords: Water-clear cell carcinoma, parathyroid carcinoma, parathyroid adenoma, primary hyperparathyroidism

Introduction

Primary hyperparathyroidism caused by parathyroid carcinoma is relatively rare. Many researchers have discussed the criteria for distinguishing parathyroid carcinoma from adenoma (1-3). It is generally agreed that the pathological criteria for malignant parathyroid tumors are the invasive features and metastases, rather than cellular atypia, while the most important features indicating invasion are tumor cells invading into vessels, perineural space, and surrounding capsule (1-3). Histologically, majority of the functioning tumors including adenoma and carcinoma consist of an admixture of chief cells and oncocyts with a predominance of chief cells, although clear cells are also encountered. Up to now, only eight cases of water-clear cell adenoma with primary hyperparathyroidism have been reported in literature (4-11). To the best of our knowledge, no cases of water-clear cell type carcinoma of the parathyroid gland have been described in English and Japanese literature. We encountered a case of parathyroid water-clear cell tumor exhibiting vascular invasion. We diagnosed this tumor as water-clear cell carcinoma of the parathyroid gland, and report it here as the first case of water-clear cell type carcinoma.

Case Report

Clinical history

The patient is a 74-year-old Japanese woman who was admitted to our hospital in January 2011 for evaluation of hyperparathyroidism. She had been treated for Hashimoto's thyroiditis since 2008. General examination showed that the patient had slightly elevated serum calcium (10.9 mg/dl, reference range 7.8-10.6 mg/dl) and decreased serum phosphorous (2.7 mg/dl, reference range 2.5-4.5 mg/dl) before admission. Further examination revealed an elevated level of parathyroid hormone (intact PTH, 137 pg/dl; reference range 4.0-65.0 pg/dl). Other laboratory tests including Na, K, CI, alkaline phosphatase, free triiodothyronine, free thyroxine, human stimulating hormone, thyroglobulin antibody, thyroid peroxidase antibody were all within normal ranges. Her physical examination was unremarkable. Ultrasound examination of the patient's neck demonstrated a well-defined tumor (1.5 x 2 cm) in the lower pole of the left lobe of thyroid gland (Fig. 1a). ^{99m}Tc-MIBI subtraction scintigraphy defined a tumor with increased uptake of radionuclide at the same location revealed with ultrasound. Based on these findings, the patient was diagnosed with parathyroid adenoma, and surgical resection was performed in our hospital in February 2011.

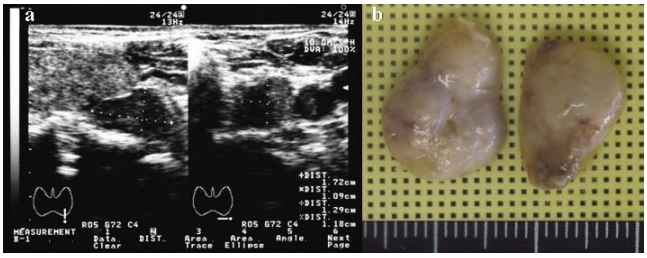

Figure 1. 1a: Ultrasound sonogram showing a well-defined tumor (1.5 x 2 cm) in the lower pole of the left lobe of thyroid gland. 1b: Macroscopic appearance of the tumor measured 1.5 x 1.2 x 0.5 cm and weighed 1.0 gram.

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Gross findings

The tumor involved a single gland (the left lower gland) without apparent invasion to the thyroid gland and other adjacent structures. The excised tumor was soft in consistency, brownish in appearance and covered with a thin capsule. The cut surface of the tumor was brown-yellow in color. The tumor measured 1.5 x 1.2 x 0.6 cm and weighed 1.0 gram (Fig. 1b).

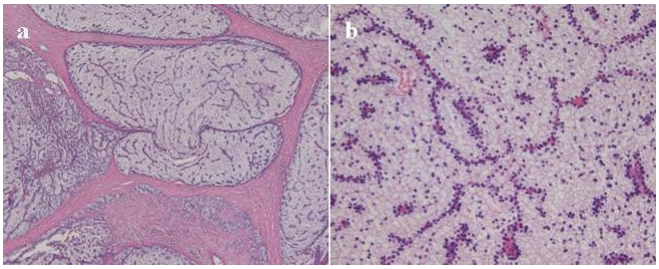

Figure 2. Histology of the tumor. 2a showing water-clear cells with abundant foamy cytoplasm and arranged in large nests with band-forming fibrosis in the stroma (40X). 2b showing the water-clear cells at high magnification (100X) (H&E stain).

Histopathology

The tumor had a dense fibrous capsule and the tumor cells were arranged in nests with band-forming stromal fibrosis (Fig. 2a). A rim of normal parathyroid tissue was identified outside the capsule. The tumor was composed of pure water-clear cells with abundant foamy cytoplasm (Fig. 2b). These cells contained abundant glycogen as demonstrated by diastase-sensitive Periodic-acid-Schiff reactivity (Fig. 3a and 3b). Neither nuclear atypia nor mitotic figures were remarkable, giving a bland impression. However, prominent vascular invasion was identified in the periphery of this tumor (Fig. 4a and 4b), which led us to diagnose the present case as water-clear cell carcinoma of the parathyroid gland.

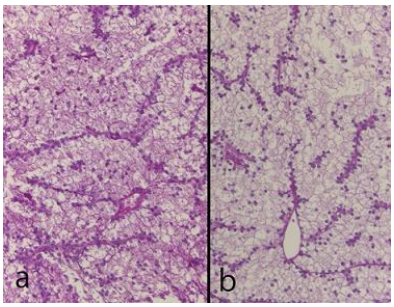

Figure 3. Periodic-acid-Schiff (PAS) staining. 3a shows granules in the water-clear cell cytoplasm with PAS staining (100X). 3b shows decreased granules with PAS staining after diastase digestion, supporting that the granules were glycogen (100X).

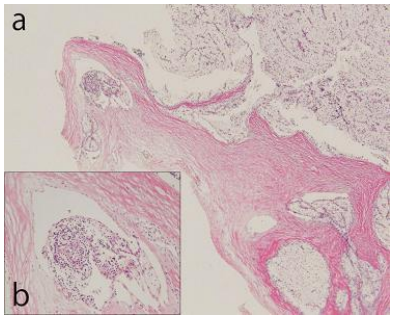

Figure 4. 4a shows the tumor cells invading into blood vessels in the tumor capsule (40X) and 4b shows the high magnification of the intravascular aggregate of tumor cells (200X).

Immunohistochemistry

On the immunohistochemical studies with the formalin-fixed paraffin-embedded tumor tissue, the tumor cells were strongly positive for PTH (Novocastra, Newcastle upon Tyne, UK) (Fig. 5a) and negative for CD10 (Nichirei, Tokyo, Japan). Labeling of the vascular endothelial cells with CD34 staining (Nichirei, Tokyo, Japan) confirmed the intravascular invasion of tumor cells (Fig. 5b). The labeling index of tumor cells was <1% with Ki-67 staining (DAKO, Glostrup, Denmark).

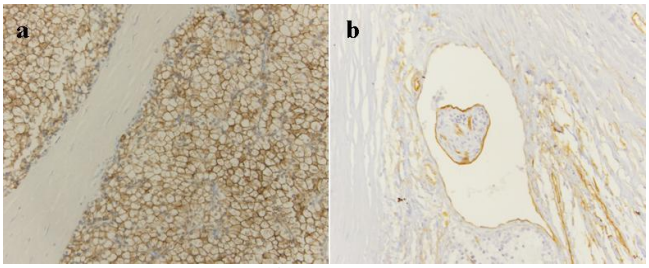

Figure 5. 5a: Immunostaining for PTH demonstrating strong positivity in the tumor cytoplasm and cell membrane (200X). 5b: Immunostaining for CD34 showing endothelial cell lining of blood vessels with an intravascular tumor aggregate, a definite evidence of vascular invasion by the tumor cells (200X).

Clinical follow-up

Postoperative course was uneventful. The patient experienced no hypocalcemic symptoms and required no medication of either calcium or vitamin D. The serum levels of calcium and intact PTH of the patient remained within the normal range 34 months after surgery.

Discussion

Parathyroid carcinoma is a rare disease accounting for 1-5% of all patients with primary hyperparathyroidism (1, 12-14). Careful attention is required to the pathological features for malignancy of tumors from endocrine organs. Various factors such as tumor size, histological appearance and Ki-67 labeling index must be considered when malignancy is diagnosed. In general, large tumors are more likely to be malignant. In a series of six patients with early parathyroid carcinoma reported by Uematsu et al., all tumors were ≥2 cm in diameter and two of them were ≥4 cm (15). Many pathologists have pointed out that band-forming fibrosis, rosettes formation, and high mitotic activity are features of carcinoma (1, 3, 16). A Ki-67 labeling index of >5% indicates potential malignancy of a parathyroid tumor (17, 18). Nevertheless, the most reliable criteria for diagnosis of malignancy are the invasive growth and distant metastases of tumor cells. The former includes vascular invasion, perineural space invasion, and capsular penetration with growth into adjacent tissues (1). These criteria are identical to those of follicular carcinoma of the thyroid gland. In the present case, the tumor exhibited vascular invasion although other features such as nuclear atypia and mitotic activity were unremarkable, and the tumor was relatively small. Furthermore, the Ki-67 labeling index of this tumor was <1% and its histological appearances, except for the vascular invasion, were similar to those of adenoma. These features made the tumor difficult for clinical doctors to suspect carcinoma before surgery.

Regarding the cell types, most parathyroid adenomas are composed of an admixture of chief cells and oncocytes. Clear cells are encountered as one type of tumor cells in some parathyroid adenomas. But pure water-clear cell type adenoma (a tumor composed exclusively of water-clear cells) is rare, and only eight such cases have been reported to date with none of them meeting

the criteria of malignancy (4-11). To the best of our knowledge, this is the first case of parathyroid carcinoma with pure water-clear cells in literature. Clear cell carcinoma should be differentiated from other tumors, especially the metastatic renal cell carcinoma. The tumor cells in the present case were positive for PTH and negative for CD10, demonstrating its parathyroid cell origin, although the exact etiology for the development of water-clear cells is unclear.

The clinical manifestations of parathyroid carcinoma are largely due to the effects of excessive PTH secretion. Severe hypercalcemia, a very high PTH level, and elevated serum alkaline phosphatase activity are more commonly present in patients with parathyroid carcinomas than those with adenoma (19-21). In the present case, the serum levels of calcium and PTH were only mildly increased. Kanda et al. have postulated that water-clear cell adenoma may have a low endocrinological activity, thereby the serum calcium concentration may not reach a high abnormal level until that the adenoma is of considerable size (3). This may explain why the present case presented mildly increased endocrinological activity.

To reduce recurrence, aggressive initial treatment is critical and en bloc resection with ipsilateral thyroid lobectomy is usually recommended (22, 23). In the present case, simple resection of the tumor was performed under the clinical diagnosis of parathyroid adenoma, which might be insufficient for treatment of parathyroid carcinoma. Although the postoperative course (34 months after surgery) of the patient was uneventful, the intact PTH and serum calcium levels remained within the normal ranges, and there was no evidence of residual tumor and tumor recurrence, the surgeons were advised to follow-up the patient carefully considering the potential risk of recurrence (12, 24).

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