Endocr Pathol (2012) 23:196–200
DOI 10.1007/s12022-012-9211-1

Water-Clear Parathyroid Adenoma: Report of Two Cases and Literature Review

Shuting Bai · Virginia A. LiVolsi · Douglas L. Fraker · Zhanyong Bing

Published online: 26 May 2012

Introduction

Water-clear cell parathyroid adenoma is very rare. Based on our institution database of parathyroid adenoma in 2010 and 2011, water-clear cell parathyroid adenoma is about 0.4 % of parathyroid adenomas in this period. Only ten cases have been reported in English literature [1–10]. Water-clear cell adenoma consists of large polygonal cells with abundant clear cell cytoplasm; most of the patients presented as primary hyperparathyroidism. Water-clear cell adenoma can morphologically mimic numerous tumors composed of clear cells, especially metastatic clear cell renal cell carcinoma. We reported here additional two cases of water-clear cell adenoma with review of the literature.

Case Report

Clinical Information

Case 1

The patient was an 81-year-old man with biochemical hyperparathyroidism. The ultrasound of the neck was negative. The Tc99m nuclear scan showed a lower neck lesion with isotope uptake and persisted on the delayed images. The preoperative parathyroid hormone (PTH) was 22.2 pmol/L (normal 1.3–6.8 pmol/L), which decreased to 3.2 pmol/L postoperatively.

Case 2

The patient was a 55-year-old man with biochemical hyperparathyroidism. His parathyroid nuclear scan was negative. Ultrasound study did not show abnormality of parathyroid. In addition, he had a biopsy-proven papillary thyroid carcinoma. He underwent total thyroidectomy, right neck lymph node dissection and parathyroidectomy. His PTH level returned to normal after parathyroidectomy (from preoperative 15.9 pmol/L to postoperative 1.6 pmol/L).

Pathology

Gross Examination

For case 1, the lesion from the right upper parathyroid site measured 4.0×2.5×1.6 cm and weighed 6.91 g. It was yellow tan on cut surface. For case 2, the left upper parathyroid measured 1.4×0.8×0.6 cm and weighed 0.27 g. In addition, the case 2 patient also had a papillary thyroid carcinoma in the right lobe of thyroid.

Microscopic Findings

Microscopically, both parathyroids were composed of hypercellular follicles with predominant large polygonal cells. The cytoplasm was water-clear (Fig. 1b), which appeared to be filled with numerous vacuoles (Fig. 1c or f) by toludine blue stains. The cells were well demarcated. The tumor nuclei were small, round, with smooth nuclear contours, and located

S. Bai · V. A. LiVolsi · Z. Bing (✉)
Department of Pathology and Laboratory Medicine, 6 Founders,
Hospital of the University of Pennsylvania,
3400 Spruce Street,
Philadelphia, PA 19104, USA
e-mail: bingz@uphs.upenn.edu

D. L. Fraker
Department of Surgery, University of Pennsylvania Health System,
Philadelphia, PA, USA

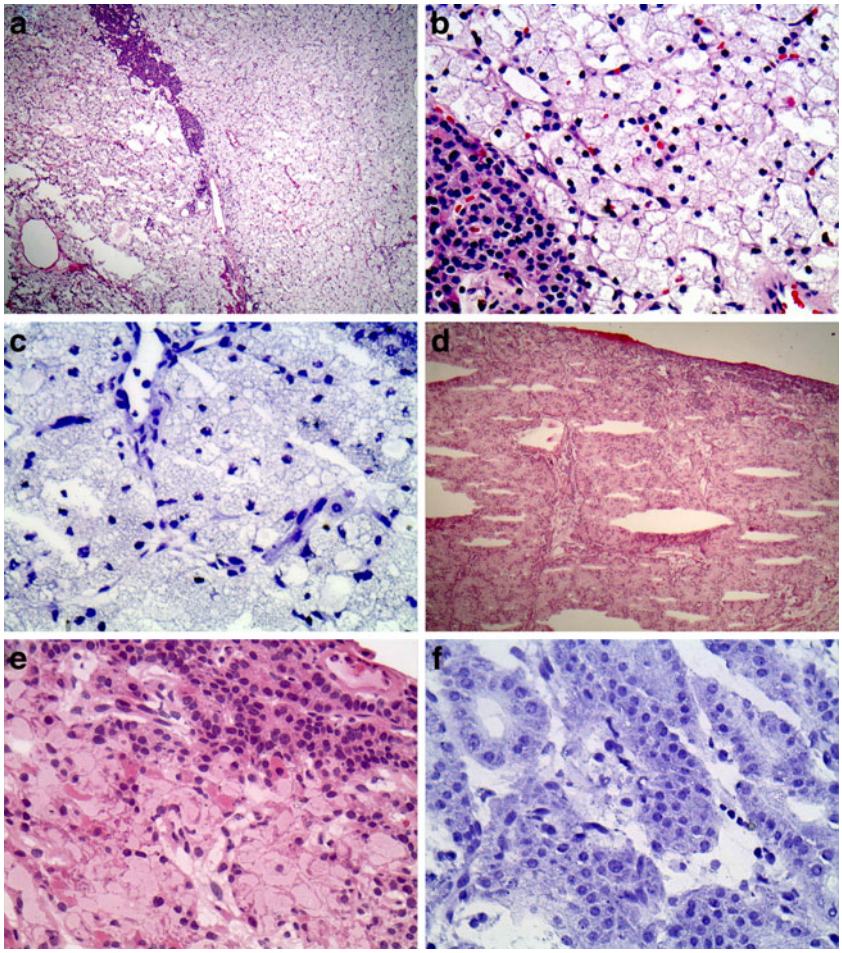

Fig. 1 Morphology of water-clear cell parathyroid adenoma: **a**–**c**: Case 1. **a** H&E 50X; **b** H&E, ×400; **c** toludine blue, ×400. **d**–**f**: Case 2. **d**: H&E ×50; **e** H&E, ×400; **f** toludine blue, ×400

centrally or at a side (Fig. 1b/e). No mitosis or coagulative necrosis was seen. In addition to these water-clear cells, there were small clusters of normal appearing parathyroid cells located in the periphery of the glands or adjacent to the blood vessels in both cases (Fig. 1a/d). The tumors were subjected to the immunohistochemical stain. The tumor cells were strongly positive for PTH (Fig. 2a) and chromogranin (Fig. 2b), and interestingly, they are also focally positive for renal cell carcinoma marker (2 C). By using parathyroid carcinoma as the negative control, parafibromin stain revealed positive nuclear expression in both tumors (Fig. 2d).

Discussion

Primary parathyroidism predominantly results from solitary parathyroid adenoma (85 %), less commonly from hyperplasia (10 %), multiple adenoma (4 %), and carcinoma (1 %) [11]. Most of the adenomas are composed of a mixture of chief and oxyphilic cells. Water-clear cell parathyroid adenoma is extremely rare. To our knowledge, only ten cases have been reported in the English literature [2–10]. In this report, we presented two new cases of water-clear parathyroid adenoma. Both lesions were solitary, composed of large polygonal cells with clear cytoplasm and round small nuclei without prominent nucleoli. Both patients showed intraoperative PTH levels returned to normal after removing the adenomas. The combined findings supported the diagnosis of water-clear parathyroid adenoma.

Among the 12 water-clear cell parathyroid adenomas cases (including the current two cases), only one patient presented double parathyroid adenomas. There were six males and six females. The average age of these patients is 52 years old (range 18 to 81 years old). The clinical symptoms are mainly dependent on the length and severity of hypercalcemia and increased PTH levels. Ten patients had high PTH and two patients presented with kidney stones.

The ultrastructure of water-clear cells from human's parathyroid clear cell hyperplasia [12, 13], normal parathyroids from golden hamsters [14], rabbits [15], possums [16], monotremes [17], and SAMP6 mice [18] have been examined. Ultrastructural study was also reported previously in a water-clear cell parathyroid adenoma [3]. The water-clear cells appear to be derived from the chief cells. The cytoplasm of water-clear cells is largely filled with spherical, 0.2–2 um in diameter, membrane-limited vacuoles. The

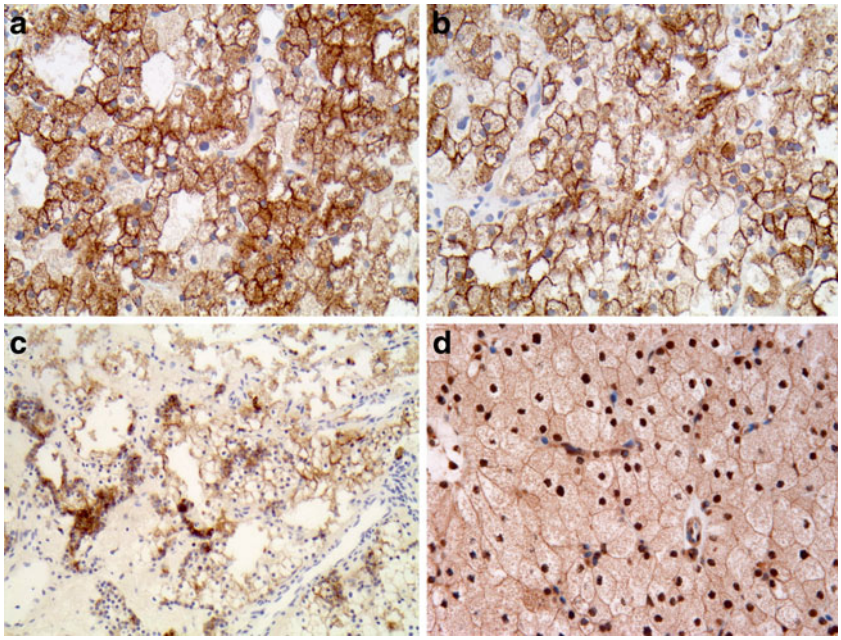

Fig. 2 Immunohistochemical study. **a** PTH, ×400; **b** chromogranin, ×400; **c** RCC Ma, ×400; **d** parafibromin, ×400

membranes of the vacuole consist of the trilaminar membranes. Most vacuoles appeared empty or contained a finely granular or thread-like material [12, 13, 18]. Ultrastructural examination was performed on our paraffin-embedded tissue and the preservation was suboptimal. The cytoplasm of the tumor cells were filled with various-sized vacuoles. Due to the suboptimal preservation, it was difficult to determine whether there were ribosomes attached to the surfaces of the vacuoles.

The origin of the vacuoles is still controversial. Several hypotheses are presented. Some believe that the vacuoles arising from the golgi region and resulting from the manufacture of cytomembranes by this organelle [3, 12, 16], as the contents in these vacuoles resembles those of the Golgi vesicles, and small vacuoles, larger than the usual Golgi vesicles, are often present in the Golgi region. Some authors believe that the vacuoles derive from distended cisternae of the granular endoplasmic reticulum, citing the presence of ribosomes on the surfaces of the vacuoles [14, 19] as evidence. Some authors think that the vacuoles arise from the secretory granules, arguing that appearance of membrane structures with characteristics intermediate between secretory granules and water-clear vacuoles [20].

The appearance of water-clear cells may represent hyperfunction of the parathyroid glands in SAMP6 mice [18] as with the aging of the animals, the number of water-clear cells in the parathyroids increases parallel to the increasing of the level of PTH.

The differential diagnosis includes metastatic clear cell renal cell carcinoma (ccRCC), chromophobe renal cell carcinoma as well as tumors with clear cells as a major component. Water-clear cell parathyroid adenoma can vividly mimic the metastatic renal cell carcinoma, and may lead to misdiagnosis, especially during intraoperative frozen section. In this situation, patient's history, especially preoperative imaging, and intraoperative PTH test will be helpful in reaching a correct diagnosis. Morphologically, the adenomas may have small clusters of cells with normal parathyroid morphology which are usually in the periphery or perivascular areas of the glands; this may aid in the diagnosis. On permanent sections, immunohistochemical stain for PTH and chromogranin can be helpful.

Renal cell carcinoma can synthesize PTH-like protein and lead to the symptoms of hyperparathyroidism and hypercalcimia [21, 22] and mimic primary hyperparathyroidism clinically. Parathyroid tissue can be positive for immunohistochemical markers commonly used in renal epithelial neoplasm such as renal cell carcinoma marker (RCC Ma) and Pax8. RCC Ma is a monoclonal antibody against a normal human proximal tubular brush border antigen [23]. RCC Ma highlights approximately 80 % of primary renal cell cancers, and is a useful marker in small biopsies. In addition, it is useful for the differential diagnosis from renal oncocytoma when the tumor is mainly composed of eosinophilic cells [23]. RCC Ma can be positive in parathyroid carcinoma [24]. RCC Ma was detected as positive in both of our cases. Therefore one should be prudent in using this marker to differentiate these two identifies. Pax2 is a useful marker for renal cell tumors [25–28]. Pax2 is a transcriptional factor of paired box family expressed in the ductal and mesanchymal components of the genitourinary system [29–32]. Rarely, benign parathyroid tumor can be positive for this marker (6 %) [25–28]. Pax2 is a relatively specific marker in differentiating these two identities.

Parafibromin is a tumor suppressor gene encoded by HRPT2, locating in human chromosome 1q31.2. Parafibromin

mutations have been detected in 66 to 100 % of sporadic parathyroid carcinoma [33, 34]. Parathyroid carcinomas in both Hyperparathyroidism–jaw tumor syndrome–related and sporadic cases are characterized by loss of nuclear parafibromin immunoreactivity [35], which may function as a diagnostic and prognostic marker for parathyroid lesions [36]. Furthermore, decreased expression of parafibromin was found to be inversely correlated with depth of invasion, lymph node metastasis, and tumor staging in gastric and colorectal carcinomas [37, 38]. The expression of parafibromin in renal epithelial tumors appears to correlate with tumor type, with ccRCC having only about 8 % positivity [39]. No report for parafibromin expression in English literature was noted for water-clear parathyroid adenoma. The Immunohistochemical stain for parafibromin in our cases show nuclear staining for both cases. Since there are some morphological and immunohistochemical staining overlap between ccRCC and water-clear parathyroid adenoma, to distinguish metastatic ccRCC from water-clear parathyroid adenoma, extensive clinical and radiological examination is critical. The positive nuclear staining of parafibromin in our two cases is consistent with a benign behavior of these tumors and may aid in the differential diagnosis.

In summary, water-clear cell parathyroid adenoma is extremely rare and can be a diagnostic pitfall for a metastatic renal cell carcinoma or other carcinomas with clear cell components. Correlation with clinical history, intraoperative PTH testing, diligently searching for small portion of conventional parathyroid tissue, usually at the periphery or perivascular foci can help to reach a correct diagnosis. In difficult cases, immunohistochemical stain may be helpful; however, it should be noted that some commonly used renal cell carcinoma markers, such as RCC Ma and Pax8 can be positive in parathyroid tumors. Parafibromin is positive in this tumor, consistent with its benign behaviors and may aid in the differential diagnosis.

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