Water-Clear Cell Adenoma of Parathyroid Gland: A Case Report and Literature Review

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Abstract

Parathyroid adenoma of water-clear cell type is an extremely rare neoplasm, and only very few cases have been reported to date. Here we report a case of water-clear cell adenoma of the parathyroid in a 59-year old female patient who presented with hypercalcemia and high parathyroid hormone (PTH) level. Sestamibi scan showed a possible parathyroid adenoma involving the right superior parathyroid gland. The surgically excised specimen weighed 13.3 grams and contained a cystic hemorrhagic mass measuring 1 x 1 x 0.8 cm. Histologically, the tumor mass was surrounded by a thin fibrous capsule with a compressed thin rim of normal parathyroid tissue. High power examination revealed the tumor to be composed of cells with vacuolated cytoplasm, and with minimal nuclear pleomorphism. Immunohistochemical analysis demonstrated positive staining for PTH and chromogranin. Histological examination of the right inferior parathyroid gland showed unremarkable parathyroid tissue. Post-operatively, the patient's serum calcium level returned to normal. These findings support the diagnosis of water-clear cell adenoma of the parathyroid gland. In this report, we also reviewed related literature and compared our case with similar cases reported before.

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Introduction

Adenoma of parathyroid gland is the most common cause of hyperparathyroidism.[1] Parathyroid adenomas are mainly composed of chief cells or mixed cell type, whereas oxyphil cell type is less common. Most parathyroid adenomas are solitary and in rare cases can be multiple.[2] Water-clear cell adenoma of parathyroid gland is a very rare neoplasm, composed of cells with vacuolated or granular cytoplasm. Up to now, only seven cases have been described in English literature.[3-9] In general, it is not difficult to differentiate water-clear cell adenoma (WCCA) from water-clear cell hyperplasia (WCCH), because WCCH usually involves all four glands while water-clear cell adenoma very rarely affects more than one gland. However, the confusion still exists because WCCH can happen in an asymmetric pattern. The four glands may vary considerably in size and may not be completely replaced by water-clear cells.[10-12] Differentiation between the hyperplasia and adenoma is important in terms of the clinical management. The resection of the adenoma is considered curative, while the surgeon needs to remove three glands and possibly a portion of the fourth to treat hyperplasia. As a result, strict criteria have been proposed for diagnosing adenomas of parathyroid gland.

Here we report another case of water-clear cell adenoma of parathyroid gland as a cause of hyperparathyroidism diagnosed at our hospital.

Case Report

The patient is a 59-year old African-American female, and first presented at the Ear, Nose and Throat (ENT) clinic for evaluation for her thyroid and parathyroid in 2009. She had elevated calcium on a routine exam and complained of mood changes and lethargy, though she denied any history of renal calculi. She had a serum calcium level of 11.8 mg/dL (reference range 8.5 - 10.5 mg/dL) and a PTH level of 265 pg/mL (reference range 12 - 72 pg/mL). Sestamibi scan of the parathyroid glands showed a probable "adenoma" in the left superior location. Ultrasound also showed thyroid nodules. The patient then underwent surgical excision of the "parathyroid adenoma" and thyroid nodule one month later. The pathology review demonstrated "Parathyroid tissue showing focally decreased adipose tissue". However, the patient had persistent hypercalcemia of 12.3 mg/dL and PTH of 371 pg/mL after the surgery. Another Sestamibi scan showed "a possible parathyroid adenoma involving the right

superior gland". The patient underwent a second surgery to excise the lesion 2 months later, and the specimen was sent to pathology. The patient's calcium level went down to 10.4 mg/ml one day after, and 8.8 mg/ml and 7.4 mg/ml two days after the second surgery.

Grossly, the specimen of the right superior gland was an oval-shaped fragment, yellow-pink in color. It weighed 13.3 grams and measured 4.5 x 3.5 x 1.3 cm. Serial sectioning revealed a hemorrhagic cystic lesion of 1 x 1 x 0.8 cm. The specimen was extensively sampled for both frozen section diagnosis and paraffin embedded histological diagnosis as well as immunohistochemistry (IHC) studies.

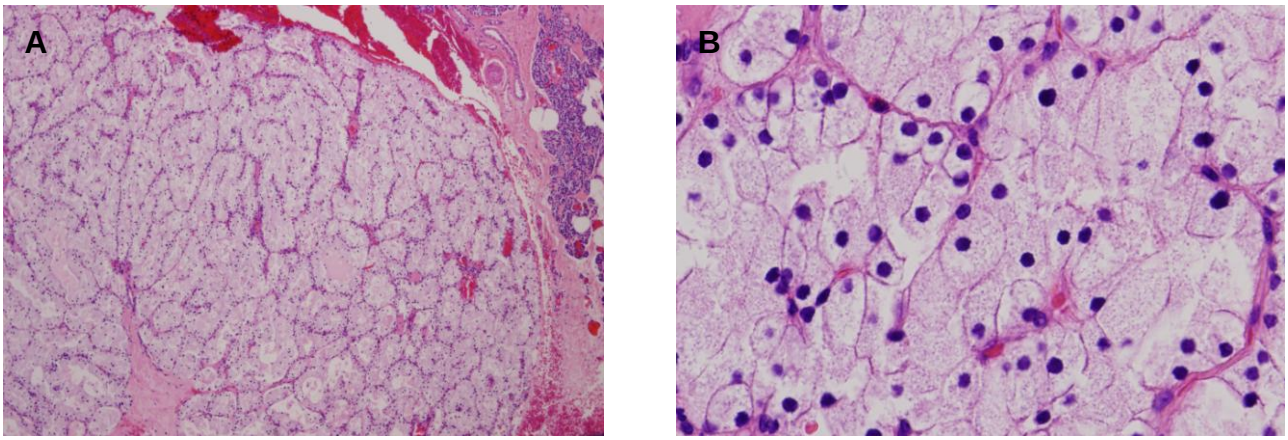

Figure 1. Histology of water-clear cell adenoma by H&E staining. **A.** Low power view shows a well-circumscribed and thin-capsulated mass composed of nests of neoplastic cells with eosinophilic cytoplasm. Compressed normal parathyroid gland can be seen at right upper corner. **B.** High power view shows neoplastic cells have round to oval hyperchromatic nuclei and plump eosinophilic granular cytoplasm with distinctive cell border.

Microscopic review of the H&E stained sections, shown in **Figure 1**, revealed that the tumor was well circumscribed with a thin fibrous capsule. The tumor was composed of sheets of uniform, intermediate sized water-clear cells. The cells had distinct borders and the cytoplasm was finely vacuolated or granulated. The nuclei had finely stippled chromatin with minimal pleomorphism. In some areas the cells were arranged in nests separated by fine fibrovascular septa. A thin rim of extracapsular normal parathyroid tissue was present. Histological examination of the right inferior parathyroid gland biopsied during the surgery showed unremarkable parathyroid tissue with intercellular fat (not shown). Based on these typical histological findings,[13] the diagnosis of water-clear adenoma of parathyroid gland was given. The diagnosis was further supported by the immunohistochemistry studies shown in **Figure 2**, which demonstrated that the tumor cells to be positive for PTH and chromogranin, and negative for synaptophysin. The negative staining results of CD10 and EMA made the differential diagnosis of metastatic renal cell carcinoma unlikely and the negative staining S-100 excluded the possibility of granular cell tumor.

Discussion

Adenoma of the parathyroid gland is the most common cause of hyperparathyroidism accounting for 80-85% of the cases. Other causes include multigland hyperplasia (15%) and parathyroid carcinomas (1%).[1] Most patients having adenomas are between 50 to 60 years of age. Approximately half of the patients are asymptomatic and with high serum calcium levels found on routine chemistry tests, like the patient in our case. Other patients can have renal stones and skeletal diseases. The diagnosis of hyperparathyroidism is confirmed by high serum calcium and high PTH levels. The hyperfunctioning tumor in the parathyroid gland can be detected by the sensitive Tc-99m-labeled Sestamibi scan. Surgical excision of the tumor is usually curative, however the rate of recurrence is estimated at 10%.[14]

Parathyroid adenoma typically involves a single gland, however multiple adenomas, either unilateral or bilateral, have been reported.[14] Patients with two adenomas usually have higher PTH levels. When adenomas involve two parathyroid glands, the distinction from parathyroid hyperplasia can be difficult. Parathyroid gland hyperplasia, by definition, involves all four parathyroid glands, but hyperplasia can happen in an asymmetric form, with two glands being more prominent than the others. So strict clinical criteria must be applied to diagnose double adenomas, even though these criteria are sometimes confusing:[2]

1) More than 1 and less than 4 enlarged parathyroid glands are present, confirmed histologically;
2) At least one normal parathyroid gland;
3) No evidence of multiple endocrine neoplasia or familial hyperparathyroidism;
4) Permanent normalization of calcium level after resection of the enlarged glands.

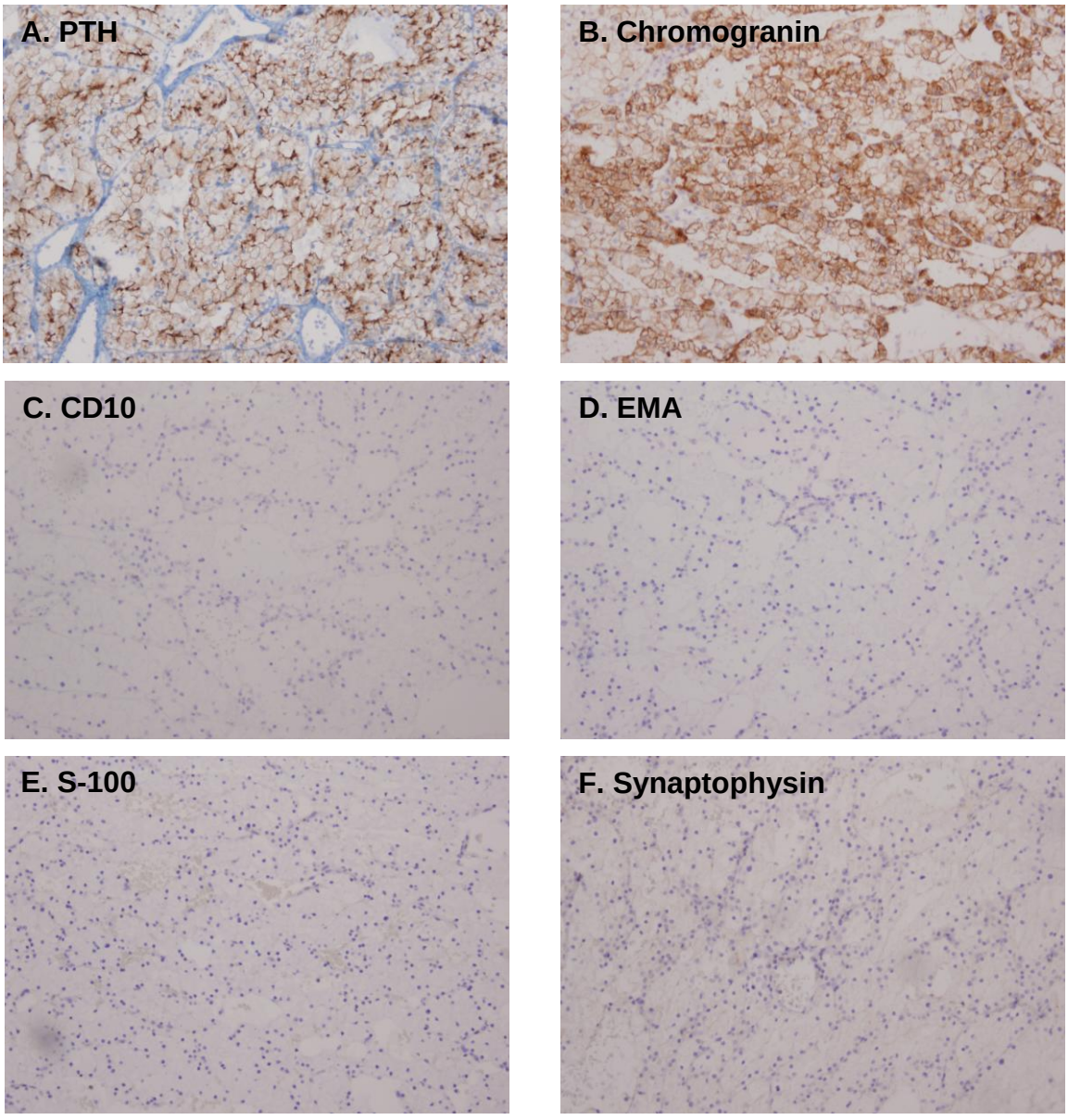

Figure 2. Immunohistochemistry staining of the parathyroid tumor. Positive staining for PTH in **A**, and Chromogranin in **B**; Negative staining for CD10 in **C**, EMA in **D**, S-100 in **E** and Synaptophysin in **F**.

The distinction between double adenomas and hyperplasia has significant clinical importance because of the difference in surgical management. For double adenomas, resection of the two involved glands is considered curative, however, for hyperplasia the recommended treatment is to resect three and a half of the parathyroid glands or resect all four glands and do a parathyroid tissue implant.[15] As a result, correct differentiation between adenomas and hyperplasia can avoid unnecessary surgery and its complications, such as nerve palsy and hypoparathyroidism.

Histologically, parathyroid adenoma is well circumscribed and has a thin rim of compressed normal-appearing parathyroid tissue. Parathyroid adenoma is usually composed of chief cells or functioning oxyphilic cells. The tumor cells form sheets, cords, acinars, and microcysts, with a delicate capillary or sinusoidal network. The nuclei are usually dark, round and uniform. The chromatins are finely stippled.

Compared to the conventional adenomas, water-clear cell variant of the parathyroid adenoma (or water-clear cell adenoma, WCCA) is a rare pathological entity. So far, only seven cases have been described in English literature.[3-9] Water-clear cell changes in parathyroid hyperplasia as a cause of hyperparathyroidism was first described by Albright et al in 1934,[17] where all four glands are entirely composed of water-clear cells. Interestingly, for unknown reasons, the incidence of water-clear cell hyperplasia decreased from 12.8% to only 1% in the following decades in a series of cases from Massachusetts General Hospital.[10] The water-clear cells are polygonal with distinct cell borders. The

cytoplasm is often vacuolated, foamy, or granular rather than "clear". The origin of the vacuoles is still unknown, but is proposed be derived from Golgi apparatus in an electron microscopic study reported by Roth.[18] Many authors have observed that superior glands are usually larger than the inferior ones in asymmetric water-clear cell hyperplasia.[11-12,16]

WCCA of parathyroid gland has most features of the regular adenoma, i.e. being well-circumscribed, with a thin fibrous capsule and a thin rim of relatively normal extra-capsular parathyroid tissue. However, WCCA is composed of uniform cells with granular to finely-vacuolated cytoplasm. Some important features of the seven published cases are summarized in **Table 1**. In our case, the tumor in right superior parathyroid gland is composed of water-clear cells with a thin rim of compressed unremarkable parathyroid tissue present outside the fibrous capsule. However, the histologic examination of the right inferior parathyroid gland showed no specific pathologic abnormality without any signs of water-clear cell changes. All these findings are consistent with the diagnosis of WCCA. In addition, the patient has normalized calcium level after the second surgery.

Table 1. Summary of water-clear cell adenoma of parathyroid gland cases.

Author	Patient Age/gender	Clinical Presentation	Tumor	Management	Outcome
Kovacs et al,[7] 1994	48 yo/Male	Acromegaly, history of renal stone; increase serum Ca^{++}	Left lower gland; tumor with large clear cells and fibrous capsule; unknown size and weight.	Total parathyroidectomy	Serum Ca^{++} returned to normal after the surgery.
Grenko et al,[4] 1995	40 yo/Male	Fatigue, cramps; hypercalcemia; high PTH	Right superior gland; 5 x 3 x 1.5 cm, 7.6 grams.	Excision of right superior gland	Both Ca^{++} and PTH were normal at one and half years after the surgery.
Dundar et al,[3] 2001	43 yo/Female	Progressive tiredness; lethargy, cramps, high Ca^{++} and high PTH	Intra-thyroid parathyroid adenoma with water-clear cells; unknown size and weight.	Near total thyroidectomy	Normocalcemic with 5-year follow up.
Kuhel et al,[8] 2001	56 yo/Female	High Ca^{++}	Both right (2.8 cm, 1.7 g) and left (1.5 cm, 0.5 g) superior glands; encapsulated lesions of water-clear cells.	Excision of right and left parathyroid glands	Normocalcemic for 2 years postoperatively.
Kanda et al,[5] 2004	52 yo/Female	High Ca^{++} and high PTH	Left inferior parathyroid gland; 6.8 x 2.8 x 1.9 cm, 15.4 grams.	Excision of the left inferior parathyroid gland	PTH and Ca^{++} level returned to normal after the surgery.
Prasad et al,[9] 2004	40 yo/Female	Fatigue, cramps, muscle weakness; high serum Ca^{++} and high PTH	Left superior parathyroid gland; 3 x 1.5 x 1 cm, 4.2 grams.	Excision of left superior parathyroid gland	Normocalcemic for 9 years after the surgery.
Kodama et al,[6] 2007	18 yo/Female	Hypercalcemia with renal stones; and high PTH.	Right superior parathyroid tumor; 5 x 3.3 x 3 cm, 21.7 grams.	Excision of right superior parathyroid tumor	Normal Ca^{++} and normal PTH at 30 months after the surgery.
Liang et al (this case), 2009	59 yo/Female	Mood changes and lethargy; hypercalcemia and high PTH	Right superior parathyroid WCCA; 4.5 x 3.5 x 1.3 cm, 13.3 grams.	Excision of right superior parathyroid tumor	Serum Ca^{++} returned to normal after the surgery.

The H&E slides of the left superior parathyroid gland from the first surgery were also reviewed. The histologic feature showed the tissue was mainly composed of parathyroid chief cells with reduced adipose content. Although a microscopic focus of cells showed transparent cytoplasm, majority of cells were not "water-clear" cells. Since the specimen was small without a capsule, a diagnosis of "adenoma" could not be given. Based on the evidence we had, the patient did not have double water-cell adenomas of the parathyroid gland.

Besides water-clear cell hyperplasia, another differential diagnosis of this case is the chief cell adenoma of parathyroid. Although clear cells can be present in a conventional adenoma, the entire tumor should not be completely replaced by clear cells, as in the case of the water-clear cell variant. The clear cells in typical chief cell adenoma are admixed with chief cells and are positive for glycogen staining, which can be confirmed by PAS-diastase

sensitivity. On the other hand, water-clear cell adenoma is negative for glycogen according to one report by Grenko et al.[4] Other clear cell lesions in the neck may also be considered as differential diagnoses, including metastatic conventional renal cell carcinoma, paraganglioma, and clear cell changes in salivary gland tumors, such as mucoepidermoid carcinoma and acinar cell carcinoma.[4] Immunohistochemical staining of CD10, S-100, and PTH should be helpful in the suspected cases.

In summary, we describe a case of hyperparathyroidism with a diagnosis of water-clear cell adenoma of parathyroid gland. The tumor is completely composed of water-clear cells and has a well circumscribed capsule with compressed normal parathyroid gland tissue. The IHC studies demonstrate the tumor cells to be positive for PTH and chromogranin. The inferior gland is grossly and histologically normal. The patient's hypercalcemia was corrected after resection of the tumor. The overall histopathological and clinical features support the diagnosis of water-clear cell adenoma of parathyroid gland.

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