Double water-clear cell parathyroid adenoma: a case report and literature review

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Abstract. Water-clear cell parathyroid adenoma is an uncommon cause of primary hyperparathyroidism. Herein, we report an interesting case of a 56-year-old man who presented with weight loss, bone pain, fatigue, and a palpable right neck mass. Laboratory tests indicated hypercalcemia, elevated parathyroid hormone (PTH) levels, and normal thyroid function. Further examinations detected osteoporosis and kidney stones. The ultrasound of neck revealed bilateral extrathyroidal tumors, which were sestamibi-avid. The patient underwent resection of the large right inferior and left inferior parathyroid tumors. Histopathology revealed a double water-clear cell parathyroid adenoma. His serum calcium and PTH levels normalized after surgery. The literature review identified 37 cases of water-clear cell parathyroid adenoma between 1985 and 2021. The median age at diagnosis was 56 years. Classic complications were common, including nephrolithiasis in nine and skeletal presentations in 10 patients. Before surgery, the median calcium and PTH levels were 12.0 mg/dL and 290 pg/mL, respectively. Overall, 89% were localized on ultrasonography, and 60% were positive on scintigraphy. Four patients had double adenomas. The median maximum diameter was 3.8 cm, and the median weight of the resected adenoma was 5.27 g. In summary, water-clear cell parathyroid adenoma has certain unique features. These include larger tumor size, relatively indolent biochemical profile, high prevalence of complications and nonspecific symptoms, an isoechoic appearance on ultrasonography, and reduced scintigraphic sensitivity.

Key words: Water-clear cell, Parathyroid, Double adenoma, Primary hyperparathyroidism

PRIMARY HYPERPARATHYROIDISM is the most common cause of hypercalcemia [1]. The underlying pathophysiology is the loss of feedback suppression of serum calcium upon the synthesis and secretion of parathyroid hormone (PTH) owing to increased parathyroid cell mass and/or reduced expression of the calcium-sensing receptor. The diagnosis of hyperparathyroidism is based on hypercalcemia and non-suppressed PTH levels.

In 80% of cases of primary hyperparathyroidism, excessive secretion of PTH results from a solitary parathyroid adenoma. It has been documented that four-gland hyperplasia accounts for 10%–15% of cases, multiple adenomas in 5%, and parathyroid cancer in less than 1%. Histologically, parathyroid adenomas are composed of varying proportions of cell types that make up the normal parathyroid gland, but there is a typical predominance of

chief cells [2]. Uncommon variants include oxyphil adenomas, lipoadenomas, and water-clear cell adenomas.

Water-clear cells are characterized by optically clear cells with abundant foamy-to-granular cytoplasm, which is attributed to the presence of numerous small vacuoles derived from the Golgi apparatus [2]. Water-clear cell parathyroid adenoma is a rare cause of primary hyperparathyroidism [3]. In this report, we present a patient with double water-clear cell parathyroid adenoma and review the literature highlighting the unique features of this entity.

Case Report

A 56-year-old man was noted to have persistently high serum calcium levels on regular blood tests. His medical history was remarkable for essential hypertension and chronic tophaceous gout treated with medications. He reported a weight loss of 3 kg, intermittent bone pain, and fatigue for a few months. He had no voice changes, neck pain, or swallowing symptoms. There was no radiation exposure in the past, and neither a family history for multiple endocrine neoplasia or neurofibromatosis.

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Physical examination revealed a firm, non-tender mass in the right thyroid region. The ultrasound of neck showed well-defined homogeneous extrathyroidal tumors with similar or slightly decreased echogenicity compared to the thyroid parenchyma at the bilateral lower neck (Fig. 1A and 1B). The thyroid gland, though otherwise unremarkable, was compressed by the tumor. The nodules measured $4.7 \times 3.1 \times 3.6$ cm on the right side and $2.8 \times 1.8 \times 1.8$ cm on the left. There was no evidence of tumor invasion to adjacent structures or lymphadenopathy. Fine-needle aspiration biopsy was not performed as the tumors were suspected to be of parathyroid origin.

Laboratory tests showed a serum calcium level of 12.7 mg/dL (reference range 8.9–10.3 mg/dL), serum phosphorus of 2.1 mg/dL (reference range 2.7–4.5 mg/dL), and intact PTH level of 936.94 pg/mL (reference range 10.00–60.00 pg/mL). He was euthyroid with a TSH level of 0.75 μ U/mL (reference range 0.25–4.00 μ U/mL) and calcitonin level of 14.00 pg/mL (reference range <18.2 pg/mL). Though his chest X-ray was essentially normal, the plain abdominal radiographs revealed radiopaque lesions over the bilateral renal

shadows. Subsequent renal ultrasonography confirmed the presence of bilateral kidney stones. Dual-energy X-ray absorptiometry disclosed bone mineral density of 0.579 g/cm² with a T-score of –2.6 and Z-score of –1.3, corresponding to osteoporosis. Dual-phase Tc-99m sestamibi scintigraphy with three-dimensional assessment using single-photon emission computed tomography (SPECT) was performed. Increased radioactivity was observed in the right and left lower thyroid regions (Fig. 1C), corresponding to the two enlarged parathyroid glands seen on ultrasound.

The patient was admitted with an initial diagnosis of a double parathyroid adenoma. Bilateral neck exploration was performed through a low-collar incision under general anesthesia. Large parathyroid tumors with no adhesion to the thyroid were resected from the inferior poles of the bilateral thyroid lobes. The superior parathyroid glands on both sides appeared to be normal.

Gross examination of the resected tumors revealed tan-white lesions covered with a thin capsule (Fig. 2A). The tumor on the right side was $5.6 \times 3.5 \times 3.0$ cm in size and weighed 32 g; the other on the left side measured $2.7 \times 2.0 \times 1.5$ cm and had a weight of 4.3 g.

Fig. 1 Preoperative imaging studies of the patient with double water-clear cell parathyroid adenoma. (A) Transverse and longitudinal scan of the right extrathyroidal tumor. (B) Transverse and longitudinal scan of the left extrathyroidal tumor. (C) Tc-99m sestamibi SPECT imaging.

Fig. 2 Pathologic imaging of double water-clear cell parathyroid adenoma. (A) Macroscopic view of double parathyroid adenoma. (B) Overview of the right parathyroid tumor (H&E, original magnification 40 $\times$). (C) High-power view of the left parathyroid tumor (H&E, original magnification 400 $\times$).

Microscopically, both tumors were composed exclusively of uniform, large, clear cells without intervening fat cells or necrosis (Fig. 2B). No rim of compressed normal parathyroid tissue was identified at the tumor periphery. At high magnification, the cytoplasm was finely vacuolated (Fig. 2C). The nuclei of tumor cells exhibited no pleomorphism or atypical mitosis.

The patient recovered uneventfully and was discharged from the hospital on postoperative day 2. His intact PTH level dropped to 15.54 pg/mL after the surgery, and he remained normocalcemic during follow-up.

Literature Review

A systematic search of relevant literature published between January 1985 and August 2021, identified 37 cases of water-clear cell parathyroid adenoma, including the present case (Table 1). The median age at diagnosis was 56 years (range, 18–81 years). Twenty-seven (73%) were women and 10 were men. Classic complications were common. Nine patients were diagnosed with nephrolithiasis, and 10 patients had fragility fractures, brown tumors, osteoporosis, or osteopenia. Two patients had pancreatitis. The majority of others presented with non-specific symptoms such as fatigue, muscle aches, bone pain, abdominal pain, depression, and lethargy.

Before surgery, the median calcium and PTH levels were 12.0 mg/dL and 290 pg/mL, respectively. Imaging localization studies were performed in some of the patients. Most adenomas (25/28, 89%) were localized by ultrasonography. Interestingly, only 60% (15/25) of the patients had positive scintigraphy results and these had higher preoperative PTH levels (Mann-Whitney *U* test, $p = 0.027$) and heavier or larger parathyroid adenomas ($p = 0.001$, Fig. 3A).

Four patients had double parathyroid adenomas, and 33 had a single adenoma. Among 41 adenomas, 14 (34%) were on the right side, and 26 (63%) were on the

left. One ectopic adenoma was found in the postero-superior mediastinum. All patients with double adenomas had a crossed bilateral distribution. Water-clear cell parathyroid adenoma most frequently occurred in the left inferior parathyroid gland (16/41, 39%).

The tumor size of water-clear cell parathyroid adenomas was relatively large compared to that of classic parathyroid adenomas. The median maximum diameter in the pooled analysis was 3.8 cm (range, 0.8–6.8). The median weight of the resected adenoma was 5.27 g (range, 0.27–36.3). Preoperative calcium levels did not correlate with PTH levels (Spearman rank correlation, $p = 0.295$) or adenoma weight ($p = 0.551$, Fig. 3B). Nonetheless, it was noted that preoperative PTH levels were closely correlated with size (Spearman $\rho = 0.659$, $p < 0.001$) and weight ($\rho = 0.727$, $p < 0.001$) of the adenoma. Adenoma size and weight were highly correlated ($\rho = 0.904$, $p < 0.001$, Fig. 3C).

Discussion

Water-clear cell hyperplasia of the parathyroid glands was described as early as 1934. However, for reasons largely unknown, this type of hyperplasia has gradually disappeared in recent times [4]. In contrast, sporadic reports of water-clear cell adenomas are increasingly getting documented in the literature.

In our literature review, two series that compared the clinical and biochemical features between chief cell adenomas and clear cell adenomas were excluded because of the lack of individual information [5, 6]. It was considered that Kovacs and colleagues reported the first case of water-clear cell parathyroid adenoma [7]. Nonetheless, our survey revealed that the case described by Stout is better classified as double adenoma instead of hyperplasia in which normal right inferior parathyroid tissue was confirmed by a frozen section [8]. We also included an additional case that was previously classified as

Table 1 Summary of cases reported in literature on water-clear cell parathyroid adenoma

First author (year)	Age (year)	Sex	Presentations	Calcium (mg/dL)	PTH (pg/mL)	Ultrasound	Scintigraphy	Adenoma No.	Location ^a	Diameter (cm)	Weight (g)
Stout (1985) [8]	46	F	Nephrolithiasis	11.6	21			2	RS LS	3.8	5.2
Kovacs (1994) [7]	48	M	Nephrolithiasis	11.8				1	LI		
Grenko (1995) [21]	40	M	Fatigue, leg cramps	11.3	945			1	RS	5	7.6
Begueret (1999) [22]	73	M	Nephrolithiasis	13.8	207			1	LI	2.8	
Dundar (2001) [23]	43	F	Fracture	13.3	1,667	+	–	1	IT(L)	6	
Kuhel (2001) [12]	56	F	Osteopenia	13.2	52	+	–	2	RS LS	2.8	2.2
Kanda (2004) [17]	52	F	Nephrolithiasis, gastric ulcer	11.7	643	+	+	1	LI	6.8	15.4
Prasad (2004) [24]	40	F	Osteopenia	12.4	346			1	LS	3	4.2
Kodama (2007) [19]	18	F	Nephrolithiasis	11.6	356	+	+	1	RS	5	21.7
Liang (2010) [25]	59	F	Mood changes, lethargy	12.3	371		+	1	RS	4.5	13.3
Burstein (2011) [26]	57	F	Fatigue, brown tumors	15.9	1,905	+	+	1	LI	5	22
Bai (2012) [27]	81	M			209	–	+	1	RS	4	6.91
	55	M			150	–	–	1	LS	1.4	0.27
Ezzat (2013) [9]	61	F		11.6	389	+	+	1	LS		18
	73	M		13.0	290	+	+	1	LI	3.7	8
	74	F		11.6	111	+	–	1	LI	1.6	0.9
Papanicolaou-Sengos (2013) [28]	64	M						1	LI	4.7	
Piggott (2013) [29]	74	F	Abdominal pain, lethargy	12.5	489	+	+	1	LI	5.5	13
Chou (2014) [30]	81	F	Pancreatitis	12.0	450	+	+	1	LS	3.8	
Murakami (2014) [31]	59	F	Nephrolithiasis, fracture, gastric ulcer	11.9	72	+	–	1	LI	0.8	0.5
Tassone (2014) [32]	54	F	Bone pain, weakness	12.4	130	+	+	1	LI	2.8	
Pirela (2016) [33]	34	F		9.3		+		1	IT(R)	2.5	
Boutzios (2017) [34]	53	F		11.1	398	+	+	1	LI	5.4	
Yazar (2017) [20]	47	M	Nephrolithiasis, abdominal pain	16.6	744	+	–	2	RI LI	2.5	2.8
Ioannis (2018) [35]	58	F		10.4	902	+		1	R	4.5	12
Arik (2019) [36]	70	M	Back pain					1	Mediastinum	6	
Radaideh (2019) [37]	50	F	Pancreatitis, osteoporosis	12.1	429	+	+	1	R	5	36.3
	33	F	Bone pain, abdominal pain	10.5	156	+	–	1	LI	1.2	0.3
Zinovkin (2020) [38]	64	F	Osteopenia	12.0	117			1	LS	3	5.34
Mohamed (2021) [39]	56	F		12.5	1,036	+	+	1	LS	3	9
Juhlin (2021) [40]	53	F			113	+	–	1	LI		0.538
	78	F	Nephrolithiasis		160	+	–	1	RS		3.48
	52	F	Muscle pain		85	+	+	1	RI		0.47
	38	F	Fatigue, depression		179	+		1	LI		1.34
	61	F	Osteopenia, depression		123	–	–	1	RI		0.883
	58	F	Osteopenia, fatigue, muscle pain		198	+		1	LS		0.577
Present case	56	M	Nephrolithiasis, osteoporosis	12.7	937	+	+	2	RI LI	5.6	36.3

^a IT, intrathyroidal; LI, left inferior; LS, left superior; RI, right inferior; RS, right superior

Fig. 3 Scatter plots of water-clear cell parathyroid adenomas reported in the literature. (A) PTH levels and adenoma weight grouped by negative or positive scintigraphy results. Black horizontal lines represent medians. (B) PTH levels and adenoma weight *versus* preoperative calcium levels. (C) PTH levels and adenoma weight *versus* maximum diameter of the adenoma.

hyperplastic [9]. The patient had normal calcium and PTH levels postoperatively, although only two parathyroids were resected. In all, 37 cases of water-clear cell parathyroid adenoma are presented in Table 1.

Despite controversy concerning the possibility of asymmetric hyperplasia, double adenoma has been considered a distinct clinical entity based on the observation that selective resection leads to a durable cure [10].

Interestingly, double adenomas seem to have a nonuniform anatomic distribution, namely, abnormal glands disproportionately involved in both sides of the neck [11]. Some authors propose that double adenoma may be an abnormal proliferation of embryologic origin (*e.g.*, bilateral superior parathyroids arising from the fourth branchial pouch) rather than isolated neoplastic events. In our review, double water-clear cell adenoma occurred as a bilateral disease rather than a one-sided disease in all four patients. Intriguingly, in one case, both lesions were noted to be monoclonal using X-linked clonality analysis [12].

Water-clear cell hyperplasia has a reversed sex ratio with male predominance compared to chief cell hyperplasia [4, 13]. It is suggested that water-clear cell hyperplasia may be etiologically different from the common form of primary hyperparathyroidism. Nonetheless, we found that water-clear cell adenomas had a 2:1 to 3:1 ratio of females to males. The most striking difference between the classic and water-clear cell adenomas was related to the size and weight of adenomas. For classic adenomas, tumor size commonly ranges from 1–3 cm and weight from 0.3–5 g [14]. Water-clear cell adenomas were remarkably larger and heavier. In addition, a positive correlation between the serum calcium and PTH levels is usually observed in patients with classic primary hyperparathyroidism [15]. The association unexpectedly disappeared in our pooled analysis of patients with water-clear cell adenomas.

Hyperplasia of water-clear parathyroid cells was shown to have low PTH levels in tissue extracts and high levels of circulating PTH, suggesting that PTH was excessively secreted and storage was markedly reduced [16]. Kanda *et al.* first speculated that water-clear cell parathyroid adenomas have low endocrine activity, and serum calcium concentration does not reach highly abnormal values until the adenoma is large enough [17]. Despite their enormous size, the malignancy of water-clear cell parathyroid tumors is exceptional. In a singular case, vascular invasion was the only malignant feature [18]. It is noteworthy that although serum calcium levels are not proportional to the large tumor burden, water-clear cell adenomas are not free of adverse consequences. We found that renal and skeletal complications were common in patients with water-clear cell adenomas. Considering the low proliferative activity of these tumors, it is likely that a long latent period elapses before the symptoms become clinically apparent.

Given the relatively large tumor size, visualization of lesions on ultrasonography is not difficult. However, water-clear cell adenomas are frequently isoechoic, as in our patient, which makes them sometimes indistinguishable from thyroid nodules [19]. Previous studies have

Table 2 Comparison of characteristics between water-clear cell adenomas and classic adenomas in patients with primary hyperparathyroidism (pHPT)

First author (year)	Type	<i>n</i>	Age (year)	Sex (M:F)	Presentations	Calcium (mg/dL)	PTH (pg/mL)	Ultrasound	Scintigraphy	Diameter (cm)	Weight (g)
Roizen (2014) [41]	pHPT (12% hyperplasia)	2,405				11.2	174.5				1.19
Howson (2015) [42]	Non-oxophilic	91	66.5	72:19 (3.8:1)	3% nephrolithiasis 48% osteoporosis	10.44	63.94	63%	66%		
	Oxophilic	91	66.6	72:19 (3.8:1)	10% nephrolithiasis 41% osteoporosis	10.8	138.59	47%	54%		
Stern (2016) [6]	Single adenoma	378	63.4	287:91 (3.2:1)	21% nephrolithiasis 40% osteoporosis	11.5	165			1.8	1.4
Nafisi (2017) [43]	Adenoma	1,137	57.5	836:301 (2.8:1)				80%	84%		
Lam (2019) [15]	pHPT (13% hyperplasia)	95	59	72:23 (3.1:1)	34% nephrolithiasis 5% fracture	11.4	148				0.586
Zafereo (2019) [44]	pHPT (review)							74–91%	70–86%		
Present study	Water-clear cell adenoma	37	56	27:10 (2.7:1)	24% nephrolithiasis 27% bone complications	12.0	290	89%	60%	3.8	5.27

Note: estimates are mean or median values.

suggested decreased sensitivity of preoperative scintigraphic localization [20], probably due to the low content of mitochondria in water-clear cells and the paucity of oxyphilic cells. Overall, our analysis showed that nearly two-thirds of the patients were positive for sestamibi scintigraphy. A comparison between the characteristics of water-clear cell adenomas and those of the classic adenomas reported in recent series or reviews is compiled in Table 2.

In summary, we report a rare case of double water-clear cell parathyroid adenoma that was successfully treated by surgery without residual hyperparathyroidism. A review of the literature reveals several notable features of water-clear cell adenomas, including large tumor size, relatively indolent biochemical profile, high prevalence of complications and nonspecific symptoms, an isoechoic appearance on ultrasonography, and reduced

scintigraphic sensitivity.

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Disclosure Statement

The authors have no potential conflicts of interest.

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