Primary hyperparathyroidism-related giant parathyroid adenoma (Review)

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Abstract. Primary hyperparathyroidism (PHPT), an endocrine condition caused by a parathyroid adenoma (PTA) in 80-85% of the cases, has shifted in the modern era to a mildly symptomatic phenotype due to the prompt recognition of hypercalcemia and to a minimally invasive surgical approach which has a curative potential. Clinical complications of PHTH are either related to high calcium or parathyroid hormone [also parathormone (PTH)] or both, while the originating tumor typically is small, without local mass effects. A distinct entity is represented by giant PTA (GPTA) which is considered at a weight of more than 3 (3.5) grams. The present article is a review of the literature involving practical points of non-syndromic PHPT-related GPTA. Most authors agree that pre-operatory calcium and PTH are higher in GPTA vs. non-GPTA. However, the clinical presentation of PHPT may be less severe, probably due to local mass effects that bring the patient to an early medical evaluation. Age distribution, sex ratio, rate of successful pre-operatory location do not differ from non-giant PTA. Hypovitaminosis D is more frequent in PTA of higher dimensions. Post-operative hypocalcemia, but not recurrent/persistent PHPT, is expected, even hungry bone disease. A higher rate of atypia is described although the tumor is mostly benign. Unusual presentations such as cystic transformation, initial diagnosis during pregnancy or auto-infarction have been reported. The ectopic localization of PTA presented in almost 15% of all cases may also be found in GPTA. What are the exact cutoffs for defining GPTA is still an open issue.

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Abbreviations: CT, computed tomography; cm, centimeter; g, grams; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone or parathormone; PTA, parathyroid adenoma; GPTA, giant PTA; PC, parathyroid carcinoma

Key words: parathyroid adenoma, primary hyperparathyroidism, parathyroidectomy, calcium, vitamin D, parathyroid tumor, parathormone, giant parathyroid adenoma, incidentaloma, cyst

Contents

1. Introduction

Primary hyperparathyroidism (PHPT), an endocrine condition caused by a parathyroid adenoma (PTA) (80-85%), hyperplasia or carcinoma, has shifted in the modern era to a mildly symptomatic phenotype due to the

prompt recognition of hypercalcemia and to a minimally invasive surgical approach which has a curative potential (1,2). An overlap with a vitamin D deficiency-related secondary component is also common due to the global prevalence of hypovitaminosis D (1-3). The incidence of PHPT of 27 to 30 per 100,000 person-years increases with age and is 2 to 3 times higher in women (4,5). In addition, a potential association of increased incidence and obesity has been described, but this condition has also experienced an increased general prevalence worldwide in addition to other multiple complications, whether they are bone-related or not (6,7).

The clinical complications of PHTH are either related to high calcium levels (acute or chronic) or increased parathyroid hormone [also parathormone (PTH)] or both such as osteoporosis and associated low-trauma fractures, neuropsychiatric disorders, neuromuscular manifestations, gastrointestinal disturbances, nephrocalcinosis, and urolithiasis, eventually complicated with urinary infections and kidney failure (8). When it comes to the primary tumor itself, typically the lesion is small and there are no local mass effects unless a carcinoma is the underling diagnosis which is positive in less than 1% of all cases, and also some exceptional cases of very large/giant parathyroid adenoma (GPTA) have been described (9). GPTA is an extremely rare type generally defined as having a weight of at least 3.5 grams (g) or 3 g (depending on the study), and some authors consider this particular endocrine mass as a distinct entity (9). Large PTA is usually considered a tumor weighing between 1 and 3 g (9). PTA, regardless of the size, are identified based on anterior cervical ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) as well as functional imagery such as ^{99}Technetium-labelled sestamibi-single photon emission CT or scintigraphy (1,9). Regardless of the dimension, surgical removal of a PTA cures the disease with a considerable improvement of many of the associated complications (unless severe kidney disease is already established) (10).

2. Aim

This article is a review of the literature regarding GPTA that causes PHPT focusing on different aspects including pre-operative biochemistry correlates, post-parathyroidectomy outcome, histological issues, unusual locations as ectopic/intra-thyroid, and particular clinical aspects such as diagnosis during pregnancy. The main research tool was the PubMed database. A number of 90 references are cited. We systematized in a table the papers published between 2010 and 2020 displaying HPTH-related GPTA. The level of evidence varied from case report or series to retrospective studies or meta-analyses. Cases with parathyroid carcinoma or hyperplasia or associated multiple endocrine neoplasia syndromes were not included.

3. Giant parathyroid adenoma: Concept around the size considerations

Spanheimer *et al* considered that a GPTA may represent a particular condition characterized by a larger lesion, a paradoxically less severe phenotype at presentation and a more severe evolution after surgical removal in terms of low calcium levels, not of persistent/recurrent hypercalcemia (9). This study included 300 patients that identified 15 GPTAs with a weight >3.5 g or ≥95th percentile (median GPTA weight of 5.65 g) vs. non-giant PTA group of 285 subjects (median PTA weight of 0.56 g) (9). Analyzing the clinical and laboratory features, the patients with a giant lesion had a statistically significant higher value of calcium (11.07 vs. 10.9 mg/dl) and PTH (227.6 vs. 136.7 pg/ml) before surgery and a lower percent of symptomatic PHPT (9). The pre-operative success rate of localization using different imaging techniques was similar between the two groups (9). The risk of post-operative symptomatic hypocalcemia was higher in GPTA (9). The groups were similar regarding age at diagnosis, sex ratio, location, and the rate of post-operative persistent/recurrent hyperparathyroidism (9).

4. Pre-operative biological correlates

Leong *et al* published a retrospective study between 2013 and 2018 of 555 patients (a mean PTA weight of 1.022 g) and found a strong positive correlation between preoperative PTH levels and parathyroid weight ($r=0.602$, $P<0.001$), a medium correlation between calcium before surgery and parathyroid gland ($r=0.474$, $P<0.001$). Thus, PTH appears to be a better predictor of PTA weight than calcemic levels (11). Another cohort of 378 cases presenting with PHPT found a statistically significant correlation of preoperative calcium, respective PTH values and adenoma dimensions and weight. A calcium level >11.5 mg/dl and PTH >165 pg/ml were found to predict a PTA of more than 2.18 cm and 2.7 g (12). A statistically significant correlation ($P=0.0001$) between adenoma weight with serum calcium, respective PTH (and not serum phosphate) was pointed out in a retrospective study of 69 cases with a mean age of 54 years (mean PTH of PTA of 770.971 pg/ml before surgical removal in association with mean total calcium of 11.47 mg/dl) (13). A study in 2019 of 519 candidates for parathyroidectomy considered 'dwarf' PTA the cases with a tumor weight of <3 g (N=100, median 2 g) vs. 'giant' PTA, tumors more than 3 g (N=56, median weight of 4.3 g) (14). 'Dwarf' when compared with GPTA had statistically significant lower values of calcium and PTH, but overall a weak correlation of biochemistry parameters to adenoma size was established (14). During 40 months of post-operative follow-up, none of the GPTA cases had recurrent disease; the fact that the tumor was large did not underline a malignancy (14). Grover *et al* published a study in 2020 of 79 patients with PHPT and PTA; 11.3% of them had a giant tumor (maximum diameter between 3.5 and 5.5 cm) without pre-operative correlations in biochemical elements and adenoma size (15). Another potential useful correlation was described in one study between neutrophil/lymphocyte ratio and PTA size (a study on 32 parathyroid tumors, mean age of 53 years, 75% of them were females) (16).

5. Relationship with vitamin D status

Vitamin D deficiency is a stimulus for parathyroid hyperplasia; the component of secondary hyperparathyroidism may be

additional to a primary one and it may cause a supplementary increase in parathyroid tumor, regardless of the positive diagnosis of associated osteoporosis, menopausal status or body weight (17). Agarwal *et al* studied the influence of vitamin D levels and parathyroid tumor weight on 59 patients that were included in a retrospective case-control study based on the PTA weight as small <1 g (N=12 patients), large PTA of 1-3 g (N=34 subjects), GPTA of >3 g (N=13 patients) and based on the 25-hydroxyvitamin D level (deficient, insufficient, sufficient). PTH was higher in vitamin D deficient vs. sufficient subjects while 25-hydroxyvitamin D was lower in patients with larger vs. smaller tumors (18). A prospective study on 51 consecutive patients (mean age of 43 years) with PTA also grouped the PTA based on weight: small <1 g, large 1-3 g, GPTA >3 g and it showed a higher percentage of hypovitaminosis D in GPTA (19).

6. Histological issues

Authors have questioned whether GPTAs have a higher risk of malignancy (20). A retrospective analysis of 3,643 PTAs included 52 atypical PTA (N=34) and 18 malignant parathyroid carcinoma (PC) concluded that PCs have statistically significant higher dimensions (20). Another retrospective analysis of 353 PTA patients divided the lesions into small and large tumor weight (a cut-off of 2 g) and found a statistically significantly higher frequency of atypical lesions among the large tumors (21). Chandramohan *et al* published a retrospective analysis of 264 patients with PHPT, and 26 patients of these exhibited atypical ultrasound features associated with a larger lesion of the adenoma (22). In 2020, an exceptional case presenting with a GPTA mimicking PC was published. The histological report showed a tumor with dimensions 6.5x5x3 cm; weight of 90 g with preoperative hypercalcemia of 12.5 mg/dl and PTH of 2,747 pg/ml, noting that in the literature the largest weight was 145 g in a female with a GPTA (23,24).

Another unexpected situation is the process of apoplexy in GPTA (25). Garrahy *et al* reported a case of a 45-year-old female with acute airway compromise due to PTA apoplexy with a mass effect (hypercalcemia of 13.3 mg/dl, and PTH of 367 pg/ml) due to a PTA of 10.7x5.2x4.2 cm (25).

Cystic GPTA associated or not with PHPH have been reported, and liquid accumulation is expected to increase the tumor size (26-28). The parathyroid cysts, functional or non-functional, represent less than 1% of all neck cysts of different etiologies (26-28). Here a few studies are presented. Pontikides *et al* published 9 cases of cystic parathyroid lesions (female/male ratio of 7/2), of nonfunctioning type (6/9) and with HPTH (3/9) (27). Ghasemi-Rad *et al* published a retrospective study of 109 cystic (26/109, mean age 43.3 years) and solid (83/109, mean age 48.6 years) adenomas associated with a serum calcium level statistically significant higher in the solid PTA group (11.18 vs. 11.95 mg/dl) while size was higher in the cystic group (28). Hu *et al* published a retrospective study of 907 patients. The cystic PTAs (37/907) when compared with the solid PTAs (870/907) showed higher PTH, calcium values, and increased risk of hypercalcemic crisis (29). Papavramidis *et al* published a meta-analysis of cases with 359 cystic PTAs of mean age 49.24 years (females/males: 65/35%), either asymptomatic or running as HPTH, of mean 4.81 cm (ranging from 0.5 to 15 cm) (30).

7. Ectopic PTA of large dimensions

Ectopic PTA tissue is not uncommon, with an incidence of approximately 16% of all cases according to one study from 2019, and some of them are GPTA without a clear incidence (31). The most common sites are the mediastinum, thymus and thyroid (31). A previously mentioned case that was published in 2011, introduces a female with giant mediastinal PTA measuring 7x5x4 cm and weighing 145 g (PTH of 642 pg/ml and calcium of 13.2 mg/dl) (24). Intra-thyroid PTA of large dimensions have been reported (32,33). For instance, Yalcin *et al* published such a case of a 76-year-old female with preoperative biochemistry revealing hypercalcemia (12 mg/dl) with high levels of parathyroid hormone (512 pg/ml), and a lesion of 2.4x1.9x1.6 cm (33). Vilallonga *et al* reported a giant inthra-thyroidal parathyroid adenoma of 3 cm maximum diameter, weighing 70 g in a 19-year-old patient with hypercalcemia (14.2 mg/dl) and elevated PTH (1207 pg/ml) (34). Silaghi *et al* reported an intra-thyroid PTA of 4 cm, complicated with brown tumors (35). Another case with high dimensions at ultrasound was that of a 82-year-old male who presented with classical PHPT symptoms, increased calcium levels and high PTH of 210.4 pg/ml, with a thyroid ultrasound revealing a giant intra-thyroidal nodule (a PTA) of 6.9x5.2x4.8 cm (36).

8. Risk of post-operative hypocalcemia

Most authors agree that after removal of a GPTA, the risk of developing low PTH-related hypocalcemia is higher than seen in patients with smaller tumors (37,38). Hungry bone syndrome may be expected especially if pre-operative PTH is highly increased (37,38). A cases series of 3 GPTAs exhibited severe hypocalcemia after surgery: a 57-year old male with PTH of 1,780 pg/ml, calcium of 14.14 mg/dl, ultrasound features of the PTA of 5x3x2 cm, a weight of 30.6 g; a 60-year old female, with calcium of 16.17 mg/dl, PTH of 863 pg/ml, tumor dimension 5.5x4x3 cm, a weight of 35.2 g, and also a 33-year old subject with calcium of 12.58 mg/dl, PTH of 1,174 pg/ml, and 30 g weight for the PTA (39).

Another exceptional condition is hypocalcemia following an auto-infarction of a previously known or unknown PTA (40). For instance, a reported case from 2018 revealed such a situation involving a GPTA auto-infarction resulting in hungry bone syndrome (40). This case was a 71-year-old man known with atrial fibrillation, treated with rivaroxaban, who was found with severe hypercalcemia of 14.6 mg/dl and elevated PTH of 2,555 pg/ml; ultrasound size of PTA was 4.1x3.6x3.1 cm (40). Therefore, a parathyroidectomy was planned, rivaroxaban was halted 5 days prior to surgery, but the patient developed hypocalcemia before surgery due to spontaneous infarct of the tumor (40). Whether the use of an anticoagulant is a trigger for self-infarction as seen in adrenal glands, it is difficult to establish due to the limited published data (40). Novodvorsky *et al* reported a series of two cases with auto-infarction: a 51-year-old subject with hypercalcemia of 12.44 mg/dl, PTH of 253.66 pg/ml, PTA at ultrasound of

Table I. A review of published articles[a] between 2010 and 2020 involving giant PTA complicated with PHPH.

Study: First author, year of publication	Age (years)/sex of the subjects	Type ofstudy/ number of patients	Dimensions of the parathyroid adenoma (cm)	Weight of PTA (g)	Type of lesion (pathological report)	Serum calcium (mg/dl)	Blood PTH (pg/ml)	(Refs.)
Hong *et al*, 2010	52/M	Case report/1	8x5.6x4.6	87	Cystic PTA	13.28 (N: 8.2-10)	93 (N: 16-87)	(53)
Tahim *et al*, 2010	53/M	Case report/1	3.5x2.0x1.5	9.25	Giant PTA	20.8 (N: 8.48-10.6)	3,957 (N: 12-75)	(54)
Jayant *et al*, 2011	45/F	Case report/1	5.0x4.0x3.0	35	Giant PTA	14.2	1,543	(55)
O'Neal *et al*, 2011	Mean age 58/ F:M=3.5:1	Retrospective analysis/353	Mean max diameter 1.24	<2 g	PTA	Mean 11.3	Mean 145	(21)
	Mean age 56/ F:M=1:1		Mean max diameter 2.52	≥2 g	Parathyroid carcinomas (n=3)	Mean 12.0	Mean 297	
Asghar *et al*, 2012	55/F	Case report/1	11x7.0x6.0	-	Giant cystic PTA	22 (N: 8.6-10.2)	1,182 (N: 16-87)	(56)
Agarwal *et al*, 2012	41/F 18/M; Mean age 36.3 (24-78)	Retrospective case-control study/59	-	Mean 3.543	PTA	Mean 13.6 (N: 8.5-10.2)	Mean 683 (N: 9-55)	(18)
Mazeh *et al*, 2012	79/F	Case report/1	3.5x1.0x0.4	3.1	Cystic PTA	13.5 (N: 8.5-10.2)	325 (N: 15-65)	(57)
Pontikides *et al*, 2012	52/F	Case series/9	3.4x3.8x3.5	-	Cystic PTA	-	58	(27)
	35/F		3.4x2.9x2.3				-	
	48/F		2.6x1.8x3.0				28	
	49/F		6.0x3.1x2.5				32	
	31/F		4.5x3.5x5.0				-	
	22/F		1.2x2.5x3.1				41	
	82/M		5.6x4.0x4.2				1,064	
	51/M		3.3x2.5				881	
	43/F		4.0x3.6x2.1				171	
Khan *et al*, 2012	58/F	Case report/1	3.5x4.5x3.2	-	Cystic PTA	23.3 (N: 8.6-10.6)	1,364 (N: 10-65)	(58)
Zaman *et al*, 2012	54/F	Case report/1	-	-	Giant cystic PTA	17.4	1,182	(59)

Table I. Continued.

Study: First author, year of publication	Age (years)/sex of the subjects	Type ofstudy/ number of patients	Dimensions of the parathyroid adenoma (cm)	Weight of PTA (g)	Type of lesion (pathological report)	Serum calcium (mg/dl)	Blood PTH (pg/ml)	(Refs.)
Vilallonga *et al*, 2012	19/F	Case report/1	Maximum diameter 3.0	70	Giant intrathyroidal PTA	14.2 (N: 8.8-10.2)	1,207 (N: 7-82)	(34)
Kamani *et al*, 2013	F (n=52) M (n=17)	Prospective study/69	-	Mean 8.6 (1.5-31.5)	PTA	Mean 11.74	Mean 770	(13)
Suzuki *et al*, 2013	67/F	Case report/1	1.68x1.62x2.00	-	Cystic PTA	11.68	270	(60)
Spanheimer *et al*, 2013	Mean age 59.7 years Mean age 59.3 years	Retrospective study/300	-	0.56 (0.05-3.2) 5.65 (3.5-29.93)	Non-giant PTA (n=285) Giant PTA (n=15)	Mean 10.9 Mean 11.7	Mean 136.7 Mean 227.6	(9)
Sisodiya *et al*, 2013	52/F	Case report/1	3.9x2.0x1.7	-	Giant PTA	17	598	(61)
Singh *et al*, 2013	Mean age 49.7 42.5 45.3	Prospective study/51	Mean diameter 1.6 2.1 3.6	Meanweight 0.504 1.902 9.134	Small <1 g Large 1-3 g Giant >3 g parathyroid	Mean values 11.32 12.6 12.32	-	(19)
Dutta *et al*, 2013	24/F	Case report/1	0.6x1.0	-	Intrathyroidal parathyroid cyst	12.1 (N: 8.6-10.8)	1,283 (N: 7-65)	(62)
Kim *et al*, 2013	67/M	Case report/1	Maximum diameter 5.4	-	Cystic PTA	10.3	113	(63)
Haldar *et al*, 2014	61/F	Case report/1	6.5x3.0x1.5	12	Giant PTA	12.8 (N: 8.4-10.2)	179 (N: 11.31-87.69)	(64)
Salido *et al*, 2014	47/M	Case report/1	-	-	Giant PTA	9.88	140.5	(65)
Neagoe *et al*, 2014	57/M 60/F 33/F	Case report/3	5.0x3.0x2.0 5.5x4.0x3.0	30.6 35.2 30.0	Giant PTA	14.14 16.17 12.58 (N: 9-11)	1,780 863 1,174 (N: 15-68)	(39)
Kawashima *et al*, 2014	67/F	Case report/1	1.2x1.1x5.4	-	Cystic PTA	14 (N: 8.5-10.2)	239 (N: 15-65)	(66)
Yalcin *et al*, 2014	76/F	Case report/1	2.4x1.9x1.6	-	Intrathyroidal parathyroid cyst	12 (N: 8.8-10.2)	512 (N: 13-92)	(33)
Zeren *et al*, 2015	53	Retrospective study/32	Maximum diameter 2.9	-	Parathyroid adenoma Parathyroid carcinoma	11.7	663	(16)

Table I. Continued.

Study: First author, year of publication	Age (years)/sex of the subjects	Type ofstudy/ number of patients	Dimensions of the parathyroid adenoma (cm)	Weight of PTA (g)	Type of lesion (pathological report)	Serum calcium (mg/dl)	Blood PTH (pg/ml)	(Refs.)
Garas *et al*, 2015	53/F	Case report/1	7.0x3.7x2.7	27	Giant PTA	15.9 (N: 8.4-10.5)	4,038 (N: 10-65)	(67)
Sumana *et al*, 2015	46/F	Case report/1	6.0x4.0x3.0	21	Cystic PTA	16.9 (N: 8.5-10.2)	880.1 (N: 12-88)	(68)
Colsa-Gutiérrez *et al*, 2015	76/F	Case report	-	25	Cystic PTA	-	-	(69)
Dogan *et al*, 2015	69/F	Case report/1	2.8x1.5	-	Intrathyroidal PTA	13.7 (N: 8.2-10.9)	507 (N: 15-88)	(70)
Taghavi Kojidi *et al*, 2016	70/M	Case report/1	-	75	PTA	14.4 (N: 8.4-10.2)	930 (N: 10-65)	(71)
Rutledge *et al*, 2016	21/F	Case report/1	8.0x5.5x3.0	58.8	Giant intrathyroidal PTA	15.84 (N: 8.81-10.42)	1,305 (N: 15-65)	(38)
Pecheva *et al*, 2016	72/F	Case report/1	3.9x3.7x1.9	19	Giant PTA	12.1	-	(72)
Krishnamurthy *et al*, 2016	50/M	Case report/1	6.0x4.0	-	Giant PTA	11.2	669	(73)
Taguchi *et al*, 2016	85/F	Case report/1	3.6x2.5x2	11.3	Cystic PTA	10.4 (N: 8.1-10.5)	1,348 (N:10.3-65.9)	(74)
Sahsamanis *et al*, 2017	42/F	Case report/1	3.3x2.0x1.4	5.39	Giant PTA	10.4 (N: 8.1-10.5)	151	(75)
Araujo Castro *et al*, 2017	40/F	Case report/1	6.4x1.6x2.0	10.8	Giant PTA	12.8	825 (N: 14-72)	(76)
Garrahy *et al*, 2017	45/F	Case report/1	5.2x4.2x10.7	-	Giant PTA	13.2	367 (N: 15-65) (N: 8.81-10.42)	(25)
El-Housseini *et al*, 2017	87/F 31/F 34/F	Case report/3	3.5x3.0x2.0 3.5x2.0x1.0 5.0x4.5x4.0	-	Cystic PTA	13.84 10.76 11.04	305 259 1,410	(77)
Papavramidis *et al*, 2018	Female (n=228) Male (n=123); Mean age 49	Meta-analysis/ 359	Mean diameter 4.81	-	Cystic PTA	-	-	(30)
Ebrahimpur *et al*, 2018	67/F	Case report/1	3.3x3.4	-	'Huge' ectopic PTA	13 (N: 8.4-10.2)	291 (N: 10-65)	(78)
Mantzoros *et al*, 2018	73/F	Case report/1	5.0x2.5x2.5	30	Giant PTA	14.5	1629	(37)
Verzijl *et al*, 2018	71/M	Case report/1	4.1x3.6x3.1	-	Giant PTA	14.6 (N: 8.8-10.48)	2,555 (N: 13.2-71.66)	(40)

Table I. Continued.

Study: First author, year of publication	Age (years)/sex of the subjects	Type ofstudy/ number of patients	Dimensions of the parathyroid adenoma (cm)	Weight of PTA (g)	Type of lesion (pathological report)	Serum calcium (mg/dl)	Blood PTH (pg/ml)	(Refs.)
Hu *et al*, 2018	M:F=1:2.9; Mean age 52.8 M:F=1:1.3; Mean age 54.6	Retrospective study/907	Mean diameter 2.1 Mean diameter 4.05	-	Solid PTA (n=870) Cystic PTA (n=37)	Mean 11.56 Mean 12.52	Mean 408 Mean 620	(29)
Anagnostis *et al*, 2018	70/F	Case report/1	Maximum diameter 6.5	-	Cystic PTA	10.8 (N: 8.4-10.4)	187 (N: 10-53)	(79)
Novodvorsky *et al*, 2019	51/M 54/F	Case report/2	3.3x1.9x2.3 Maximum diameter 4.4	- -	PTA	12.44 18.32 (N: 8.8-10.4)	253.66 486.58 (N: 15-65)	(41)
Çayir *et al*, 2019	52/F	Case report/1	Maximum diameter 8.0	-	'Doughnut shaped' PTA	12.37 (N: 8.8-10.6)	356.5 (N: 12-88)	(80)
Al-Hassan *et al*, 2019	52/F	Case report/1	4.0x2.5x1.5	7.7	Giant PTA	12.48	503	(81)
Mirza and Wei, 2019	31/F	Case report/1	5.0x4.0x3.0	37	Giant PTA	14.1	622	(43)
Wang and Yuan, 2019	54/F	Case report/1	5x3.2	-	Giant PTA	13.88 (N:8.48-11.68)	592.66 (N:6.5-36.8)	(82)
Abdel-Aziz *et al*, 2019	Mean age 69 (24-89) Mean age 65 (25-89)	Cohort study/519	-	Mean 0.2 Mean 4.3	Dwarf adenomas (<3 g) Giant adenomas (>3 g)	Mean 11.36 Mean 12	Mean 110 Mean 241	(14)
Miller, *et al*, 2019	53/M	Case report/1	8.0x3.0x3.0	30.9	Giant PTA	11.2	179	(83)
Chen *et al*, 2019	82/F	Case report/1	6.9x5.2x4.8	-	Intrathyroidal PTA	-	210.4 (N: 12-68)	(36)
Nastos *et al*, 2021	54/F	Case report/1	Maximum diameter 6.5	8.3	Giant PTA	12.1 (N:8.1-10.4)	277 (N:15-65)	(84)
Grover *et al*, 2020	Range from 13-52 years	Prospective study/79 Out of these n=9 (11.3%) had giant PTA	Maximum diameter ranged from 1.5 to 5.5	-	PTA	Range from 9 to 12.38	Range from 225 to 2,444	(15)
Leong *et al*, 2020	Mean age 63.3 (17-93)	Retrospective study/555	-	Mean 1.022	PTA	Mean 10.86	Mean 168	(11)
Gücek Haciyanli *et al*, 2020	Mean age 55.7 (40-71)	Retrospective study/537	Mean longest diameter 2.87 (ranges: 1-5.5)	Mean 14.9 (4-38)	PTA	Mean 15.9	-	(85)

Table I. Continued.

Study: First author, year of publication	Age (years)/sex of the subjects	Type ofstudy/ number of patients	Dimensions of the parathyroid adenoma (cm)	Weight of PTA (g)	Type of lesion (pathological report)	Serum calcium (mg/dl)	Blood PTH (pg/ml)	(Refs.)
Evola *et al*, 2020	52/F	Case report/1	6.5x5.0x3.0	90	Giant PTA	12.5 (N: 8.4-10.2)	2,747 (N: 19-65)	(23)
Werner *et al*, 2020	56/F	Case report/1	5.5x3.1x3.3	-	Cystic PTA	13.52 (N: 8.8-10.6)	190 (N: 6.7-38.8)	(86)
Monsour *et al*, 2020	69/F	Case report/1	3.5x2.1x2.0	-	Cystic PTA	20.4	731.8	(87)
Güneş *et al*, 2020	69/M	Case report/1	5.8x3.2	-	Cystic PTA	-	-	(88)
Papanikolaou *et al*, 2020	43/F	Case report/1	3.7x2.5x4.0	-	Intrathyroidal PTA	12.97 (N: 8.4-10.2)	457.2 (N: 15-65)	(32)
Krishnaraju *et al*, 2021	64/F	Case report/1	Maximum diameter 3.5	-	Cystic PTA	12.8	547	(89)
Abdulsalam *et al*, 2021	63/F	Case report/1	7.0x5.0x4.0	145	Giant PTA	13.2	642 (N: 8-97)	(90)

[a]The studies appear (lines) in the order of the publication year. PTA, parathyroid adenoma; PTH, parathyroid hormone; F, female; M, male; g, grams; cm, centimeter; N, normal values; n, no. of cases.

3.3x1.9x 2.3 cm and a 54-year-old patient admitted for severe hypercalcemia of 18.32 mg/dl in addition to increased PTH of 486.58 pg/ml associated with a PTA of 4.4 cm at MRI (41). The two cases with auto-infarction were managed differently, the first case underwent surgery and the second case was conservatively approached (41).

Table I introduces the review of the literature of cases/studies identified between 2010 and 2020 available via PubMed in the field of HPTH-related GPTA.

9. Future considerations

Several topics are still an open issue since, to date, only a limited amount of published data are available. We mention three such categories.

Diagnosis of GPTA during pregnancy. PHTP is exceptionally diagnosed during pregnancy starting most probably from the detection of high calcium values which might be completely asymptomatic (42,43). The newborn may experience convulsions after birth due to calcium metabolism anomalies (42). Some single case reports introduce such situations such as a 29-year-old pregnant female with double PTAs causing PHTP (a calcium level of 11.3 mg/dl, and a PTH of 678 pg/ml) or a diagnosis of HPTP during the first trimester of pregnancy in a female with a serum calcium of 14.1 mg/dl due to high PTH of 622 pg/ml underling a GPTA of 5x4x3 cm with a weight of 37 g (42,43).

Syndromic PHTP-related parathyroid tumors. PHTP is associated with a multitude of other non-parathyroid endocrine/neuroendocrine and non-endocrine tumors such as type IIA multiple endocrine neoplasia; but in cases with specific gene background as *RET* mutations, the parathyroid tumors actually underline a hyperplasia, not an adenoma (44-48). Since the relationship with genetic makeup and the presence of other tumors influence the timing of PHTP diagnosis and its frequency among a particular syndrome such as other less described neoplasia associations are still incompletely understood (for instance, meningioma and PTA), we consider this heterogeneous chapter a completely different topic and thus we did not discuss it here (47,48).

Parathyroid incidentaloma. The detection of a parathyroid tumor, even very large (especially it is posterior cervical or ectopic), may be incidental, and the assessment of the biochemistry and endocrine panel may become irrelevant, meaning that PHPT is not confirmed (49,50). The diagnosis of PHPT is based exclusively on biological data, a synchronous increase in both calcium and PTH, at least two assays; thus imaging findings, even impressive like in cases of large/giant PTA, do not impact the diagnosis of PHPT itself (1,49,50). Surgical removal of a non-functioning PTA depends mostly on the size and local compressive effects (1,49,50). However, when it comes to a GPTA respecting an incidentaloma scenario, the tumor may be non-functional, but in most cases the clinical identification comes first because of the neoplasia size, thus the accidental imaging detection as part of traditional endocrine incidentaloma definition is not applicable (49). Incidentalomas at the level of the parathyroid gland, regardless of the size, are

still a controversy issue in relationship to a clear definition, standards or protocol of management and follow-up, contrary to the massive amount of medical information we have up to this moment about adrenal and pituitary incidentaloma, regardless of whether they are cystic or solid or mixed, of small or large dimensions (49,50). We report here two cases of giant non-functioning PTA. Mossinelli *et al* described a case of a 46-year-old male with a giant retro-tracheal non-functioning PTA (measuring 5.5x4x2.5 cm and weighing 42 g; normal calcium levels of 9.2 mg/dl and PTH of 70.03 pg/ml) (51). Zhang *et al* described a 56-year-old male with a compressive giant non-functional parathyroid cyst of 9x6 cm associated with a serum calcium value of 9 mg/dl, and a PTH level of 37.98 pg/ml (52).

Table I introduces the review of the literature of cases/studies identified between 2010 and 2020 available via PubMed in the field of HPTH-related GPTA (11,13-16,18,19,21,23,25,27,29,30,32-34,36-41,43,53-90).

10. Conclusions

A GPTA represents a fascinating particular entity that is associated, in most cases, with PHPT with higher calcium/PTH values at detection, but less complications of PHPT vs. non-giant PTA, probably due to the local mass effects that bring the patient to an early medical evaluation. Post-operative hypocalcemia, but not necessarily recurrent/persistent PHPT, is expected, and even hungry bone disease. A higher rate of atypia is described although the tumor is mostly benign. Unusual presentations such as cystic transformation or diagnosis during pregnancy have been reported. An ectopic PTA localization of almost 15% of cases may also be found. The cut-off for defining a GPTA is still an open issue; but, the values used so far, include a weight of >3-3.5 g.

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Availability of data and materials

All information is documented by relevant references.

Authors' contributions

AG drafted the manuscript and critically revised the final form. AIT drafted the manuscript in light of the literature studies. EP researched the literature data. MC drafted the manuscript in light of the literature studies. AV researched the literature. AF is the corresponding author and helped the manuscript drafting in light of the literature studies. AMO researched the literature in connection with all cases of giant parathyroid adenoma and wrote the article according to the requirements of the journal. FS drafted the manuscript, revised the English language of the article and researched the literature with the selection of all the data necessary for the writing of the article. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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