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Cohort Study

Giant versus regular parathyroid adenoma: A retrospective comparative study

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ABSTRACT

Background: A fraction of Parathyroid Adenoma (PTA) is considered giant if they weigh more than 3.5 g. There is no clear consensus whether this subgroup has a distinct clinical or biochemical presentation that could have implications on PTA localization and management. In this study, we investigate the difference between regular and giant PTA patients regarding their clinical and laboratory findings as well as their postoperative outcomes.
Materials and methods: Clinical and PTA-related data were retrospectively retrieved from all patients undergoing parathyroidectomy from 2010 to 2019 at our hospital.
Results: A total number of 84 PTA (Females 76.2%) patients were included, of which 24 (28.6%) qualified as a giant with a mean weight of 7.86 g and the rest were regular adenomas (71.4%) with a mean weight of 1.45 g. Giant adenomas were more likely to present at a younger age compared to regular adenoma patients, (44.4 vs 50.8, P = 0.053, D = 0.470). Preoperative PTH levels were significantly higher in the giant PTA group (650.8 vs 334.2 pg/mL, P = 0.044, r = 0.22). Hospital stay was on average 1.6 days longer in giant PTA patients compared to regular PTA patients.
Conclusion: Giant PTA compromised a significant percentage of all adenomas, which was higher than what is reported in the literature and might reflect a delay in diagnosis and lack of screening tests. Both giant and regular adenomas seem to run a similar clinical course, yet biochemical abnormalities in PTH levels may have a predictive value for adenoma weight.

1. Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that typically affects postmenopausal women [1]. In the majority of cases, PHPT arises as a result of parathyroid adenoma, as 80% of PHPT were reported in single benign parathyroid adenoma (PTA) whereas 15–20% were seen in multiglandular cases [2]. Over the past years, sestamibi parathyroid scintigraphy along with neck ultrasound have become the mainstay in confirming the diagnosis and localizing PTAs after a suspected clinical presentation and elevated Calcium (Ca) and Parathyroid Hormone (PTH) laboratory findings.

The majority of PTA patients present with hypercalcemia, bone pain, fatigue as well as neuropsychiatric disturbances such as depression [3]. In extreme cases, patients can present with nervous system failure and coma as a result of extremely elevated calcium levels, usually more than 15 mg/dL, a condition known as a parathyroid crisis [4]. Yet, in the case of moderate hypercalcemia, the classical presentation is absent and as a result, these patients are mostly diagnosed during blood tests or while screening for other bone-related pathologies.

PTA is typically less than 1 g in weight [5]. Rarely when the adenoma is 3.5 g or more, it is described as a giant adenoma [6]. Whether this variation in size is due to late detection of disease or due to the hyperproliferative nature of adenoma cells is still unclear. In this context, oxyphil adenomas despite representing only 3% of cases, are more likely to attain a large size in comparison to chief cell adenoma [7].

Over the last couple of years, it has been noticed in our institute that a respectable percentage of those adenomas removed do qualify as giant. This triggered this research project to examine all PTAs removed over the last 10 years. The main objective of this study is to describe the clinical characteristics and outcomes of PTA patients in our tertiary

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hospital and compare the clinical presentation, laboratory findings, and postoperative outcomes of regular and giant PTAs.

2. Materials and methods

In this retrospective study, PTA patients' data were retrieved from the electronic reports system consecutively from 2010 to 2019 at King Abdullah University Hospital (KAUH) located in the north of Jordan. Patients were stratified into two groups according to adenoma weight; < 3.5 g were considered regular PTAs and ≥3.5 g were considered giant PTAs. Extracted data from both PTA groups included: patient's age, sex, clinical presentation, lab findings (Pre and postoperative Ca and PTH levels), adenoma weight, localization outcome, whether patients received postoperative IV Ca infusion, and length of hospital stay for both regular and giant PTAs. We excluded patients with an abnormal renal function such as end-stage renal disease, or those with a familial disease as well as PTA patients undergoing revision surgery.

Diagnosis is mostly established through clinical symptoms coupled with elevated serum calcium and PTH. Preoperative localization of the adenoma is done in our institute using neck ultrasonography and Sestamibi scan. Computed Tomography (CT) scan was employed in a few giant PTAs where a retrosternal extension was present. Parathyroidectomy is the primary treatment in PTA.

This study was done following the Strengthening the reporting of cohort studies in surgery (STROCSS) guidelines [8]. Ethical approval was obtained from the Institutional Review Board (IRB) at Jordan University of Science and Technology.

Descriptive measures used included mean, Standard Deviation (SD) for quantitative variables, and for categorical variables, counts and percentages were used. Independent T-test was used to compare means in case of data normality, which was investigated using the Shapiro-Wilk test, and when this assumption was violated, we used the Mann–Whitney U instead. To analyze associations between categorical data across the regular and giant PTA groups we used the Chi-square test, or Fisher's exact test if cell count was less than 5. Pairwise deletion was used in case of missing data. Effect size measures included Cramer's V for nominal data and Cohen's D and r correlation statistic for continuous data. Effect size measures reference ranges are detailed in Table 1 [9–11]. Spearman's coefficient (rho) was calculated to assess the correlation between adenoma weight and preoperative Ca and PTH levels. A two-sided p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS version 26 [12].

3. Results

3.1. Overall PTA patients' characteristics

A total number of 84 patients were identified and included in the study. Twenty-four of these qualified as giant adenomas (28.6%) and the rest were regular adenomas (71.4%). A mean age of 48.94 ± 13.7 and female predominance (76.2%) were reported in all included cases. The distribution of PTAs weights was right-skewed and not normally distributed (Shapiro-Wilk test P-value = 0.000). The average adenoma weight was 3.58 ± 4.8 g for both groups, which is slightly over the cutoff point for giant PTAs.

Upon clinical presentation, 27 patients (32.14%) were diagnosed incidentally, whereas symptomatic patients were most likely to present with bone pain (15.5%), renal stones (9.5%), painless neck masses (9.5%), fatigue (8.3%) or bone fractures (8.3%). Preoperative localization using Sestamibi and US was used in the majority of patients and was positive in (83.3%).

Average preoperative Ca and PTH levels were 2.47 ± 0.31 mmol/L and 428 ± 460.5 pg/mL, respectively. The correlation between preoperative serum Ca and PTH with adenoma weight were both weakly direct but not significant (Ca and weight: rho = 0.125, P-value = 0.315, PTH and weight: rho = 0.231, P-value = 0.053, Figs. 1 and 2).

Upon parathyroidectomy, the mean hospital stay was 4.52 ± 5.1 days and only 17 patients (20.2%) received IV calcium infusion as a result of postoperative hypocalcemia. Reoperation was not carried out in any of the patients. Full patients' characteristics are presented in Table 2.

3.2. Giant versus regular PTA

Among the entire cohort of PTA patients, 24 were identified as giant PTAs with a mean weight of 7.86 ± 6.46 g, and the remaining 60 patients were classified as having regular adenoma with a mean weight of 1.45 ± 0.8 g. Giant adenomas ranged from 3.5 to 32 g and were more likely to present at a younger age compared to regular adenoma patients, (44.4 vs 50.8, P = 0.053, D = 0.470 "small effect"). Preoperative PTH levels were significantly higher in the giant PTA group (650.8 vs 334.2 pg/mL, P = 0.044, r = 0.22 "small effect"). Scatter plots for preoperative Ca and PTH levels and adenoma weight grouped by PTA size are presented in Figs. 1 and 2, respectively.

Patients with giant PTA were more likely to present with pancreatitis (12.5% vs 1.67%) and muscle weakness (16.7% vs 3.3%), whereas regular PTA patients presented more frequently with fatigue (11.67% vs 0%) or diagnosed incidentally (33.3% vs 25%) than giant PTA.

Both groups had a high percentage of preoperative localization (Giant: 79.2% and Regular: 87.9%). Patients with giant PTAs tended to

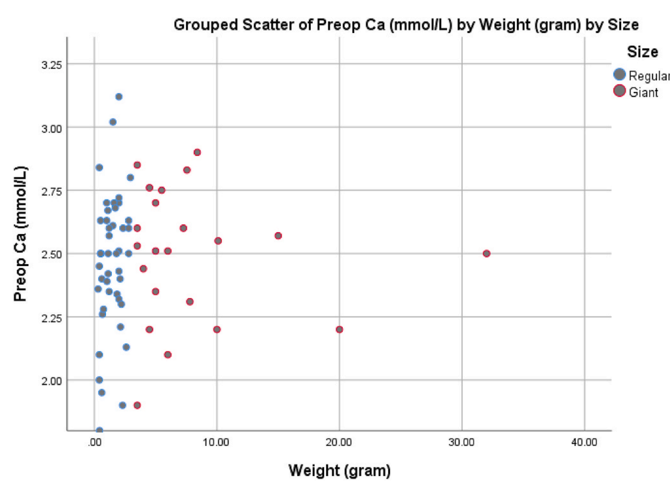

Fig. 1. Scatter plot for preoperative Ca levels (mmol/L) and adenoma weight (gram) grouped by adenoma size.rho = 0.125, P-value = 0.315.

Table 1
Effect size measures reference ranges.

Cramer's V		Cohen' D		r statistic	
Range	Interpretation[9]	Range	Interpretation[10]	Range	Interpretation[11]
0.1 - < 0.3	small effect	<0.35	trivial effect	0.1 - < 0.3	small effect
0.3 - < 0.5	medium effect	0.35 - < 0.80	small effect	0.3 - < 0.5	medium effect
0.5 - ≤ 1	large effect	0.80 - < 1.5	moderate effect	0.5 - ≤ 1	large effect
		≥1.5	large effect		

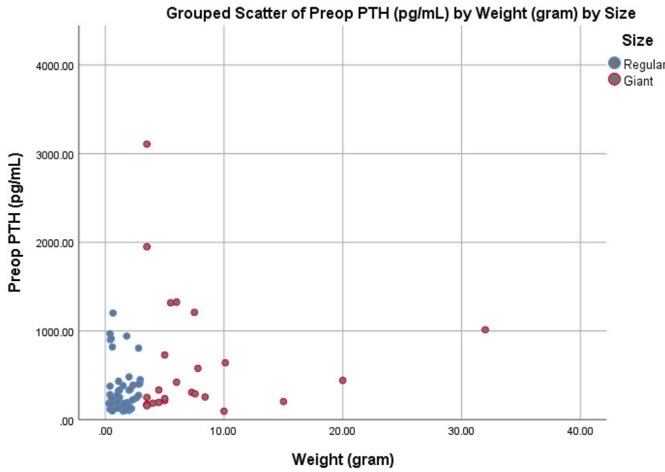

Fig. 2. Scatter plot for preoperative PTH levels (pg/mL) and adenoma weight (gram) grouped by adenoma size.rho = 0.231, P-value = 0.053.

Table 2
Overall PTA patients characteristics.

Patient Characteristics	Overall (N = 84)
Age	
Mean (SD)	48.94 (13.71)
Sex (%)	
Male	20 (23.8)
Female	64 (76.2)
Weight (g)	
Mean (SD)	3.58 (4.82)
Median (IQR)	2 (3.28)
Size (%)	
Regular	60 (71.4)
Giant	24 (28.6)
Preoperative Ca levels (mmol/L)	
Mean (SD)	2.47 (0.31)
Preoperative PTH levels (pg/mL)	
Mean (SD)	428 (460.50)
Median (IQR)	272.5 (252.9)
Clinical presentation (%)	
Symptomatic	57 (67.86)
Bone pain	13 (15.48)
Pancreatitis	4 (4.76)
Fatigue	7 (8.3)
Constipation	5 (5.95)
Weakness	6 (7.14)
Painless neck mass	8 (9.52)
Renal stones	8 (9.52)
Bone fracture	7 (8.3)
Others (dysphagia, numbness, mood ——changes, polyuria, dysrhythmia)	18 (21.43)
Incidental	27 (32.14)
Localization using Sestamibi/US	70 (83.3)
Length of hospital stay (days)	
Mean (SD)	4.52 (5.12)
Median (IQR)	3 [2]
Postoperative Ca on Day 1 (mmol/L)	
Mean (SD)	2.28 (0.29)
Postoperative Ca on Day 2 (mmol/L)	
Mean (SD)	2.16 (0.24)
Postoperative PTH levels (pg/mL)	
Mean (SD)	37.90 (36.27)
Median (IQR)	24.3 (40.63)
Patients receiving postoperative IV Ca infusion (%)	17 (20.24)
Reoperation (%)	0 (0)

receive postoperative IV Ca infusion more likely than those with regular PTAs (33.3% vs 15%, P = 0.059, V = 0.206 "small effect"). Hospital stay was on average 1.6 days longer in giant PTA patients compared to regular PTA patients (P = 0.032, r = 0.23 "small effect"). Differences in postoperative Ca levels were not statistically significant across both groups. Detailed comparison of patients' characteristics between giant and regular PTAs are presented in Table 3.

Our cohort included five cases with extreme giant adenomas (≥10 g). Detailed characteristics for these patients are presented in Table 4.

4. Discussion

In this retrospective comparative study, we present our unique hospital's experience with PTAs as the prevalence of giant adenomas

Table 3
Comparison of patient characteristics between giant and regular PTA.

Patient Characteristics	Giant Adenoma (N = 24)	Regular Adenoma (N = 60)	P-value	Effect Size
Age				
Mean (SD)	44.38 (13.86)	50.77 (13.32)	0.053	D = 0.470
Sex (%)				
Male	7 (30.43)	13 (21.67)	0.466	V = 0.080
Female	16 (69.57)	47 (78.33)		
Weight (g)				
Mean (SD)	7.86 (6.46)	1.45 (0.81)	**0.000**	r = 0.81
Preoperative Ca levels (mmol/L)				
Mean (SD)	2.52 (0.23)	2.46 (0.32)	0.644	r = 0.086
Preoperative PTH levels (pg/mL)				
Mean (SD)	650.79 (711.01)	334.21 (255.13)	**0.044**	r = 0.22
Clinical presentation (%)				
Incidental	6 [25]	21 (33.33)	0.375*	V = 0.097
Symptomatic	17 (70.83)	39 (65)		
Bone pain	4 (16.67)	9 [15]		
Pancreatitis	3 (12.5)	1 (1.67)		
Fatigue	0 (0)	7 (11.67)		
Constipation	1 (4.17)	4 (6.67)		
Weakness	4 (16.67)	2 (3.33)		
Painless neck mass	3 (12.5)	5 (8.33)		
Renal stones	2 (8.33)	6 [10]		
Bone fracture	2 (8.33)	5 (8.33)		
Others (dysphagia, numbness, mood – changes, polyuria, dysrhythmia)	3 (12.5)	15 [25]		
Localization using Sestamibi/US	19 (79.17)	51 (87.93)	1.000	V = 0.021
Length of hospital stay (days)				
Mean (SD)	5.67 (5.05)	4.07 (5.12)	**0.032**	r = 0.23
Postoperative Ca on Day 1 (mmol/L)				
Mean (SD)	2.24 (0.26)	2.29 (0.29)	0.474	D = 0.182
Postoperative Ca on Day 2 (mmol/L)				
Mean (SD)	2.11 (0.24)	2.19 (0.23)	0.234	D = 0.340
Postoperative PTH levels (pg/mL)				
Mean (SD)	36.97 (37.20)	37.63 (36.25)	0.887	r = 0.016
Patients receiving postoperative IV Ca infusion (%)	8 (33.33)	9 [15]	0.059	V = 0.206
Reoperation (%)	0	2 (3.17)		

* P value for Chi square test to examine the relation between weight groups and the presence of symptoms or not (symptomatic vs incidental)

Table 4
Characteristics of patients with giant adenomas over 10 g.

#	Sex	Age	Adenoma weight (g)	Preop PTH (pg/mL)	Preop Ca (mmol/L)	Presentation	Hospital Stay (days)	Postoperative IV Ca infusion	Sistamibi/US Localization	Postop PTH (pg/mL)
1	F	37	32	1014	2.5	Bone pain Constipation	14	Yes	Yes	65
2	F	37	20	441	2.2	Renal stones	3	No	Yes	11
3	M	61	15	201.9	2.57	Weakness	2	No	Yes	6.6
4	M	59	10.1	640.4	2.55	Dysrhythmia	3	No	Yes	23.7
5	F	42	10	93.6	2.2	Painless neck mass	3	No	NA	37.2

over 10 years was notably higher than what is previously reported in the literature [13]. In 84 PTA patients, excellent outcomes were reported across both giant and regular adenoma patients. There was an increased need for IV calcium infusion in the immediate postoperative period due to the bone hunger syndrome.

Our sample had a high success rate in localization studies. This may be explained by the relatively high mean adenoma weight that was marginally eligible to be considered giant adenoma. This in return reduces the need for revision surgery in case of multiglandular involvement which is reflected in our low percentage of reoperation. Incidental cases only accounted for almost a third of the patients whereas the majority were symptomatic, bone pain being the most common, followed by renal stones and painless neck masses. This further confirms the predominance of the classical presentation of primary hyperparathyroidism characterized by “stones, bones and groans” in the Middle East, Asia, and South Africa [14–18]. The insufficiency of routine calcium screening in these regions is thought to contribute to low asymptomatic primary hyperparathyroidism diagnosis compared to the USA and Western Europe [1,19,20].

When stratifying patients based on PTA weight, a high percentage (28.6%) of giant adenoma was reported over ten years compared to cohorts reported in the literature [21,22]. TE et al. reported in his prospective database study a percentage of 10.7% from 519 patients for giant adenomas over eleven years despite using 3 g as their cutoff point for giant adenomas compared to our 3.5 g [13]. Also, five patients in our cohort presented with giant adenomas weighing over 10 g, the maximum was 32 g. These giant adenomas are unusual and were presented only as case reports in the literature [23,24]. These elevated numbers are more likely to be inflated as a result of the lack of routine calcium screening rather than PTAs displaying unique hyperproliferative patterns. Yet, more studies in the region are certainly needed to confirm this conclusion.

In our sample, there was no association between adenoma weight and preoperative Ca levels, but PTH levels were significantly higher in giant PTH preoperatively. This is in accordance with findings from previous studies. Hamidi et al. and Mozes et al. found a moderate direct correlation between PTH levels and adenoma’s weight in 71 and 155 patients in their retrospective cohort studies, respectively while Mortez et al. in their retrospective analysis on 30 patients reported a significant association only when PTH levels were extremely high or low [22,25,26]. Other studies reported invariable and sometimes contradictory significant correlations between preoperative PTH levels, and PTA weight as Williams et al. showed in their retrospective cohort study on 44 patients that PTAs heavier than 750 mg had a significantly lower circulating PTH level per mg of adenoma than patients with glands lighter than 750 mg [27].

The explanation for such inconsistent results is not clear but can be partially owed to the variation in baseline characteristics in studies, one of those factors being the investigated population. For instance adenomas in our study were much heavier compared with western studies from Canada and the USA [21,22]. This is because of corresponding variations in levels of vitamin D deficiency. The Middle East has some of the highest rates of vitamin D deficiency despite having abundant sunlight [28]. In return, vitamin D deficiency is associated with more severe primary hyperparathyroidism and larger adenomas [29]. Other important variant confounding factors include calcium intake, serum albumin, and renal function. Stern et al. hypothesized that a higher proportion of chief cells would be associated with higher PTH levels, yet this difference failed to appear in their historical cohort study on 378 patients [30]. Another retrospective study on 66 patients also found that both chief cell and clear cell PTAs secrete PTH at similar levels [31].

In our series, patients with giant adenomas were nearly twice as likely to need postoperative IV calcium infusion. This is because of bone hunger syndrome after a sudden fall in PTH levels following surgery. Consequently, these patients had longer hospital stays. TE et al. in their prospective database study on 519 patients reported a notably shorter hospital stay in both giant and regular PTA patients from the United Kingdom compared to our sample which again reflects changes in underlying populations [13].

While disturbances in Ca and PTH levels still have a debatable role in predicting adenomas’ size, it has been suggested that their concentrations can be good indicators of multiglandular involvement in PTA [32]. In our sample, only two patients had more than one adenoma.

This study presents valuable insight on PTA from an underreported population from Jordan in the Middle East. The high prevalence of giant adenomas within a single tertiary institute over a relatively small period presents unique data that warrant a more comprehensive understanding of the landscape of PTAs. Limitations of this study include the retrospective nature of this study which prevents appropriate control of potential confounders that were not taken into consideration such as vitamin D levels. Our small sample size limits the ability to draw generalizations from our findings. This further highlights the need for prospective national-based large studies.

5. Conclusion

In this cohort study, giant parathyroid adenoma compromised a significant percentage of all adenomas. This is higher than what is reported in the literature and might reflect a delay in diagnosis and lack of screening tests. Despite the difference in size, both giant and regular adenomas seem to run a similar clinical course, and the success of surgical treatment was found to be comparable. Biochemical abnormalities in PTH levels could have a potential role in predicting the weight and size of PTA.

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Ethical Approval

This research has got the institutional board review approval (IRB) at King Abdullah University Hospital. Ref. No 20200643

Consent

Not applicable. The IRB waived the need for signing a consent form from each patient because of the retrospective nature of the study based on reviewing the patients' records.

Author contribution

Wisam Algargaz: Study concept and design, data collection, manuscript writing. Hassan Abushukair: Data analysis, manuscript writing. Haitham Odat: Data collection. Shadi Hamouri: Data interpretation and manuscript writing. Raneem AbuAshour: Data interpretation and manuscript writing

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102454.

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