Giant Parathyroid Adenoma versus Parathyroid Carcinoma: Differentiating Two Entities

Hazwani Aziz1 and Zanariah Hussein2

1Hospital Tuanku Jaafar, Ministry of Health Malaysia
2Hospital Putrajaya, Ministry of Health Malaysia

Abstract

Giant parathyroid adenoma (GPA) is defined as adenoma larger than 3.5 g. Twenty-one cases of parathyroid mass >3.5 g in patients with primary hyperparathyroidism who underwent parathyroidectomy in Hospital Putrajaya, Malaysia were identified. Most cases presented with nephrolithiasis. Two cases are reported as parathyroid cancer. GPA has significantly higher serum calcium and iPTH levels and can be asymptomatic. Parathyroid carcinoma patients are frequently symptomatic, with large tumors. Differentiating GPA from parathyroid cancer is important as it determines the subsequent surgical intervention.

Key words: hyperparathyroidism, primary, parathyroid neoplasm, parathyroidectomy, calcium, adenoma

INTRODUCTION

Primary hyperparathyroidism is a common endocrine disorder with a reported incidence of 25 per 100,000 in the general population. Only less than 1% of cases of primary hyperparathyroidism are due to parathyroid cancer, and 85% are due to parathyroid adenoma. Giant parathyroid adenoma is a rare condition as parathyroid adenomas are commonly reported as small lesions, weighing less than 1 gram. Giant parathyroid adenoma is defined as an adenoma of more than 3.5 g weight. There has been no reported prevalence data of giant parathyroid adenoma among ASEAN countries. This case series adds to the body of knowledge generally lacking in the incidence of parathyroid disease in the Asian population.

This case series describes the different demographics, clinical presentations, laboratory data, tumor sizes and histopathological reports of patients who underwent parathyroidectomy in Hospital Putrajaya, Malaysia with parathyroid mass larger than 3.5 g.

CASE SERIES

Twenty-one cases of parathyroid mass larger than 3.5 g in patients with primary hyperparathyroidism who underwent parathyroidectomy in Hospital Putrajaya, Malaysia from 2012 till 2019 were identified from the electronic medical records. A total of 87 patients with primary hyperparathyroidism were collected and 21 of the patients (24%) had large parathyroid mass. The majority of patients were male (62%), and between 50 to 65 years old (62%) at presentation (Table 1).

Eleven cases (52%) presented with nephrolithiasis. Six cases had osteoporosis and two were asymptomatic. A case of severe parathyroid bone disease with osteoporotic fracture occurred in a 17-year-old female with markedly elevated serum parathyroid hormones (iPTH) of 89.8 pmol/L. Two cases presented with pancreatitis and severe hypercalcaemia of 3.21 mmol/L and 4.0 mmol/L.

Average serum calcium at presentation was 3.2 mmol/L, with only 2 cases having serum calcium levels of less than 3.0mmol/L. Average iPTH level was 71.5 pmol/L, with highest iPTH level of 176.6 pmol/L. The tumor sizes ranged from 3.5 g to 38 g.

Two cases developed hungry bone syndrome post-surgery. The first case was a patient with an adenoma size of 32.4 g, with serum calcium of 3.14 mmol/L and serum alkaline phosphatase (ALP) of 3046 U/L at presentation. The second case was a patient with an adenoma size of 6 g, and serum calcium of 3.22 mmol/L and serum ALP of 405 U/L.

Upon histopathological review, two cases were reported as parathyroid cancer and a single case was classified with atypical histology suggestive of cancer. Both had significantly high iPTH levels.

The first case was a 28-year-old female, presenting with nephrocalcinosis and chronic pancreatitis, with serum calcium of 3.2 g, iPTH level of 3.14 mmol/L, and serum alkaline phosphatase (ALP) of 3046 U/L at presentation. The second case was a patient with an adenoma size of 6 g, and serum calcium of 3.22 mmol/L and serum ALP of 405 U/L.

The first case was a 28-year-old female, presenting with nephrocalcinosis and chronic pancreatitis, with serum calcium of 4.0 mmol/L, iPTH level of 176 pmol/L and tumor size of 4.2 g. The second case was a 78-year-old female who presented with symptomatic hypercalcaemia and osteoporosis, with serum calcium of 3.61 mmol/L, iPTH level of 88.2 pmol/L and tumor size of 38 g. A case...
Thus, it can be concluded that in patients with giant parathyroid tumours with significantly high serum calcium, in the absence of symptoms, the likely diagnosis is giant parathyroid adenoma rather than parathyroid cancer. However, this subject requires further evaluation.

Parathyroid carcinoma patients are frequently symptomatic with more severe symptoms. Two cases with parathyroid cancer presented with severe symptoms requiring admission with significantly high calcium of 3.61 mmol/L and 4.0 mmol/L, with one of them having the largest tumour in our series weighing 38 g.

It is important to differentiate the clinical presentations of both conditions prior to surgery as fine needle aspiration is not recommended due to low discriminatory capacity and risk of dissemination. Absence of adjacent structural invasion and distant metastases made the diagnosis even more challenging. Ultrasound plays an important part in discriminating giant parathyroid adenoma and parathyroid cancer as parathyroid cancers have lobulated and heterogenous appearance but giant adenomas have smooth borders and homogenous echogenicity. The depth/width ratio is greater than 1 in 95% of parathyroid cancers and less than 1 in 94% of giant adenomas.

Only histopathology examinations will confirm parathyroid carcinoma. Presence of dense fibrous bands, of atypical parathyroid adenoma with focal capsular and perivascular invasion occurred in a 52-year-old female with serum calcium of 2.77 mmol/L, serum iPTH of 87.8 pmol/L and tumour size of 6.9 g.

Two cases were associated with Multiple Endocrine Neoplasm 1 (MEN1), each showed histopathological features of parathyroid hyperplasia with tumor size of 15.6 g and 4.1 g, respectively (Figures 1-4).

### DISCUSSION

Differentiating giant parathyroid adenoma and parathyroid carcinoma is a diagnostic challenge. It is important to determine the risk of parathyroid carcinoma in all giant parathyroid tumour as this will determine the surgical approach of the tumour, including the resection margin and the possibility of ipsilateral thyroidectomy in the presence of nodular thyroid disease.

Giant parathyroid adenoma and parathyroid cancer share some of the common characteristics including significantly large tumour size, higher serum calcium and higher iPTH levels.

One of the distinct properties of giant parathyroid adenoma is it can be asymptomatic as presented by two cases of giant parathyroid adenoma despite high calcium and large adenoma. Thus, it can be concluded that in patients with giant parathyroid tumours with significantly high serum calcium, in the absence of symptoms, the likely diagnosis is giant parathyroid adenoma rather than parathyroid cancer. However, this subject requires further evaluation.

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### Table 1.
The summarized relevant data of all the patients with parathyroid mass of more than 3.5 g, with relevant laboratory investigations; serum calcium, serum inorganic phosphate, serum alkaline phosphatase (ALP), serum parathyroid hormone (iPTH), their clinical presentations, associated syndromes and the results of their biopsies

| Case | Age/Gender | Calcium (mmol/L) | Inorganic Phosphate (mmol/L) | ALP (U/L) | iPTH (pmol/L) | Clinical presentations/associated syndromes | Weight (g) | HPE |
|------|------------|------------------|-----------------------------|----------|--------------|---------------------------------------------|------------|-----|
| 1    | 50/M       | 3.70             | 0.81                        | 101      | 67.2         | Nephrolithiasis                             | 14.2       | Adenoma |
| 2    | 35/M       | 3.05             | 0.90                        | 78       | 16.8         | Recurrent PHPT                               | 4.3        | Adenoma |
| 3    | 61/M       | 3.34             | 0.81                        | 179      | 113.5        | Asymptomatic                                | 9.1        | Adenoma |
| 4    | 57/M       | 3.26             | 0.85                        | 77       | 37.1         | Nephrolithiasis                             | 4.9        | Adenoma |
| 5    | 63/M       | 4.23             | 0.90                        | 95       | 67.0         | Nephrolithiasis                             | 5.8        | Adenoma |
| 6    | 53/F       | 3.21             | 0.69                        | 139      | 34.1         | Pancreatitis                                | 10.1       | Adenoma |
| 7    | 63/F       | 3.26             | 1.00                        | 80       | 83.5         | Constipation                                | 8.7        | Adenoma |
| 8    | 53/F       | 3.85             | 0.64                        | 194      | 99.2         | Osteoporosis                                | 15.6       | Adenoma |
| 9    | 48/M       | 3.06             | 0.68                        | 171      | 28.5         | Nephrolithiasis                             | 3.7        | Adenoma |
| 10   | 63/F       | 3.00             | 0.51                        | 204      | 50.3         | Nephrolithiasis                             | 5.3        | Adenoma |
| 11   | 26/F       | 4.00             | 0.69                        | 173      | 176.0        | Nephrolithiasis Pancreatitis                | 4.2        | Carcinoma |
| 12   | 58/M       | 3.22             | 0.56                        | 405      | 40.4         | Polyuria                                    | 6.0        | Adenoma |
| 13   | 37/M       | 3.00             | 0.89                        | 73       | 36.5         | Constipation                                | 4.1        | Hyperplasia |
| 14   | 60/M       | 3.59             | 0.60                        | 142      | 40.8         | Confusion                                   | 5.8        | Adenoma |
| 15   | 17/F       | 3.14             | 0.40                        | 3046     | 89.8         | Fractures                                   | 32.4       | Adenoma |
| 16   | 24/M       | 2.60             | 0.60                        | 142      | 63.7         | Abdominal pain                              | 3.9/10     | Hyperplasia |
| 17   | 51/M       | 3.03             | 0.57                        | 90       | 56.8         | Nephrolithiasis                             | 3.5        | Adenoma |
| 18   | 52/F       | 2.77             | 0.50                        | 1396     | 87.8         | Constipation                                | 6.9        | Atypical adenoma |
| 19   | 59/M       | 3.21             | 0.56                        | 143      | 41.2         | Asymptomatic                                | 7.6        | Adenoma |
| 20   | 39/M       | 4.64             | 0.66                        | 388      | 176.6        | Lethargy                                    | 14.6       | Adenoma |
| 21   | 78/F       | 3.61             | 0.67                        | 146      | 88.2         | Confusion                                   | 38.0       | Carcinoma |

Abbreviations: M, male; F, female; ALP, alkaline phosphatase; iPTH, intact parathyroid hormones; HPE, histopathological examination; MEN, multiple endocrine neoplasia.
thyroid adenoma are less severe compared to patients with parathyroid carcinoma. Reported median size and weight of atypical parathyroid adenomas by Cetani et al., are 2.5 cm (range 0.7–7.2 cm) and 4.15 g (range 0.3–101 g), which is more than the weight definition of giant parathyroid adenoma (Table 2). Interestingly, O’Neal et al., reported that presence of atypical parathyroid adenoma was significantly higher than that of carcinoma among tumors weighting ≥2 g (17.5% vs 1.3%, P < 0.05).

Study Limitations
Our case series is limited by the information gained from the electronic medical record review. Prospective case study is the optimal research methodology to further assess the differentiating criteria, the proper diagnostic approaches prior to surgery and the outcome of the approaches for better understanding of giant parathyroid adenoma and parathyroid carcinoma.

The major issue in this case series is the ethical considerations during electronic medical record review.

trabecular architecture, vascular and capsular invasion, and mitotic activity are proposed morphology criteria to identify parathyroid carcinoma although sensitivity and specificity of each isolated criterion is limited. Loss of staining for parafibromin and Ki-67 of more than 5% are good indicators for parathyroid carcinoma.

Another entity that is described in this case series is atypical parathyroid adenoma. Atypical parathyroid adenoma is defined by a group of intermediate form of parathyroid neoplasms of uncertain malignant potential which show some atypical histological features that represent a challenge for the differential diagnosis with parathyroid carcinomas. The described atypical features include solid growth pattern, fibrous bands, and cellular atypia. In our featured case, the atypical features are presence of focal capsular and perivascular invasion.

In contrast to parathyroid carcinoma, atypical parathyroid adenoma has no evidence of local invasion or metastases. The outcome of patients with atypical para-

Figure 1. **Case 21.** Neoplastic cells arranged in compactly arranged trabecular pattern and pseudo-follicular configurations. The tumor cells are extending beyond the capsule into the attached adipose tissue (H&E, 40x).

Figure 2. **Case 21.** Immunohistochemical studies chromogranin stain shows the tumour cells are expressing chromogranin (40x).

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Figure 3. **Case 15.** Tumour cells with clear cytoplasm that are arranged in sheets and cords traversed by delicate blood vessels (right lower) and some cells with bizarre enlarged nuclei (left) (H&E, 100x).

Figure 4. **Case 15.** Tumour cells exhibit enlarged hyperchromatic nuclei (H&E, 400x).
Table 2. Clinical, radiographic and histomorphological features comparing giant parathyroid adenoma and parathyroid carcinoma

| Criteria                  | Giant parathyroid adenoma                      | Parathyroid carcinoma               |
|---------------------------|-------------------------------------------------|-------------------------------------|
| Clinical Features         | Can be asymptomatic                             | Frequently symptomatic with severe symptoms |
| Symptomatology            | High                                            | High                                |
| Tumour Size               | Greater than 1                                  | Lobulated and heterogeneous appearance |
| Serum Calcium             | High                                            | Greater than 1                      |
| Serum iPTH                | Less than 1                                     | Dense fibrous bands, trabecular architecture, vascular and capsular invasion and mitotic activity |
| Ultrasonography           | Smooth borders and homogenous echogenicity      |                                    |
| Features                  | Well circumscribed, with thin fibrous capsule, absent of fat cells within the mass, absent of lobular pattern12 |                                    |
| Depth/Width ratio         | Present                                         |                                    |
| Histomorphologic features | Less than 5%                                    | Loss                                |
| Staining for parafibromin | Present                                         | More than 5%                        |
| Ki-67                     | Present                                         |                                    |

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