Parathyroid Cancer: Two Case Reports with a Review of the Literature

KS Aljabri1*, SA Bokhari1, MA Alshareef1, PM Khan1, DA Abdulhafez2 and BK Aljabri3

1Department of Endocrinology, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia
2Department of Pathology, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia
3Medical Student, College of Medicine, Um Alqura university, Makkah, Kingdom of Saudi Arabia

*Corresponding Author: Khalid S Aljabri, Department of Endocrinology, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia.

Received: September 18, 2017; Published: October 21, 2017

Abstract

Parathyroid cancer (PTC) is a rare disease. It is most often diagnosed incidentally based on multi-organ non-specific symptoms of hypercalcemia as a consequence of parathyroid hormone over secretion. We report two cases of PTC initially presented with severe hypercalcemia and elevated parathyroid hormone levels. The diagnosis was confirmed histologically following a thyroidectomy and parathyroidectomy.

Keywords: Parathyroid Cancer; Saudi Arabia

Introduction

Parathyroid cancer (PTC) is an uncommon endocrine malignancy. It accounts for 0.4% to 5.2% of all reported cases of hyperparathyroidism. It is estimated to comprise from 0.2 - 1% in the US and Europe to 0.5% in Japan and Italy of malignant endocrine tumors which is approximately 0.005% of all cancers overall [1-15]. Two cases were reported from Saudi Arabia [16,17]. The first known case, described by Fritz De Quervain in 1904 [9]. The 45 - 55 year age group is the most affected, with a slight predominance of cases in women [18]. It has not been described and preponderance concerning race, income level or geographic distribution [19]. It may be sporadic or part of a genetic syndrome such as hyperparathyroidism jaw-tumor syndrome, and the majority of PTC are functional, with fewer than 10% of cases being nonfunctional [1]. We report two cases of PTC presented with severe hypercalcaemia and elevated parathyroid hormone levels.

Case Report

Case 1

A 62-year-old Saudi male, who was known to have type 2 diabetes mellitus, osteoporosis and hyperlipidaemia, complained of bone and muscle pain of several years of duration. Neck examination revealed goitre. Clinical picture and the conducted tests showed primary hyperparathyroidism (Tables 1). Thyroid ultrasound showed right complex thyroid nodule 1.0 cm and 0.8 cm solid on the left thyroid gland. Tc99m-sestamibi scintigraphy showed no evidence of parathyroid adenoma. Patient was treated for hypercalcemia with hydration preoperatively and his calcium level reached the day of surgery 2.51 mmol/L. Subtotal thyroidectomy was done November 2016. Postoperative histopathology showed PTC with a Size of 5.5 x 4.5 x 1.5 cm and weight of 33.6 gm PTC (Figure 1A and 1B). Six months later, his serum calcium was 2.3 mmol/L, albumin 45 gm/L, parathyroid hormone 9.6 pmol/L, TSH 4.8 mIU/L and vitamin D was 90.7 nmol/L.

Parathyroid Cancer: Two Case Reports with a Review of the Literature

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal reference</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>2.15 - 2.55 (mmol/L)</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Albumin</td>
<td>34 - 52 (gm/L)</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.7 - 1.2 (mmol/L)</td>
<td>0.6</td>
<td>0.97</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>40 - 129 U/L</td>
<td>90</td>
<td>224</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.66 - 1.06 mmol/L</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>1.6 - 6.9 (pmol/L)</td>
<td>73.4</td>
<td>61.5</td>
</tr>
<tr>
<td>25-hydroxyvitamin D</td>
<td>75 - 250 (nmol/L)</td>
<td>20.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Creatinine</td>
<td>62 - 106 (umol/°)</td>
<td>76</td>
<td>132</td>
</tr>
<tr>
<td>TSH</td>
<td>0.27 - 4.2 (mIU/L)</td>
<td>1.67</td>
<td>3.5</td>
</tr>
<tr>
<td>FT4</td>
<td>12.1 - 22 (pmol/L)</td>
<td>12.7</td>
<td>12.04</td>
</tr>
</tbody>
</table>

Table 1: Laboratory values for the two cases.

Figure 1: Case 1 showed nodules of parathyroid tissue within thick fibrous bands. Red arrow points the fibrous band (A) and invasion to the thyroid gland (blue arrow) by nodules of parathyroid neoplastic tissue (red arrows) (B). Case 2 showed multiple blood vessels lined by flat layer of endothelial cells with attached tumor emboli. Red arrows point the blood vessels (c) and islands of parathyroid tissue infiltrating the surrounding fat and sizable blood vessels which make the resection of the tumor difficult. Red arrows indicating the fat component and one large blood vessel (D).

Case 2

A 72-year-old Saudi female was referred to the endocrinology department clinic for hyperparathyroidism after routine blood work drawn by her primary care physician revealed a calcium level as high as 3.7 mmol/L as well as an intact parathyroid hormone level that was significantly increased at 199 pmol/L. The patient complained of generalized body aches and had history of chronic renal impairment and osteoporosis. She denied any radiation exposure or any personal or family history of cancer. On examination, diffuse goitre with thyroid mass was detected in the right neck without evidence of cervical lymphadenopathy. Subsequent work-up included blood work (Table 1) and thyroid ultrasound and neck MRI showed a large inhomogeneous mass of the right lower thyroid lobe that measured 3.7 cm (Figure 2A and 2B). Fine needle aspiration of the right thyroid nodule showed Benign colloid nodules, Bethesda Category II. Tc99m-sestamibi scintigraphy demonstrated thyroid adenoma. At this time, the patient was scheduled for a neck exploration in the operating room with a differential diagnosis of a large adenoma. Total thyroidectomy was performed June 2017. The pathology report described a right thyroid lobe with a PTC, The tumor was extending beyond the capsule and is reaching to the inked resection margins. Foci of vascular invasion and surrounding soft tissue invasion identified. The tumor cells are positive for Cyclin-D1 and glactin-3, negative for thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK7) are positive in 5-6% of the tumor cells (Figure 1C and 1D). At follow-up one month after surgery, the patient appeared disease free, her serum calcium was 1.6 mmol/L, albumin 34 gm/L, parathyroid hormone 1.9 pmol/L and TSH 0.9 mIU/L.

**Figure 2:** Ultrasound thyroid (A) and MRI neck (B) showed a large inhomogeneous mass of the right lower thyroid lobe that measured 3.7 cm (Arrow).

Discussion

There has not been established any etiology for PTC and no predisposing factors were identified, it seems to be a result of a complex interaction of environmental factors and inherited genetic predispositions. There have not been established a definite progression sequence of benign to malignant lesions. The absence of conclusive data is attributed to the rarity of this tumor [20]. Neck radiation, adenoma, secondary and tertiary hyperparathyroidism have been reported in patients with parathyroid carcinoma [21]. A single glandular adenoma or hyperplasia are the most frequent cause of primary hyperparathyroidism. It is rarely caused by hyperfunctioning carcinoma, that accounts for 0.5% up to 5% of the patients with primary hyperparathyroidism. In one review of 4,239 patients with hyperparathyroidism, 2.1% had functioning parathyroid carcinomas [11]. A systematic review of 22,225 cases of primary hyperparathyroidism

Parathyroid Cancer: Two Case Reports with a Review of the Literature

reported between 1995 and 2003 revealed that parathyroid carcinoma accounted for 0.74% of the cases [12]. The SEER (Surveillance, Epidemiology, and End Results) cancer registry identified 224 patients with parathyroid carcinoma from 1988 to 2003. During this time period, the incidence of parathyroid cancer was found to be very low (< 1 per million population per year), however, incidence was shown to increase from 3.58 to 5.73 per 10 million population when comparing the first three years to the last three years of the study [7], table 2. The reported median ages from 54.5 years (14 - 88 years) to 57 years (10 - 89 years). Although our patients were older than the reported median age, they are within the age range [22]. Diagnosis of PTC is not easy, in fact 86% of the patients with primary hyperparathyroidism receive no pre-operative or intra-operative diagnosis of malignancy [22,23]. The first case was described over 100 years ago, but because of its rarity is difficult to establish clinical, histopathological and radiologic criteria of malignancy. The clinical presentation with symptoms of hypercalcaemia, including anorexia, weight loss, fatigue, weakness, nausea, vomiting, bone pain, polyuria and polydipsia, complications such as pathologic fracture, renal colic, acute pancreatitis, peptic ulcer, occur more frequently than in benign disease. Hypercalcaemia in parathyroid carcinoma tends to be more severe (> 3.5 mmol/L in 65 - 75% of patients) and recalcitrant to treatment. The positive predictive value and sensitivity of hypercalcaemia were found to be 14% and 56% respectively. On the other hand, parathyroid hormone levels and tumor weight emerged as the more reliable surrogate indicators of parathyroid carcinoma. A tumor weight in excess of 2.5g. strongly favors a diagnosis of parathyroid carcinoma over that of adenoma. Serum parathyroid hormone levels tend to hover at about 10.3 times the upper limits of normal in parathyroid carcinomas as was the case in our patient. In contrast, mean parathyroid hormone levels in benign primary hyperparathyroidism will usually reach 2.6 times the normal values [24]. A palpable neck mass is present in up to 50% of PTC; hoarseness of voice due to recurrent laryngeal nerve palsy increase the possibility of malignancy; cervical lymph node metastases are present in 15 - 20% of cases. However, up to 30% of cancers haven’t these characteristic features and benign disease can be similar to malignancy; then, a definitive diagnosis based on clinical or biochemical criteria is virtually impossible. Most of PTC are hyperfunctioning, with marked serum parathyroid hormone levels, and symptoms occurs more frequently than in benign disease [24].

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1920 - 1972</td>
<td>70</td>
<td>9</td>
</tr>
<tr>
<td>1920 - 2009</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>1933 - 1968</td>
<td>41</td>
<td>13</td>
</tr>
<tr>
<td>1969 - 1981</td>
<td>62</td>
<td>12</td>
</tr>
<tr>
<td>1981 - 1988</td>
<td>163</td>
<td>10</td>
</tr>
<tr>
<td>1985 - 1995</td>
<td>286</td>
<td>4</td>
</tr>
<tr>
<td>1988 - 2003</td>
<td>224</td>
<td>7</td>
</tr>
<tr>
<td>1990 - 1999</td>
<td>94</td>
<td>14</td>
</tr>
<tr>
<td>1995 - 2003</td>
<td>150</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 2: Published collective series of parathyroid carcinoma.

Pre-operative imaging study with ultrasonography, Tc99m-sestamibi scintigraphy and CT scan can’t make differential diagnosis between benign disease or malignancy. Tc99m-sestamibi scintigraphy is the most sensitive imaging modality used for localizing abnormal parathyroid tissue, with an accuracy of 90% [24]. Sestamibi is a lipophilic cation that accumulates almost exclusively in the mitochondria; the oxyphil cells have an intensely eosinophilic cytoplasm rich of mitochondria. Principal cells are the active endocrine cells, with slight eosinophilic cytoplasm containing few mitochondria. A positive sestamibi scan is more frequent in adenomas rich in oxyphil cells than in predominance of chief cells. In absence of metastatic disease, it is difficult to establish a pre-operative diagnosis of PTC. The sensitivity for localizing parathyroid carcinoma in the neck using ultrasonography, 99mTc sestamibi scan, CT and MRI were, respectively, 83%, 79%, 69% and 93% [24].

Parathyroid Cancer: Two Case Reports with a Review of the Literature

Although the histopathological characteristics of PTC described in 1973 by Schantz and Castleman [9] are still used for diagnosis; none of them is pathognomonic of PTC and occur frequently in typical and atypical parathyroid adenoma as well as in parathyromatosis and it is often difficult to make diagnosis of PTC only on the basis of histology; but the presence of several findings in the same histological picture increase the possibility of malignancy [25]. Serum parathyroid hormone immunopositivity affirms the parathyroid origin of the tumor whereas proliferation markers serve a limited role in differentiating parathyroid carcinomas from adenomas. Ki-67 is one such marker staining cells which are actively cycling. A higher proportion of Ki-67-positive cells will usually be present in a carcinoma as opposed to an adenoma because of the higher proportion of proliferating cells in the former, but discrimination between the two on this basis alone is difficult because considerable overlap exists. Immunostaining with Ki-67 was performed in one of our patient in addition to evidence of thyroid gland and vascular invasion at the time of presentation had made it already amply clear that the tumor was malignant [26].

The treatment of parathyroid carcinoma aims not only to cure the disease but to obtain its biochemical remission: normalization of blood calcium and parathyroid hormone levels, arrest of bone calcium depletion and regression of vascular, renal and neurological disorders. The majority of parathyroid neoplasms are found in the inferior gland position, which is likely related to the different embryologic descent paths taken by the superior and inferior glands [27].

Patients suspected of having parathyroid carcinoma should not undergo pre-operative biopsy procedures since the breaking away of cells in transit may serves as a nidus for ectopic dissemination of active parathyroid tissue [27-29]. Continued high postoperative calcium and parathyroid hormone levels are a sign of the disease’s persistence (metastasis or residual disease). Follow up involves periodic monitoring of calcium and PTH levels, markers for the disease’s recurrence. Surgical approach of PTC is the gold standard treatment, with en bloc resection of pathologic parathyroid gland, ipsilateral thyroid lobe and muscles. Continued high postoperative calcium and parathyroid hormone levels are a sign of the disease’s persistence (metastasis or residual disease). Local recurrence occurs in up to 30%, in the primary site rather than in distant ones, and can be treated with a palliative surgical reexploration. One well recognized surgical complication in patients in whom the tumor is completely excised is the development of the "hungry bone syndrome. The sudden postoperative withdrawal of PTH induces abrupt cessation of osteoclastic bone resorption without affecting osteoblastic activity. Consequently, an increased bone uptake of calcium, phosphate and magnesium is observed [30]. Local recurrence as well as distant metastases occurring due to lymphatic and haematogenous spread may and do occur in parathyroid carcinomas. Since radiotherapy and chemotherapy are generally ineffective, surgery may also have a role in the palliative management of recurrent or metastatic disease, through the extirpation of lesions in the neck, lungs or liver providing symptomatic relief and reducing serum calcium and hormone levels in most patients. The potential morbidity caused by these re-operations must be borne in mind [31]. Hypercalcaemia is the principal cause of morbidity and mortality from parathyroid carcinoma. The carcinomas grow slowly in most patients, but can occasionally be aggressive. The disease typically follows one of three courses: one third of patients are cured at initial or follow-up surgery, one third experience a recurrence after a prolonged disease-free survival but may be cured with re-operation, and one third experience a short and aggressive course [32]. The combined 5- and 10-year survival rates for patients with parathyroid carcinomas varied from 50 to 70 and 13 to 35 percent respectively, with a mean survival time of 6 to 7 years.

Competing Interests
The authors declare that they have no competing interests.

Bibliography


Parathyroid Cancer: Two Case Reports with a Review of the Literature


Parathyroid Cancer: Two Case Reports with a Review of the Literature


Volume 2 Issue 1 October 2017
© All rights reserved by Khalid S Aljabri., et al.