Case Reports

Hyperfunctioning intrathyroidal parathyroid carcinoma

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ABSTRACT

Intrathyroidal parathyroid carcinoma is an exceedingly rare cause of primary hyperparathyroidism with difficulties in the diagnosis and management. We report a case of hypercalcemia from intrathyroidal parathyroid carcinoma in a 63-year-old Saudi female. She was diagnosed 2 years earlier with osteoporosis in a primary care clinic and was on alendronate since then. This year she was noted to have hypercalcemia, but in retrospect she had more than 10 years history of multiple medical problems related to hypercalcemia. Parathyroid 99mTc-(SestaMIBI) scintigraphy revealed parathyroid adenoma in the left inferior parathyroid gland. She had successful video-assisted parathyroidectomy that relieved most of her symptoms. The extreme rarity of such a case, the interesting clinical presentation and review of the literature are discussed.

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Primary hyperparathyroidism clinical profile had shifted, over the last 2 decades, from a symptomatic disease with hypercalcemic symptoms, nephrolithiasis, skeletal disease more towards asymptomatic state in western countries.[1] However, symptomatic disease is so far, the predominant form in developing countries with renal and skeletal manifestations. Parathyroidectomy is a curative procedure but parathyroid glands are known to vary in anatomic location, requiring knowledge by the surgeon of the atypical sites.[2] Parathyroid carcinoma is a rare cancer but relatively more frequent in Japan compared to western countries.[3] We present a case initially diagnosed with osteoporosis and 2 years later was found to have hypercalcemia, caused by primary hyperparathyroidism from parathyroid carcinoma.

Case Report. A 63-year-old Saudi lady referred to the endocrine clinic in our tertiary hospital with severe hypercalcemia for management. She was diagnosed 2 years earlier in a primary care center with osteoporosis and was started on oral alendronate 70 mg every week. However, she had more than 10 years-history of hypertension, nephrolithiasis, body aches, fatigue, constipation, reflux disease, depression and renal insufficiency. She gave history of passing small stones in multiple occasions and did have lithotripsy 8 years earlier. Her hypertension was controlled with 2 antihypertensives. However, the depression was marked and was treated by various antidepressants with no improvement. Just prior to presentation, a calcium level test was carried out showing hypercalcemia of 4.10 mmol/L [Normal Range (NR) 2.10-2.55].

On examination, she looked depressed and weak. Blood pressure 145/70 mm Hg, pulse rate 65 per minute and regular. Chest and cardiovascular examinations revealed no abnormalities. Neurological examination was within normal, as well as the rest of physical examination. She had palpable 2 cm dominant firm nontender mass in the left thyroid area. Investigations showed, repeat calcium was high 3.17 mmol/L (NR:

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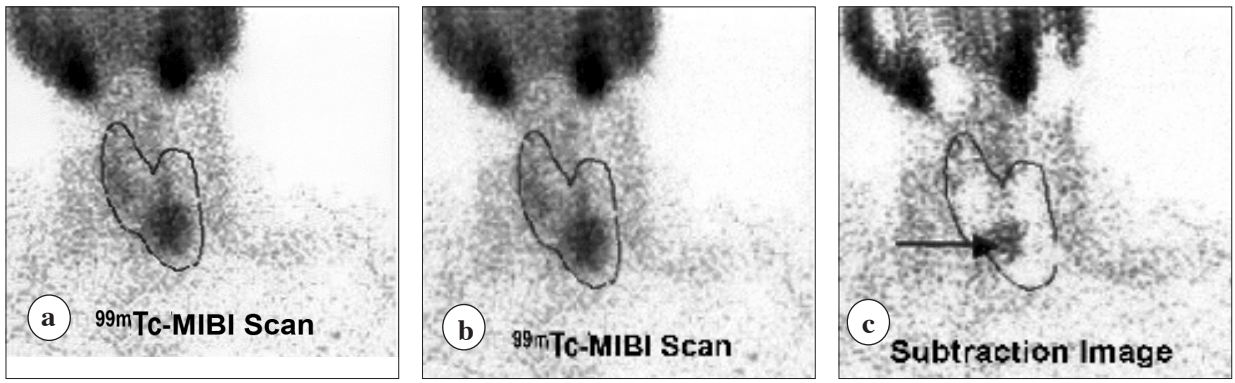

Figure 1 - The preoperative ^{99m}Tc-SestaMIBI-^{99m}Tc-Pertechnetate subtraction parathyroid scintigraphy revealing the abnormal parathyroid uptake. **a)** The thyroid scan shows a nodular left lobe with sizable lower pole. There is a cold area in the medial aspect of the lower pole. **b)** ^{99m}Tc-SestaMIBI scan showing a prominent focal area in the lower pole of the left thyroid lobe likely to be in the inferior parathyroid region. **c)** The subtraction image showed the prominent hot area (arrow) to be likely located in the cold area seen in the thyroid scan image (a).

2.10-2.55), low phosphorus 0.76 mmol/L (NR: 0.81-1.45), intact parathyroid hormone (PTH) 80.6 pmol/L (NR: 1.3-7.6) with alkaline phosphatase 628 u/L (NR: 17-142). Urea was up to 14.9 mmol/L (NR: 2.5-6.1) and creatinine 153 μmol/L (NR: 62-106). She had normal albumin, magnesium, thyrotropin and complete blood count. Chest x-ray and abdominal ultrasonography were unremarkable.

Preoperative parathyroid imaging was carried out using dual Phase ^{99m}Tc-(SestaMIBI) scintigraphy and was carried out in conjunction with a ^{99m}Tc-Pertechnetate thyroid scan for the purpose of subtraction. The subtraction images showed a positive uptake in the medial aspect of the thyroid nodule seen in the thyroid scan raising the possibility of parathyroid adenoma in the region of the left inferior parathyroid gland (**Figure 1**). Patient was taken to surgery using a video-assisted parathyroidectomy approach, the left side of the thyroid area was explored but the left lower parathyroid was not found. However, due to the nodular nature of the left thyroid lobe and the hard consistency, the left thyroid lobe was resected. Histopathology of the left thyroid lobe revealed a large, hard and fibrous mass occupying most of the left thyroid lobe weighing 8.5 gm and measuring 6 x 3.5 cm. Sections showed solid growth with tumor cells arranged in diffuse masses or in trabeculae pattern with thick acellular fibrous band dividing the tumor into lobules. The features were compatible with the diagnosis of parathyroid carcinoma. The parathyroid cancer is however, seen in the thyroid gland destroying entirely the thyroid gland and leaving only a thin rim of normal thyroid tissue on the periphery. Four lymph nodes resected and showed reactive changes only. The diagnosis was conclusively established by external pathology review in a tertiary center.

Discussion. Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients and the second cause of hypercalcemia, after malignancies, in hospitalized patients. It occurs in 0.2-0.5% of the population with more than 100,000 new cases identified each year in the United States of America. The peak incidence is between the 5th and 6th decades of life with a sharp increase in the 5th decade. Females are affected more commonly than males with 3.5:1 ratio.[1] Available reports from the Kingdom of Saudi Arabia indicate low prevalence of the disease but does report late symptomatic presentation with complications of the disease due to lack of routine serum calcium testing.[4] The diagnosis is made by the demonstration of inappropriately high intact PTH in the presence of hypercalcemia. Serum phosphorus may be decreased, and mild hyperchloremic acidosis could be found in some cases. Approximately 80-85% of primary hyperparathyroid cases harbor a single adenoma with double adenoma in only 2%. In the remainder 12-15%, poly-glandular parathyroid hyperplasia is responsible, which may be part of the multiple endocrine neoplasia type I, IIA.[1]

Parathyroid carcinoma is exceedingly an uncommon endocrine malignancy and in most series of hyperparathyroidism it is less than 1% but with a higher rate of 5% reported in Japan.[3] The first description of this cancer was in 1904 and since then approximately 500 cases have been reported in the literature.[5] The

natural history of parathyroid carcinoma has been described as slow but progressive disease. Majority of tumors are functional resulting in hypercalcemia and mortality is typically secondary to metabolic complications of hypercalcemia. Nonfunctional tumors present at advanced age as an expanding neck mass and generally, they have poorer prognosis. For unknown reasons parathyroid carcinoma occur almost exclusively in the inferior parathyroid glands.[3] Most reports indicate equal gender distribution and a mean age of 48 years, which is a decade younger from the mean age for primary hyperparathyroidism from an adenoma. A palpable neck mass is found in 30-76% of the cases with parathyroid carcinoma, with a median size of 3 cm, however a palpable mass is less than 10% in primary hyperparathyroidism. Usually parathyroid carcinoma cases exhibit more profound hypercalcemia (>3.5 mmol/L), alkaline phosphatase, PTH levels and metabolic abnormalities than do patients with parathyroid adenoma or hyperplasia.[6] Renal and skeletal systems involvement is reported to be much higher with parathyroid carcinoma. Recurrent laryngeal nerve palsy seen in any patient with hyperparathyroidism is highly suggestive of parathyroid carcinoma.[7]

The parathyroid glands could be variable in location and usually the inferior glands are more variable than the superior ones. In parathyroidectomies series, atypically located parathyroid lesions were found to be up to 20.3%. [5] Intrathyroidal parathyroid gland is defined as one situated totally within the thyroid and surrounded by thyroid parenchyma. Intrathyroidal location is normal for mammalian species but rare in humans. The true incidence of intrathyroidal parathyroid glands remains unknown; in some series the frequency of intrathyroidal parathyroid glands ranged from 2.4-8%. This location is a cause of failed cervical exploration for hyperparathyroidism. [8] With the advancement of surgical procedures like the unilateral neck exploration or the minimally invasive parathyroidectomies, preoperative localizations are very beneficial and desirable for surgeons. In our case, the finding in the left lower parathyroid area by ^{99m}Tc-SestaMIBI/^{99m}Tc-Pertechnetae parathyroid subtraction scintigraphy have helped to decide for left thyroid lobectomy and precluded the need for unnecessary cervical or mediastinal dissection for an ectopic parathyroid gland.[9] Most surgeons believe that the prognosis is most favorable after 'en bloc' resection of tumor in the first surgical procedure as it offers the patient the best chance for cure.[10] However, this is very challenging since it is difficult to recognize this rare endocrine malignancy preoperatively and often not conclusively identified intraoperatively. This makes the intraoperative therapeutic decisions made by the skilled operating surgeon based on what limited findings and information available.

Post-parathyroidectomy, apart from expected hypocalcemia, and rarely injury to the recurrent laryngeal nerve, most patients have rapid recovery from the related hypercalcemia symptoms. As with our patient, they experience improvement in their symptoms, marked reduction in the rate of nephrolithiasis, improvement in bone mass and in blood pressure.[8] Recurrence following surgical excision is common, with rates ranging from 33-78%. The reported time from surgery to first recurrence varies from 1 month to 20 years with a mean of 2-5 years. It tends to recur locally and spread to contiguous structures in the neck. Metastases occur late in the course of the disease with spread via both lymphatic and hematogenous routes. Most common sites are cervical nodes (30%), lung (40%), the liver (10%), and less to the bone and adrenal glands.[5] Data from the National Cancer database in 1999 reported the 5 year and 10 year overall relative survival rates to be 85% and 49.1%, respectively.[6] Data on stage specific survival are not available because specific staging criteria for parathyroid carcinoma have yet to be defined. If the initial parathyroidectomy fails, the treatment should be aimed at lowering hypercalcemia, the cause of the fatal sequel, by use of various drugs including the calcimimetic drug Cinacalcet, adjuvant radiotherapy or anti-PTH immunotherapy in certain cases. Chemotherapy has a very limited role in the management of parathyroid carcinoma.[10] However; surgical excision of recurrence or metastases may provide excellent palliation by reducing tumor burden and, consequently, amount of parathyroid hormone production and the symptoms of hypercalcemia.

In conclusion, this 63-year-old Saudi lady may have a delayed diagnosis but her symptoms did improve dramatically and became normocalcemic after removal of the intrathyroidal parathyroid cancer. She was seen one month after surgery in our hospital but maintains follow up with her physician in a rural primary clinic and continue to be normocalcemic. We report this case to highlight the intrathyroid parathyroid carcinoma, and the value of parathyroid imaging with dual Phase ^{99m}Tc-Pertechnetate Subtraction scintigraphy in localization of abnormal parathyroid tissue. Also, to emphasize the importance of evaluating all nodularity within or associated with the thyroid gland and the criticality of a more aggressive surgery during the first surgical excision.

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