PARATHYROID CARCINOMA, PARATHYROID CRISIS AND HUNGRY BONE SYNDROME

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Abstract

Parathyroid carcinoma is a rare endocrine malignancy accounting for <1% of cases of sporadic primary hyperparathyroidism (PHPT) and is associated with more severe clinical disease than its much more common benign counterpart, parathyroid adenoma. Clinical suspicion of a parathyroid cancer, therefore, should lead the surgeon to an aggressive initial operative approach as a complete resection of all malignant tissue at the time of initial surgery allows for the greatest likelihood of a cure. We report a case of parathyroid carcinoma induced parathyroid crisis with development of hungry bone syndrome in the postoperative period.

Keywords: Hyperparathyroidism; Parathyroid carcinoma; Parathyroid crisis; Hungry bone syndrome

Introduction

Parathyroid carcinoma is one of the rarest known malignancies that may occur sporadically or as part of a genetic syndrome. The first known case, described by De Quervain in 1909, was a non-functional tumor whose malignancy was only revealed by the lesion’s macroscopic features. This cancer is responsible for less than 1% of cases of primary hyperparathyroidism (1). The majority of parathyroid cancer tumors are hormonally functional and hypersecrete parathyroid hormone. Thus most patients exhibit strong symptomatology of hypercalcemia at presentation. Patients often present with severe fatigue, nephrolithiasis, pathologic fractures, brown tumors, hypercalcemic crises, and if not recognized, obturate hypercalcemia (2). Serum calcium and PTH levels are also much higher in parathyroid cancer patients than in patients with functional parathyroid adenoma. However, patients have been identified with nonfunctional non-secreting cancers, and they are often associated with a poor prognostic outcome (3). A case of parathyroid carcinoma that came to our attention prompted this paper and literature review.

Case Report

50-year-old housewife with no other co-morbidities presented with complaints of vomiting, fatigue, anorexia, generalized weakness and inability to get up from bed, for two months duration. She had undergone surgery for intervertebral disc prolapse 4 years back. There was no history of abdominal pain, altered bowel habits, jaundice, bone pain, altered behavior, loss of weight or loss of appetite.

Examinations of neck revealed a single ovoid 3x2cm non-tender swelling in front of neck, extending between the anterior border of lower third of Sternocleidomastoid and midline, which was firm in consistency. Overlying skin was normal and there were no cervical lymph nodes palpable. There were no signs of toxicity.

Figure 1: Neck showing swelling towards the right side

We proceeded with a provisional diagnosis of Solitary nodule Right lobe of thyroid. Investigations revealed an abnormally high level of serum calcium -15mg/dl, alkaline phosphatase— 398U/l, S.PTH – 1638 pg/ml.
(normal: 15 to 65 pg/ml), Phosphorus: 2.4mmol/liter, Albumin: 3.7g/dl, Creatinine: 2.5mg/dl, and Urea: 65mg/dl.

Figure 2: X-ray skull lateral view showing osteolytic lesion

Figure 3: X-ray hand showing osteopenia & Subperiosteal erosion of 2, 3, and 4 middle phalanges

USG neck showed - Hypo echoic nodule of 28mm in lower pole of right lobe of thyroid with well defined margins, showing areas of cystic degeneration and micro calcification. Another Hypo echoic nodular lesion of 10mm seen posterior to and abutting the nodule in lower pole of right lobe of thyroid. USG abdomen showed B/L grade 1 renal parenchymal changes, and FNAC right thyroid nodule shows Bethesda category 2 (Benign follicular nodule). Following a suspicion of parathyroid neoplasm a Pertechnetate Scan and MIBI scan was done.

**Pertechnetate scan** showed impaired patchy tracer uptake in both lobe of thyroid. Photopenic area was seen in relation to lower pole of right lobe of thyroid.

Figure 4: Pertechnetate scan

Figure 5: MIBI SCAN shows focal increased uptake in the lower pole of right lobe of thyroid
Subtracted image—showed focal abnormal tracer uptake noted in relation to lower pole of right lobe of thyroid gland.

Figure 6: Subtracted image

Our diagnosis after Sestamibi was right inferior parathyroid adenoma. The patient was pre-operatively managed for hypercalcemic crisis with aggressive hydration along with loop diuretic (furosemide) so as to maintain a Urine output >100ml/hr and IV hydrocortisone (Diagnosis of parathyroid crisis based on S.Ca >15mg/dl) following which the level of creatinine progressively decreased from 2.5mg/dl to 1.2mg/dl.

As the tumor was localized in the inferior pole of right lobe of thyroid, along with a Benign follicular nodule in the same lobe, patient was prepared for excision of parathyroid adenoma and right Hemithyroidectomy.

Intra-operatively a 3x1.5x1cm mass was found near the lower pole of right lobe of thyroid with loose areolar connection to the lower pole of thyroid without any invasion.

The mass was enucleated intact and sent for imprint cytology. The pathologist could not give a definite opinion. A right hemithyroidectomy was also done as a treatment for the solitary nodule right lobe.

Figure 7: Per Operative photograph

Figure 8: Parathyroidectomy specimen

The mass was enucleated intact and sent for imprint cytology. The pathologist could not give a definite opinion. A right hemithyroidectomy was also done as a treatment for the solitary nodule right lobe. Intra-operative PTH measurement was done after removal of the parathyroid neoplasm which showed a value of serum PTH (238 pg/ml).
On third postoperative day, patient developed severe hypocalcaemia along with hypophosphatemia not responding to IV calcium and a diagnosis of intractable hungry bone syndrome was made. Patient was managed with Vitamin D3 60,000 Units BD and calcium supplementation and the hypocalcemic symptoms could be controlled.

Histopathology report was indicative of Parathyroid carcinoma. Haematoxylin and eosin (H&E) staining at 100x showed capsular invasion by malignant cells with fibrous tissue invasion of the parathyroid gland.

Discussion
Parathyroid carcinoma is an exceedingly rare clinical entity, which occurs equally in males and females with a median age of 45 years. The diagnosis of parathyroid carcinoma typically relies on the patient’s clinical presentation, laboratory studies, imaging, and ultimately histopathology (4).

Histological diagnosis is on the basis of capsular, vascular, or perineural invasion or metastasis (5, 6). The suspicion for malignancy should be high with hypercalcemia greater than 14 mg/dl, extremely high serum PTH levels (> five times the upper limit of normal), as well as large masses and unilateral vocal cord paralysis. The main signs and symptoms of parathyroid carcinoma are due to high calcium and PTH levels. They present with the classic quartet of stones, bones, abdominal groans, & psychic moans. Other features include fatigue, polyuria and polydipsia, muscular asthenia, nausea, vomiting, loss of appetite and weight loss (7). These signs and symptoms are typical of primary hyperparathyroidism and also arise in patients who do not have a parathyroid carcinoma. They should therefore not be considered cancer-specific. Parathyroid Crisis is usually associated with hypercalcemia >15mg/dl, PTH levels are 5-10 times higher than normal, with progressive or rapid deterioration of CNS, GI & Renal function & patients will be grossly dehydrated (8).

Diagnosis is more problematic in non-functional lesions and the prognosis is worse due to delay in diagnosis. A visible or palpable lump in the front of the neck or
ultrasound or CT evidence may give rise to the suspicion of parathyroid carcinoma (9). Histopathological examination will ultimately prove the final diagnosis. Ultrasound and Sestamibi scans are of additional benefit in localizing lesions and determining active vs. non-active lesions (10).

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 (11). Patients suspected of having parathyroid carcinoma should not undergo pre-operative biopsy procedures since the breaking away of cells in transit may serve as a nidus for ectopic dissemination of active parathyroid tissue. Measurement of intraoperative PTH level has been widely adopted to confirm removal of the hyperactive gland, and is considered satisfactory when the value is <50% of the pre-excision PTH level (12).

Molecular pathogenesis of parathyroid carcinoma has in part been revealed through studying Hyperparathyroidism-Jaw Tumor (HP-JT) syndrome.

HP-JT is a rare autosomal dominant disease in which patients develop ossifying bone tumors of the maxillary and/or mandibular regions in conjunction with primary hyperparathyroidism, renal masses, and uterine masses. About 15% of the parathyroid lesions causing hyperparathyroidism in HP-JT syndrome are parathyroid carcinomas (13). Due to different histopathological approaches used to diagnose parathyroid carcinoma, identifying a HPRT2/CDC73 mutation would be a definitive clue to a malignant parathyroid lesion (14). Case reports of histologically benign but metastatic parathyroid lesions have been reported that tested positive for the mutation, further advocating the use of genetic testing in suspected parathyroid malignancy.

Surgery is the gold standard for the treatment of parathyroid carcinoma. En bloc dissection of the tumor with the thyroid lobe with avoidance of capsular violation or tumor spillage should be the initial surgery (15). The radicalism of the surgery is important and it is essential to avoid damaging the tumor capsule, as any residual or dispersed cells could lead to a fast recurrence. Sometimes it is possible to remove local recurrences. Later cervical and central lymphadenectomy is generally carried out only if necessary.

Nonsurgical therapies such as radiation and chemotherapy have yielded poor results in the treatment of PTC although some authors consider radiotherapy to have some effect on preventing recurrences when used as a complementary treatment (16). The treatment of parathyroid carcinoma aims not only to cure the disease but to obtain its biochemical remission, normalization of blood calcium and PTH levels, arrest of bone calcium depletion and regression of vascular, renal and neurological disorders (17). Continued high postoperative calcium and PTH levels are a sign of the disease’s persistence (metastasis or residual disease).

Hypercalcemic-crisis or severe hypercalcemia represents a life-threatening emergency. The clinical presentation and prognosis depend on the acuity of the development of hypercalcemia, the degree of hypercalcemia, and the underlying cause. General measures must be implemented to reverse the dehydration, to promote urinary calcium excretion, to avoid prolonged immobilization, and to identify the underlying cause of hypercalcemia. Specific measures directed at inhibiting bone resorption, increasing renal sodium and calcium excretion, and occasionally at decreasing intestinal absorption of calcium (or more specifically blocking vitamin D metabolism) should also be implemented. Obviously, the more reversible the underlying cause of hypercalcemia, the more aggressive one should be with the therapy.

Hungry bone syndrome is one of the problems encountered postoperatively which is a reversal of acute osteodystrophy. Hungry bone syndrome as a cause of hypocalcemia, known to occur after parathyroidectomy in 12.6% cases. As a result there is rapid “rebound” recalcification of bones causing prolonged hypocalcaemia. It is characterized by increased calcitriol, markedly decreased calcium (6mg/dl or lower), decreased phosphorus and decreased magnesium (one of the main differential for hungry bone syndrome is hypoparathyroidism which is characterized by increased phosphorous and low calcium). Hypocalcemia, hypophosphatemia and hypomagnesia is due to excessive and unregulated rapid bone demineralization following parathyroidectomy. Redistribution of magnesium from plasma into bone and soft tissue can occur after parathyroidectomy. Hungry Bone Syndrome treatment requires duration of at least 6 months and is indicated by normalization of ALP.

Hungry Bone Syndrome is managed by oral & IV calcium preparation, vitamin D₃ (calcitriol) 0.5-1mcg/day and oral or IM magnesium preparations (19). Magnesium sulphate is provided in 10-50% solution. Total replacement dose is 2-4 meq/kg which is adjusted over 3-5 days followed by 0.5meq/kg for the next 3 to 4 days. Oral magnesium supplementation is limited by diarrhea, however it can be provided as magnesium oxide 400 mg 1-2 tabs per day.

Recurrence is possible, and it is recommended that patients undergo long-term follow-up clinically and with measurements of serum, calcium and PTH. The outcome of surgery mainly depends upon early diagnosis (20).
**Conclusion**

Parathyroid carcinoma is a rare neoplasm with an incidence of less than 1%. Histopathological diagnosis is mainly based on the capsular and vascular invasion. When the size of parathyroid neoplasm is more than 1 cm, a high index of suspicion for carcinoma should be kept in mind and in suspected cases En Bloc dissection of Ipsilateral thyroid gland along with parathyroid tissue must be done.

**References**


