Parathyroid Carcinoma, Parathyroid Crisis and Hungry Bone Syndrome

Dayananda Babu R[a], Srijith Prasad T[a]

a. Department of Surgery, Sree Gokulam Medical College & Research Foundation, Trivandrum, Kerala, India*

ABSTRACT

Published on 21st December 2020

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

*See End Note for complete author details

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 <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 of 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 Sterno-

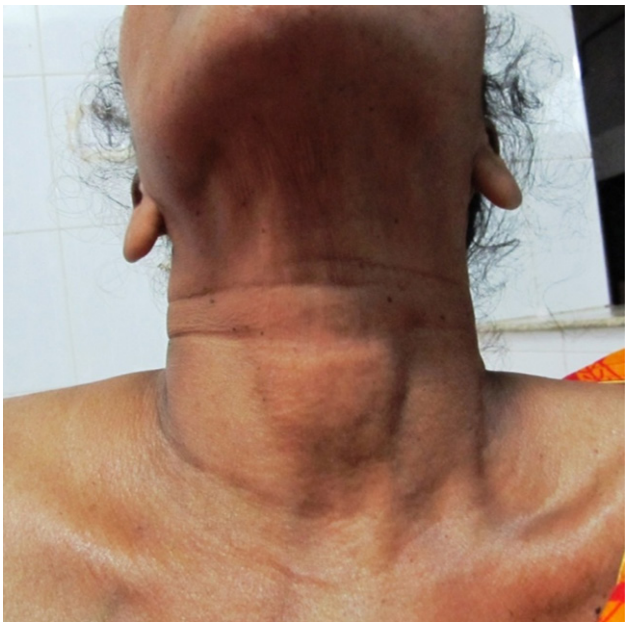

Figure 1. **Neck showing swelling towards the right side**

Cite this article as: Babu DR, Prasad ST. Parathyroid Carcinoma, Parathyroid Crisis and Hungry Bone Syndrome. IMA Kerala Medical Journal. 2020 Dec 21;13(4):154–9.

Corresponding Author:
Dr Dayananda Babu R, Professor & HOD, Department of Surgery, Sree Gokulam Medical College & Research Foundation, Trivandrum, Kerala, India. E-mail: rdayanandababu@yahoo.com

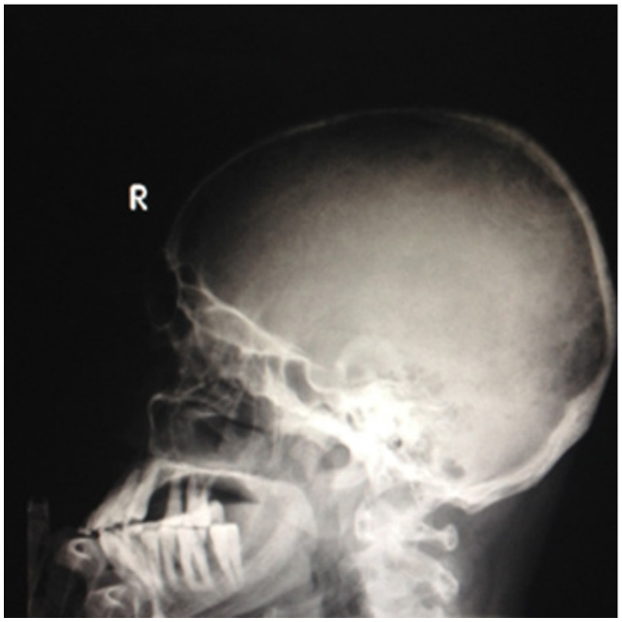

Figure 2. **X-ray skull lateral view showing osteolytic lesion**

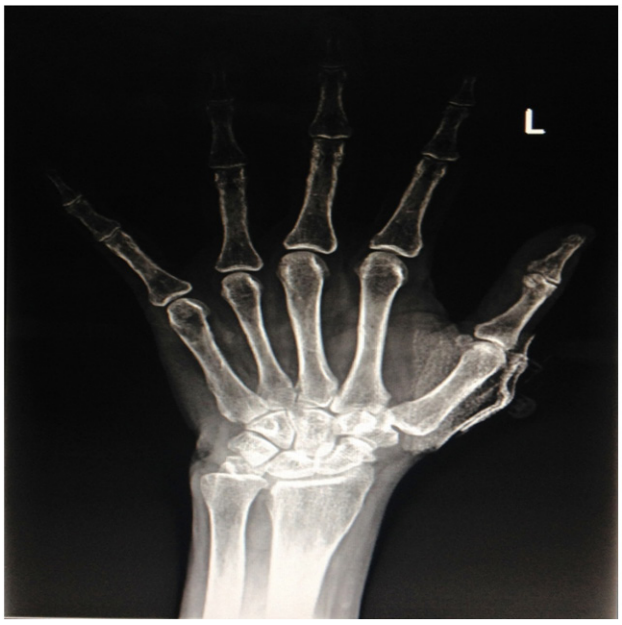

Figure 3. **X-ray hand showing osteopenia & Sub-periosteal erosion of 2, 3, and 4 middle phalanges**

cleidomastoid 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.

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.

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.

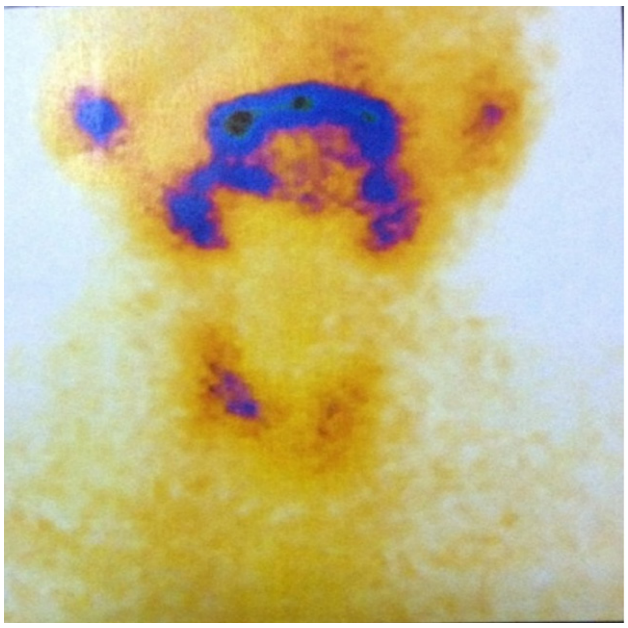

Figure 4. **Pertechnetate scan**

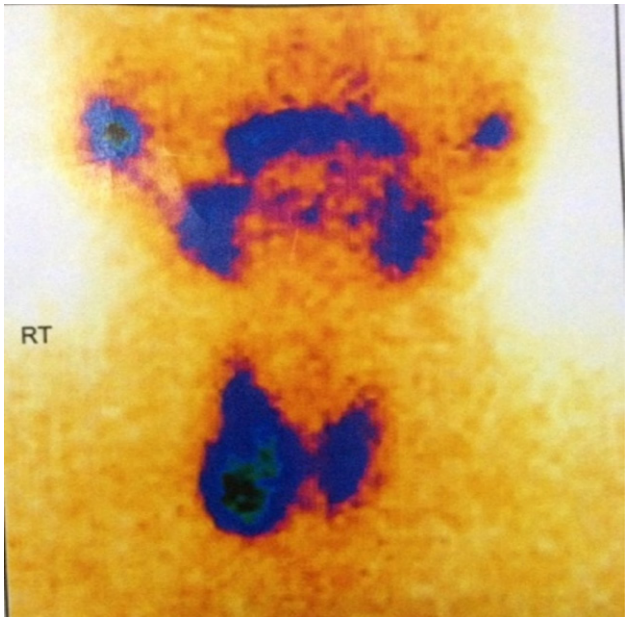

Figure 5. **MIBI SCAN shows focal increased uptake in the lower pole of right lobe of thyroid**

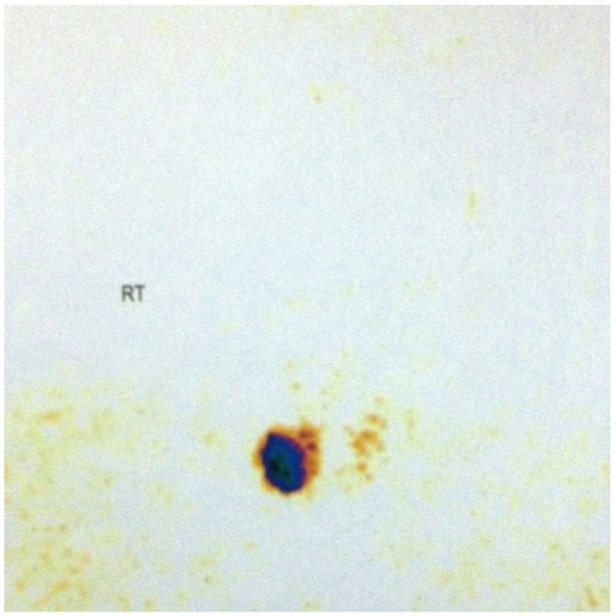

Figure 6. **Subtracted image**

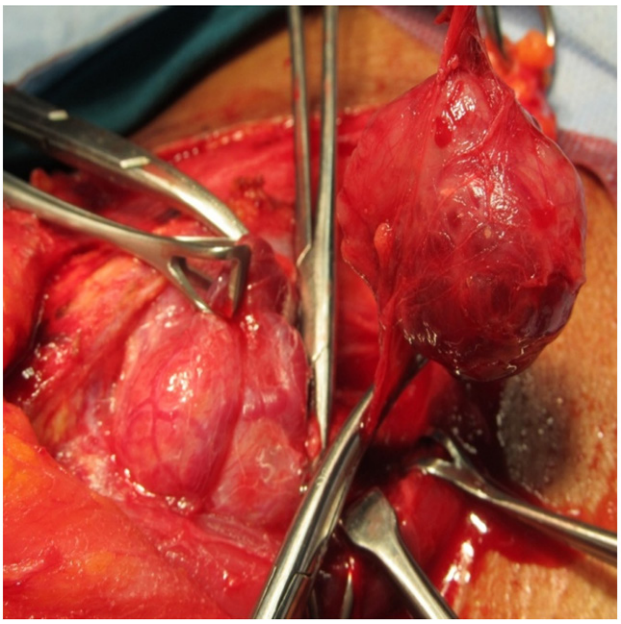

Figure 7. **Per Operative photograph**

Subtracted image-showed focal abnormal tracer uptake noted in relation to lower pole of right lobe of thyroid gland.

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 ofthyroid with loose areolar connection to the lower pole of thyroid without any invasion.

The mass was enucleated intact and send 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.

The mass was enucleated intact and send 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 wit 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

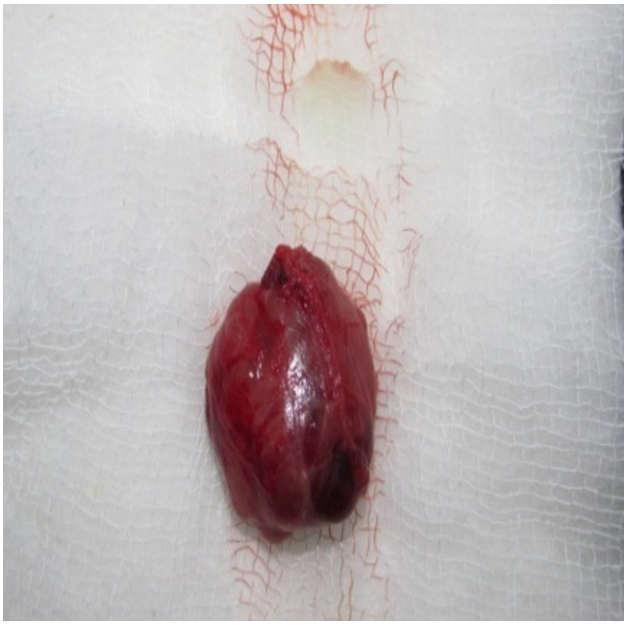

Figure 8. **Parathyroidectomy specimen**

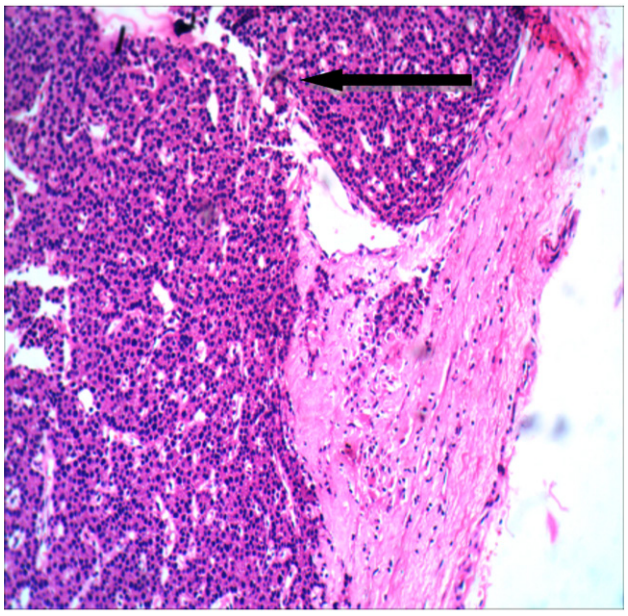

Figure 9. **Histopathology showing capsular invasion**

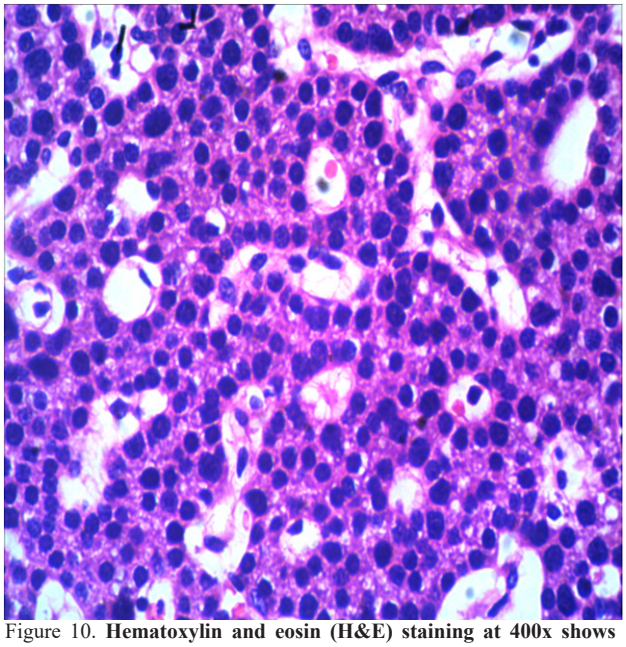

Figure 10. **Hematoxylin and eosin (H&E) staining at 400x shows nests of large pleomorphic cells with scattered mitoses**

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 preoperative biopsy procedures since the breaking away of cells in transit may serves 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 is 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 6months 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 a 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.

END NOTE

Author Information

1. Dr Dayananda Babu R, Professor & HOD, Department of Surgery, Sree Gokulam Medical College & Research Foundation, Trivandrum, Kerala, India.
2. Dr Srijith Prasad T, Junior resident, Department of Surgery, Sree Gokulam Medical College & Research Foundation, Trivandrum, Kerala, India

Conflict of Interest: None declared

REFERENCES

1. Brown S, O'Neill C, Suliburk J, Sidhu S, Sywak M, Gill A, et al. Parathyroid carcinoma: increasing incidence and changing presentation. ANZ J Surg.
2. Dilli A, Gultekin SS, Ayaz UY, Ayaz S. Parathyroid carcinoma. JBR-BTR;96(4):224–5.
3. Wynne AG, van Heerden J, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathologic features in 43 patients. Medicine (Baltimore). 1992 Jul ;71(4):197–205.
4. Sharretts JM, Kebebew E, Simonds WF. Parathyroid cancer. Semin Oncol. 2010 Dec [cited 2015 Jun 24];37(6):580–90.
5. Rodriguez C, Nadéri S, Hans C, Badoual C. Parathyroid carcinoma: a difficult histological diagnosis. Eur Ann Otorhinolaryngol Head Neck Dis. 2012 Jun;129(3):157–9.
6. Smith JF, Coombs RR. Histological diagnosis of carcinoma of the parathyroid gland. J Clin Pathol. 1984 Dec;37(12):1370–8.
7. Kolluri S, Lal K, Chang R, Mandava N. Parathyroid carcinoma: a silent presentation. Gland Surg. 2014 Aug;3(3):211–4.
8. Wang CA, Guyton SW. Hyperparathyroid crisis: clinical and pathologic studies of 14 patients. Ann Surg 1979 Dec;190(6):782–90.
9. Okamoto T, Iihara M, Obara T, Tsukada T. Parathyroid carcinoma: etiology, diagnosis, and treatment. World J Surg. 2009 Nov;33(11):2343–54.
10. Kebebew E, Arici C, Duh QY, Clark OH. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. Arch Surg. 2001 Aug;136(8):878–85.
11. Ali K, Sarangi R, Dhawan S, Agarwal BB, Gupta MK. Malignancy of parathyroid: An uncommon clinical entity. Indian J Endocrinol Metab. 2013 Mar;17(2):329–31.
12. Zawawi F, Mlynarek AM, Cantor A, Varshney R, Black MJ, Hier MP, et al. Intraoperative parathyroid hormone level in parathyroidectomy: which patients benefit from it? J Otolaryngol Head Neck Surg. 2013 Jan;42:56.
13. Kutcher MR, Rigby MH, Bullock M, Trites J, Taylor SM, Hart RD. Hyperparathyroidism-jaw tumor syndrome. Head Neck. 2013 Jun;35(6):E175–7.
14. Howell VM, Haven CJ, Kahnoski K, Khoo SK, Petillo D, Chen J, et al. HRPT2 mutations are associated with malignancy in sporadic parathyroid tumours. J Med Genet. 2003 Sep.
15. Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. Curr Treat Options Oncol. 2012 Mar;13(1):11–23.
16. Kebebew E. Parathyroid carcinoma. Curr Treat Options Oncol. 2001 Aug;2(4):347–54.
17. Pelizzo MR, Piotto A, Bergamasco A, Rubello D, Casara D. [Parathyroid carcinoma. Therapeutic strategies derived from 20 years of experience]. Minerva Endocrinol. 2001 Mar;26(1):23–9.
18. Kim K-M, Park J-B, Bae K-S, Kang S-J. Hungry bone syndrome after parathyroidectomy of a minimally invasive parathyroid carcinoma. J Korean Surg Soc. 2011 Nov;81(5):344–9.
19. Adam MA, Untch BR, Olson JA. Parathyroid carcinoma: current understanding and new insights into gene expression and intraoperative parathyroid hormone kinetics. Oncologist. 2010 Jan;15(1):61–72.
20. Harari A, Waring A, Fernandez-Ranvier G, Hwang J, Suh I, Mitmaker E, et al. Parathyroid carcinoma: a 43-year outcome and survival analysis. J Clin Endocrinol Metab. 2011 Dec;96(12):3679–86.