DOI: 10.7860/IJARS/2023/59022.2887

Case Report

Surgery Section

Parathyroid Carcinoma with Low Values of Elevated Parathyroid Hormone: A Case Report

MARIYA JACOB[1], KRISHNA SHANKAR GOPAL SANKAR[2], SARVESWARAN VENUGOPAL[3]

ABSTRACT

Parathyroid Carcinoma (PC) is a rare endocrine malignancy, accounting for <1% of sporadic Primary Hyperparathyroidism (PHPT) cases. A preoperative and even intraoperative diagnosis of PC is rarely reported due to its close resemblance to parathyroid adenoma with respect to symptoms- hypercalcaemia, renal stones and/or failure, osteoporosis, and cardiac/neurocognitive dysfunction. The mean serum calcium in PC is reported to be greater than 14 mg/dL along with serum Parathyroid Hormone (PTH) levels often above 1000 g/mL. When serum PTH levels are 10 times the upper limit of the normal, it is considered diagnostic of PC. Surgical en-bloc resection without capsular breach is the only definitive cure for PC. The present case report included two patients (39-year-old male, 55-year-old female) who presented with features of single parathyroid glandular enlargement, hypercalcaemia, its consequences and with normal ionised calcium, but relatively low levels of elevated serum PTH (<300 pg/mL). They were operated and identified postoperatively as having PC. This rare presentation of PC where the preoperative serum PTH values were lower than usually seen in carcinoma, should alert endocrinologists and surgeons that lower levels of elevated serum PTH do not primarily exclude the possibility of carcinoma.

Keywords: Adenoma, Hypercalcaemia, Hyperparathyroidism

CASE REPORT

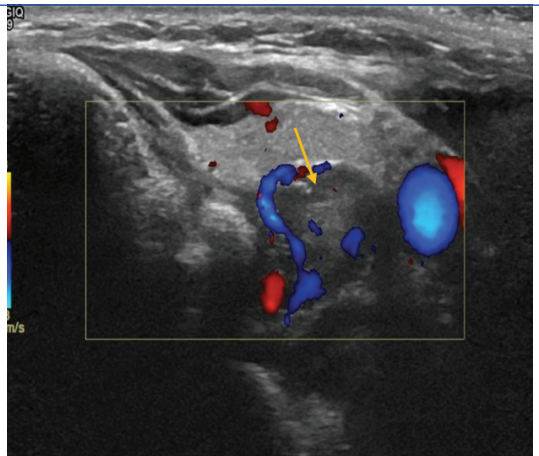
Case 1

A 39-year-old male, a known case of neurofibromatosis and left superior parathyroid adenoma, diagnosed outside the institute from which the cases were reported by Ultrasonography (USG) neck six months before, was presented with acute, intermittent, severe, non-radiating epigastric pain, intermittent bilious vomiting, decreased appetite and weight loss for one month. The patient gave a history of similar complaints of pain in the past. The patient was not a consumer of alcohol/tobacco and had no significant family history. At presentation vitals were stable and had a left-sided palpable neck mass. Perabdominal examination revealed epigastric tenderness with no guarding, rigidity or palpable mass. The patient was diagnosed with acute pancreatitis, based on clinical, radiological and laboratory findings and managed conservatively. Due to history of parathyroid adenoma with elevated PTHs in the past (outside peak-value: 245.7 pg/mL), a complete endocrinology work-up was done to rule out Multiple-Endocrine-Neoplasia (MEN) syndrome. This included serum total/ionised calcium, PTH, Vitamin D, phosphorus, TSH, Prolactin, Cortisol USG abdomen, and Bone Marrow Density (BMD) scan. Patient was non compliant with bisphosphonate therapy prescribed at the time of diagnosis (outside) and hence presented with effects of uncontrolled hypercalcaemia [Table/Fig-1].

Parameters	Patient value	Normal value
Calcium (mg/dL)	12.2 mg/dL	8.5-10.2 mg/dL
Ionised calcium (mg/dL)	5.72 mg/dL	4.5-5.6 mg/dL
Vitamin D (ng/dL)	19.7 ng/mL	5-75 ng/mL
Serum PTH (pg/mL)	278.6 pg/mL	11-55 pg/mL
Phosphorus (mg/dL)	2.1 mg/dL	2.5-4.5 mg/dL
Prolactin (ng/mL)	36.9	<14 ng/mL
TSH (mIU/L)	0.737	0.5-5 mIU/L
Cortisol (mcg/dL)	10.6	4.3-22.4 mcg/dL

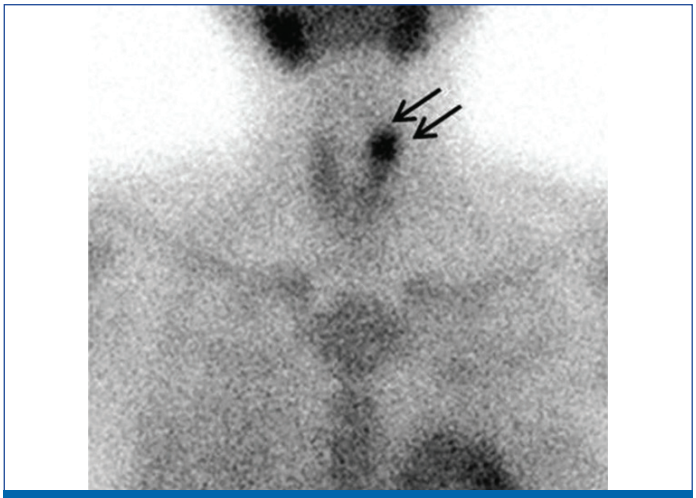
[Table/Fig-1]: Patient parameters chart.

Initially, diagnosis of acute pancreatitis was made due to elevated calcium levels. It led to the primary diagnosis of PHPT. Serum calcitonin was normal. The patient had hypophosphataemia (2.1 mg/dL), which was suspected as an adjunctive cause of vomiting. It was simultaneously corrected by administration of intravenous sodium phosphate. BMD scan showed ostopaenia at the spine and osteoporosis of bilateral forearm. USG neck showed left superior parathyroid adenoma and a normal thyroid gland [Table/Fig-2]. A 99 mTc-Sestamibi-parathyroid scan showed left-superior parathyroid adenoma with no evidence of ectopic parathyroid tissue [Table/Fig-3]. After attaining sufficient levels of serum vitamin-D (81.4 ng/mL) with oral supplementation and mild control of serum calcium post bisphosphonate therapy, the patient underwent left-superior parathyroidectomy. There was no local adherence/invasion of lymph nodes or intraoperative gross capsular-breach. Serum levels on postoperative day one were-PTH: 54.5 pg/mL, Phosphorus: 2.8 mg/dL, Ionised calcium: 4.4 mg/dL.



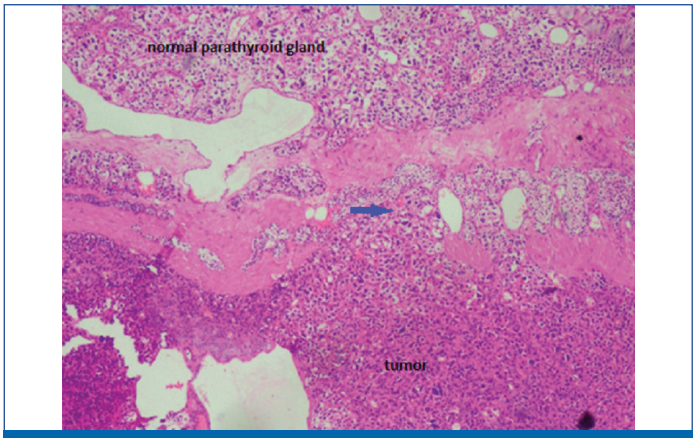
[Table/Fig-2]: USG neck showing left superior parathyroid adenoma (yellow arrow) of size 1×1.4×3 cm.

Histopathological examination of the specimen revealed PC, with mild to moderate nuclear-pleomorphism, mitotic activity of 2-3/10 High Power Field (HPF) and multiple foci of capsular invasion



[Table/Fig-3]: A 99mTc-Sestamibi-parathyroid scan showing left superior parathyroid adenoma (arrow).

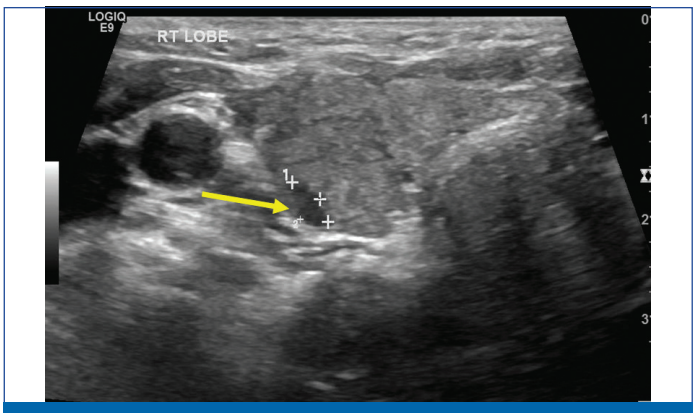
[Table/Fig-4]. Computed Tomography (CT) thorax (to rule out metastasis) in addition to the preoperative 99 mTc Sestamibi scan was negative. The patient had been on frequent follow-ups with no evidence of recurrence to date.



[Table/Fig-4]: Parathyroid Carcinoma (PC) with capsular invasion (blue arrow) (x40 magnification, H&E stain).

Case 2

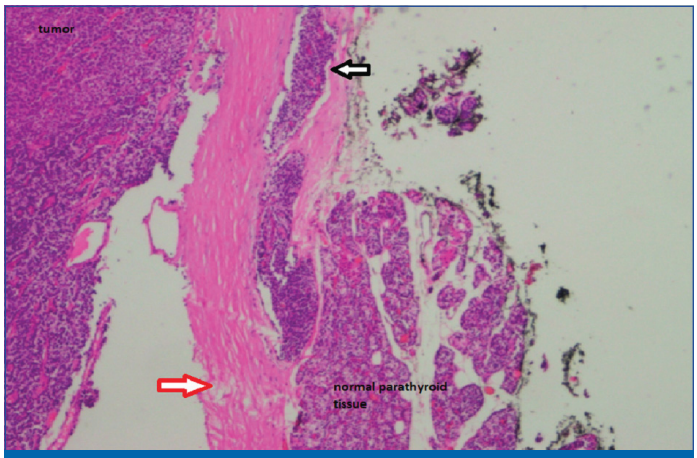
A 55-year-old women known case of hypothyroidism presented with complaints of neck swelling since three months, with a history suggestive of primary-hyperparathyroidism, due to multiple attacks of ureteric calculi and recurrent Transient Ischaemic Attacks (TIA), for one year. No significant personal/family history. On examination, USG neck revealed a normal thyroid gland and right-inferior parathyroid-adenoma of size 2×1.8 cm which was confirmed in the carotid and vertebral doppler study done for the recurrent attacks of TIA [Table/Fig-5]. Computed Tomography of Kidneys, Ureters, Bladder (CT KUB) showed left renal calculus with mild pyeloureteritis. The serum ionised calcium was 5.49 mg/dL with normal Vitamin-D, serum



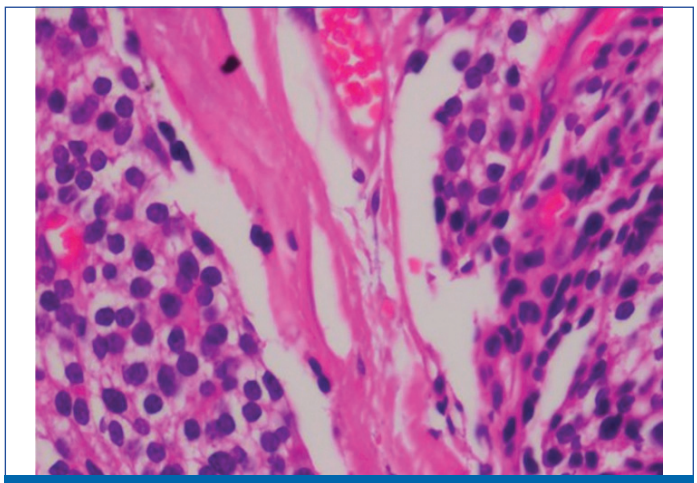
[Table/Fig-5]: USG neck showing right inferior parathyroid-adenoma (yellow arrow) of size 2×1.8 cm.

phosphorus of 2 mg/dL and serum PTH levels were 260.2 pg/mL. The patient underwent right inferior parathyroidectomy with Double-J-stenting of the left ureter. Intraoperative findings were suggestive of a benign swelling with no gross capsular breach or lymphnode Involvement.

Postoperative serum values were: Ionised calcium- 4.95 mg/dL, Phosphorus- 3.1 mg/dL and PTH- 71.1 pg/mL. Histopathological examination revealed PC with mild nuclear pleomorphism, inconspicuous mitotic activity, focal capsular and vascular invasion but free tumour margins [Table/Fig-6,7]. The patient underwent a 99mTc-Sestamibi scan along with CT thorax and bone scan to rule out metastasis, which was negative. The patient had been on frequent follow-ups to date with no evidence of recurrence.



[Table/Fig-6]: Shows Parathyroid Carcinoma (PC) with vascular invasion (black arrow) and capsular invasion (red arrow). (x100 magnification, in H&E).



[Table/Fig-7]: Showing large pleomorphic tumour cells with hyperchromatic nuclei within parathyroid specimen (x400 magnification, H&E stain).

DISCUSSION

The PC is a rare endocrine malignancy, frequently diagnosed in the 5th decade, irrespective of gender. It is often misdiagnosed as benign adenoma until after postoperative histopathology report [1]. More than 90% of PC are functional and present with effects of elevated serum PTH, which was true in both the cases. They both had elevated serum calcium and PTH levels and had been suffering from the effects of hypercalcaemia with hypercalcaemia-induced acute pancreatitis in the first case and nephrolithiasis in the second case.

The mean serum calcium in PC patients reported in the past is 14.6-15.0 mg/dL and about 60-65% of patients present with a calcium level greater than 14 mg/dL [2]. PTH levels in PC are on average 5-10 times the upper limit of the normal range and are often defined as unsuppressed which in reality, is as much as 1,230 pg/mL above the upper limit of normal. A level 10 times the upper limit of the normal range is considered diagnostic of PC due to a positive-predictive-value of 81% [3]. In both the cases serum PTH level was below

300 pg/mL, which is elevated and higher than normal. But PC often presents with PTH levels above 1000 pg/mL. Benign adenomas may present with PTH levels (<300 pg/mL). Another characteristic feature of PC is the presence of a single palpable neck mass seen in almost 76% of cases as multiglandular disease is uncommon. This was true in both cases [4].

It is often difficult to grossly differentiate between parathyroid adenoma and carcinoma without the presence of local infiltration/metastasis/recurrence [5]. The biochemical parameters are reported to be more pronounced in PC than in adenomas [6]. The histologic features distinguishing PC from adenoma which were identified by Schantz A and Castleman B, are the presence of parenchymal mitoses, trabeculated parenchyma including often thick fibrous bands and capsular or vascular invasion [7]. Since, these individual features can also be found in atypical parathyroid adenomas, the criteria of PC have been redefined by World Health Organisation (WHO) for tumours with evidence of invasion or to those tumours with documented metastases-local (neck/lymphnodes) or distant (spine/lungs). PC tumours lose their encapsulation and infiltrate into adjacent structures. Vascular invasion is defined as the presence of the affected vessel within/outside the tumour capsule. The presence of endothelial cells around the tumour embolus and identification of thrombus within the tumour cells is regarded as evidence of angioinvasion. Thus, perineural, capsular and lymphovascular invasion remains PC's most specific histopathologic feature [8,9]. Both cases were identified as PC due to the presence of focal capsular invasion in the first case and focal capsular and vascular invasion for the second case, in the postoperative specimen [1,8].

Investigations like USG, Tc-99m-Sestamibi scans and high-resolution CT can help in preoperative localisation of parathyroid disease but despite the modality used, differentiation between benign and malignant disease is difficult. More often, the PC is diagnosed intraoperatively and confirmed by histopathology. PC tumours are described as firm, fixed and grey-white on gross appearance, but the affected gland may appear indistinguishable from a benign adenoma [10].

Surgery-en-bloc tumour resection with ipsilateral-thyroidectomy, without tumour-capsule rupture and tumour cell-spillage, is the only effective cure for PC identified preoperatively [11]. Long-term results in terms of local recurrence and distant metastasis are significantly improved in this. Since, most often PC is a postoperative histopathological diagnosis, this doesn't happen and local dissemination is highly possible. Newer literature, recommends re-operation with ipsilateral thyroid lobo-isthmusectomy, as conservative resection is associated with risk of capsule-rupture and subsequent local dissemination [1,12]. The mean time to recurrence is three years, although intervals of upto 20 years have been reported. Prolonged survival is possible with palliative surgery [6], with five year survival rates varying from 40% to 86%. Currently, chemotherapy and radiotherapy have no significant role in the management of PC [6]. Patients thus diagnosed are followed-up postoperatively with regular calcium and PTH levels as well as neck ultrasounds. Based on the symptoms, other imaging tests to rule out metastasis are added.

CONCLUSION(S)

Hypercalcaemia and its consequences were the presenting complaint of the patient mentioned in the first case report while normal ionised calcium level was noticed in second patient. Both patients were found to have PC with low values of elevated PTH (<300 pg/mL). Lower values of elevated serum PTH do not exclude the possibility of carcinoma. Since, the presence of metastasis is the only obvious preoperative criterion between parathyroid adenoma and carcinoma, mandatory preoperative neck, spine, and chest imaging for all cases of parathyroid adenoma to rule out the possibility of metastasis is recommended as these are the most common locations in carcinoma. This case report reaffirms the need for en-bloc resection with an intact capsule in all cases of parathyroid surgery, and a mandatory resurgery in the event of an inadequate tumour margin or breached capsule, in cases identified postoperatively as PC.

Acknowledgement

We wish to thank all the healthcare workers involved in the diagnosis and treatment of the above two patients.

REFERENCES

[1] Rodrigo JP, Hernandez-Prera JC, Randolph GW, Zafereo ME, Hartl DM, Silver CE, et al. Parathyroid cancer: An update. Cancer Treatment Reviews. 2020;86:102012.
[2] Schaapveld M, Jorna F, Aben K, Haak H, Plukker J, Links T. Incidence and prognosis of parathyroid gland carcinoma: A population-based study in The Netherlands estimating the preoperative diagnosis. Am J Surg. 2011;202(5):590-97.
[3] Fernandez-Ranvier GG, Khanafshar E, Jensen K, Zarnegar R, Lee J, Kebebew E, et al. Parathyroid carcinoma, atypical parathyroid adenoma, or parathyromatosis? Cancer. 2007;110(2):255-64.
[4] Long KL, Sippel RS. Current and future treatments for parathyroid carcinoma. Int J Oncol. 2018;5(01):IJE06.
[5] Ippolito G, Palazzo FF, Sebag F, De Micco C, Henry JF. Intraoperative diagnosis and treatment of parathyroid cancer and atypical parathyroid adenoma. BJS. 2007;94(5):566-70.
[6] Sawhney S, Vaish R, Jain S, Mittal N, Ankathi SK, Thiagarajan S, et al. Parathyroid Carcinoma: A review. Indian J Surg Oncol. 2022;13(1):133-42.
[7] Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. Cancer. 1973;31(3):600-05.
[8] Lloyd RV, Osamura RY, Klöppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs, 4th edn IARC Press. 2017.
[9] Schulte JJ, Pease G, Taxy JB, Hall C, Cipriani NA. Distinguishing parathyromatosis, atypical parathyroid adenomas, and parathyroid carcinomas utilizing histologic and clinical features. Head Neck Pathol. 2021;15(3):727-36.
[10] Sharretts JM, Kebebew E, Simonds WF. Parathyroid cancer. Semin Oncol. 2010;37(6):580-90.
[11] Ullah A, Khan J, Waheed A, Sharma N, Pryor EK, Stumpe TR, et al. Parathyroid Carcinoma: incidence, survival analysis, and management: A study from the SEER database and insights into future therapeutic perspectives. Cancers. 2022;14(6):1426.
[12] Schulte KM, Talat N, Galata G, Gilbert J, Miell J, Hofbauer LC, et al. Oncologic resection achieving r0 margins improves disease-free survival in parathyroid cancer. ASO. 2014;21(6):1891-97.

PARTICULARS OF CONTRIBUTORS:
1. Registrar, Department of General Surgery, Sri Ramakrishna Hospital, Coimbatore, Tamil Nadu, India.
2. Consultant, Department of Endocrinology, Sri Ramakrishna Hospital, Coimbatore, Tamil Nadu, India.
3. Consultant, Department of General Surgery, Sri Ramakrishna Hospital, Coimbatore, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mariya Jacob,
Registrar, Department of General Surgery, Sri Ramakrishna Hospital,
Coimbatore-641044, Tamil Nadu, India.
E-mail: theeditor13@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 14, 2022
- Manual Googling: Nov 05, 2022
- iThenticate Software: Nov 07, 2022 (8%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 11, 2022**
Date of Peer Review: **Aug 24, 2022**
Date of Acceptance: **Nov 08, 2022**
Date of Publishing: **May 01, 2023**