CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Persistent Primary Hyperparathyroidism Secondary to an Ectopic Mediastinal Adenoma in a Young Adult: A Case Report

Karl Homer Nievera and Rebecca Alba

Section of Endocrinology, Diabetes and Metabolism, Chinese General Hospital and Medical Center, Manila, Philippines

Abstract

Primary hyperparathyroidism commonly affects elderly women. When present in the young population, it is usually asymptomatic, most frequently due to a parathyroid adenoma and the definitive management is surgical excision. Uncommonly, 5-10% of patients fail to achieve long-term cure after initial parathyroidectomy and 6-16% of them is due to an ectopic parathyroid adenoma that will require focused diagnostic and surgical approaches.

We report a 21-year-old male who had bilateral thigh pain. Work-up revealed bilateral femoral fractures, brown tumors on the arms and multiple lytic lesions on the skull. Serum studies showed hypercalcemia (1.83 mmol/L), elevated parathyroid hormone [(PTH) 2025.10 pg/mL], elevated alkaline phosphatase (830 U/L), normal phosphorus (0.92 mmol/L) and low vitamin D levels (18.50 ng/mL). Bone densitometry showed osteoporotic findings. Sestamibi scan showed uptake on the left superior mediastinal region consistent with an ectopic parathyroid adenoma. Vitamin D supplementation was started pre-operatively. Patient underwent parathyroidectomy with neck exploration; however, the pathologic adenoma was not visualized and PTH levels remained elevated post-operatively. Chest computed tomography with intravenous contrast was performed revealing a mediastinal location of the adenoma. A repeat parathyroidectomy was done, with successful identification of the adenoma resulting in a significant drop in PTH and calcium levels. Patient experienced hungry bone syndrome post-operatively and was managed with calcium and magnesium supplementation. A high index of suspicion for an ectopic adenoma is warranted for patients presenting with hypercalcemia and secondary osteoporosis if there is persistent PTH elevation after initial surgical intervention. Adequate follow-up and monitoring is also needed starting immediately in the post-operative period to manage possible complications such as hungry bone syndrome.

Key words: hyperparathyroidism, reoperation, hypercalcemia, ectopic parathyroid adenoma

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disorder of mineral and bone metabolism that often presents with high calcium levels with elevated parathyroid hormone (PTH).[1] This may result in kidney stones and pathologic fractures. Once treated, 5-10% of patients may fail to achieve long-term cure after initial parathyroidectomy[2] and is considered persistent hyperparathyroidism if calcium and PTH are still elevated within 6 months of neck exploration. One of the reasons includes an ectopic location of the gland[3] – which only occurs in 6-16% of patients[4] such as in our case.

CASE

This is a 21-year-old Filipino male, with no known comorbidities presenting at the emergency room due to severe pain of both thighs. Three months prior, the patient experienced bilateral leg and thigh pain with no prior trauma or injury. No consult was done until 1 day prior to consult while he was walking on the pavement, he suddenly felt his legs give way, causing him to fall and land on his buttocks. The patient had no previous admissions and had an unremarkable past medical, personal-social, genetic and family history. He had a BMI of 17.3 kg/m^2 and physical examination showed no remarkable findings other than pain on movement.

On work-up, skeletal survey revealed brown tumors on the arms (Figure 1) and multiple nonaggressive lytic lesions on the skull. His legs had multiple fractures described as complete linear displaced fracture at the left femoral neck and complete oblique fracture at the left and right femoral proximal shafts (Figure 2). Laboratory tests showed elevated calcium with a normal phosphorus and low 25-hydroxyvitamin D level. Additional work-up was then performed with a consideration of PHPT. Bioactive parathyroid hormone (PTH) assay was requested twice, showing markedly elevated levels. Other remarkable findings were a low magnesium, elevated alkaline phosphatase (ALP), elevated urinary calcium excretion and presence of non-obstructing nephrolithiasis on the left (Table 1). Bone densitometry also showed z-scores

eISSN 2308-118x (Online)
Printed in the Philippines

Received: February 6, 2023. Accepted: April 4, 2023.
Published online first: July 15, 2023.
https://doi.org/10.15605/jafes.038.02.16

Corresponding author: Karl Homer V. Nievera, MD
Fellow, Chinese General Hospital and Medical Center
286 Blumentritt Road, Santa Cruz, Brgy. 372, Manila, Philippines, 1014
Tel. No.: +632-87114141
E-mail: endokarldiologist@gmail.com
ORCiD: https://orcid.org/0000-0002-3394-8573

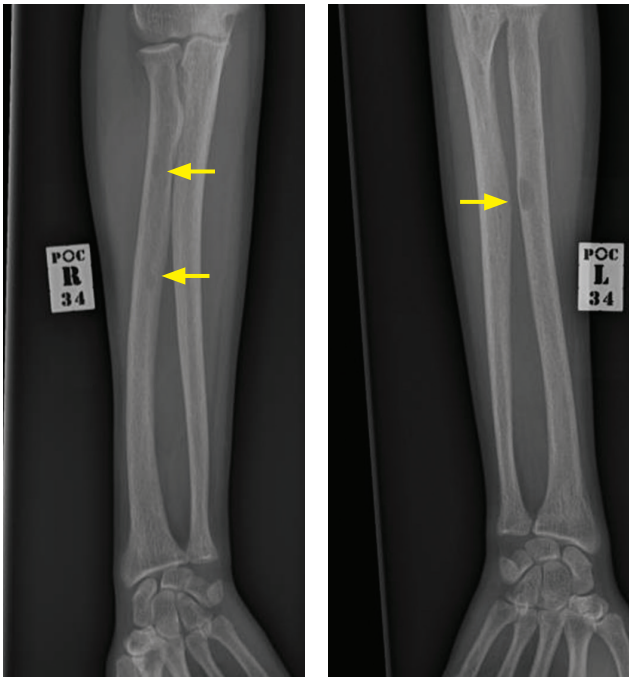

Figure 1. Technetium 99m sestamibi scan shows intense focal tracer uptake and retention in the left superior mediastinal region.

below the expected range for age. With a high suspicion of PHPT, a technetium 99m sestamibi scan was performed which revealed an intense focal sestamibi accumulation and retention in the left superior mediastinal region consistent with an ectopic parathyroid adenoma (Figure 3). This prompted transfer to our institution for surgical intervention.

The patient was referred to a head and neck surgeon and underwent parathyroidectomy and neck exploration with frozen section via low collar incision. Fifteen minutes after excision of the suspicious parathyroid adenoma, PTH assay was done showing persistently elevated levels. Frozen section identified thymic tissue and benign thyroidal tissue. Neck exploration to remove other suspicious lesions was then performed. PTH level 15 minutes thereafter remained elevated and frozen section only identified unremarkable lymph nodes. The procedure was terminated with plan to reopen once further imaging is performed.

To further localize the parathyroid adenoma, a computed tomography (CT) scan with intravenous contrast was performed on the neck and chest (Figure 4) which showed an avidly enhancing soft tissue nodule in the aorto-pulmonary window/anterior left mediastinum region

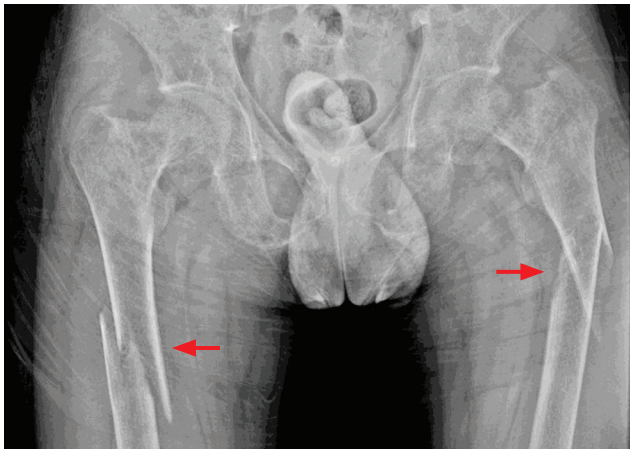

Figure 2. Frontal radiograph of both upper femurs shows badly displaced fractures of both upper femoral shafts *(red arrows)*. These pathological fractures have occurred through bilateral underlying osteolytic lesions consistent with brown tumors.

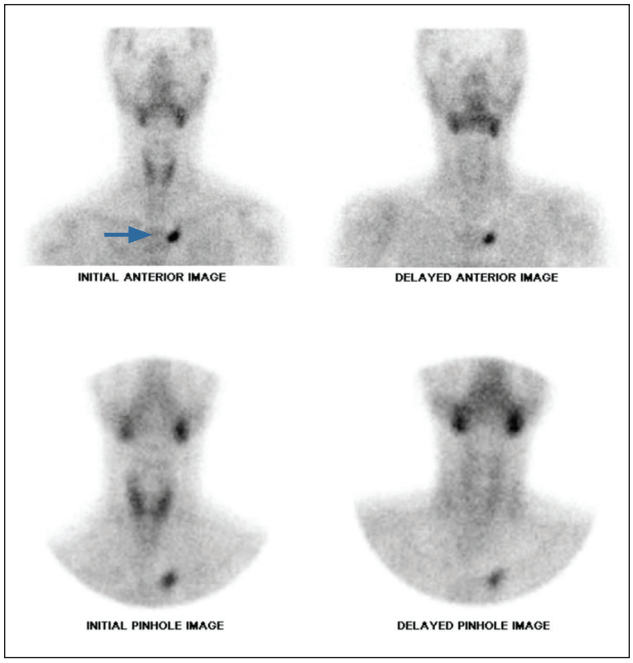

Figure 3. Technetium 99m sestamibi scan shows intense focal tracer uptake and retention in the left superior mediastinal region.

consistent with a thymoma and/or residual ectopic parathyroid adenoma. The second operation was then performed with a referral to a thoracic and cardio-vascular surgeon in order to proceed with an ectopic parathyroidectomy via midline sternal incision. To aid with

Table 1. Pertinent laboratory findings

	First operative attempt			After second operative attempt		
	Day 1	Post parathyroidectomy with frozen section	After neck exploration	Day 1	Day 2	Day 3
Magnesium (Normal Value: 1.8-2.6 mg/dL)	1.41	1.68		1.43	1.39	1.29
Ionized Calcium (Normal Value: 1.12-1.32 (mmol/L)	1.83	1.60		1.23	0.93	1.07
PTH (Normal Value: 15-65 pg/mL)	2025.10	1553.90	2180.40	208.80		

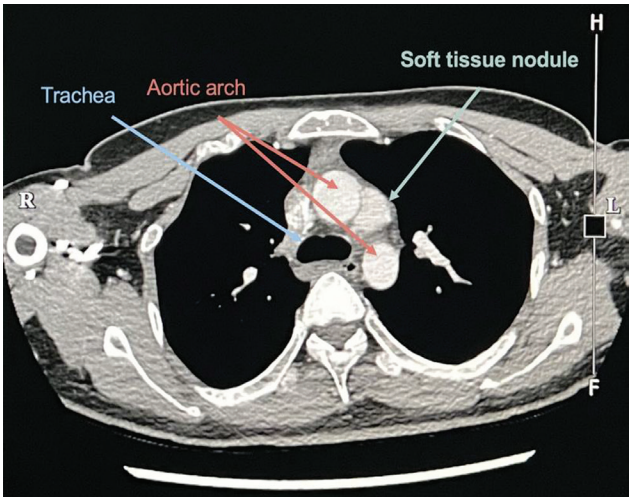

Figure 4. Axial contrast-enhanced CT image shows an enhancing soft tissue nodule in the aortopulmonary window *(labelled)* consistent with an ectopic parathyroid adenoma. This corresponds to the focus of tracer uptake detected on the Tc-99m sestamibi scan.

localization, technetium 99 m sestamibi was administered prior to the procedure and a gamma probe was utilized to confirm the presence of the adenoma. Fifteen minutes after excision of the suspected adenoma, PTH markedly dropped by 89%. Frozen section further confirmed parathyroid adenoma. On gross examination, the specimen obtained was a light brown to light red, irregular, soft to rubbery tissue measuring 2.2 x 1.8 x 0.7 cm and weighing 2.0 grams. Final histopathology report revealed a parathyroid adenoma.

Immediately postoperatively, the patient was started on calcium gluconate drip and transitioned to calcium tablet once he was able to tolerate oral medications together with calcitriol and magnesium supplementation. Ionized calcium and magnesium levels were monitored postoperatively and medications were titrated accordingly. Patient was then cleared for discharge without signs and symptoms of hypocalcemia. On follow-up after 1 week, calcium levels were still low hence, calcitriol was adjusted and compliance to the regimen provided was emphasized. Fracture repair is still on hold while waiting for the prostheses from social services but is planned to be done immediately once available.

DISCUSSION

PHPT is predominant among postmenopausal women although the prevalence varies by country and race.[5] In countries such as the Philippines, screening is not routine hence, PHPT is infrequently seen. According to a report by Lou et al.,[6] the incidence of PHPT is less common in the young (2-5 cases per 100,000) and were usually asymptomatic, unlike in our case.

Hypercalcemia is usually caused by either PHPT or malignancy in 90% of patients.[7] Hence, the approach to diagnosis is to distinguish between the two by using serum PTH. A high serum PTH in the background of hypercalcemia is likely due to PHPT[8] and is most commonly due to an adenoma. Ectopic adenomas have been reported to account for only 4 to 16 % of patients with hyperparathyroidism and are classically described as occurring anywhere from the angle of the mandible to the mediastinum.[9]

Since our patient had elevated serum calcium on top of elevated PTH levels, ultrasound of the neck and sestamibi scan was done to locate the causative etiology similar to the recommendation of Roy et al., for localization in unexplored patients (REF).[4] This then revealed an adenoma in the left superior mediastinal area which the head and neck surgeon operated on with a consideration of an intrathymic parathyroid adenoma based on the imaging studies done.

Due to the persistently elevated PTH levels and histopathology report of thyroid and thymic tissues, a CT scan of the neck and chest was done. This is in line with the algorithm proposed by Yen et al.,[10] for further localization before a second operation. It was recommended that if there is persistent or recurrent PHPT localized with sestamibi studies, a CT or MRI may be done and once with localization, re-operation may be performed. If additional imaging yields no findings, parathyroid angiography with selective vein sampling may be considered. If the lesion remains elusive, conservative management is advised. This was applied to our case, where a CT was done prior to re-operation and revealed a focus on the superior mediastinal area consistent with a residual ectopic parathyroid adenoma.

Surgery is the definitive management of adenoma(s) and when presented with an ectopic location, imaging studies can be used to further locate the lesion. However, the ultimate factor in the success of operations would still be surgical volume as shown by Zarebczan et al.[11] They reported cure rates as high as 95% in initial operations but decreases to 80% for re-operation cases. However, the use of SPECT-CT may be able to localize the ectopic lesions more precisely.[12] The limiting factor for its use in this case was the availability and cost of the SPECT-CT. On a side note, intraoperative gamma probe, PTH monitoring and frozen section were facilitated by the team in this case which contributed to the success of the operation. The PTH levels normalized post-operatively which is consistent with the studies performed for these various intraoperative adjuncts.[13-15]

Post-operatively, hungry bone syndrome (HBS) was observed in this case and was anticipated due to the presence of risk factors such as elevated ALP and high pre-operative PTH levels consistent with the study of Bollerslev et al.[16] Calcium replacement may be done intravenously for symptomatic patients or if there are ECG changes consistent with hypocalcemia. Oral calcium supplements at a range of 6-12 g/day may be given for asymptomatic patients.[17] Magnesium should be replaced if needed since persistently low magnesium would hinder calcium replacement because it may impair PTH production leading to a state resembling hypoparathyroidism.[18]

As to its prognosis, there appears to be a great degree of variability regarding how long it can last. In some case reports, the need for calcium and active vitamin D replacement may last for up to 1 year post-operatively.[19] Hence, follow-up care should also be emphasized to adjust the medications prescribed, with proper monitoring of calcium level post-operatively to avoid further complications.

CONCLUSION

Since calcium levels are frequently included in general laboratory screens, hyperparathyroidism predominantly presents asymptomatically and is common in elderly females. However, in low to middle-income countries, classic manifestations of hyperparathyroidism may be seen, even in the young. Hence, a high index of suspicion is warranted for patients presenting with hypercalcemia and secondary osteoporosis. Furthermore, an ectopic adenoma should be considered especially with persistent PTH elevation after initial surgical intervention. Complete laboratory workups and imaging studies should be performed to better localize the pathologic adenoma. We highlight the value of additional diagnostic tests including CT scan of the neck and chest, intraoperative gamma probe, serial PTH monitoring and frozen section in the success of surgery.

Ethical Considerations
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
KHN: Conceptualization, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision; **RA:** Conceptualization, Validation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References
1. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: A method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417-27. PMID: 11444092. https://doi.org/10.1007/s001980170112.
2. Mazotas IG, Yen TWF, Doffek K, et al. Persistent/recurrent primary hyperparathyroidism: Does the number of abnormal glands play a role? J Surg Res. 2020;246:335-41. PMID: 31635835. https://doi.org/10.1016/j.jss.2019.08.007.
3. Smith G, Prinz RA. Chapter 9. Persistent and recurrent hyperparathyroidism. McGraw-Hill Manual: Endocrine Surgery; 2010. https://accesssurgery.mhmedical.com/content.aspx?bookid=440&sectionid=40161242
4. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013;37(1):102-6. PMID: 22968537. https://doi.org/10.1007/s00268-012-1773-z.
5. Bilezikian JP. Primary hyperparathyroidism. J Clin Endocrinol Metab. 2018;103(11):3993-4004. PMID: 30060226. PMCID: PMC6182311. https://doi.org/10.1210/jc.2018-01225.
6. Lou I, Schneider DF, Sippel RS, Chen H, Elfenbein DM. The changing pattern of diagnosing primary hyperparathyroidism in young patients. Am J Surg. 2017;213(1):146-50. PMID: 27392754. PMCID: PMC5154878. https://doi.org/10.1016/j.amjsurg.2016.03.019.
7. Walls J, Ratcliffe WA, Howell A, Bundred NJ. Parathyroid hormone and parathyroid hormone-related protein in the investigation of hypercalcaemia in two hospital populations. Clin Endocrinol (Oxf). 1994;41(4):407-13. PMID: 7955450. https://doi.org/10.1111/j.1365-2265.1994.tb02569.x.
8. Walker MD, Bilezikian JP. Primary hyperparathyroidism. [Updated 2021 Apr 19]. In: Feingold KR, Anawalt B, Blackman MR, et al. (eds). Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. https://www.ncbi.nlm.nih.gov/books/NBK278923/.
9. Chang BA, Sharma A, Anderson DW. Ectopic parathyroid adenoma in the soft palate: A case report. J of Otolaryngol Head Neck Surg. 2016;45(1):53. PMID: 27756384. PMCID: PMC5069995. https://doi.org/10.1186/s40463-016-0165-z.
10. Yen TW, Wang TS, Doffek KM, Krzywda EA, Wilson SD. Reoperative parathyroidectomy: An algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results in a successful focused approach. Surgery. 2008;144(4):611-9. PMID: 18847646. https://doi.org/10.1016/j.surg.2008.06.017.
11. Zarebczan B, Chen H. Influence of surgical volume on operative failures for hyperparathyroidism. Adv Surg. 2011;45:237-48.
12. Taubman ML, Goldfarb M, Lew JI. Role of SPECT and SPECT/CT in the surgical treatment of primary hyperparathyroidism. Int J Mol Imaging. 2011;2011:141593. PMID: 21776381. PMCID: PMC3139123. https://doi.org/10.1155/2011/141593.
13. Jaskowiak NT, Sugg SL, Helke J, Koka MR, Kaplan EL. Pitfalls of intraoperative quick parathyroid hormone monitoring and gamma probe localization in surgery for primary hyperparathyroidism. Arch Surg. 2002;137(6):659–69. PMID: 12049536. https://doi.org/10.1001/archsurg.137.6.659.
14. Naik AH, Wani MA, Wani KA, Laway BA, Malik AA, Shah ZA. Intraoperative parathyroid hormone monitoring in guiding adequate parathyroidectomy. Indian J Endocrinol Metabol. 2018;22(3):410-6. PMID: 30090736. PMCID: PMC6063190. https://doi.org/10.4103/ijem.IJEM_678_17.
15. Li J, Vasilyeva E, Hiebert J, Britton H, Walker B, Wiseman SM. Limited clinical utility of intraoperative frozen section during parathyroidectomy for treatment of primary hyperparathyroidism. Am J Surg. 2019;217(5):893-8. PMID: 30771863. https://doi.org/10.1016/j.amjsurg.2019.01.032.
16. Bollerslev J, Rejnmark L, Zahn A, et al. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: Recommendations of the ESE educational program of parathyroid disorders. Eur J Endocrinol. 2022;186(2):R33-63. PMID: 34863037. PMCID: PMC8789028. https://doi.org/10.1530/EJE-21-1044.
17. Anwar F, Abraham J, Nakshabandi A, Lee E. Treatment of hypocalcemia in hungry bone syndrome: A case report. Int J Surg Case Rep. 2018;51:335-9. PMID: 30245357. PMCID: PMC6153392. https://doi.org/10.1016/j.ijscr.2018.08.011.
18. Cartwright C, Anastasopoulou C. Hungry bone syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK549880/.
19. Ho LY, Wong PN, Sin HK, et al. Risk factors and clinical course of the hungry bone syndrome after total parathyroidectomy in dialysis patients with secondary hyperparathyroidism. BMC Nephrol. 2017;18(1):12. PMID: 28073343. PMCID: PMC5223390. https://doi.org/10.1186/s12882-016-0421-5.