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CASE REPORT

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Unravelling a hidden pathology of a vertebral fracture in a teenage girl

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Abstract

Background Although the skeleton remains a common target of primary hyperparathyroidism, the classic bone disease "osteitis fibrosa cystica" is currently rare due to early diagnosis. This case represents severe classic bone manifestations of primary hyperparathyroidism due to delayed diagnosis and delayed medical attention.

Case presentation A 19-year-old young female was symptomatically managed for chronic back pain and nonspecific bone pain in the small joints of both hands over 2 months by a general practitioner. The patient had delayed seeking for treatment for 3 months. Later, she was evaluated for tuberculosis, hematological malignancies and rheumatic disorders following a fractured T12 vertebra and underwent pedicle screw fixation. However, clinical examination and investigations, including biochemistry, imaging and histology, ruled out the above conditions. Unfortunately, serum calcium level was not performed at the initial presentation. Later, primary hyperparathyroidism was diagnosed on the basis of moderate hypercalcaemia and elevated intact PTH levels (2064 pg/ml). She had sufficient vitamin D levels and normal kidney function. Her DXA scan revealed severe secondary osteoporosis with the lowest Z score of -8 at the total lumbar spine. Ultrasonography of the thyroid revealed a hypo echoic mass in the left lower neck, and localization studies with technetium-99 m sestamibi and 4D-CT revealed a left inferior parathyroid adenoma (1.6 × 1.5 × 1.6 cm). CT scan also revealed brown tumors in the mandible and vertebrae and diffuse bony changes in the skull, sternum, humerus and vertebrae. Her radiographs revealed subperiosteal bone resorption on the radial aspects of the middle and distal phalanges and brown tumors in both the ulna and fibula. We excluded MEN and other hereditary syndromes in our patient with a personal and family history and with a normal pituitary hormone profile because of poor resources for genetic testing. She underwent parathyroid adenoma excision, and the postoperative period was complicated with hungry bone syndrome, requiring high doses of calcium and active vitamin D supplements. These supplements were gradually weaned off over 6 months, and she recovered with normal biochemical investigations. Histology revealed parathyroid adenoma without malignant features.

Conclusion In developing countries where routine calcium screening is not available, clinicians should be aware of various manifestations of primary hyperparathyroidism to allow diagnosis as soon as possible without delay to prevent further progression, as it is a treatable condition.

Keywords Primary hyperparathyroidism, Osteitis fibrosa cystica, Hungry bone syndrome, Delayed diagnosis

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Background

Primary hyperparathyroidism (PHPT) is a common endocrine disorder of calcium metabolism characterized by hypercalcaemia and inappropriately normal or elevated parathyroid hormone (PTH) secretion from one or more parathyroid glands.

Previously, PHPT was diagnosed as symptomatic classical kidney or skeletal disease with moderate to severe hypercalcaemia. The classic bone disease of PHPT is "osteitis fibrosa cystica", which is characterized by bone pain clinically and subperiosteal bone resorption on the radial aspect of the middle phalanges, tapering of the distal clavicle, salt and pepper skull appearance, bone cysts and brown tumors of long bones radiographically. Furthermore, patients with PHPT have decreased bone mineral density (BMD), in particular at more cortical sites (forearm and hip) than at more trabecular sites (spine) and an increased risk of vertebral fractures [1].

However, early detection of PHPT during the asymptomatic phase is the most common presentation, with routine biochemical screening in the modern era. Unfortunately, target organ damage at presentation predominates in developing countries, such as most Asian countries, where routine biochemical screening is not in practice [2, 3].

Furthermore, delayed medical attention of the patient also results in delayed diagnosis. Additionally, a lack of awareness among clinicians regarding the manifestations of the disease can lead to delayed diagnosis of PHPT, severe progression of disease and unnecessary evaluation. Therefore, early prompt diagnosis is crucial to prevent severe progression, as PHPT is a treatable condition.

Case presentation

A 19-year-old previously healthy teenage girl was evaluated for chronic back pain and pain in the small joints of both hands for 2 months by a general practitioner after delayed medical attention for 3 months. During that time, specific investigations were not conducted and only managed symptomatically. Later, she was admitted to the orthopedic discipline with a fractured T12 vertebra.

The back pain was mechanical in nature, and there was no history of trauma. She reported nonspecific bone pain in the small joints of the hand without early morning stiffness. There was no history of other large or small joint pain, oral ulcers or alopecia suggesting a rheumatic disorder. There was no history of constitutional symptoms such as fever, weight loss or loss of appetite. She denied having chronic cough, or a past or contact history of tuberculosis. There was no personal or family history suggestive of malignancies, particularly hematological malignancies.

Initially, she was evaluated for tuberculosis, hematological malignancies such as leukemia and lymphoma, and rheumatic disorders, which are common diseases among young females in Sri Lanka. Unfortunately serum calcium evaluation was not performed at the initial presentation. Her clinical examination and investigations, including biochemistry, imaging and histology, ruled out the above conditions. She underwent pedicle screw fixation for the fractured T12 vertebra.

She was subjected to further extended investigations for diagnosis. A few weeks later, PHPT was diagnosed as moderate hypercalcaemia with elevated second-generation intact parathyroid hormone (PTH) levels.

On further questioning, she was not aware of polyuria, polydipsia or constipation. She did not have obvious psychiatric manifestations. She was not on any medications, particularly steroids. Family history was not significant for recurrent young-onset fractures, hypercalcaemia, neck surgeries or other features suggestive of MEN and other syndromes. She had regular menstruation. There were no palpable neck masses during examination.

She had sufficient vitamin D levels. Her renal function was normal, and there was no ultrasonic evidence of nephrolithiasis or nephrocalcinosis. Compared to the

Table 1 Laboratory results of the patient

Laboratory tests	Preoperative value	Postoperative value		Reference	Unit
		Soon after surgery	After 6 months		
Albumin corrected calcium	12.4	7.5	9.0	8.40–10.20	mg/dL
Phosphate	1.9	1.5	3.75	2.3–4.7	mg/dL
Alkaline phosphatase	1244		250	40–150	U/L
Intact PTH	2064	157	52	16-60.4	pg/mL
Magnesium		1.2		1.7–2.2	mg/dL
Erythrocyte sedimentation rate (ESR)	15				mm/ 1st hour
Serum creatinine	0.60	0.69		0.57–1.1	mg/dL
Spot urine calcium/ creatinine ratio	0.478			< 0.14	mg/mg
Vitamin D level	42			30–100	ng/mL
9am cortisol	224			101–536	nmol/L
Thyroid stimulating hormone (TSH)	2.76			0.35-4.94	mU/L
Prolactin	301			102–496	mIU/mL

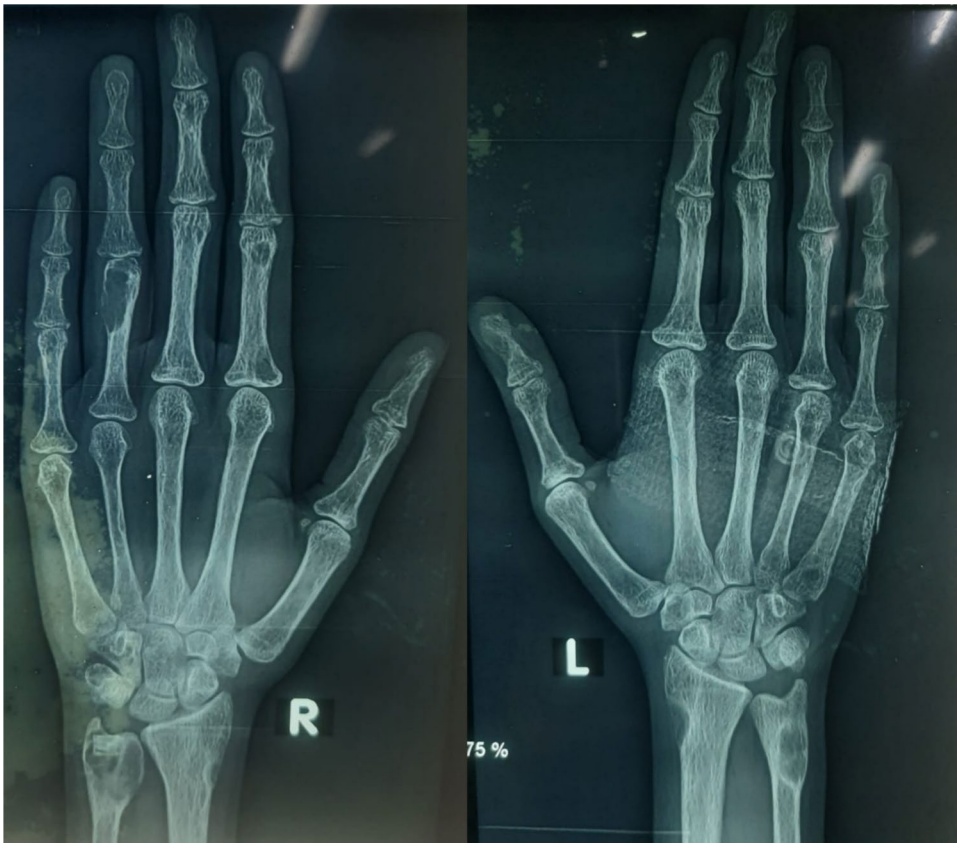

Fig. 1 X-ray of both hands showing subperiosteal bone resorption on the radial aspects of the middle and distal phalanges and brown tumors in the proximal phalanges and in both the ulna and radius

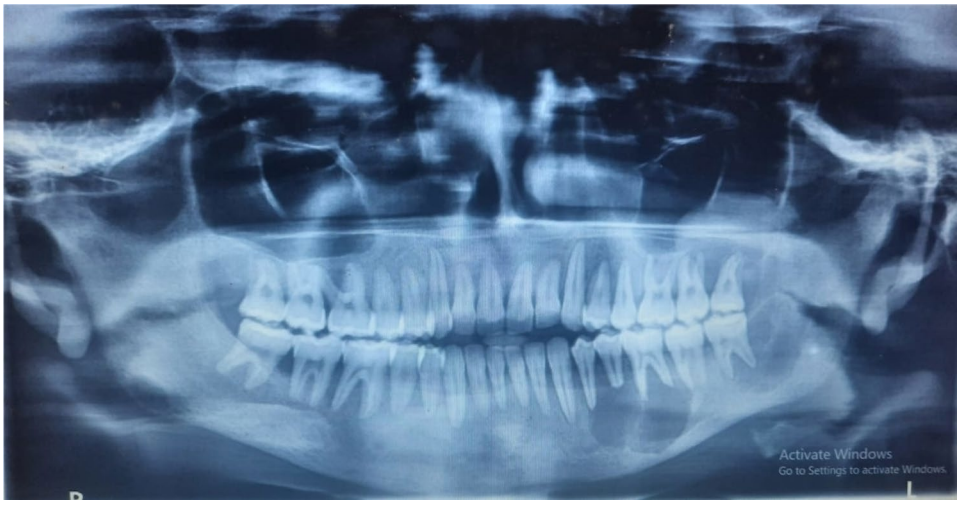

Fig. 2 orthopantomography image of a brown tumor in the mandible

age- and sex-matched population, she had the lowest Z score of -8 at the total lumbar spine on the DXA scan. This finding indicated the presence of a cause for secondary osteoporosis. Her radiographs revealed subperiosteal bone resorption on the radial aspects of the middle and distal phalanges and brown tumors in both the ulna and fibula.

In parallel, imaging studies for localization were arranged. The USS thyroid revealed a hypo echoic mass in the left lower neck, and a technetium-99 m sestamibi scan revealed an active left inferior parathyroid adenoma.

4D-CT revealed a left inferior parathyroid adenoma measuring 1.6×1.5×1.6 cm. CT scan also revealed brown tumors in the mandible and vertebrae and diffuse bony changes in the skull, sternum, bilateral humerus and vertebrae.

Association between MEN and other syndromes were excluded with a personal and family history and with a normal pituitary profile, as genetic studies are widely not available in Sri Lanka. Biochemical screening for pheochromocytoma was not performed because of poor resources.

Her hypercalcaemia was managed with adequate hydration. She underwent minimally invasive left-sided inferior parathyroidectomy with intraoperative PTH monitoring. Macroscopically, the tumor appeared benign without suspicious features for malignancy, such as irregularity, lobulation, a hard capsule or attachment to adjacent structures. An intraoperative PTH reduction of more than 50% from baseline within 10 min was observed. [Baseline and 10 min values were 2064 pg/mL and 157 pg/mL, respectively.)

Unfortunately, her postoperative period was complicated by hungry bone syndrome, with an albumin-corrected calcium concentration of 7.5 mg/dL, a phosphate concentration of 1.5 mg/dL and a magnesium concentration of 1.2 mg/dL. She was treated with higher doses of both intravenous and oral calcium and active vitamin D supplements and was discharged on day 10 with oral supplements. These supplements were gradually weaned off over 6 months after surgery, and she currently has normal calcium, phosphate and PTH levels and is cured of the disease. Currently, she has started to mobilize independently, with improved quality of life. Her DXA scan at 6 months after surgery was completely normal.

Histology was compatible with parathyroid adenoma without suspicious malignant features such as capsular invasion, vascular invasion, thick fibrous septa, nuclear atypia, an infiltrative growth pattern or atypical mitosis.

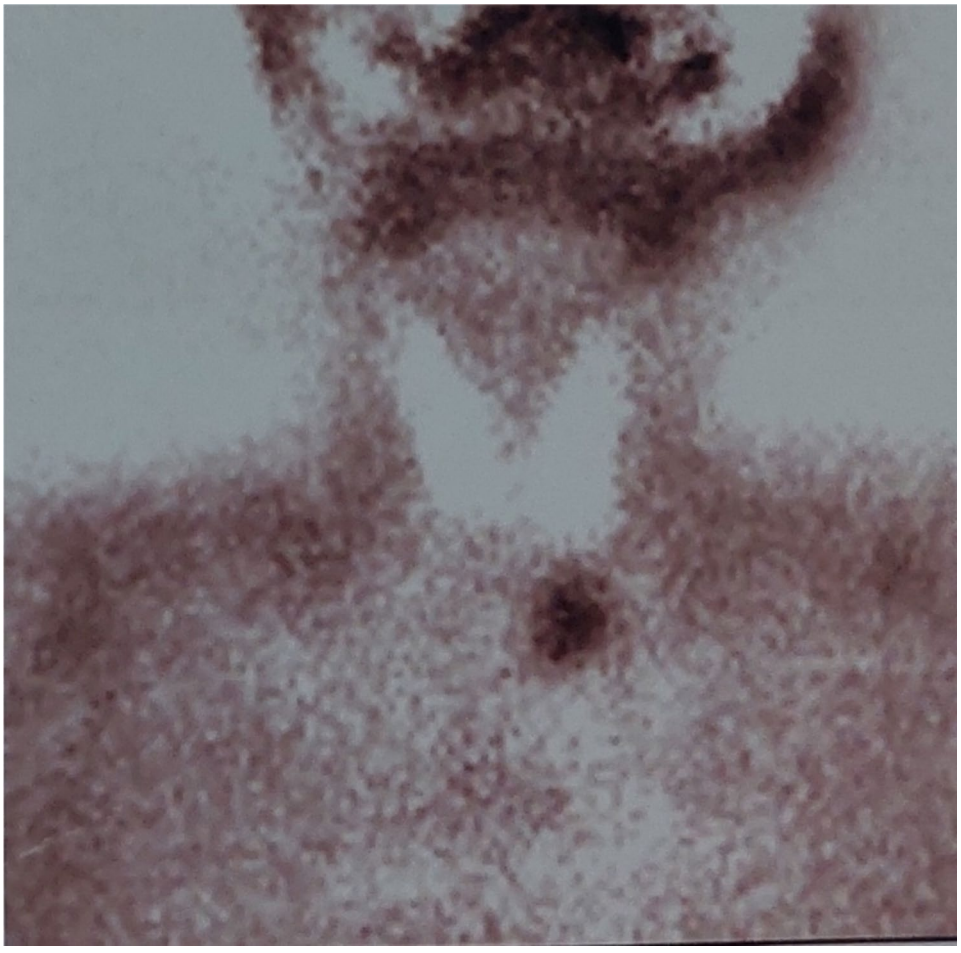

Fig. 3 Technetium-99 m sestamibi scan showing increased tracer activity just below the lower pole of the left thyroid gland

Discussion

The most common presentation of PHPT is asymptomatic hypercalcaemia with routine biochemical screening. However, symptomatic disease is more common in resource-limited countries.

Normocalcaemic PHPT is another variant of PHPT, is diagnosed in the context of nephrolithiasis or metabolic bone disease and is characterized by normal serum calcium levels when measured at least twice over 6 months despite elevated PTH levels after excluding the causes for secondary hyperparathyroidism [4].

The important factors determining the presentation of disease are the availability of routine biochemical screening, the prevalence of vitamin D deficiency, screening for PHPT with a diagnosis of osteoporosis or osteopenia and awareness among clinicians regarding the manifestations of disease.

Although the incidence of target organ damage has greatly decreased in the modern era, classical manifestations of PHPT are still present in our country setting, where universal biochemical screening of PHPT is not available.

A lack of awareness among clinicians regarding the various manifestations of the disease also leads to delayed diagnosis. Furthermore, delayed medical attention of the patient also contributes to delayed diagnosis. Our patient was evaluated for 2 months by a general practitioner after delayed medical attention for 3 months. During that time, specific investigations were not conducted and only managed symptomatically. Later, she was admitted to the orthopedic discipline with a vertebral fracture. Initially, she was evaluated for tuberculosis, hematological malignancies and rheumatic disorders, which are common in our country. Unfortunately calcium evaluation was not performed at initial presentation. A few weeks later, PHPT was identified as having a hidden etiology for the vertebral fragility fracture through serum calcium and further investigations. However, PHPT should be suspected quickly in a young patient presenting with fracture or bone lesions and serum calcium evaluation should be performed as soon as possible. Therefore, clinicians must be aware of the spectrum of manifestations of PHPT for prompt diagnosis without delay to prevent progression and to avoid unnecessary evaluation.

Bone disease and kidney stones are classical target organs affected in PHPT. Back pain is one of the most frequent symptom in general practice that can lead patients to consult various specialties, including general practitioners, rheumatologists, orthopedists and neurosurgeons. Therefore, interdisciplinary collaboration is necessary in this situation.

The classic imaging appearance is osteitis fibrosa cystica (OFC), which is relatively rare today. OFC is characterized by bone pain clinically and subperiosteal bone resorption on the radial aspect of the middle phalanges, tapering of the distal clavicle, a salt and pepper skull appearance, bone cysts and brown tumors of long bones radio graphically. Parathyroidectomy results in complete regression of brown tumors in most patients [5].

Decreased BMD is a well-recognized skeletal manifestation of PHPT. PHPT preferentially affects the peripheral skeleton rather than the axial skeleton. On the other hand, postmenopausal osteoporosis tends to affect the axial skeleton more prominently. Therefore, BMD should be measured at the lumbar spine, hip and distal third of the forearm in the evaluation of PHPT.

A recent population-based study revealed that patients with PHPT had an increased overall risk of fractures including fractures of the vertebrae, distal forearm and the pelvis, with a mild increase in the risk of femoral fractures. These findings indicate that PHPT has an impact on cancellous bone in addition to cortical bone. All of the above bone manifestations can be prevented if early diagnosis of PHPT is warranted [6].

MEN and other hereditary syndromes associated with PHPT should be considered when evaluating young patients with PHPT [7]. However, we excluded hereditary associations in our patient with a personal and family history and a with normal pituitary hormone profile because of poor resources for genetic testing.

After the biochemical diagnosis of PHPT, preoperative localization studies help with planning a minimally invasive approach for patients with single-gland disease. Approximately 80% of patients have a single parathyroid adenoma, 10% have more than one adenoma, another 10% have hyperplasia in 4 glands, and less than 1% of patients have parathyroid carcinoma. Multiple imaging modalities are available for localization. Commonly utilized first-line imaging methods include ultrasonication, technetium-99 m sestamibi scanning and 4D-CT scanning [8].

Symptomatic patients with PHPT should undergo parathyroid surgery because it cures the disease, improves BMD, decreases fracture risk and decreases the formation of renal stones. However, there are proposed criteria by a fourth international workshop on PHPT for asymptomatic patients to proceed with surgery, as most of them do not have disease progression. Surgery is recommended for asymptomatic patients for whom one or more of the following conditions are present [9].

1. Age younger than 50 years.
2. Serum calcium greater than 1 mg/dL above the upper limit of normal.
3. A T-score greater than – 2.5 was given at the lumbar spine, total hip, femoral neck or distal 1/3 of the radius.
4. Vertebral fracture on imaging.

5. eGFR < 60 mL/min/1.73 m^2.
6. Twenty-four-hour urinary calcium > 400 mg/day.
7. Presence of nephrolithiasis or nephrocalcinosis on imaging.

The rapid intraoperative PTH assay method is useful for confirming the successful removal of adenoma. It takes advantage of the short half-life (three to five minutes) of PTH. In Sri Lanka, the ">50% reduction criterion" is commonly used to assess success [10]. A "Cure" in PHPT can be established when normocalcaemia lasts at least 6 months after surgery [11].

Postoperative hypocalcaemia can occur due to hypoparathyroidism or hungry bone syndrome (HBS). HBS is caused by the massive transfer of calcium into bone tissue and is associated with rapid, severe and prolonged hypocalcaemia, hypophosphatemia and hypomagnesemia. High PTH levels, large parathyroid adenoma, severe hypercalcaemia, the presence of bone disease and vitamin D deficiency are risk factors for HBS. Treatment requires very high doses of calcium and active vitamin D supplements. High-risk patients should be monitored carefully during the postoperative period for the development of HBS [12].

Conclusion

Patients with PHPT still present with severe skeletal and other end-organ damage due to delayed diagnosis, especially in developing countries, where routine calcium screening is lacking, in addition to delayed medical attention. Therefore, awareness among clinicians regarding cases and details of manifestations of PHPT is valuable for prompt diagnosis and management to prevent further progression of the disease and avoid unnecessary evaluation.

Abbreviations

PHPT	Primary hyperparathyroidism
OFC	Osteitis fibrosa cystica
PTH	Parathyroid hormone
DXA	Dual energy X-ray absorptiometry
BMD	Bone mineral density
4D	CT scan-4 dimensional computed tomography scan
MEN	Multiple endocrine neoplasia
HBS	Hungry bone syndrome

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Author contributions

S.S - prepared the main manuscript text, S.W.G - prepared Table 1; Fig. 1, M.F - prepared Fig. 2, U.B - prepared Fig. 3, All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

Consent from the patient was obtained.

Consent for publication

Written informed consent has been obtained from the patient for publication of the case report and accompanying images.

Competing interests

The authors declare no competing interests.

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References

1. Jouan A, Zabraniecki L, Vincent V, Poix E, Fournié B. An unusual presentation of primary hyperparathyroidism: severe hypercalcemia and multiple brown tumors. Joint Bone Spine. 2008;75(2):209–11. https://doi.org/10.1016/j.jbspin.2007.03.00
2. Bilezikian JP. Primary hyperparathyroidism. J Clin Endocrinol Metabolism. 2018;103(11):3993–4004. https://doi.org/10.1210/jc.2018-01225
3. Pradeep PV, Jayashree B, Mishra A, Mishra SK. Systematic review of primary hyperparathyroidism in India: the past, present, and the future trends. Int J Endocrinol. 2011;2011:921814. https://doi.org/10.1155/2011/921814
4. Cusano NE, Cetani F. Normocalcemic primary hyperparathyroidism. Archives Endocrinol Metabolism. 2022;66(5):666–77. https://doi.org/10.20945/2359-3997000000556
5. Noriega-Jalil AB, Valverde-García YA, García-Barajas J, Hernández HG, González-Torres JA, Ramos-Armengol DC, Garrido-Mendoza AP, González-Virla B, Vargas-Ortega G, López-Juárez NG, Mendoza-Zubieta V. Mandibular brown tumor as atypical presentation of primary hyperparathyroidism: two case reports and literature review. AACE Clin Case Rep. 2018;4(3):203–8. https://doi.org/10.4158/EP171967.CR
6. Khosla S, Melton LJ 3rd, Wermers RA, Crowson CS, Wm OF. Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Min Res. 1999;14(10):1700–7. https://doi.org/10.1359/jbmr.1999.14.10.1700
7. Simonds WF. Familial syndromes of primary hyperparathyroidism. In Mineral deficiencies-electrolyte disturbances, genes, diet and disease interface. 2020 Jul 7. IntechOpen. https://www.intechopen.com/chapters/72573#:~:text=DOI%3A 10.5772/intechopen.93036
8. Uludağ M. Preoperative localization studies in primary hyperparathyroidism. Şişli Etfal Hastanesi Tip Bülteni. 2019;53(1):7–15. https://doi.org/10.14744/SEMB.2019.78476
9. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. The Journal of Clinical Endocrinology & Metabolism. 2014;99(10):3561-9. https://doi.org/10.1210/jc.2014-1413
10. Wharry LI, Yip L, Armstrong MJ, Virji MA, Stang MT, Carty SE, McCoy KL. The final intraoperative parathyroid hormone level: how low should it go? World J Surg. 2014;38(3):558–63. https://doi.org/10.1007/s00268-013-2329-6
11. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, Doherty GM, Herrera MF, Pasieka JL, Perrier ND, et al. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2016;151:959–68. https://doi.org/10.1001/jamasurg.2016.2310
12. Rolighed L, Bollerslev J, Mosekilde L. Vitamin D treatment in primary hyperparathyroidism. Curr Drug Saf. 2011;6:100–7. https://doi.org/10.1210/jc.2013-3978

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