The importance of laboratory analyses in unmasking parathyroid adenoma in a patient with breast cancer: a case report of persistent hypercalcemia with low vitamin D status

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European Journal of Medical Case Reports
Volume 9(9):234–238
DOI: 10.24911/ejmcr.9-2277

ABSTRACT

Background: Parathyroid adenoma is a frequent cause of hyperparathyroidism. Its association with D hypovitaminosis can complicate this pathological state, especially in the case of delayed surgical intervention.

Case presentation: This case report presents a 77-year-old female patient with a complex medical history, including dyslipidemia, hypertension, who developed primary hyperparathyroidism due to a parathyroid adenoma. The persistent hypercalcemia, elevated parathyroid hormone, and parathyroid scintigraphy led to the diagnosis, but the low 25-hydroxyvitamin D level complicated the picture. Due to personal decisions and the COVID-19 pandemic, surgery was delayed for 6 years, resulting in complications such as vitamin D deficiency-induced immunosuppression and osteoporosis. Post-surgical outcomes were favorable, with normalization of biochemical markers and stabilization of comorbid conditions.

Conclusion: This case highlights that timely multidisciplinary management is essential in primary hyperparathyroidism, as surgical delay worsens complications, yet parathyroidectomy can still reverse outcomes even after years of progression.

Keywords: Case report, hypercalcemia, low vitamin D status, primary hyperparathyroidism.

Type of Article: CASE REPORT **Specialty:** Endocrinology

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Received: 06 July 2025
Revised (1): 18 September 2025
Accepted: 22 September 2025

Introduction

The most common cause of primary hyperparathyroidism (PHPT) is a parathyroid adenoma [1]. The usual presentation encompasses biochemical abnormalities such as hypercalcemia and elevated parathyroid hormone (PTH). PTH causes increased bone resorption and renal tubular reabsorption of calcium. However, vitamin D deficiency, characterized by low serum levels of 25-hydroxyvitamin D (25-OH-D), can complicate this condition further. Treatment delays can result in systemic complications, including osteoporosis and immunological deficits [2]. This delay in surgical intervention and its consequences are notable in this patient with a history of breast cancer.

Case Presentation

A 77-year-old female patient with a history of dyslipidemia and hypertension was followed for a remote history of breast cancer (1994) managed with surgery, chemotherapy, and radiotherapy (Table 1) with negative axillary nodes and chronic left-arm lymphoedema. Tumor markers (CA 15-3 and CA 125) remained within reference intervals on surveillance. Routine testing between 2016 and 2022 (Table 2) showed persistent hypercalcemia with preserved renal function and progressively elevated PTH; the first increase in calcemia was observed in January 2015 with a value of 10.53 mg/dl.

Vitamin D deficiency work-up considered dietary intake, sun exposure, and malabsorption, but no alternative cause was identified beyond PHPT-related dysregulation. The patient's hypercalcemia was initially attributed to prior breast cancer or chronic illness, delaying endocrinology referral. This is a frequent pitfall, given that 10%-30% of cancer patients develop hypercalcemia [3]. This, therefore, shows the importance of routine inclusion of serum PTH levels in the evaluation of unexplained hypercalcemia, especially in patients with prior malignancy. Further follow-up analyses demonstrated elevated PTH and a decrease in 25-OH-D levels. This warranted an endocrinology referral. Physical examination was unremarkable with no palpable neck masses, leading to imaging examinations being done (scintigraphy and ultrasound) (Figures

Table 1. *Timeline of key clinical events.*

DATE	EVENT
1994	Breast cancer diagnosis and treatment
2016-2022	Persistent hypercalcemia detected on routine laboratory examinations
2022	Diagnosis of parathyroid adenoma, surgery performed
2022-2024	Postoperative normalization and continuous follow-up

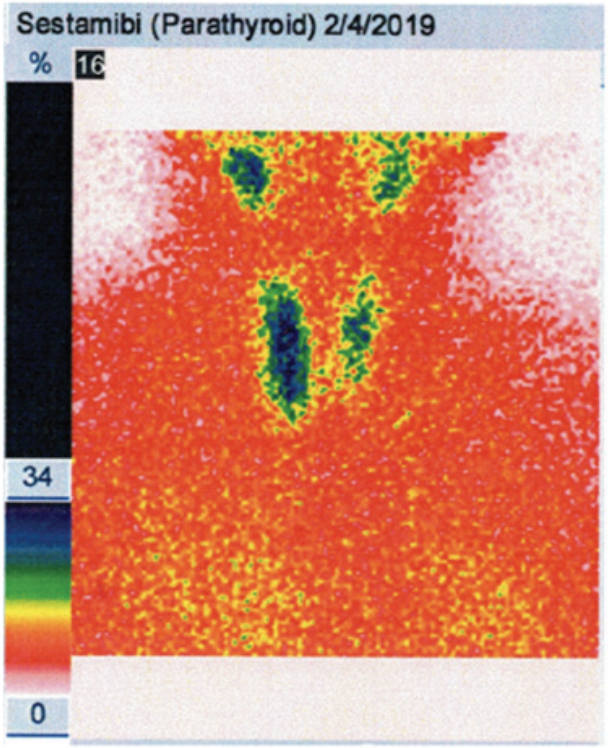

Figure 1. *Parathyroid scintigraphy with Tc-99m Sestamibi, showing increased focal radiotracer uptake in the left of the image (seen as darker blue/green zones), localizing the lesion and informing surgical planning.*

1 and 2) [4]. Through these investigations, a left-sided parathyroid tumor could be identified.

Despite the diagnosis, surgical treatment was delayed due to the COVID-19 pandemic and personal reasons (mainly fear of surgery). During the 6-year delay, the patient developed immunosuppression secondary to vitamin D deficiency and was diagnosed with osteoporosis (Figure 3). Bisphosphonate therapy with *ibandronate* was initiated with the patient reporting adverse oromaxillofacial (OMF) effects.

On the 4th of May 2022, after excluding multiple endocrine neoplasia type 1 and type 2 syndromes, the patient underwent successful parathyroidectomy. Histopathology confirmed a parathyroid adenoma. Postoperative recovery was uneventful. Total and ionic calcium, and PTH were normalized within a few months with subsequent correction of 25-OH vitamin D with supplementation (Table 3). Vitamin D supplementation was continued to maintain adequate levels. Tumor markers associated with breast cancer (CA 15-3 and CA 125) monitoring remained within normal limits with no signs of recurrence; CA 15-3 was 21.3 IU/ml (NR: 1-32.4 IU/ml) and CA 125 was 7.4 IU/ml (NR: 0-35 IU/ml), respectively, measured in July, 2016. The patient is followed up every six months with no pathological findings to date.

Discussion

PHPT is characterized by excessive secretion of PTH, most commonly due to a benign parathyroid adenoma. PTH plays a central role in calcium homeostasis, and its dysregulation can have many systemic effects. This case report shows the clinical trajectory of prolonged, untreated PHPT and the resulting systemic complications, offering insight into the underlying hormonal mechanisms and the importance of prompt intervention.

Serum calcium levels are tightly regulated through a complex interaction between the parathyroid glands, kidneys,

Table 2. *Laboratory data from 2016 to 2022 (NR: normal range).*

DATE	TOTAL SERUM CALCIUM	IONIC SERUM CALCIUM	SERUM PTH LEVEL	5-OH-VIT. D LEVEL
17.11.2016	11.82 mg/dl (NR: 8.8-10.2 mg/dl)	5.4 mg/dl (NR: 3.82-4.82 mg/dl)	161 pg/ml (NR: 15-65 pg/ml)	22 ng/ml (NR: 30-50 ng/ml)
06.04.2017	11.1 mg/dl (NR: 8.8-10.2 mg/dl)	5 mg/dl (NR: 3.82-4.82 mg/dl)	214 pg/ml (NR: 15-65 pg/ml)	16 ng/ml (NR: 30-50 ng/ml)
09.05.2018	12.63 mg/dl (NR: 8.8-10.2 mg/dl)	5.21 mg/dl (NR: 3.82-4.82 mg/dl)	250.9 pg/ml (NR: 15-65 pg/ml)	15.3 ng/ml (NR: 30-50 ng/ml)
20.11.2019	11.1 mg/dl (NR: 8.8-10.2 mg/dl)	4.93 mg/dl (NR: 3.82-4.82 mg/dl)	299.4 pg/ml (NR: 15-65 pg/ml)	12.9 ng/ml (NR: 30-50 ng/ml)
02.03.2020	10.74 mg/dl (NR: 8.8-10.2 mg/dl)	4.93 mg/dl (NR: 3.82-4.82 mg/dl)	303.5 pg/ml (NR: 15-65 pg/ml)	11.9 ng/ml (NR: 30-50 ng/ml)
15.10.2021	12.83 mg/dl (NR: 8.8-10.2 mg/dl)	5.73 mg/dl (NR: 3.82-4.82 mg/dl)	242.3 pg/ml (NR: 15-65 pg/ml)	-
21.03.2022	11.9 mg/dl (NR: 8.8-10.2 mg/dl)	5.3 mg/dl (NR: 3.82-4.82 mg/dl)	211.5 pg/ml (NR: 15-65 pg/ml)	-

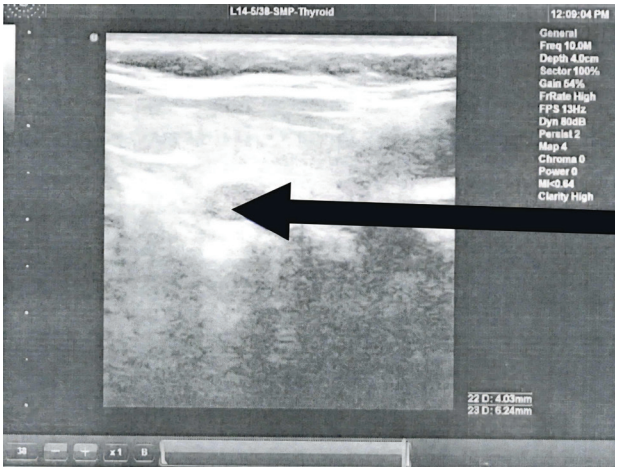

Figure 2. *Ultrasound image showing an inferior 4.03 × 6.24 mm, hypoechogenic nodule, confirmed by scintigraphy as a parathyroid adenoma, marked with a black arrow.*

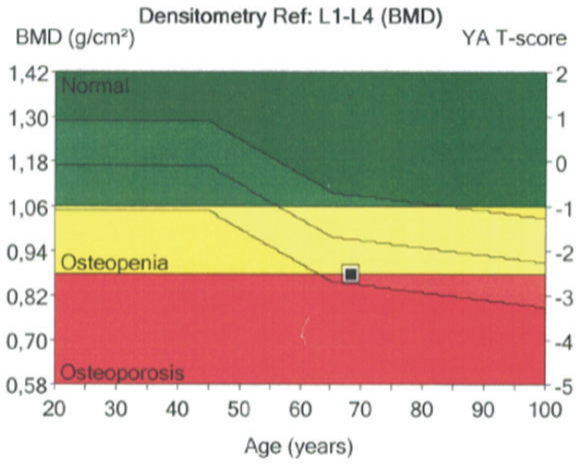

Figure 3. *Dual-energy X-ray absorptiometry scan result showing BMD for the L1-L4 spinal region, plotted against age with a T-score of approximately –2.5, indicating osteoporosis. This influenced perioperative management and the decision to initiate antiresorptive therapy.*

bones, and the gastrointestinal (GI) tract [5]. At the GI tract, the stimulation of the renal 1-alpha hydroxylase enzyme by PTH enhances intestinal calcium absorption through the conversion of the inactive 25-hydroxyvitamin D_3 (25-hydroxycholecalciferol) into the active 1,25-dihydroxyvitamin D_3 (1,25-dihydroxycholecalciferol or calcitriol) form.

In PHPT, secretion of PTH becomes autonomous, disregarding normal feedback inhibition by serum calcium levels. This results in chronic hypercalcemia, elevated PTH levels, and reduced serum 25-OH vitamin D_3, which is due to negative feedback inhibition of 1-alpha hydroxylase. The patient in this case presented with persistently elevated serum calcium and PTH levels over several years, accompanied by vitamin D deficiency. This patient's condition came with a significant diagnostic challenge due to the overlap in clinical manifestations of PHPT and malignancy-associated hypercalcemia. These two pathologies represent 80%-90% of all cases of hypercalcemia. Parathyroid hyperfunction is more frequent in ambulant patients, while cancer-related hypercalcemia is more common in hospitalized subjects [6]. In oncological practice, hypercalcemia in a patient with a history of breast cancer often triggers concern for bone metastases or paraneoplastic syndromes due to ectopic production of PTH-related peptide (PTHrP) [6,7]. Humoral hypercalcemia of malignancy (HHM) is a well-characterized syndrome where elevated levels of PTHrP lead to hypercalcemia, resembling the effects of elevated PTH, but originating from non-parathyroid tumors [8]. In patients with HHM, the presence of cancer often results in markedly decreased to undetectable serum PTH levels, contrasting sharply with the elevated calcium levels typically noted. Rarely, parathyroid carcinoma can produce excessive PTH, leading to significant metabolic disturbances, particularly hypercalcemia [9]. However, in our patient, thorough laboratory analysis, imaging studies, and histopathological examination confirmed a left-sided parathyroid adenoma as the underlying cause of hypercalcemia. Vitamin D deficiency in this context was likely multifactorial; chronic PTH elevation depleting vitamin D stores and low 25-OH vitamin D_3 reducing intestinal calcium absorption, further worsening PTH secretion. The delayed surgical intervention for six years, due to the pandemic and patient-related factors, led to significant secondary complications, including immunosuppression and osteoporosis. The pathophysiology behind these findings can be related to inadequate levels of vitamin D and PTH. Since vitamin D is crucial for immune function, through enhancing innate immunity and modulating adaptive responses, its deficiency has been associated with increased susceptibility to infections and impaired wound healing [10]. Chronic PTH excess accelerates bone resorption, particularly in cortical bone, predisposing patients to osteopenia and fractures [11]. Bone mineral density (BMD) loss is a well-documented consequence of PHPT. To mitigate osteoporosis, the patient was treated with *ibandronate* but reported adverse OMF symptoms. A well-known and serious risk associated with bisphosphonate use is osteonecrosis of the jaw (ONJ) [12]. This complication can also occur as a manifestation of cancer or metabolic bone disease in patients; therefore, implementing pre-treatment dental evaluations and balancing antiresorptive therapy in patients with overlapping skeletal and oncological comorbidities is crucial. The coexistence of breast cancer and parathyroid adenoma, although not pathophysiologically linked, complicated the differential diagnosis by producing overlapping biochemical consequences such as hypercalcaemia. While both conditions are relatively common in elderly

Table 3. *Post-operative laboratory values (2022-2024) (NR: normal range).*

DATE	TOTAL SERUM CALCIUM	IONIC SERUM CALCIUM	SERUM PTH LEVEL	5-OH-VIT. D LEVEL
20.05.2022	8.7 mg/dl (NR: 8.8-10.2 mg/dl)	4.1 mg/dl (NR: 3.82-4.82 mg/dl)	118.2 pg/ml (NR: 15-65 pg/ml)	11.8 ng/ml (NR: 30-50 ng/ml)
16.08.2022	9.6 mg/dl (NR: 8.8-10.2 mg/dl)	4.3 mg/dl (NR: 3.82-4.82 mg/dl)	43.01 pg/ml (NR: 15-65 pg/ml)	-
04.05.2023	-	4.4 mg/dl (NR: 3.82-4.82 mg/dl)	-	45.5 ng/ml (NR: 30-50 ng/ml)
28.03.2024	9.3 mg/dl (NR: 8.8-10.2 mg/dl)	4.3 mg/dl (NR: 3.82-4.82 mg/dl)	31.54 pg/ml (NR: 15-65 pg/ml)	40.1 ng/ml (NR: 30-50 ng/ml)

women, their occurrence in the same patient is rare and confounding, underscoring the need for careful evaluation and integrated management across Endocrinology, Surgery, Oncology, Laboratory Medicine, and Pathology [7,13,14]. Postoperatively, normalization of biological markers was achieved, as well as immunological and skeletal parameters stabilized, illustrating the effectiveness of parathyroidectomy in reversing systemic complications.

Conclusion

Delayed surgery in PHPT can worsen systemic outcomes such as skeletal demineralization and immune vulnerability. In oncology patients, hypercalcemia should not be automatically attributed to malignancy; biochemical evaluation for PHPT is essential. In this case, multidisciplinary collaboration enabled accurate diagnosis, which ultimately normalized biochemical parameters and stabilized comorbidities.

The coexistence of breast cancer and parathyroid adenoma created a rare diagnostic paradox, resolved only through careful laboratory work-up and imaging. The six-year surgical delay allowed the progression of complications that might have been avoided with earlier referral. However, diligent follow-up and care across Oncology, Laboratory Medicine, Endocrinology, Surgery, and Pathology ensured successful management. This case illustrates how multidisciplinary coordination can help manage comorbidities and achieve positive outcomes even after years of disease progression.

- **Improving management:**

The 6-year delay in surgical treatment, influenced by the COVID-19 pandemic and patient hesitancy, allowed the disease to progress. During this period, the patient developed secondary conditions, including vitamin D deficiency-associated immunosuppression and osteoporosis. Earlier referral to endocrinology, more direct patient counselling on the risks of prolonged hypercalcemia, and proactive surgical planning may have prevented these complications.

- **Unexpected outcomes:**

Although appropriate for managing osteoporosis, employing bisphosphonates in this patient resulted in OMF side effects potentially indicative of ONJ. This emphasizes conducting dental evaluations before initiating bisphosphonate treatment and close monitoring for adverse effects. Additionally, the vitamin D deficiency may have masked the severity of PHPT, as low vitamin D levels can blunt calcium absorption and attenuate hypercalcemia.

- **Value of multidisciplinary monitoring:**

Despite the challenges, this case was managed successfully, and the correct diagnosis was established through biochemical profiling and confirmatory imaging, demonstrating appropriate diagnostic work-up. After the patient consented to surgery, the procedure was executed without complications, resulting in the resolution of biochemical abnormalities and stabilization of bone metabolism. Postoperative follow-up was diligent, with routine monitoring of serum calcium, PTH, vitamin D levels, and tumor markers - all of which remained within normal limits. The interdisciplinary collaboration between specialists in Oncology, Laboratory Medicine, Endocrinology, Surgery and Pathology facilitated a comprehensive management approach, particularly given the patient's history of breast cancer. Continued surveillance of tumor markers also ensured there was no recurrence of malignancy.

The patient expressed relief after surgery and satisfaction with the resolution of symptoms. She is compliant with the current therapy and follow-up regimen and has been in good health.

What is new?

Persistent hypercalcemia in patients with cancer history should not be assumed malignant without excluding PHPT using PTH and vitamin D testing. This case highlights how timely diagnosis and management of PHPT can prevent long-term complications such as osteoporosis and immunosuppression. Multidisciplinary collaboration is essential for achieving optimal outcomes in complex clinical scenarios, even after delays.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

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

Ethics approval

Not required for single patient, anonymous case report at our institution.

List of Abbreviations

BMD	Bone mineral density
CaSR	Calcium sensing receptors
DCT	Distal convoluted tubules
GI	Gastrointestinal
HHM	Humoral hypercalcemia of malignancy
OMF	Oromaxillofacial
ONJ	Osteonecrosis of the jaw
PCT	Proximal convoluted tubules
PHPT	Primary hyperparathyroidism
PTH	Parathyroid hormone
PTHrp	Parathyroid hormone-related peptide
RANKL	Receptor activator of nuclear factor kappa-B ligand

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Summary of the case

1	**Patient (gender, age)**	Female, 77 years old
2	**Final diagnosis**	Parathyroid adenoma
3	**Symptoms**	Persistent hypercalcemia, osteoporosis, vitamin D deficiency, immunosuppression
4	**Medications**	Ibandronate
5	**Clinical Procedure**	Parathyroidectomy
6	**Specialty**	Endocrinology, Laboratory Medicine, Oncology, Pathology, Surgery